Engaging Esters as Cross-Coupling Electrophiles

by

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In Memory of the Surgeon <u>Dr. Mohamed Taïeb Ben Halima</u>

I wanted to share these moments with you my Father

Miss you a lot!

Abstract

Cross-coupling reactions, where a transition metal catalyst facilitates the formation of a new carbon-carbon or carbon-heteroatom bond between two coupling partners, has become one of the most widely used, reliable, and robust family of transformations for the construction of molecules. The Nobel Prize was awarded to pioneers in this field who primarily used aryl iodides, bromides, and triflates as electrophilic coupling partners. The expansion of the reaction scope to non-traditional electrophiles is an ongoing challenge to enable an even greater number of useful products to be made from simple starting materials. The major goal of this thesis research is to improve and expand upon this field by using esters as electrophiles via the activation of the strong C(acyl)−O bond. Esters are particularly robust in comparison to other carboxylic acid derivatives used in cross-coupling reactions. Success on the activation of such inert functional group using catalysis has both fundamental and practical value. By discovering new reaction modes of this abundant functional group, synthetic routes to access novel or industrially important molecules can be improved.

Chapter 1 of this thesis describes a literature overview of what has been accomplished in the field of cross coupling reactions using carboxylic acid derivatives as electrophilic coupling partners.

Chapter 2 discloses the first palladium Suzuki-Miyaura couplings of phenyl esters to produce ketones. The method is efficient and robust, giving good yields of useful products. The reaction is proposed to proceed via an oxidative addition to the strong C(acyl)−O bond of the ester. In contrast to previous efforts in this field that use traditional catalysts such as $Pd(PPh_3)_4$, the developed reaction requires use of an electron-rich, bulky N-heterocyclic carbene ligand, which facilitates the strong bond activation.

Furthermore, a palladium-catalyzed cross-coupling between aryl esters and anilines is reported, enabling access to diverse amides. The reaction takes place via a similar activation of the C−O bond by oxidative addition with a Pd−NHC complex, which enables the use of relatively non-nucleophilic anilines that otherwise require stoichiometric activation with strong bases to react.

Chapter 3 discloses a nickel-catalyzed amide bond formation using unactivated and abundant esters. In this transformation, an accessible nickel catalyst can facilitate the activation of diverse aliphatic and aromatic esters to enable direct amide bond formation with amines as nucleophiles. No stoichiometric base, acid, or other activating agent is needed, providing exceptional functional group tolerance and producing only methanol as a by-product. This reaction is of both fundamental and practical importance because it is the first to demonstrate that simple conditions can enable Ni to cleave the C–O bond of an ester to make an oxidative addition product, which can be subsequently coupled with amines. This discovery contrasts industrially-common and wasteful methods that still require stoichiometric activating agents or multistep synthesis.

Chapter 4 describes the evaluation of different types of cross-coupling reactions using methyl esters as electrophilic coupling partner. A high-throughput screening technique has been applied to this project. A combination between specific ligands, known by their efficiency to activate strong C−O bonds, and literature-based conditions has been designed for the chosen transformations. Using this strategy, two promising hits have been obtained using the same NHC ligand: a decarbonylative Suzuki-Miyaura and a decarbonylative borylation reaction.

Acknowledgements

Starting a Ph.D in chemistry was always my dream upon finishing my Master's degree in 2012. For many reasons, this dream didn't start until January 2015. Even then, reaching this goal was not an easy path. Through the last four years, my wife, Mouna, and my two princesses, Sarah and Essraa provided me an enormous amount of power and support to succeed on completing my Ph.D. Thanks Mouna: Sorry, I'll try to be more helpful in the near future. Thanks Sarah: I know that the time that we spent together was not enough and I promise that you'll never be lonely. Thanks Essraa: the future will be for us! Thanks my great family, this accomplishment would not have been possible without you.

For being my primary source of advice and guidance, I thank my supervisor, Professor Stephen Newman. Thanks Stephen for being available and for your support. Without your help my accomplishments over the last four years would pale in comparison. Stephen has dedicated a lot of time and energy to his students to achieve great things and share his knowledge in whatever way possible.

I've had the privilege "and the responsibility" for being the first Ph.D candidate in the group. Starting one session after the actual foundation of the Newman Lab, this allowed me to earn enormous knowledge. Other than the daily learning of new chemistry techniques and fundamentals, I learned how to think about a scientific project, to defend it, and to justify the scientific merit. In addition, I have acquired experience in planning and conducting research. Moreover, I learned how to lead a project from scratch to finished publication. Also, I improved my skills on the training of researchers, and the management of time and priorities. Finally, my supervisor offered me the responsibility to manage and maintain important equipment such as a GC-MS. All these benefits would not be feasible if I started with a group where a starting point from validated projects is clear and the entire infrastructure is set "NO RISK, NO REWARD". Even if the opportunity allows, all this gain would not happen without the support of a motivated and available supervisor like Stephen! I'm 100% confident that all this will serve me well in my future career. Thanks Stephen!

I've had the pleasure of sharing my last four years in the Newman group with wonderful colleagues. I had the pleasure to work with Imane Yalaoui, with here we started the cross-coupling chemistry project. I hope she will find success in pursuing her doctoral studies. Also, I want to say thanks for Wanying for helping on the Suzuki project. In addition, I want to thank Jaya as well as Mohanad for helping on the amidation project using aryl ester electrophiles. Moreover, I want to thank Jeanne for helping on the Ni-catalyzed amidation project.

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Statement of Contributions

I here-by certify that all of the work described in this thesis is the original work of the author, with the exception of work performed by collaborators as noted in the footnotes throughout. In particular, for the first part of chapter 2 (Suzuki-Miyaura coupling of aryl esters), graduate student Wanying Zhang contributed to the optimization process and to the synthesis of most of the aryl esters starting materials. DFT calculations were performed by Xin Hong and Yun-Fang Yang from the Houk lab. For the second part of chapter 2 (amide bond formation from phenyl esters), Dr. Jaya K. Vandavasi and Dr. Mohaned Shkoor contributed to the performance of the scope table. Chapter 3: Graduate student Jeanne-Masson Makdissi contributed to the scope table and synthesized Lidocaine derivatives.

- Taoufik Ben Halima

Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
Alk	alkyl
BDE	bond dissociation energy
bipheb	2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Boc	tert-butyloxycarbonyl
Bu	butyl
Bz	benzoyl
calcd	calculated
cat.	catalytic or catalyst
cod	1,5-cyclooctadiene
CuTC	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
Cyp	cyclopentyl
CDI	1,1'-Carbonyldiimidazole
DavePhos	2-Dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl
dba	dibenzylideneacetone
dcype	1,2-bis(dicyclohexylphosphino)ethane
dcypp	1,2-bis(dicyclohexylphosphino)propane
DFT	density functional theory
DCC	N, N’-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-Butanediylbis[diphenylphosphine]

dppf	1,1′-Ferrocenediyl-bis(diphenylphosphine)
dppp	1,3-bis(diphenylphosphino)propane
E or E^+	electrophile
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
EDC	N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide
EI	electron impact
equiv	equivalent
ESI	electrospray ionization
EtOAc	ethyl acetate
EWG	electron-withdrawing group
FID	flame ionization detector
$\Delta G^{\ddagger}$	activation energy
g	gram(s)
GC-MS	gas chromatography coupled with mass spectrometry
h	hour(s)
Hex	hexyl
HMPA	Hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HTE	high throughput experimentations
Hz	hertz
i	iso
ICy	1,3-bis(1-adamantyl)imidazol-2-ylidene
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPent	1,3-bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene
^{i}Pr or *i*-Pr	iso-propyl
IPr	1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene
IR	infrared
J	coupling constant
L	generic ligand

M	generic metal, or molecular ion, or molar
m	meta or multiplet
MeCN	acetonitrile
mCPBA	meta-chloroperbenzoic acid
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mol	mole(s)
mp	melting point
MS	mass spectrometry
m/z	mass over charge
nep	neopentyl glycolato
NHS	N-Hydroxysuccinimide
NHC	N-heterocyclic carbene
NMP	1-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Nu or Nuc	nucleophile
o	ortho
OVAT	one variable at a time
p	para
Pent	pentyl
Ph	phenyl
phen	phenanthroline
pin	pinacolato
Piv	pivaloyl
pKa	acidity constant
ppm	parts per million
Pr	propyl
Py	pyridyl

Q-TOF	quadrupole time of flight
R	generic chemical group
r. t.	room temperature
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolidene
SIPr	1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolidene
SM	starting material
S_N2	bimolecular nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
temp	temperature
TBS	tert-butyldimethylsilyl
^{t}Bu or *t*-Bu	tert-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	tolyl or 4-methylphenyl
Ts	tosyl
UV	ultraviolet
X	generic halogen/heteroatom
Y	generic halogen/heteroatom

“DO NOT GO WHERE THE PATH MAY LEAD,

GO INSTEAD WHERE THERE IS NO PATH AND LEAVE A TRAIL.”

— Ralph Waldo Emerson

American Essayist 1803-1882

Chapter 1

1 Cross-coupling of esters: Introduction

1.1 Classical cross-coupling reactions: General information

Inventing new carbon−carbon and carbon−heteroatom bond-forming reactions lies at the heart of synthetic methodology. At the beginning of the 20th century, a surge of highly valuable reactions had been reported. Among these, the Grignard and Wittig reactions were discovered, which now bear the names of these pioneering, Nobel-prize winning chemists. Despite the common use of these methods in synthesizing important organic scaffolds, a shared characteristic of most of them is their stoichiometric nature. In other words, using at least one equivalent of reagent is required to activate the substrate. Given the numerous challenges, such as the utilization of non-renewable resources while generating an enormous amount of chemical waste, synthetic chemists are actively searching to develop new catalytic processes as opposed to stoichiometric ones. These greener methods would aid in ensuring sustainability in the future.

During the last half century, many homogeneous, transition metal-catalyzed processes were discovered. Among them, the Mizoroki-Heck coupling reaction was discovered in 1971,[1] the Negishi coupling in 1977,[2] and the Suzuki-Miyaura coupling in 1979.[3] In addition to these C−C bond forming reactions, the Buchwald-Hartwig amination was reported.[4] This reaction, which enables the construction of the important C−N bond, has been initially discovered by Migita and co-workers in 1983.[5] Recently, several reports have evaluated the various reactions used in drug discovery, and how these transformations have changed over time. The impressive contribution of cross-coupling reactions in organic synthesis is particularly notable. In medicinal chemistry, for example, the participation of Suzuki-Miyaura cross-coupling reactions in forming C−C bond has jumped from 10 to 20% between 2000 and 2015.[6] Using a 2010 statistical report,[7] tracking

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[1] (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Soc. Chem. Jpn*. **1971**, *44*, 581; (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

[2] Negishi, E. -I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

[3] (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. For early evidence of organoboron coupling see: (b) Dieck, H. A.; Heck, R. F. *J. Org. Chem*. **1975**, *40*, 1083; (c) Negishi, E. -I. *Acc. Chem. Res*. **1982**, *15*, 340.

[4] (a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc*. **1994**, 116, 7901; (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc*. **1994**, *116*, 5969.

[5] Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett*. **1983**, *12*, 927.

[6] Schneider, N.; Lowe, D. M.; Sayle, R. A.; Tarselli, M. A.; Landrum, G. A. *J. Med. Chem*. **2016**, *59*, 4385.

what reactions medicinal chemists use in drug discovery, it was estimated that 22% of all reactions in the pharmaceutical industry are Pd-catalyzed couplings. A recent analysis, of pharmaceutical companies' electronic lab notebooks, suggests that Buchwald-Hartwig amination was the most performed reaction in pharmaceutical industries during 2013.[8] It is thus no surprise that the 2010 Nobel-prize in chemistry was given to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki "for palladium-catalyzed cross couplings in organic synthesis".[9] In the last few decades, chemists have dedicated great effort to improving these processes even further by broadening the scope, increasing catalyst turnover numbers, improving the mildness of the reactions conditions, and finding new applications for existing transformations.

1.1.1 General mechanism

Cross-coupling reactions represent a valuable alternative to traditional nucleophilic and electrophilic aromatic substitutions. These substitutions are more efficient with highly electrophilic species such as carbocations in the case of Friedel-Crafts acylation or the presence of electron-withdrawing group on the phenyl ring in the case of S_NAr type reactions. The primary role of cross-coupling reactions is accessing complex scaffolds from simple aryl halide starting materials. These reactions traditionally occur between organohalides and organometallic reagents **(Scheme 1.1)**.

Scheme 1.1. General scheme for cross-coupling reactions.

$$\boxed{R{-}X \; + \; R'{-}M^1 \xrightarrow{ML_n} R{-}R'}$$

Transition metals such as palladium or nickel are the most common catalysts for cross-coupling reactions.[10] In homogeneous catalysis, ligands (L) are mainly used to solubilize the metal catalyst species and tune the electronic properties of the transition metal catalyst. Due to their strong influence, the nature of the ligand plays a crucial role in the efficiency and the selectivity

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[7] Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem. Int. Ed*. **2010**, *49*, 8082.

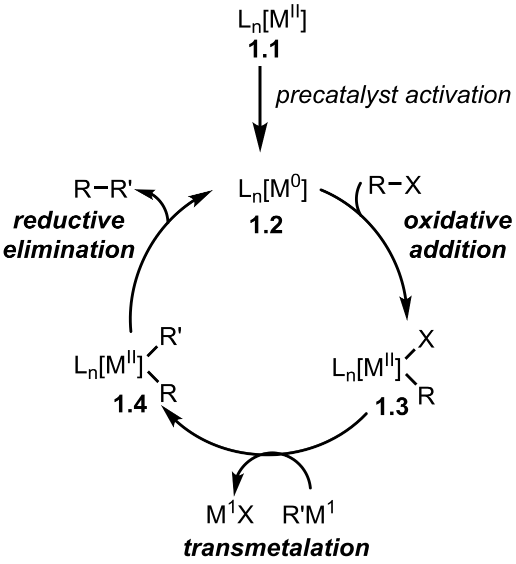
[8] https://nextmovesoftware.com/blog/2013/04/22/pharmas-favourite-reactions/

[9] The Nobel Prize in Chemistry 2010. NobelPrize.org. Nobel Media AB 2019. Wed. 20 Feb 2019. <https://www.nobelprize.org/prizes/chemistry/2010/summary/>

[10] (a) Meijere, A. de; Diederich, F.; Eds., *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed., Wiley-VCH, Weinheim, **2004**; (b) J. *Tsuji, Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**.

of the active catalyst. A general metal-catalyzed cross-coupling reaction mechanism is provided **(Scheme 1.2)**. Whenever a precatalyst L_nM^{II} **1.1** is required for a cross-coupling reaction, this entity has to be reduced to the active catalyst L_nM^0 **1.2**.[11] This reduction step is not needed if using a metal catalyst in the active M(0) oxidation state.

Scheme 1.2. General metal-catalyzed cross-coupling reaction mechanism



Oxidative addition

The above catalytic cycle is initiated when the oxidative addition step takes place via the insertion into a C−X bond of an organo (pseudo) halide, which acts as the electrophilic coupling partner to give the organometallic complex **1.3**. Usually, this step is favorable whenever electron-rich metal centers are used. Accordingly, less electronegative transition metals, such as nickel, are better at oxidative addition than palladium.[12] Ligands also play an important role, and electron donating ligands such as alkyl phosphines and N-heterocyclic carbenes (NHC)[13] facilitate the oxidative addition step. Lastly, another factor that affects the rate of this step is the strength of the C−X bond. In general, the weaker this bond is, the easier the oxidative addition step.

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[11] Fumiyuki, O.; Akihiko, K.; Tamio, H. *Chem. Lett.* **1992**, *21*, 2177.

[12] Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509,* 299.

[13] Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151.

Transmetalation

The next step involves a transmetalation with an organometallic reagent or a ligand exchange reaction, which provides complex **1.4**. Plenty of organometallic reagents of varying mildness have been reported. Organomagnesium (Grignard reagent) nucleophiles were one of the first reagents to be used in a transition metal-catalyzed cross-coupling reaction. This reagent type was reported initially by Kharasch,[14] and then independently reported by Tamao-Kumada[15] and Corriu[16] in 1972. Upon this discovery, new cross-coupling reactions involving milder nucleophilic coupling partners have been reported **(Figure 1.1)**. Among these include: organozinc species for Negishi[2] cross-couplings, organostannanes for Stille-Migita[17] cross-couplings, organoboron reagents for Suzuki-Miyaura cross-couplings,[3] and organosilicon compounds for the Hiyama reaction.[18]

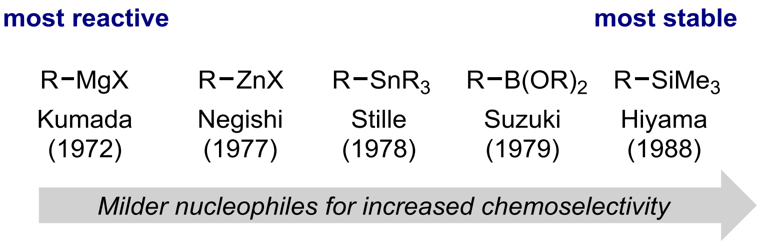

Figure 1.1. Nucleophilic coupling partner evolution

For Suzuki-Miyaura cross-coupling reactions, which use organoboron coupling partners, we still call this step of the catalytic cycle a transmetalation. However, for other cross-coupling reactions such as the Buchwald-Hartwig amination, the term “ligand exchange” is preferred. Furthermore, other types of cross couplings such as the Mizoroki-Heck[1] undergo an insertion step instead of transmetalation.

Even though the most well known nucleophilic coupling partners were discovered before the beginning of the 21st centry, other functionalities were incorporated later as transmetalating

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[14] Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc*. **1941**, *63*, 2316.
[15] Tamao, K.; Sumitani, K.; Kumada, M., *J. Am. Chem. Soc*. **1972**, *94*, 4374.
[16] Corriu, R. J. P.; Masse, J. P., *J. Chem. Soc., Chem. Commun*. **1972**, 144a.
[17] Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636.
[18] Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.

agents in the cross coupling chemistry field. This includes, but not limited to, diazo compounds,[19] alkyl nucleophiles,[20] trifluormethyl groups,[21] diboron/hydroboron reagents,[22] and the reinvestigation of organophosphorous compounds.[23]

Reductive elimination

Finally, the last step is *reductive elimination* which provides the desired cross-coupling product. During this step, the oxidation state of the metal center decreases while forming a covalent bond. Being the reverse of *oxidative addition*, more electronegative transition metals (e.g. Pd over Ni) and the use of electron-deficient ligands can accelerate the reductive elimination.[24]

1.1.2 Cross-coupling reactions: Applications

The different application areas of cross coupling chemistry made it widely applicable. Their unique selectivity and efficiency make them an excellent tool to apply in many synthetic fields.

1.1.2.1 Applications of C−N bond formation

Given the tremendous utility of Pd-catalyzed C−N cross-coupling reactions, this transformation has been applied in natural product syntheses (e.g. Murrayazoline),[25] medicinal chemistry (e.g. B-Raf inhibitors),[26] materials chemistry (e.g. Polynorbornene chromophore)[27] (**Figure 1.2**), and beyond.[28]

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[19] Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res*. **2013**, *46*, 236.

[20] (a) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc*. **2009**, *131*, 5024; (b) Joshi-Pangu, A.; Biscoe, M. R. *Synlett.* **2012**, *23*, 1103; (c) Masson-Makdissi, J.; Vandavasi, J. K.; Newman, S. G. *Org. Lett.* **2018**, *20*, 4094.

[21] (a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679; (b) Keaveney, S. T.; Schoenebeck, F. *Angew. Chem., Int. Ed*. **2018**, *57*, 4073.

[22] (a) Uematsu, R.; Yamamoto, E.; Maeda, S.; Ito, H. *J. Am. Chem. Soc*. **2015**, *137*, 4090. (b) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc*. **2010**, *132*, 17701. (c) Moldoveanu, C.; Wilson, D. A.; Wilson, C. J.; Leowanawat, P.; Resmerita, A.-M.; Liu, C.; Rosen, B. M.; Percec, V. *J. Org. Chem.* **2010**, *75*, 5438. (d) Zhu, W.; Ma, D. *Org. Lett*. **2005**, *8*, 261.

[23] (a) Belabassi, Y.; Alzghari, S.; Montchamp, J. L. *J. Organomet. Chem.* **2008**, 693, 3171; (b) Shen, C.; Yang, G.; Zhang, W. *Org. Biomol. Chem*. **2012,** *10*, 3500; (c) Yang, J.; Chen, T.; Han, L.-B. *J. Am. Chem. Soc*. **2015**, *137*, 1782.

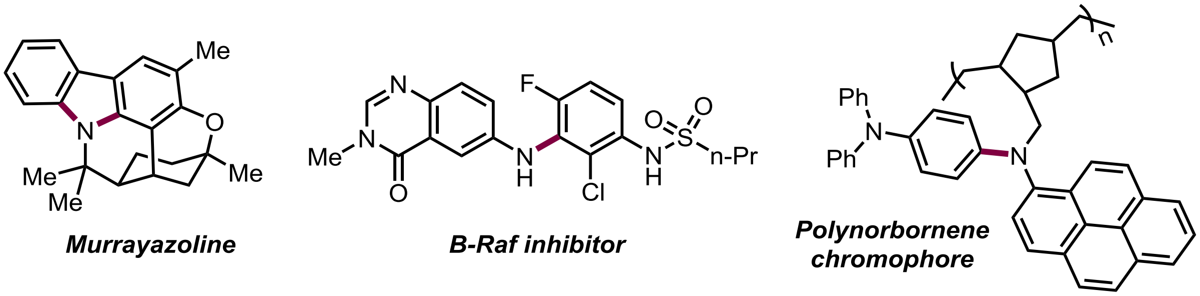
[24] Korenaga, T.; Abe, K.; Ko, A.; Maenishi, R.; Sakai, T. *Organometallics* **2010**, *29*, 4025.

[25] Ueno, A.; Kitawaki, T.; Chida, N. *Org. Lett*. **2008**, *10*, 1999.

[26] Wenglowsky, S.; Ren, L.; Grina, J.; Hansen, J. D.; Laird, E. R.; Moreno, D.; Dinkel, V.; Gloor, S. L.; Hastings, G.; Rana, S.; Rasor, K.; Sturgis, H. L.; Voegtli, W. C.; Vigers, G.; Willis, B.; Mathieu, S.; Rudolph, J. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 1923.

[27] Lian, W.-R.; Ho, C.; Huang, Y.-C.; Liao, Y.-A.; Wang, K.-L.; Liaw, D.-J.; Lee, K.-R.; Lai, J.-Y. J. *Polym. Sci., Part A: Polym. Chem*. **2011**, *49*, 5350.

[28] Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.

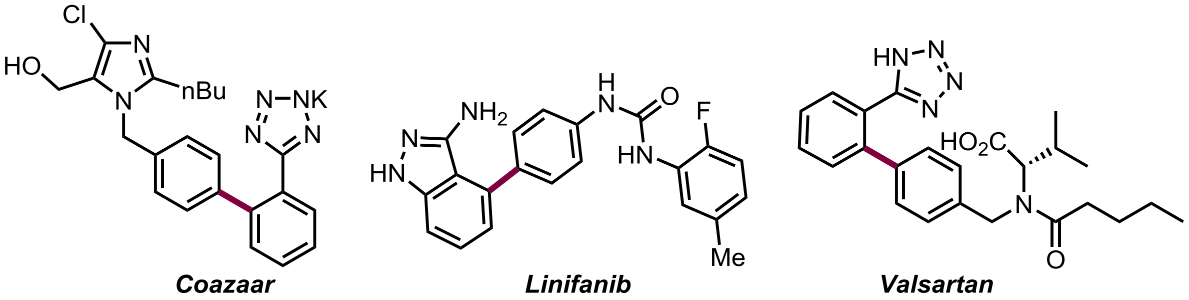


Murrayazoline ***B-Raf inhibitor*** ***Polynorbornene chromophore***

Figure 1.2. Application of C−N bond forming reaction in multiple synthetic areas

1.1.2.2 Applications of C−C bond formation

The cross-coupling of organoboron nucleophiles with C–X bonds is among the most widely used reactions for reliable, selective C–C bond formation.[29] This coupling reaction has been used to synthesize numerous drug candidates. Among those is Coazarr,[30] an important drug for treating hypertension, Linifanib (ABT-869),[31] a potent tyrosine kinase receptor inhibitor for cancer treatment, and Valsartan,[32] a drug used to lower blood pressure (**Figure 1.3**). These bioactive molecules represent some of many scaffolds manufactured from kilogram to ton scale in the pharmaceutical industry.



Coazaar ***Linifanib*** ***Valsartan***

Figure 1.3. Applications of Suzuki-Miyaura cross coupling reactions in drugs synthesis

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[29] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[30] (a) Yasuda, N., *J. Organomet. Chem*. **2002**, *253,* 279; (b) Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, R. C.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J.; Lo, Y. S.; Rossano, L. T.; Brookes, A. S.; Meloni, D.; Moore, J. R.; Arnett, J. F.; et al. *J. Org. Chem.* **1994**, *59*, 6391.

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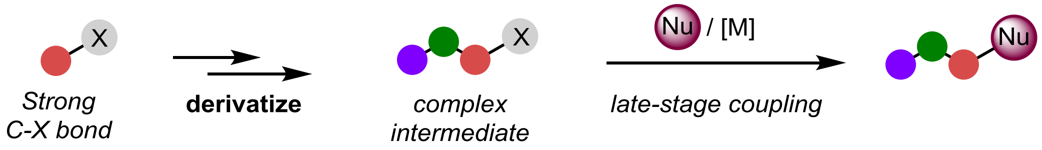
[32] Calderazzo, F.; Catellani, M.; Chiusoli, G. P. "Carbon-Carbon Bond Formation." *Metal-catalysis in Industrial Organic Processes.* Chiusoli, G. P.; Maitlis, P. M. Cambridge: *The Royal Society of Chemistry*, **2006.**

1.2 Expansion of the electrophilic coupling partners

A recent review from Snieckus and co-workers[33] classified the evolution of coupling chemistry over three different waves after the initial discovery of cross-coupling as a concept. During the first wave, great efforts were dedicated to investigate the metal catalysts, such as palladium, copper, and nickel, which are capable of promoting these transformations in a selective fashion. The second wave has been dedicated to expand the nucleophilic coupling partner scope such as alkenes for Mizoroki-Heck reaction, organozinc for Negishi coupling, organoboron for Suzuki-Miyaura coupling, and organotin reagents for Stille-Migita coupling. Lastly, the third wave has been devoted to the extension and improvement of each reaction type through ligand variation and accommodating wider electrophilic coupling partners.

While generous efforts have been made to expand the nucleophile scope, synthetic chemists are now directing the research towards the activation of more and more robust substrates for the electrophile scope. Inventing new cross-coupling methods to enable the activation of robust electrophilic coupling partners is of high importance. By doing so, these robust functional groups can be resistant/inert to reactions that activate weak functionality. Thus, these methods provide more flexibility and efficiency that could serve as a platform for late-stage elaboration of complex molecules (**Scheme 1.3**). More specifically, if the C–X bond is strong, it could be inert enough to tolerate the reagents used in the early steps of a proposed synthetic route, and then this bond could be activated towards the end of the multi-step synthesis. Examples demonstrating the activation of typically inert functionalities such as anisole derivatives, esters, and amides will be described throughout this chapter.

Scheme 1.3. Benefits of using inert strong bonds in cross-coupling reactions



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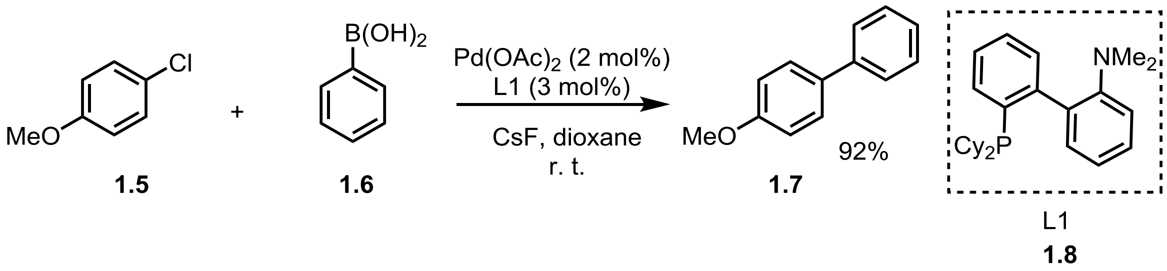
[33] Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed*. **2012**, *51*, 5062.

1.2.1 Aryl electrophiles

Despite great success in expanding the scope of nucleophilic coupling partners, the most common electrophiles used in cross-coupling reactions have historically been aryl bromides, iodides, and triflates. Even though aryl chlorides are useful because of their lower cost and the wider diversity of available compounds, these substrates were seen as highly challenging to activate until advances in ligand design in the late 1990s solved this problem.[34] The strength of this bond (BDE for Ph–X: Cl: 96 kcal mol^{-1}; Br: 81 kcal mol^{-1}; I: 65 kcal mol^{-1}), explains the requirement of novel catalyst systems to enable these cross-coupling reactions. In 1998,[35] Buchwald and co-workers reported an effective ligand (L1) for palladium-catalyzed Suzuki-Miyaura reactions of aryl chlorides **(Scheme 1.4)**.

Scheme 1.4. Efficient system using unactivated aryl chlorides for Suzuki-Miyaura coupling



This work has overcome the previous challenges associated by using only highly activated aryl chlorides. Moreover, this mild room temperature reaction affords high yield. In the same article, this ligand was also employed in the construction of C–N bonds via a Buchwald-Hartwig amination **(Scheme 1.5)**. High yielding reactions were obtained with both alkyl amine and aniline derivatives as nucleophilic coupling partners.

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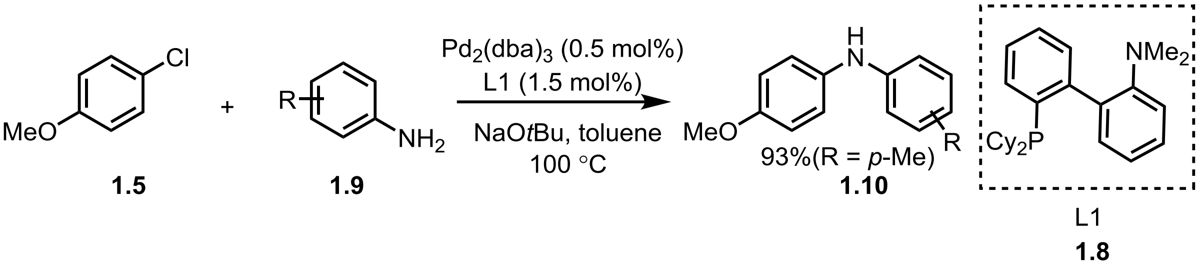
[34] Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed*. **2002**, *41*, 4176.
[35] Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **1998**, *120*, 9722.

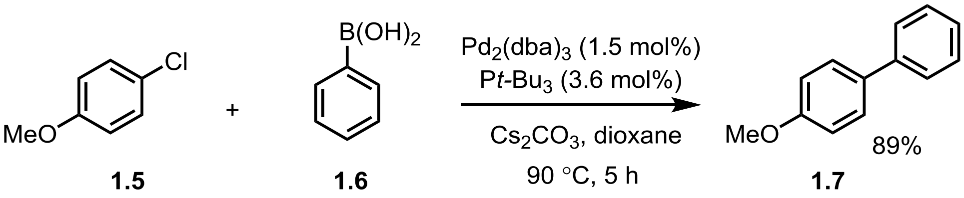
Scheme 1.5. Amination cross-coupling reaction using unactivated aryl chlorides



In contrast to traditional palladium/triarylphosphines catalyst systems, which are only effective for the coupling of aryl iodides, bromides, and certain activated aryl chlorides, the efficiency of ligand L1 is proposed to arise from two features: the electron-rich monodentate phosphine group (Cy_2PAr) and the presence of a chelating (NMe_2) group.

In parallel, the Fu group reported a general method for the cross-coupling of aryl chlorides using the electron rich alkyl phosphine P*t*-Bu_3 as ligand **(Scheme 1.6)**.[36] This ligand, which is similarly effective as the previously reported L1 ligand, enabled this Suzuki-Miyaura cross-coupling reaction with high yields regardless of the electronic character of either the boronic acid or the aryl chloride.

Scheme 1.6. General method for Pd-catalyzed Suzuki-Miyaura cross-couplings of aryl chlorides



One year later, Fu and co-workers reported the first Stille-Migita cross-couplings of aryl chlorides using the same P*t*-Bu_3 ligand and tributyl(vinyl)tin as a nucleophilic coupling partner **(Scheme 1.7)**.[37] They succeeded on accomplishing this C–C bond forming reaction, accessing

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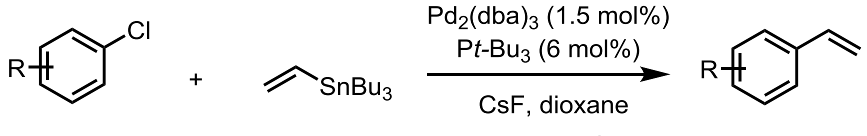
[36] Littke, A. F.; Fu, G. C. *Angew.Chem. Int. Ed*. **1998**, *37*, 3387.
[37] Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed*. **1999**, *38*, 2411.

different styrene products with a wide array of aryl chloride electrophiles including electron-poor and electron-rich substrates. Even *p*-chloroaniline could be effectively coupled.

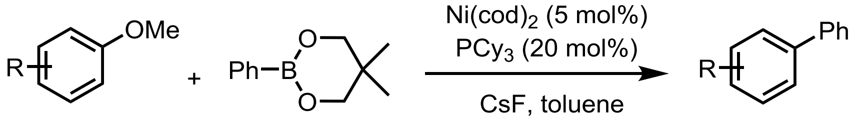
Scheme 1.7. The first Stille-Migita coupling using aryl chlorides electrophiles



1.11 **1.12** **1.13**

After these advances in the activation of strong C−Cl bonds, chemists subsequently targeted even less reactive functional groups. While nickel was reported to activate strong C−F[38] and C−O[39] ether bonds via a Kumada-Corriu coupling in the 1970s, it was not until the beginning of the 21st century that these electrophiles become relevant in cross-coupling chemistry.[40] From 2008 onwards, Chatani and co-workers reported multiple types of cross coupling reactions with various nucleophilic coupling partners and aryl ether electrophiles (**Scheme 1.8**).[41] The first achievement in this family of research described a nickel-catalyzed cross-coupling of inert and previously unreactive C−O bonds with boronic esters as nucleophilic coupling partners.

Scheme 1.8. Aryl methyl ethers activation using Ni-catalysis



1.14 **1.15** **1.16**

This procedure has been successfully applied to the coupling of a variety of electron poor and electron neutral electrophiles. Moreover, several electrophilic functionalities, including ketones and esters, are well-tolerated under these reaction conditions, which is in sharp contrast to the

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[38] (a) Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem*. **1973**, *50*, C12. (b) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn*. **1976**, *49*, 1958.

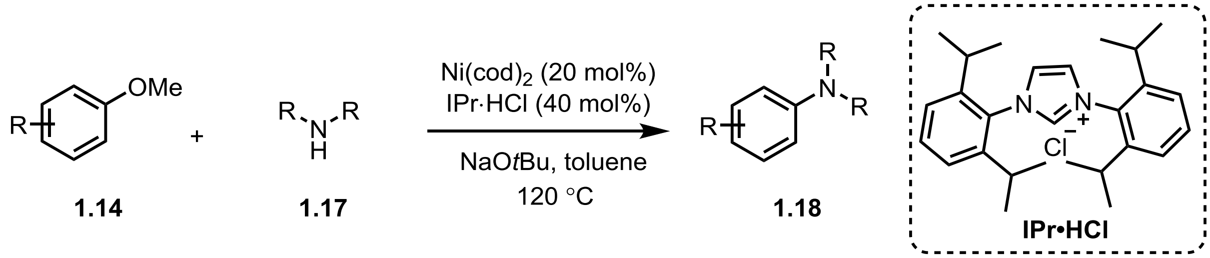
[39] Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc*. **1979**, *101*, 2246.

[40] (a) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119; (b) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717.

[41] Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed*. **2008**, *47*, 4866.

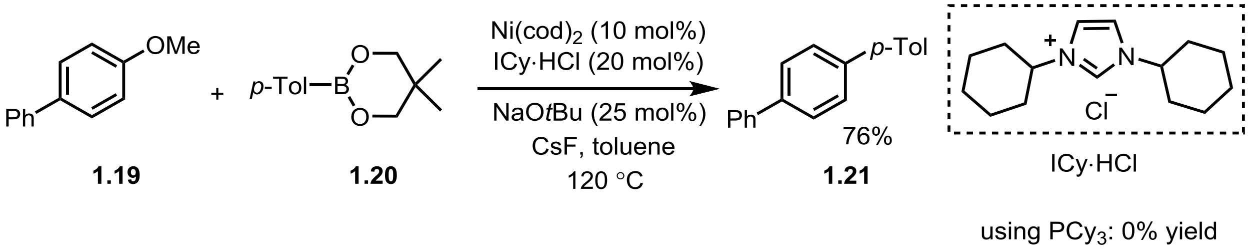
previously reported Kumada-Corriu coupling of aryl ethers.[39] Even though PCy_3 was the most effective ligand for this strong C−O bond activation with organomagnesium[42] and organoboron nucleophiles, it was less efficient for amination reactions. IPr·HCl, an N-heterocyclic carbene (NHC) ligand, evolved as a powerful tool to achieve this transformation using a variety of amine nucleophiles **(Scheme 1.9)**.[43]

Scheme 1.9. Amination reaction using strong C−O ether bond



NHC type ligands were also screened in the study of Suzuki-Miyaura-type cross-couplings using aryl ethers. Chatani and co-workers found that, for some scope examples, ICy·HCl showed even better efficiency compared to the original Ni(0)/PCy_3 system **(Scheme 1.10)**.[44]

Scheme 1.10. Ni-catalyzed cross-coupling of aryl ethers using NHC ligands.



To better illustrate the benefit of inventing new methodologies that activate strong C−O bonds, sequential synthetic modifications have been reported (**Scheme 1.11**).[40b] This strategy is useful for molecules that have two or more functional groups that are prone to react. In the ideal sequence, the first subjected conditions will selectively activate only one functional group. More specific reaction conditions will be employed to activate the remaining inert functionality. For

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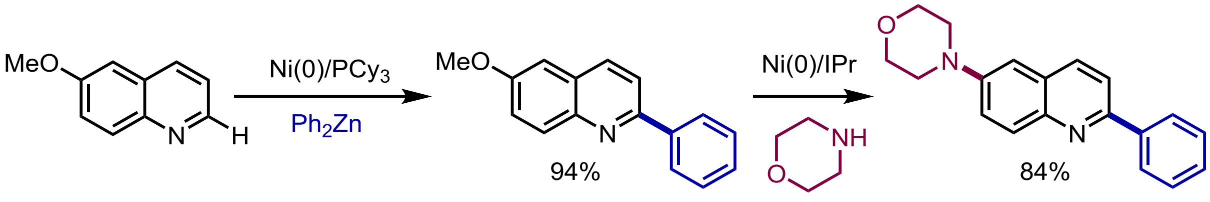
[42] Dankwardt, J. W. *Angew. Chem. Int. Ed*. **2004**, *43*, 2428.
[43] Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett*. **2009**, *38*, 710.
[44] Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K.; Chatani, N. *Org. Lett*. **2014**, *16*, 5572.

example (**Scheme 1.11**), the Ni(0)/PCy_3 system allows for arylation of the quinolines C−H bond using diphenylzinc,[45] while leaving the ether intact. A Ni(0)/NHC system can then be applied to functionalize this ether in an amination reaction, affording **1.24** in high yield.

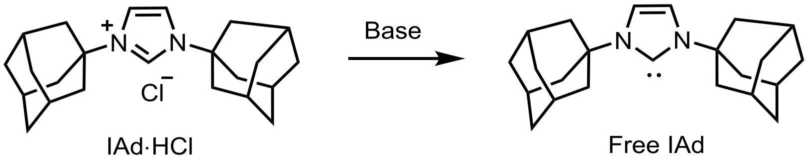
Scheme 1.11. Sequential synthetic modification of aryl ether enabled by Ni-catalysis



1.22 **1.23** **1.24**

As demonstrated above, most of these anisole derivatives have been activated via Ni-catalysis. This might be explained by the efficiency of this transition metal towards achieving challenging oxidative additions. Combining the effectiveness of the metal and the ligand together, the specific use of electron rich NHC ligands, which are strong σ-donors, pushes electron density towards the metal center and consequently facilitates the insertion into the C−O ether bond. In addition, these NHC species, first reported by Arduengo in 1991 as HCl salts and free NHCs (**Scheme 1.12**),[46] are not only electronically stabilized due to the orbital overlap with the corresponding nitrogen atoms, but also sterically stabilized by their bulky substituents on both nitrogen atoms.

Scheme 1.12. Synthesis of the first free IAd NHC



This feature protects against dimerization of the corresponding olefin, which is known as the Wanzlick equilibrium.[47] The lone pair of the nitrogen donates electron density to the empty p-

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[45] Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc*. **2009**, *131*, 12070.

[46] Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc*. **1991**, *113*, 361.

[47] Wanzlick, H. W.; Schikora, E. *Angew. Chem*. **1960**, *72*, 494.

orbital on the C2 carbon. The adjacent σ-electron-withdrawing and π-electron donating nitrogen atoms help stabilize the structure (**Figure 1.4**).[48]

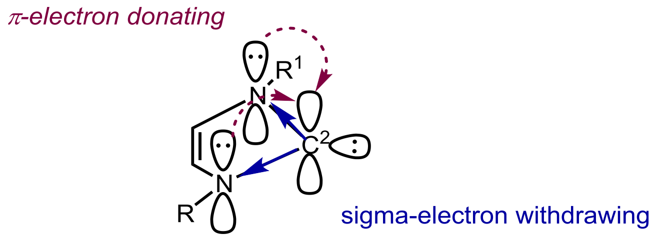

Figure 1.4. Orbital overlap for a typical NHC ligand

Overall, the evolution over time of aryl electrophilic coupling partners can be broadly illustrated by the **Figure 1.5** shown below. Common aryl iodide and bromide substrates were mostly used in the 1970s and 80s. Then, extensive efforts have been done to establish general cross-coupling reactions using aryl chlorides in late 1990s. Most recently, very strong bonds such as C−F (aryl fluorides) and C−OMe (anisoles) are becoming more relevant. This success on the activation of challenging functionalities was tightly linked to the important discoveries of efficient catalyst/ligand systems.

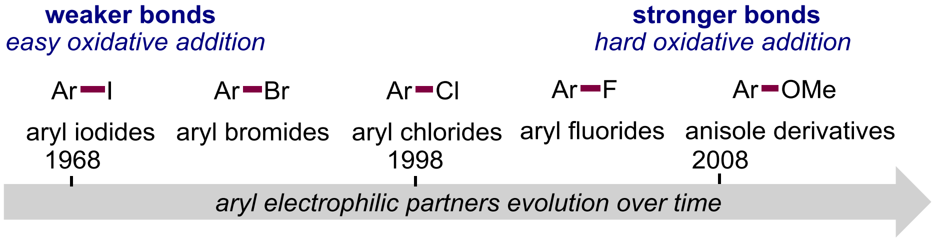

Figure 1.5. Aryl electrophilic coupling partners evolution

1.2.2 Acyl electrophiles

Throughout the years, aryl halides coupling partners have seen a drastic evolution primarily through catalyst design as described above. Similarly, carboxylic acid derivatives have been extensively studied in the cross-coupling chemistry field as potential electrophilic coupling partners.

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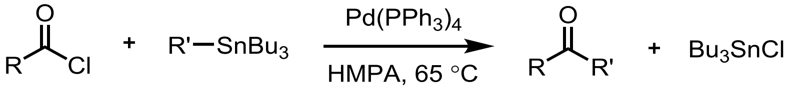
[48] Ling, K. B.; Smith, A. D. *Chem. Commun*. **2011**, *47*, 373.

1.2.2.1 Acyl chloride electrophiles

After Migita's initial report in 1977 on the use of organotin nucleophiles in cross-coupling,[49] Stille and co-workers successfully coupled acyl chlorides with organotin reagents to form ketones using Pd catalysis **(Scheme 1.13)**.[17] Despite being synthetically powerful, this Stille-Migita cross-coupling reaction requires careful handling of the toxic tin reagents.

Scheme 1.13. Stille-Migita cross-coupling reaction from acyl chlorides



1.25 **1.26** **1.27** **1.28**

Even though they are commercially available and synthetically accessible from abundant carboxylic acid functionality,[50] acyl chlorides are very reactive. For example, this highly sensitive electrophile is prone to over-addition whenever highly reactive Grignard reagent nucleophiles are used. Using less reactive organoboron reagents, acyl chloride electrophiles have been extensively used to promote Suzuki-Miyaura coupling. Following up Uemura's work on the use of sodium tetraphenylborate ($NaBPh_4$) as the nucleophile in the Pd-catalyzed phenylation of alkenes and acid chlorides,[51] the Bumagin group reported the reaction between arylboronic acids and acyl chlorides to generate interesting ketone products **(Scheme 1.14)**.[52] Quantitative yields were obtained using sterically hindered, electron-neutral, as well as electron-poor arylboronic acids. This Suzuki-Miyaura reaction, which uses basic aqueous reaction conditions, tolerates the sensitive acid chloride; no hydrolysis products were observed.

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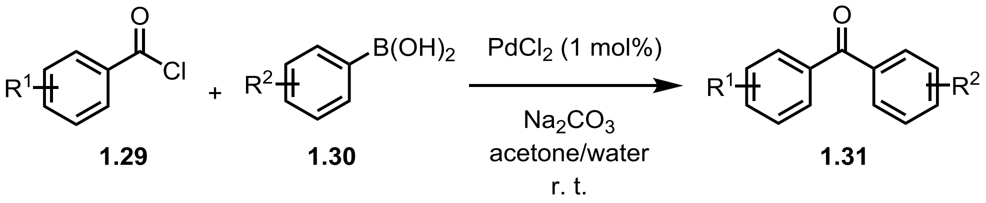
[49] Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423

[50] (a) Helferich, B.; Schaefer, W. *Org. Synth*. **1929**, *9*, 32; (b) Allen, C. F. H.; Barker, W. E. *Org. Synth*. **1932**, *12*, 16; (c) Adams, R.; Jenkins, R. L. *Org. Synth*.**1923**, *3*, 75.

[51] Cho, C. S.; Itotani, K.; Uemura, S. *J. Organomet. Chem*., **1993**, *443*, 253.

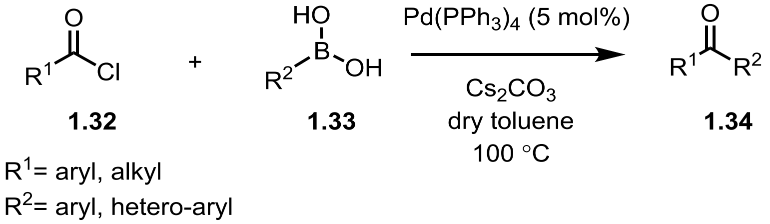
[52] Bykov, V. V.; Korolev, D.N.; Bumagin, N. A. *Russ. Chem. Bull*. **1997**, *46*, 1631.

Scheme 1.14. Bumagin's first carbon monoxide-free carbonylation of arylboronic acids



On top of the previous proposed conditions by Bumagin, the Haddach research group reported the first palladium-catalyzed coupling of organoboronic acids with acyl chlorides under anhydrous reaction conditions in 1999 **(Scheme 1.15)**.[53] By using $Pd(PPh_3)_4$ and cesium carbonate in dry toluene, several symmetric and non-symmetric aromatic ketones were synthesized in moderate to good yields.

Scheme 1.15. The first Suzuki-Miyaura coupling from acyl chlorides using anhydrous conditions



In addition to these interesting discoveries cited above, acyl chlorides have been used to couple vinylboronic acids, affording bioactive chalcone derivatives.[54]

1.2.2.2 Acid anhydrides electrophiles

Acid chlorides are readily accessible, and their transformation into ketones is a powerful reaction. However, acid chlorides are also highly sensitive functional groups that must be prepared and carefully isolated. There was thus a need to use more robust and/or diverse acyl cross-coupling electrophiles. Acid anhydrides were first reported as electrophilic coupling partners in the cross-coupling by the de Vries lab in 1998.[55] Therein, a Pd-catalyzed

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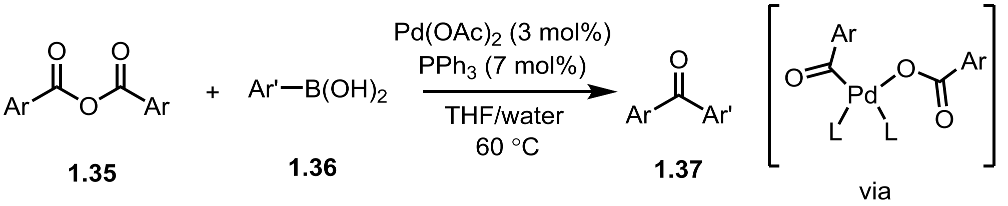
[53] Haddach, M.; McCarthy, J. R. *Tetrahedron Lett*. **1999**, *40*, 3109.
[54] Eddarir, S.; Cotelle, N.; Bakkour, Y.; Rolando, C. *Tetrahedron Lett*. **2003**, *44*, 5359.
[55] Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; de Vries, J. G. *Angew. Chem. Int. Ed.* **1998**, *37*, 662.

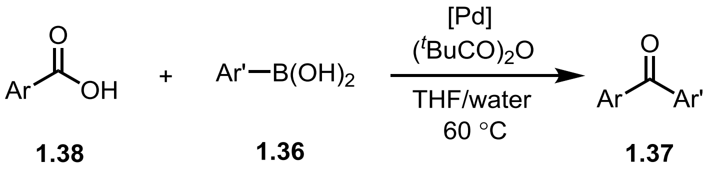
decarbonylative Mizoroki-Heck cross-coupling reaction is described. Three years later, the Gooβen group reported Pd-catalyzed Suzuki-Miyaura coupling of acid anhydrides generating ketone products **(Scheme 1.16A)**.[56] They also extended it to the coupling of the free carboxylic acids, which can be converted to acid anhydrides *in situ* with the use of stoichiometric pivalic anhydride (**Scheme 1.16B**). In 2005, the same research group supported a mechanistic study using density functional theory (DFT) calculations.[57]

Scheme 1.16. Gooβens reported Suzuki-Miyaura coupling of acid anhydrides

A) Acid anhydride as electrophilic coupling partner



B) Acid anhydride generated *in situ* from carboxylic acid



Supported by these studies, the proposed mechanism starts with an oxidative addition into the C(acyl)−O bond of the anhydride. Even though the activation of these anhydride electrophiles represents a fundamental major advance in the field compare to previously reported acyl chlorides, this method still suffers from its poor atom-economical aspect and high sensitivity of this functional group.

1.2.2.3 Thioester electrophiles

In 1998, the Fukuyama group reported novel aldehyde and ketone-forming reactions **(Scheme 1.17)**.[58] In this work, thioesters were subjected to different nucleophilic coupling partners such as triethylsilane and organozinc using Pd catalysis. Moreover, thioesters were employed in complex molecule synthesis. For example, the Fukuyama coupling, enabling the cross-coupling reaction

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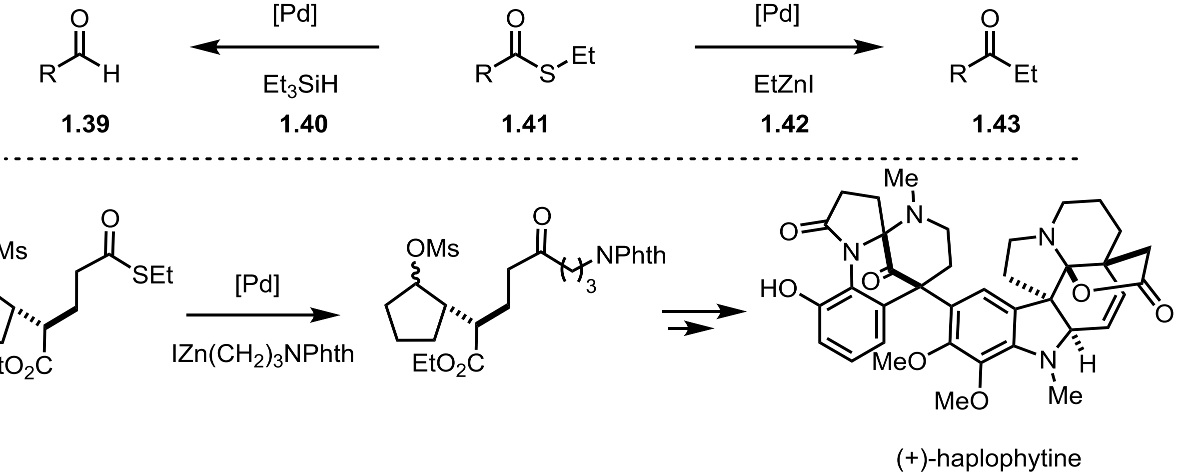
[56] Gooβen, L. J.; Ghosh, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3458.
[57] Goßen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *J. Am. Chem. Soc.* **2005**, *127*, 11102.
[58] Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.

between thioesters and organozinc, was used in the synthesis of (+)-haplophytine[59] and (+)-biotin.[60]

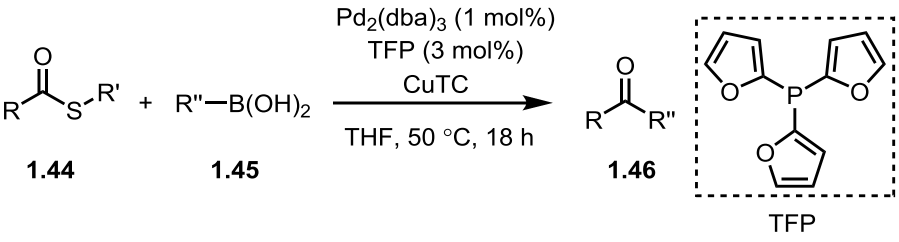
Scheme 1.17. The Fukuyama work on C−S bond activation[58] and application on the (+)-haplophytine synthesis[59]



1.39 **1.40** **1.41** **1.42** **1.43**

Two years later, Lanny Liebeskind and Jiri Srogl disclosed their method of coupling thioesters with organoboron reagents, affording ketones **(Scheme 1.18)**.[61] Due to its mild conditions and the relative robustness of thioesters, this copper carboxylate mediated “base-free” reaction offered new possibilities for the synthesis of highly functionalized and base-sensitive compounds.

Scheme 1.18. Suzuki-Miyaura cross-coupling using thioesters electrophiles



1.44 **1.45** **1.46**

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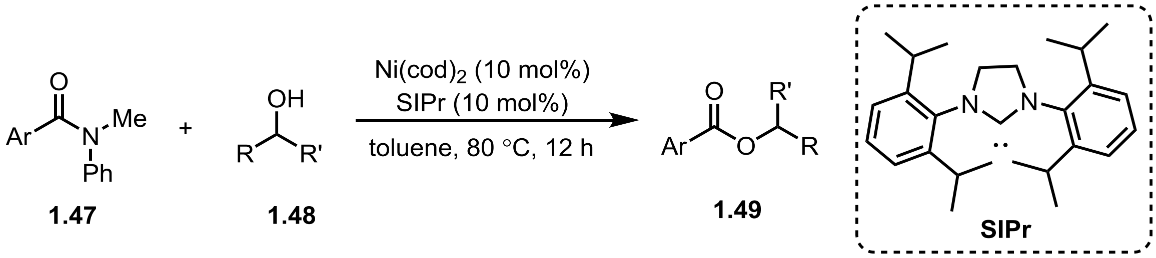
[59] Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 7600.
[60] Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2000**, *41*, 5099.
[61] Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

Thioesters are more robust electrophiles compared to acyl chlorides and anhydrides. However, thioesters are relatively rare and must be installed. C(acyl)–S activation could be achieved even if a methyl ester was present in the same molecule,[62] indicating the relative reactivity of these two groups.

1.2.2.4 Amides and twisted amide electrophiles

Since 2015, the Garg group made numerous contributions to the field of nickel-catalyzed amide C−N bond activation. In their first report **(Scheme 1.19)**,[63] they disclosed the conversion of amides to esters using alcohols.

Scheme 1.19. Esterification via nickel-catalyzed amide C−N bond activation



A Ni/SIPr catalyst system was used to activate the strong C−N bond of N-phenyl amides. After the above initial discovery, a surge of reactions that use N-Boc-amides as cross-coupling electrophiles was reported. This includes Mizoroki-Heck cyclization,[64] trans-amidation,[65] Suzuki-Miyaura coupling,[66] Negishi alkylation,[67] and the esterification cross-coupling reaction.[68]

The stability of the amide functionality is due to the lone pair delocalization of the sp^2 hybridized nitrogen that increases the double bond character. This natural phenomenon helps explain how difficult the cleavage of amide C−N bonds is and highlights the scientific merit of Garg’s discovery.[63] It is important to note that the stability of an amide is highly dependent on the nature

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[62] For the activation of thioester in the presence of the methyl ester functionality see: Shimizu, T.; Seki, M. *Tetrahedron Lett*. **2001**, *42*, 429.

[63] Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. *Nature* **2015**, *524*, 79.

[64] Medina, J. M.; Moreno, J.; Racine, S.; Du, S.; Garg, N. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6567.

[65] Dander, J. E.; Baker, E. L.; Garg, N. K. *Chem. Sci.* **2017**, *8*, 6433.

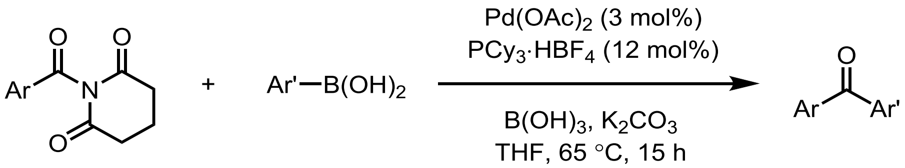
[66] Weires, N. A.; Baker, E. L.; Garg, N. K. *Nat. Chem.* **2016**, *8*, 75.

[67] Simmons, B. J.; Weires, N. A.; Dander, J. E.; Garg, N. K. *ACS Catal.* **2016**, *6*, 3176.

[68] Hie, L.; Baker, E. L.; Anthony, S. M.; Desrosiers, J.-N.; Senanayake, C.; Garg, N. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 15129.

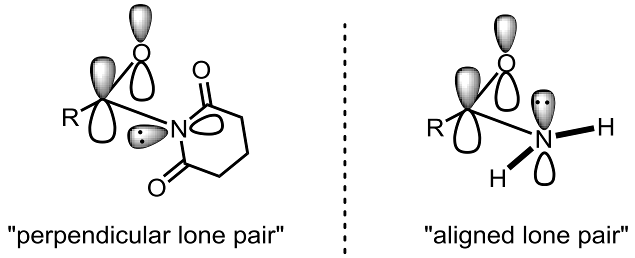
of the N-substituents. More specifically, substituents that will prevent/reduce the resonance will decrease the stability of the amide. This factor, which could lower the energetic barrier of the challenging oxidative addition, has been well explored by the Szostak group **(Scheme 1.20)**.[69]

Scheme 1.20. C−N bond activation using glutarimide amides



1.50 **1.36** **1.37**

Being the first to use the glutarimide amides as electrophilic coupling partners, Szostak and co-workers took advantage of the perpendicular geometry of the glutarimide ring versus the acyclic amide functionality (**Figure 1.6**). In other words, the lone pair on the nitrogen atom is not properly aligned for conjugation with the carbonyl π system, and thus there is no resonance stabilization. For this reason, twisted amides such as glutarimide amides are significantly easier to cleave compared to other “natural” amides.



"perpendicular lone pair" "aligned lone pair"

Figure 1.6. Aligned versus perpendicular nitrogen lone pair with the π system

Since their initial report in 2015 on Suzuki-Miyaura coupling to afford ketones, numerous types of cross-coupling reactions using glutarimide amides have been disclosed.[70]

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[69] Meng, G.; Szostak, M. *Org. Lett.* **2015**, *17*, 4364.

[70] Meng, G.; Szostak, M. *Eur. J. Org. Chem.* **2018**, 2352.

A recent study by the Hong research group,[71] supported the fact that N-boc-amides are slightly more reactive than the N-phenyl amides and less reactive than the glutarimide amides (**Figure 1.7**).

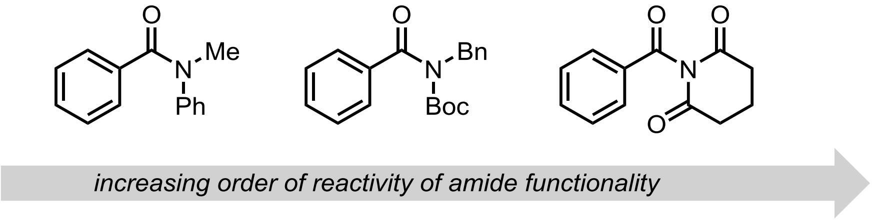

Figure 1.7. Order of amide reactivity from Hong's DFT study

1.3 Cross-coupling of esters

For the past 20 years, esters have also been explored as electrophilic reactants in the field of cross-coupling chemistry. These electrophiles are particularly robust in comparison to other carboxylic acid derivatives. Furthermore, the use of esters in cross-coupling reactions is important not only because this avoids the production of corrosive halide-containing wastes, but also because it gives access to a large number of commercially and synthetically available ester containing molecules. Moreover, ester groups are often involved in heterocyclic synthesis[72] such as the Hantzsch synthesis of pyrroles and the Feist-Benary synthesis of furans, where these functionalities are important components of the heterocycle cores.

In this section, recent milestones in the field of cross-coupling chemistry using esters as electrophilic coupling partners mediated by a Pd and Ni-based catalyst will be discussed.

Three plausible cross-coupling pathways to activate esters are accessible (**Scheme 1.21**). Path A, where the ester could be activated via C(aryl)–O cleavage. Another mode of cleavage could be achieved when the metal inserts into the C(acyl)–O with subsequent de-insertion of the carbon monoxide (path B). Finally, the C(acyl)–O could be cleaved with carbonyl retention (path C).

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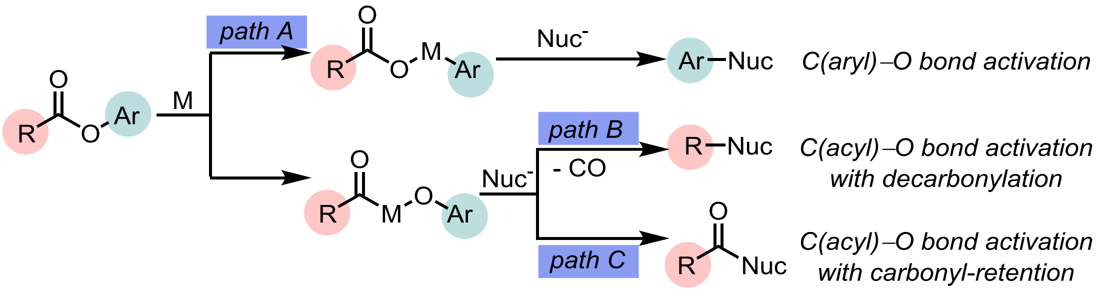
[71] Ji, C.-L.; Hong, X. *J. Am. Chem. Soc*. **2017**, *139*, 15522.

[72] (a) Hantzsch, A. *Justus Liebigs Ann. Chem*. **1882**, *215*, 1; (b) Bottorff, E. M.; Jones, R. G.; Kornfeld, E. C.; Mann, M. J. *J. Am. Chem. Soc*. **1951**,*73*, 4380; (c) Feist, F. *Ber. Dtsch. Chem. Ges*. **1902**, *35*, 1537; (d) Gopalan, A.; Magnus, P. *J. Am. Chem. Soc*. **1980**, *102*, 1756.

Scheme 1.21. Plausible activation modes of ester electrophiles



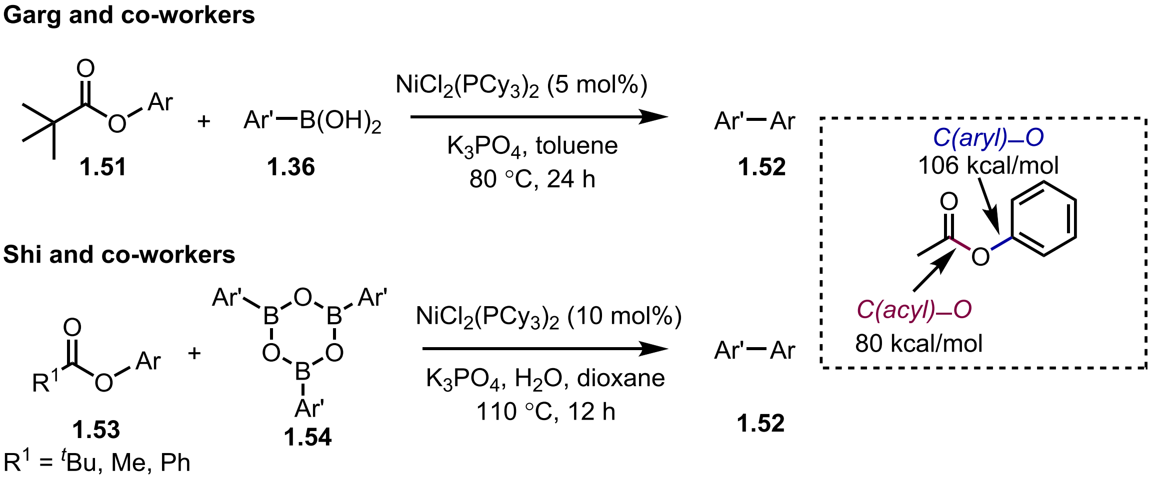
1.3.1 Cross-coupling of aryl esters

The earliest reported examples on the use of esters as cross-coupling electrophiles used significantly activated substrates.[73] Then, more robust esters have been activated using transition metal catalysis. Herein, recent achievements in the cross-coupling of aryl esters via different modes of activation as well as the mechanistic rules that dictate selectivity will be discussed.

C(aryl)–O bond activation (path A)

Among less activated acid derivatives, a particularly notable example was reported in 2008 by the Garg[74] and the Shi[75] groups **(Scheme 1.22)**.

Scheme 1.22. Garg and Shi's work on cleaving strong C(aryl)–O



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[73] Paetzold, J.; Gooßen, L. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1237.
[74] Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422.
[75] Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468.

Despite the relative weakness of the C(acyl)–O bond, these pivalate and acetate derivatives react via cleavage of the C(aryl)–O bond to provide biaryl coupling products. Furthermore, other Ni-catalyzed cross-couplings reactions of aryl pivalates generated these products arising from C(aryl)–O bond cleavage, suggesting that selectivity was in part substrate-controlled due to the steric bulk of the *t*-butyl group.[76] Nonetheless, in Shi's report (**Scheme 1.22**), C(aryl)–O activation is achieved favourably over C(acyl)–O bond cleavage with not only aryl pivalates, but also simple aryl esters, suggesting that Ni-PCy$_3$ catalyst was selective at enabling this reaction mode. Mechanistic studies later demonstrated that, particularly with monodentate phosphine ligands, selectivity for this pathway derives from a favorable C–O cleaving oxidative addition that proceeds via a 5-centered transition state **(Figure 1.8)**.[77]

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[76] (a) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem.Soc.* **2012**, *134*, 169; (b) Li, B.-J.; Xu, L.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2009**, *131*, 14656; (c) Li, B.-J.; Li, Y.-Z.; Lu, X.-Y.; Liu, J.; Guan, B.-T.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 10124.

[77] Hong, X.; Liang, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 2017.

From Houk's DFT-computed Gibbs free energies, a simplified energy diagram for the oxidative addition step with the Ni-PCy_3 catalyst is presented below **(Figure 1.8)**. Calculations for the oxidative addition of ArOPiv to Ni-PCy_3 gave a 28.5 kcal/mol activation energy barrier (**TS1.1**). Due to the highly stabilizing interaction between the oxygen atom of the carbonyl and the monoligated Ni in the 5-centered transition state **TS1.2** lowers this barrier by 10.3 kcal/mol. Consequently, the activation energy required for oxidative addition into the C(aryl)–O bond is 1.1 kcal/mol lower than what needed for C(acyl)–O bond activation (19.3 kcal/mol for **TS1.3** vs 18.2 kcal/mol for **TS1.2**).

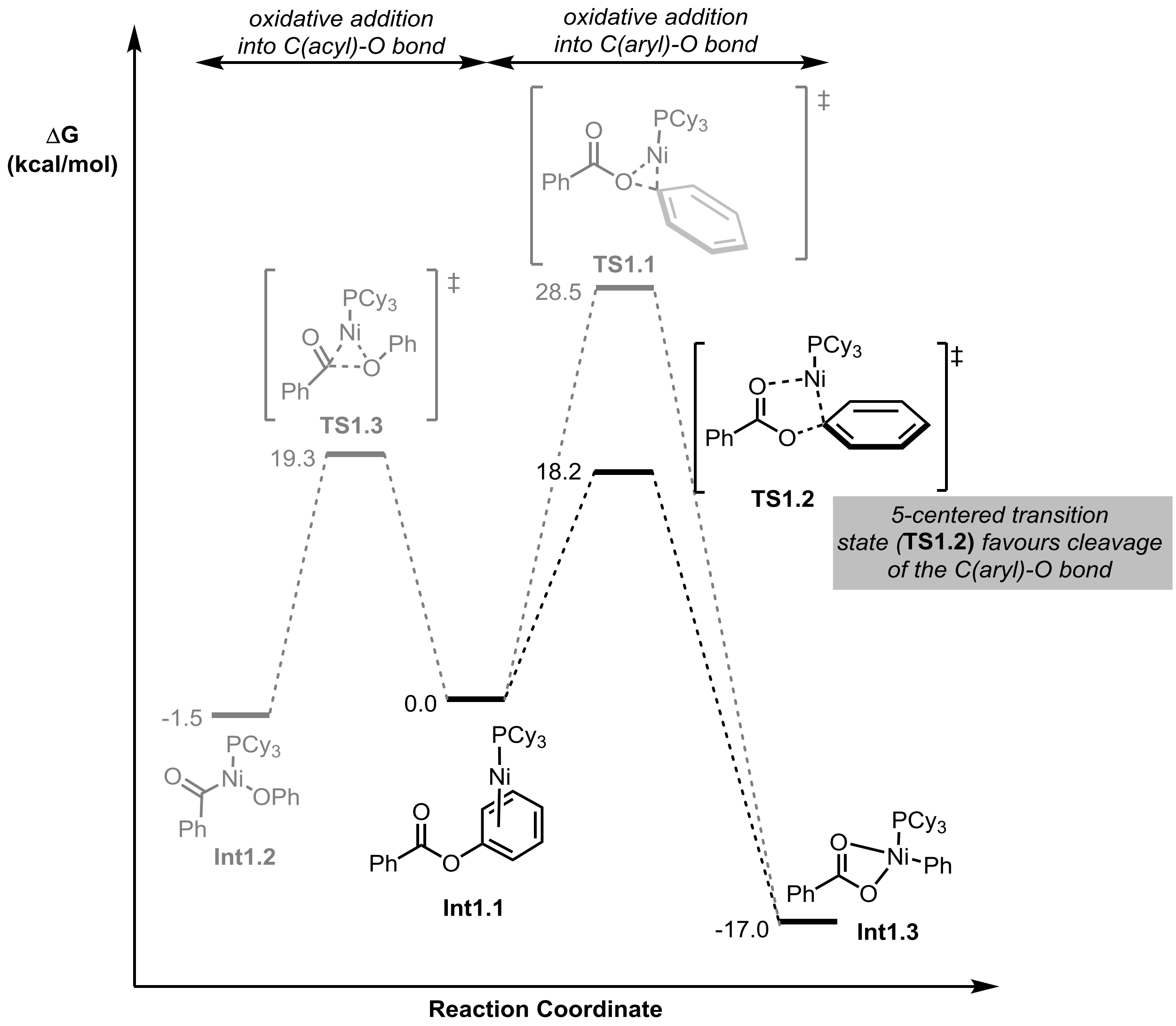
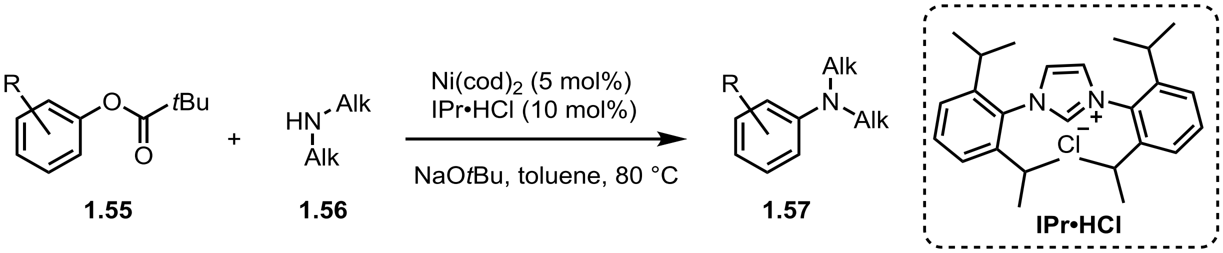


Figure 1.8. Energy diagram : Comparison of oxidative addition into C(acyl)–O vs. C(aryl)–O bond using Ni-PCy_3 system

Even though the above cleavage mode is reminiscent of the classical reactivity of aryl halides, it sharply contrasts the expected traditional functionalization of esters. This mechanistically-supported novel reactivity demonstrates the power of catalysis in tuning unusual sites of reactivity.

On top of this Suzuki-Miyaura cross-coupling that proceeds via pathway A (C(aryl)–O bond cleavage), the use of esters as coupling partners in catalytic amination reactions has also recently been explored using nickel catalysis. Chatani and co-workers reported the first example in 2010, coupling alkyl amines with aryl pivalates to prepare aniline derivatives via selective cleavage of the C(aryl)–O bond in the key oxidative addition step (**Scheme 1.23**).[78] This bond cleavage mode has been further exploited with a variety of nucleophilic coupling partners.[79]

Scheme 1.23. Ni-catalyzed amination of pivalate esters via C(aryl)–O cleavage



Using a Ni(cod)$_2$/IPr system and both electron-rich and deficient aryl pivalates, aminated products have been afforded in 70 to 99% yields. A variety of acyclic and cyclic amines such as morpholine, pyrrolidine, N-methyl benzyl amine, and piperidine derivatives has been successfully employed for the above transformation.

The choice of the substituent on the acyl group was crucial for this catalytic amination to proceed (**Table 1.1**). The same reaction conditions have been subjected to different types of acyl groups. When the phenyl acetate (entry 2) is used, no aminated product was observed. Also, the use of a

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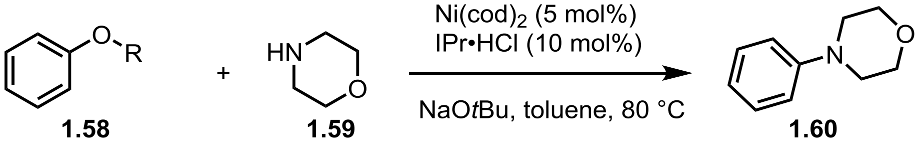
[78] Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed,* **2010**, *49,* 2929.

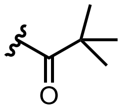
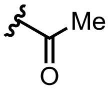
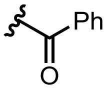
[79] (a) Molander, G. A.; Beaumard, F. *Org. Lett.* **2010**, *12*, 4022; (b) Sun, C.-L.; Wang, Y.; Zhou, X.; Wu, Z.-H.; Li, B.-J.; Guan, B.-T.; Shi, Z.-J. *Chem. Eur. J.* **2010**, *16*, 5844; (c) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346; (d) Tobisu, M.; Chatani, N. *Top. Curr. Chem.* **2016**, *374,* 41; (e) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29.

benzoyl group (entry 3) afforded the product in a much lower yield compared to the initial pivalate substrate.

Table 1.1. Screening of different acyl electrophiles towards C(aryl)–O bond activation



1.58 **1.59** **1.60**

Entry	Substrate (R)	% yield
1		91
2		0
3		26

In contrast with the “natural” C(acyl)–O site of reactivity of esters with amines nucleophiles, this work represents a novel/unusual mode of esters activation. However, the fact that this reaction is only efficient with very specific aryl pivalates electrophiles suggests that these discovered reaction conditions are limited to unique sterically hindered substrates. Further investigation of catalytic (metal/ligand) controlled activation, which helps generalizing this mode of reactivity to a variety of esters electrophiles, will be of high importance. If successful, this will certainly widen the applicability of catalytic amination in industrial settings, and increase the diversity of the electrophiles in the catalytic amination reactions.

C(acyl)–O bond activation with decarbonylation (path B)

In 1976, the Yamamoto lab reported that aryl esters could react with stoichiometric Ni(0). They hypothesized that oxidative addition of the C(acyl)–O bond produces a transient acyl Ni(II) species, which undergoes rapid decarbonylation.[80] It was not until 2012 that this pathway was exploited in selective catalytic cross-couplings, when the Itami group reported that simple phenyl

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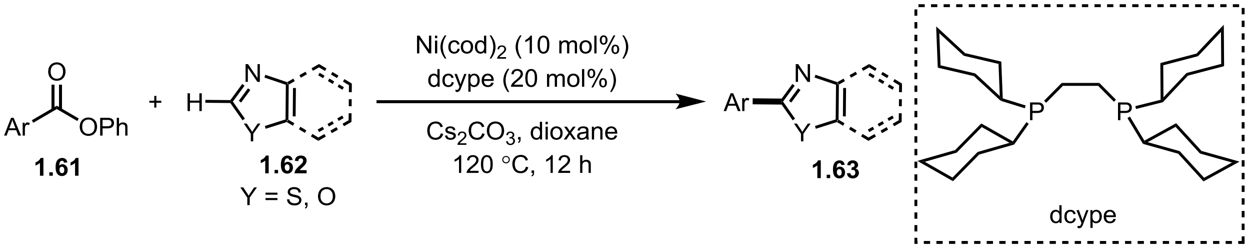
[80] (a) Ishizu, J.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1976**, *5*, 1091; (b) Yamamoto, T.; Ishizu, J.; Kohara, T.; Komiya, S.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 3758.

esters can be used in decarbonylative C-H activation with a nickel catalyst bearing a bulky bidentate (dcype) phosphine ligand **(Scheme 1.24).**[81] In addition, this established method allowed the coupling of phenyl esters with oxazole and thiazole derivatives.

Scheme 1.24. Ni-catalyzed coupling of phenyl esters via C(acyl)–O bond activation



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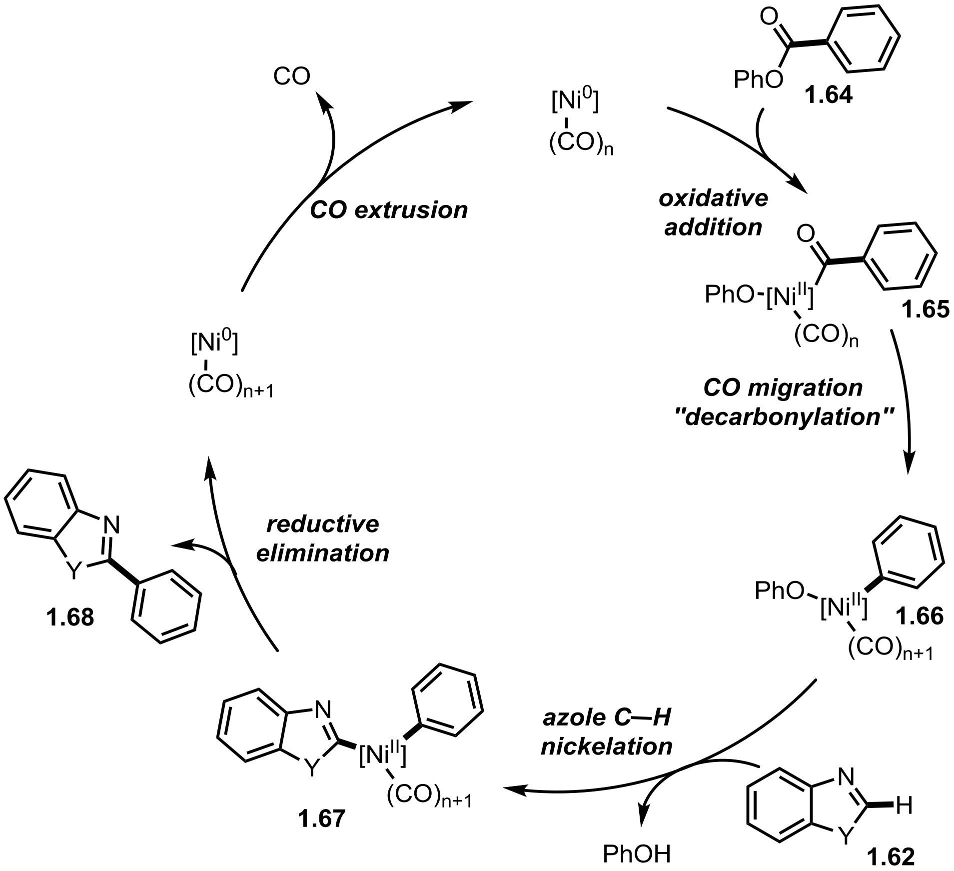
[81] Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 13573.

A plausible mechanism for this decarbonylative C−H arylation reaction was proposed (**Scheme 1.25**). The first step involves an oxidative addition into the C(acyl)–O bond of the phenyl ester. Then, a CO migration onto the nickel center followed by C–H nickelation of azole to produce **1.67**. Finally, reductive elimination occurs to release the coupling product **1.68** and generate a $Ni^0(CO)_{n+1}$ species. Moreover, the active Ni^0 catalyst could be regenerated by thermal extrusion of CO.

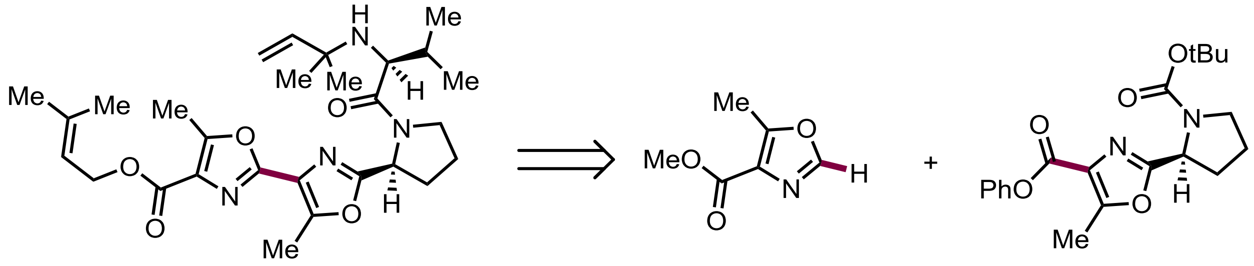
Scheme 1.25. A plausible mechanism for the decarbonylative C−H activation using a Ni−dcype catalytic system[81]



It was suggested that the selectivity for the C(acyl)–O bond cleavage originates from the inability of the bidentate Ni(0) to coordinate with the carbonyl oxygen during oxidative addition, and a rate-determining decarbonylation step that outcompetes C–C bond reductive elimination to preferentially form biaryls.[82]

Itami and co-workers applied this invention to the synthesis of muscoride A, a natural product with antibacterial activity **(Scheme 1.26)**.[81]

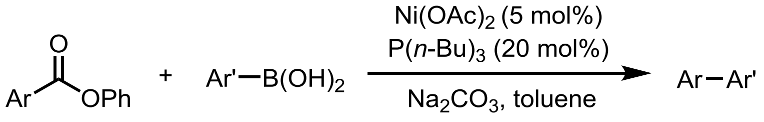
Scheme 1.26. Application of the decarbonylative C(acyl)–O bond activation in the "Muscoride A" synthesis



Muscoride A

Later, in 2015, Itami's lab reported the first Suzuki-Miyaura cross-coupling of phenyl esters that are proposed to proceed by C(acyl)–O bond cleavage (**Scheme 1.27**).[83] Therein, a nickel-based catalytic system ($Ni(OAc)_2/P(n\text{-}Bu)_3$) for the decarbonylative organoboron cross-coupling using phenyl esters as coupling partners was described. In addition to the broad organoboron scope, a variety of aryl as well as heterocyclic esters have been applied.

Scheme 1.27. Suzuki-Miyaura coupling via decarbonylative C(acyl)–O bond activation of phenyl esters



1.61 **1.36** **1.52**

Mechanistic features **(Scheme 1.28)** have been elucidated by density functional theory (DFT) calculations. Based on this data, the cross-coupling reaction is proposed to proceed through

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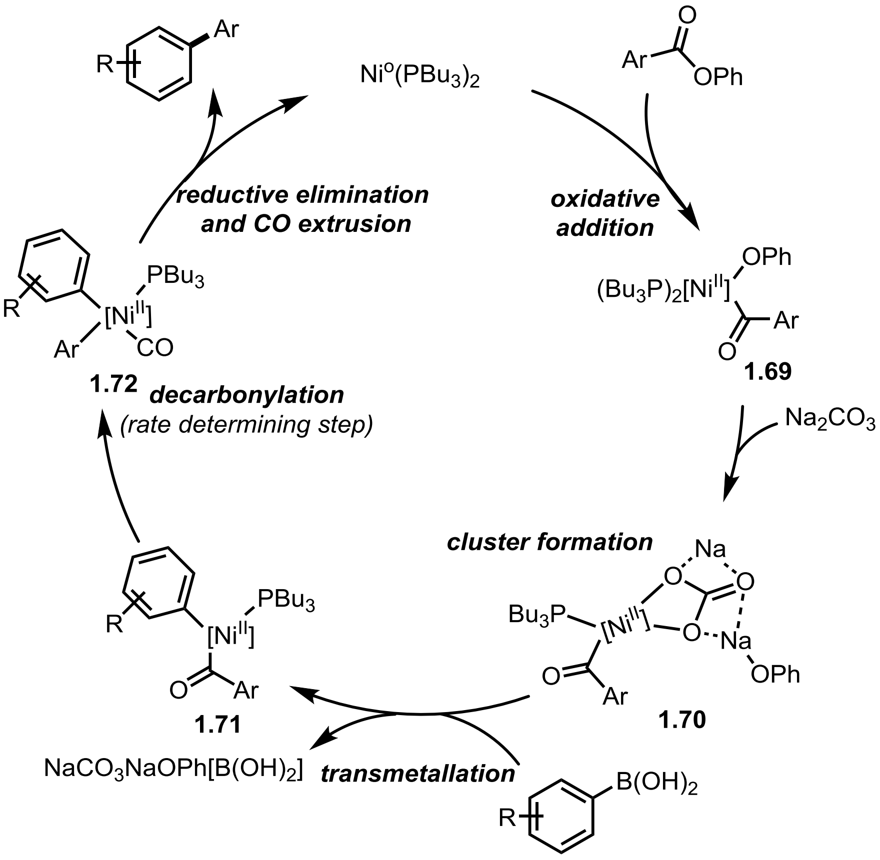
[82] Xu, H.; Muto, K.; Yamaguchi, J.; Zhao, C.; Itami, K.; Musaev, D. G. *J. Am. Chem.* Soc. **2014**, *136*, 14834.

[83] Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508.

oxidative addition step into the C(acyl)–O bond providing **1.69**. The addition of Na_2CO_3, which leads to the cluster complex formation **1.70**, does not interfere with this first step. However, it plays a determining role in the transmetalation before tackling a decarbonylative rate-determining step. It should be noted that the calculations have also demonstrated a slightly higher-energy reaction pathway in the absence of base. Using this method, aliphatic cross-couplings, a gram-scale reaction, a one-pot cross-coupling protocol starting directly from carboxylic acids, and application to complex molecular settings have all been achieved.

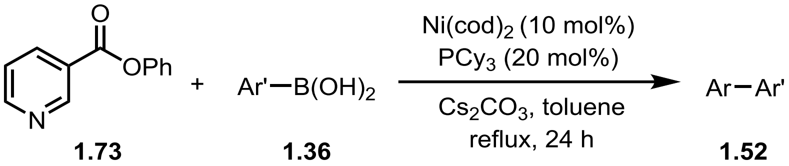
Scheme 1.28. DFT-supported mechanism of Suzuki-Miyaura coupling using phenyl ester electrophiles.[83]



The above decarbonylative Suzuki-Miyaura coupling done by Itami and co-workers featured many important "firsts" in organic synthesis. For example, it was the first clear evidence of transition-metal insertion into the C(acyl)–O bond of relatively robust phenyl ester. Also, it represents the initial report of Suzuki-Miyaura cross-coupling using esters as electrophilic coupling partner via this specific mode of cleavage C(acyl)–O bond activation with decarbonylation).

In the same year of Itami's discovery, Love and co-workers reported a similar reaction **(Scheme 1.29)**.[84] Using a Ni/PCy_3 system, they achieved decarbonylative Suzuki-Miyaura cross-coupling of aryl esters and boronic acids in modest yields. For this reaction, the electrophilic ester scope was limited to pyridine-substituted phenyl esters, which represent a clear disadvantage compared to Itami's general method.

Scheme 1.29. Love's work on Suzuki-Miyaura coupling using pyridine phenyl esters



These aryl ester decarbonylative couplings have since proven to be quite diverse. Thus, extensive efforts have been made by the Rueping[85] and the Shi[86] labs, independently, towards achieving other cross-coupling reactions, such as silylation and borylations, using phenyl esters as electrophilic coupling partner.

C(acyl)–O bond activation with carbonyl-retention (path C)

In 2004, Chatani and co-workers reported a palladium-catalyzed coupling reaction of 2-pyridyl esters with organoboron compounds **(Scheme 1.30)**.[87] For this Suzuki-Miyaura type coupling reaction, the presence of the nitrogen atom on the second position of the ester was found to be essential. Control experiments were carried out to investigate further the role of the pyridyl group by testing various coordination sites. Moreover, the accomplishment of the present reaction arises mainly from the coordination of the nitrogen atom to the Pd metal. Thus, the pyridyl group acts as good leaving and directing group.

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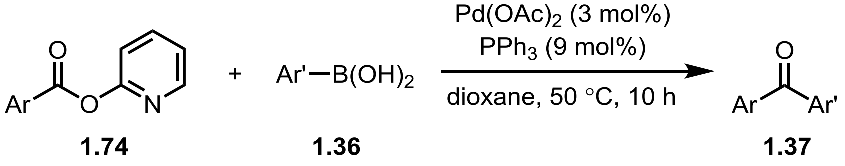
[84] LaBerge, N. A.; Love, J. A. *Eur. J. Org. Chem.* **2015**, *2015*, 5546.

[85] (a) Guo, L.; Chatupheeraphat, A.; Rueping, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 11810; (b) Guo, L.; Rueping, M. *Chem. Eur. J.* **2016**, *22*, 16787.

[86] Pu, X.; Hu, J.; Zhao, Y.; Shi, Z. *ACS Catal.* **2016**, *6*. 6692.

[87] Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, *6*, 3597.

Scheme 1.30. Suzuki-Miyaura coupling using 2-pyridyl esters electrophiles



While high yielding carbonyl-retaining couplings via C(acyl)–O cleavage (path C) from simple phenyl esters had not yet been reported at the outset of this thesis, the above discovery by Chatani and co-workers represent a preliminary evidence for the existence of this reaction mode, albeit limited to specific 2-pyridyl esters. More complex/novel catalyst systems than Pd/PPh_3 catalyst were hypothesized to be able to achieve cross-coupling reactions from more robust and simple ester functionalities to provide a general methodology that could find potential applications in the synthesis of complex molecules.

1.3.2 Cross-coupling of methyl esters

Cross-coupling reactions that proceed via the activation of the acyl functionality are known,[88] however, amination reactions proceeding by this pathway are exceedingly rare.[89] This is at least partially because of the 'natural' reactivity of amines and carboxylic acid derivatives such as acid chlorides and anhydrides, which do not require a catalyst for activation. However, for less activated coupling components such as simple esters and aryl amines, a catalyst or stronger base may be necessary.[90] Near the beginning of this thesis research, the first cross-coupling approach to amide bond formation was reported by the Garg lab[91] using a Ni-NHC catalyst system with methyl naphthoate substrates activated by $Al(O\textit{t}Bu)_3$ (**Scheme 1.31**). This C(acyl)–O activation of methyl esters, which afforded tertiary amide products, was studied by the Houk lab.

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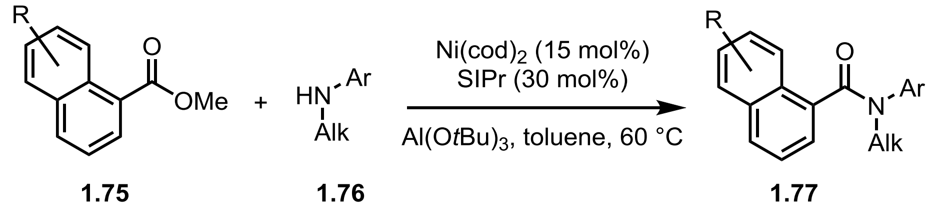
[88] (a) Kakino, R.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 371; (b) Yu, B.; Sun, H.; Xie, Z.; Zhang, G.; Xu, L.-W.; Zhang, W.; Gao, Z. *Org. Lett.* **2015**, *17*, 3298; (c) Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 14518; (d) Hu, J.; Zhao, Y.; Liu, J.; Zhang, Y.; Shi, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 8718.

[89] (a) Baker, E. L.; Yamano, M. M.; Zhou, Y.; Anthony, S. M.; Garg, N. K. *Nat. Commun.* **2016**, *7*, 11554; (b) Bao, Y.-S.; Zhaorigetu, B.; Agula, B.; Baiyin, M.; Jia, M. *J. Org. Chem.* **2014**, *79*, 803; (c) Bao, Y.-S.; Wang, L.; Jia, M.; Xu, A.; Agula, B.; Baiyin, M.; Zhaorigetu, B. *Green Chem.* **2016**, *18*, 3808.

[90] Kim, B. R.; Lee, H.-G.; Kang, S.-B.; Sung, G. H.; Kim, J.-J.; Park, J. K.; Lee, S.-G.; Yoon, Y.-J. *Synthesis* **2012**, *44*, 42.

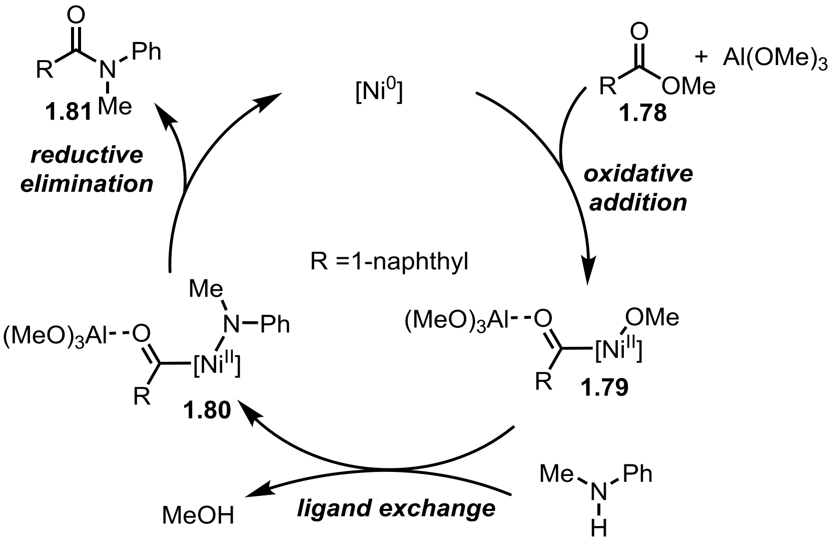
[91] Hie, L.; Fine Nathel, N. F.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Garg, N. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 2810.

Scheme 1.31. Ni-catalyzed amidation of methyl naphthoates via C(acyl)–O bond cleavage



DFT calculations supported the fact that this cross coupling reaction undergoes an oxidative addition step into the ester C(acyl)–O bond to generate intermediate **1.79**, followed by a ligand exchange, and a final reductive elimination to afford the amide product **1.81** (**Scheme 1.32**).

Scheme 1.32. DFT-supported mechanism of amidation reaction from methyl ester



The first step of this mechanism is assisted by the Lewis acid Al(O*t*Bu)$_3$. This additive is found to have a beneficial kinetic influence with regards to the rate-determining oxidative addition step. In the absence of the Lewis acid, the kinetic barrier for oxidative addition is computed to be 33.2 kcal/mol (**Figure 1.9**). However, the employment of the additive helps the oxidative addition becoming significantly more facile, with a kinetic barrier of 26.8 kcal/mol.

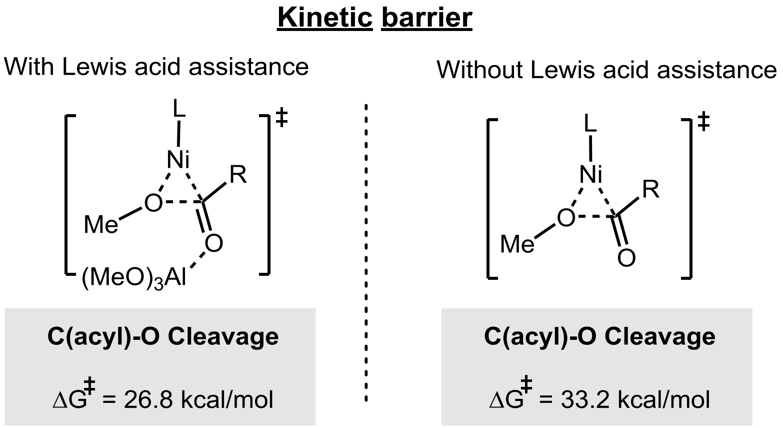
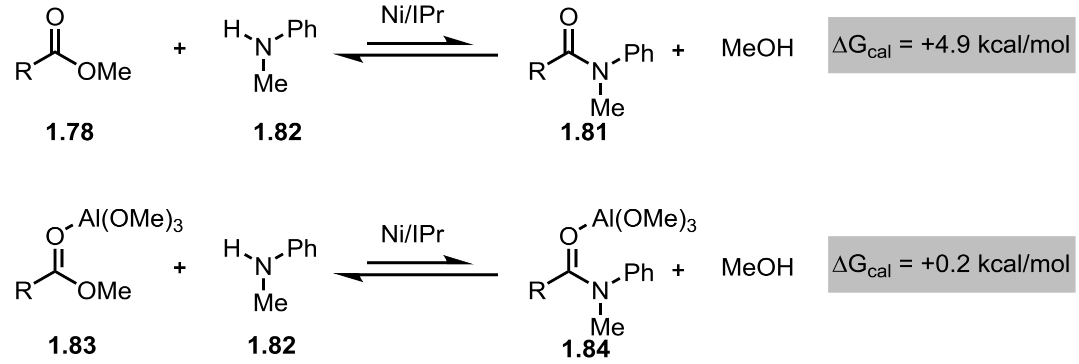


Figure 1.9. Comparison of kinetic barrier for oxidative addition with and without Lewis acid

Moreover, DFT calculations were also used to probe the beneficial influence of the Al(O*t*Bu)$_3$ additive on the thermodynamic aspect of the reaction **(Scheme 1.33)**. Without the additive, the amidation of ester with aniline is endergonic by 4.9 kcal/mol. However, upon addition of the aluminum additive, the amidation becomes almost thermoneutral.

Scheme 1.33. Influence of the Al(OR)$_3$ on thermodynamics[91]

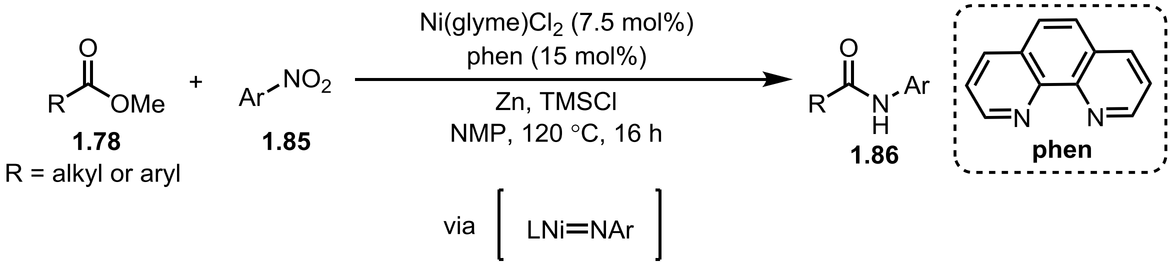


As it could be easily noticed, this reaction is highly limited to secondary N-alkyl-N-aryl amines where the N-methyl aniline dominates most of the used nucleophilic coupling partners. In parallel, methyl 1-naphthoates were the only successful ester electrophiles. Houk and Garg labs collaborated together to understand further the origin of this limitation. Using DFT calculations, it has been found that the ester-Al(O*t*Bu)$_3$ complex, in the case of methyl 1-naphthoate, is less stable than the methyl 2-naphthoate and the simple methyl benzoate. This lack of stability, which makes reactions of these substrates thermodynamically more favorable, is due to the higher distortion of this ester-Lewis acid complex.

While conceptually interesting, this discovery suffers from limited substrate scope. Furthermore, the necessity of using stoichiometric Al(O*t*Bu)$_3$ to achieve challenging oxidative addition step, will certainly limit the applications feature of this methodology.

Recently, Hu et al. disclosed the coupling of methyl esters with nitroarenes to form amides (**Scheme 1.34**).[92] In this transformation, stoichiometric zinc powder and TMSCl is required to reduce the nitroarene *in situ*. It is speculated that generation of a reactive Ni-nitrene intermediate can then facilitate insertion into the methyl ester. While this reaction does not mechanistically resemble the previously discussed C–O bond activations, the net transformation is similar. Importantly, the ester scope was greatly improved over Garg's amidation; both aliphatic and (hetero) aromatic esters could be utilized, though only N-aryl secondary amides could be prepared.

Scheme 1.34. Ni-catalyzed amidation of methyl esters using nitroarenes



Overall, different modes of ester activation have been established (**Scheme 1.21**). For example, the C(aryl)–O bond activation (path A) of simple aryl esters, which need specific conditions to tune the reaction towards the activation of these unusual bonds, was reported. This mode of reactivity has been well illustrated via the Garg, Shi, and Chatani work (**Scheme 1.22, 1.23**). Other activation modes, such as the C(acyl)–O bond cleavage with subsequent de-insertion of the carbon monoxide (path B), have been reported by the Itami and Love groups independently (**Scheme 1.24, 1.27, 1.29**). Notably, these reactions generally take place around 150 °C, a

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[92] Cheung, C. W.; Ploeger, M. L.; Hu, X. *Nature Commun.* **2017**, *8*, 14878.

substantially elevated temperature, which may facilitate this decarbonylation step. While it represents the expected natural reactivity of ester functionality, due to the weaknesses of such carbon–oxygen bond, the cleavage of the C(acyl)–O bond with carbonyl retention has barely been reported. This activation mode via path C falls into the heart of this thesis.

1.4 Conclusions and perspectives

On top of the great success of accessing inert aryl electrophiles (**Section 1.2.1**), a variety of carboxylic acid derivatives has been reported in cross-coupling chemistry (**Figure 1.10**). Methods to functionalize acyl chlorides were successfully achieved in late 1970s. Then, acid anhydrides and thioesters have been established as powerful electrophilic coupling partners in late 1990s. Most recently, extensive efforts have been done towards the activation of amides and esters in the field of cross-coupling chemistry.

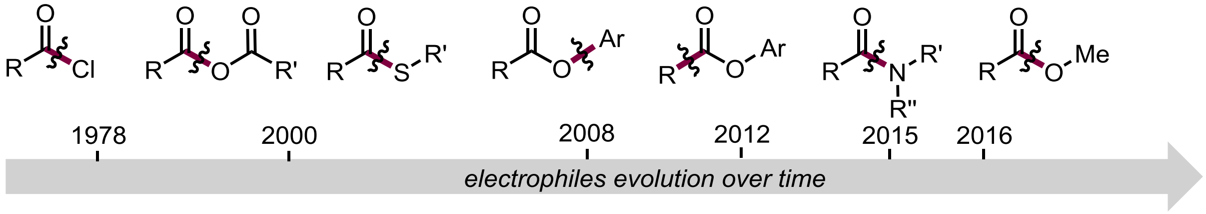


Figure 1.10. Electrophilic coupling partners evolution over time

Despite this success on the activation of ester functionality, significant improvement can be envisioned to maximize the impact of these electrophiles in cross coupling chemistry, providing researchers not only with a powerful tool to access previously inaccessible molecules but also a source of inspiration to discover new reactivities.

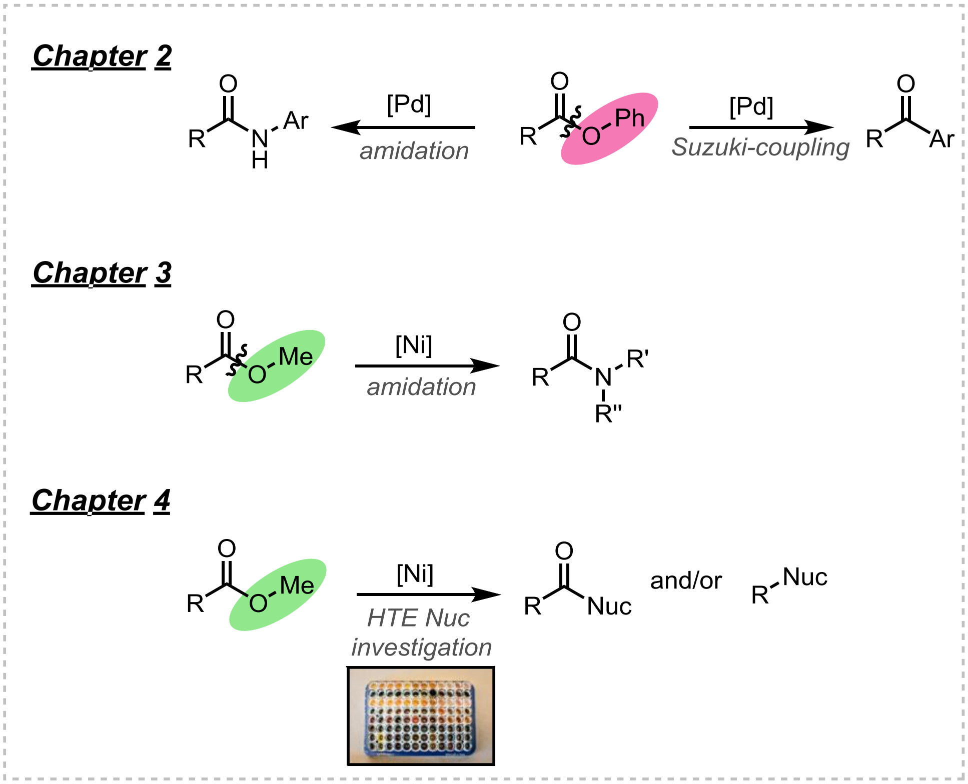
1.5 Research goals

As outlined above, several carboxylic acid derivatives emerged as powerful coupling partners in cross-coupling reactions. In the last decade, several groups presented different modes of reactivity for the cross-coupling of esters. However, the cleavage of the C(acyl)–O bond with carbonyl retention of simple aryl esters remains underdeveloped. The goal of this thesis was to determine if acylative couplings could be achieved on moderately activated and unactivated esters and to investigate the underlying rules that dictate selectivity. The development of this mode of reactivity with carbonyl retention could provide a broader range of starting materials that can give rise to diverse products. A palladium-catalyzed Suzuki-Miyaura cross-coupling of aryl esters affording ketone products and a Pd-catalyzed coupling between aryl esters and anilines generating amides is disclosed in chapter 2. Phenyl ester substrates are particularly robust in comparison to other carboxylic acid derivatives used in cross-coupling reactions, suggesting they may be applicable to the synthesis of complex molecules where chemoselectivity issues may occur. DFT calculations were performed to reveal the underlying mechanistic features that enable these reactions to selectively occur, illustrating unique differences in reactivity modes of Pd vs Ni.

While conceptually interesting, these phenol-derived substrates are considerably activated compared to abundant methyl and ethyl esters. Given the limitations of previous catalytic methodologies and seeking the practical aspect of activating such strong C(acyl)–O bond, the activation of inert methyl esters substrates is pursued in Chapter 3 in the context of amide bond formation.

Due to the acquired knowledge of activating inert methyl ester functionality via a Ni-catalyzed amide bond formation, the investigation of multiple nucleophilic coupling partners using a high-throughput screening approach is described in chapter 4. For a summary of these projects, see **scheme 1.35**.

Scheme 1.35. Summary of research projects



Chapter 2

2 Cross-coupling of aryl esters

2.1 A palladium-catalyzed Suzuki-Miyaura cross-coupling of aryl esters

2.1.1 Introduction

The Suzuki-Miyaura cross-coupling is a metal-catalyzed reaction in which boron-based nucleophiles and halide-based electrophiles react to form a new carbon–carbon bond. This is one of the most reliable tools in synthetic chemistry, and is extensively used in the synthesis of pharmaceuticals, agrochemicals and organic materials.[1]

Recently, extensive research efforts are being devoted to broadening the scope of the electrophilic partner of this cross-coupling reaction (**see Chapter 1**). At the outset of this thesis, applications of acid chlorides, anhydrides, thioesters, and select highly activated esters (e.g. pyridyl esters) were well established. Use of amide and more robust esters in Pd-catalyzed ketone synthesis had not yet been reported. Ketone synthesis from carboxylic acid derivatives is a highly valuable transformation. Stoichiometric reaction of organometallic nucleophiles with carboxylic acid derivatives such as Weinreb amides or acid chlorides are well established (**Scheme 2.1**), but issues of chemoselectivity and functional group tolerance limit applications.

Friedel-Crafts acylations represent one of the most valuable reactions in ketone synthesis. For this transformation, acyl chlorides react with electron rich arenes to afford the acylated arene. These reactions often require a strong Lewis acid additive or catalyst, such as $AlCl_3$, which may be incompatible with acid-sensitive moieties on the substrate. The Weinreb amides,[2] which could be synthesized from acyl chlorides, generate a 1,2 addition product (**2.1.8)** upon addition of the organometallic reagent **2.1.6**. The stable 5-membered intermediate **2.1.7** does not collapse until

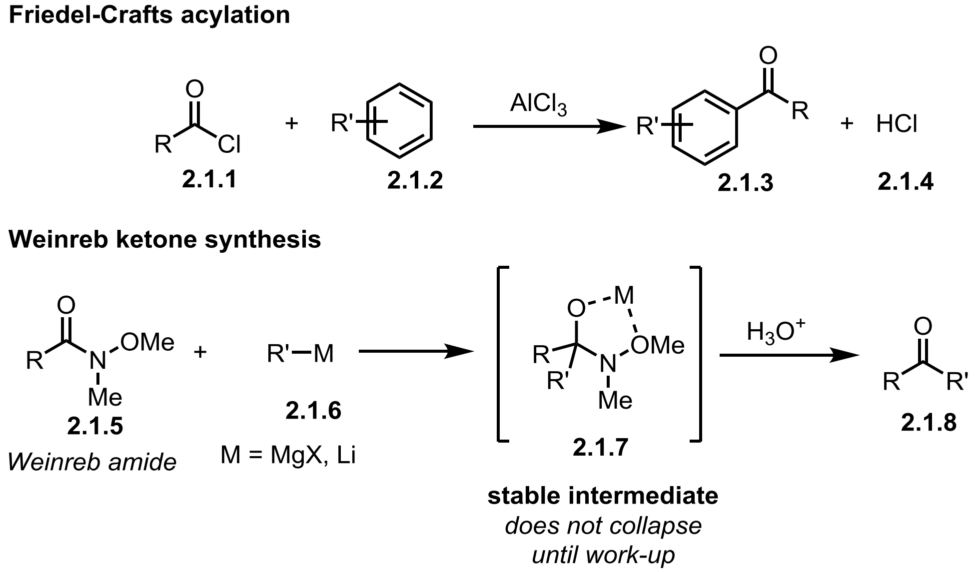
---

[1] Yasuda, N., *J. Organomet. Chem*. **2002**, *253*, 279; (b) Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, R. C.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J.; Lo, Y. S.; Rossano, L. T.; Brookes, A. S.; Meloni, D.; Moore, J. R.; Arnett, J. F.; et al. *J. Org. Chem.* **1994**, *59*, 6391; (c) Calderazzo, F.; Catellani, M.; Chiusoli, G. P. “Carbon-Carbon Bond Formation.” *Metal-catalysis in Industrial Organic Processes.* Chiusoli, G. P.; Maitlis, P. M. Cambridge: *The Royal Society of Chemistry*, **2006**; (d) Kruger, A. W.; Rozema, M. J.; Chu-Kung, A.; Gandarilla, J.; Haight, A. R.; Kotecki, B. J.; Richter, S. M.; Schwartz, A. M.; Wang, Z. *Org. Process Res. Dev*. **2009**, *13*, 1419.

[2] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

the acidic work-up and affords the corresponding ketones. Even though this method requires an additional synthetic step of the Weinreb amides starting materials, a selective monoaddition of the Grignard or organolithium reagent can be achieved. In contrast, the use of “regular” amides or esters usually leads to over-addition alcohol products instead.

Scheme 2.1.Traditional methods to synthesize ketones



On the other hand, catalytic strategies[3] towards ketone formation have mainly focused on utilizing carboxylic acid derivatives with very weak C(acyl)–X bonds that may be easily cleaved by oxidative addition, but may also be prone to other side reactions such as hydrolysis. This limits applications in multi-step synthesis, where lengthy protection, deprotection, and activation of the carboxylic acid must be carried out.[4]

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[3] (a) Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177; (b) Blangetti, M.; Rosso, H.; Prandi, C.; Deagostino, A.; Venturello, P. *Molecules* **2013**, *18*, 1188; (c) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. *Org. Lett.* **2003**, *5*, 3033; (d) Prokopcová, H.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2009**, *48*, 2276; (e) Xin, B.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2006**, *71*, 5725; (f) Chen, Q.; Fan, X.-H.; Zhang, L.-P.; Yang, L.-M. *RSC Adv.* **2014**, *4*, 53885; (g) 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; (h) 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; (i) Muto, K.; Hatakeyama, T.; Itami, K.; Yamaguchi, J. *Org. Lett.* **2016**, *18*, 5106; (j) Desnoyer, A. N.; Friese, F. W.; Chiu, W.; Drover, M. W.; Patrick, B. O.; Love, J. A. *Chem. Eur. J.* **2016**, *22*, 4070; (k) Shi, S.; Szostak, M. *Chem. Eur. J.* **2016**, *22*, 1042; (l) Shi, S.; Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6959; (m) Meng, G.; Shi, S.; Szostak, M. *ACS Catal.* **2016**, *6*, 7335.

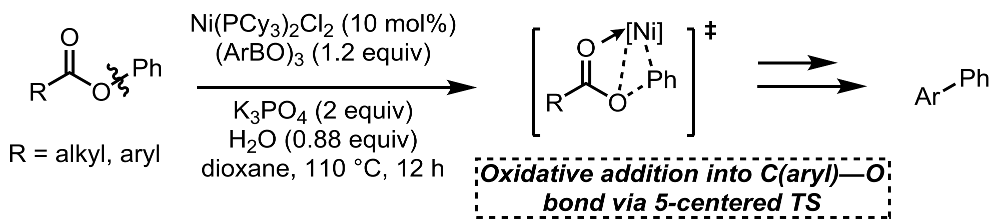
[4] For an example of a complex molecule late-stage Liebeskind-Srogl coupling that required multiple protection-deprotection steps due to the sensitivity of thioesters, see: Dandepally, S. R.; Williams, A. I. *Tetrahedron Lett.* **2010**, *51*, 5753.

2.1.2 Research goals

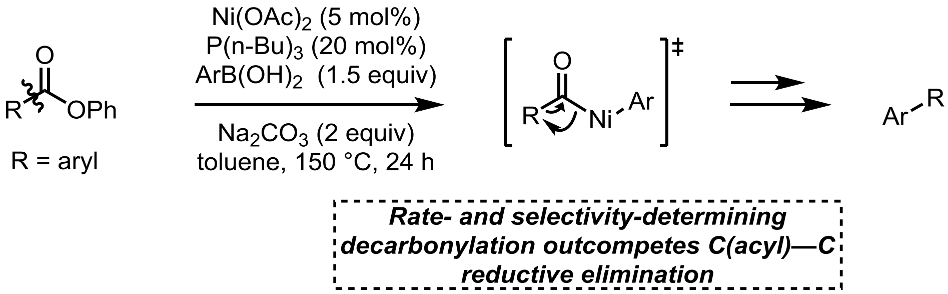
Aryl esters have recently emerged as powerful coupling partners in cross-coupling reactions. Garg[5] and Shi[6] reported Suzuki-Miyaura coupling via cleaving the C(aryl)–O bond (**Scheme 2.2**, path A), forming a biaryl species. Itami[7] and Love[8] disclosed the C(acyl)–O bond activation pathway with a loss of the carbonyl group for a Suzuki-Miyaura reaction (path B).

Scheme 2.2. Reported modes of activation using phenyl esters

Coupling via path A *(Shi and co-workers method)*



Coupling via path B *(Itami and co-workers method)*



Since cross-coupling reactions via pathway C (**Scheme 2.3**) of aryl esters remains undiscovered, an efficient catalytic methodology was sought to fill a valuable role opening access to a novel reactivity mode of ester electrophiles.

---

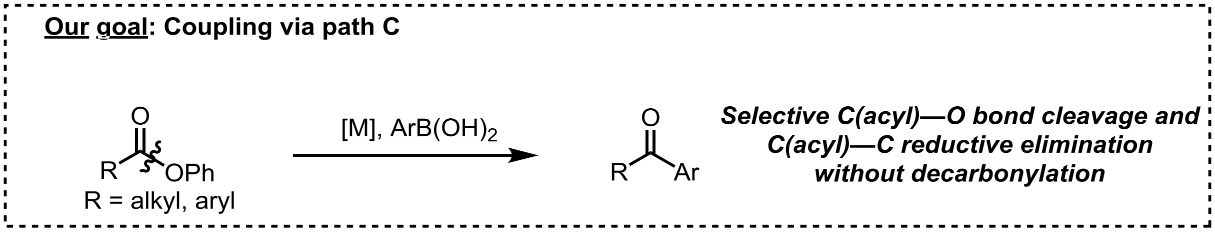
[5] Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422.

[6] Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468.

[7] Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508.

[8] LaBerge, N. A.; Love, J. A. *Eur. J. Org. Chem.* **2015**, *2015*, 5546.

Scheme 2.3. Our goal: Suzuki-Miyaura coupling via C(acyl)–O bond activation



With this motivation in mind, we sought to determine if the acyl-metal species generated by oxidative addition to phenyl esters could be efficiently utilized in a carbonyl-retentive Suzuki-Miyaura coupling via path C. Additionally, we desired to gain some fundamental understanding of the underlying rules that dictate selectivity for the three plausible coupling pathways that aryl esters may undergo.

2.1.3 Results and discussion[9]

2.1.3.1 Reaction discovery and optimization

This project was initiated using high-throughput experimentation (HTE) as a discovery tool. This technique, which will be further explained in chapter 4, is well-proven for discovering useful transformations. One of the advantages of such an approach is to screen many variables in parallel, facilitated by multi-well plates and efficient liquid transferring tools. After establishing our goal to probe new reactivity between substrates that can lead to cross-coupling reactions, a various number of parameters were screened (**Scheme 2.4**).[10] More specifically, multiple 96 well plates were performed with various numbers of esters, bases, catalysts, and solvents, whereas phenyl boronic acids were used as nucleophilic coupling partners.

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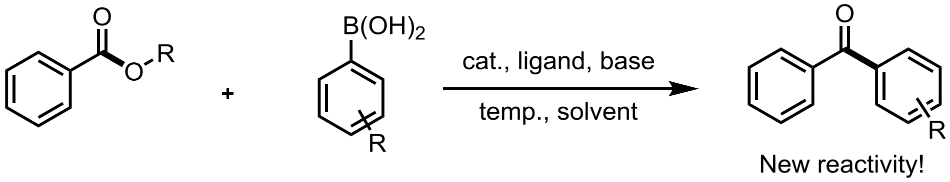
[9] The results presented in this chapter have been published in a peer-reviewed journal: Ben Halima, T.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.; Houk, K.; Newman, S. Palladium-Catalyzed Suzuki-Miyaura Coupling of Esters. *J. Am. Chem. Soc*. **2017**, *139*, 1311.

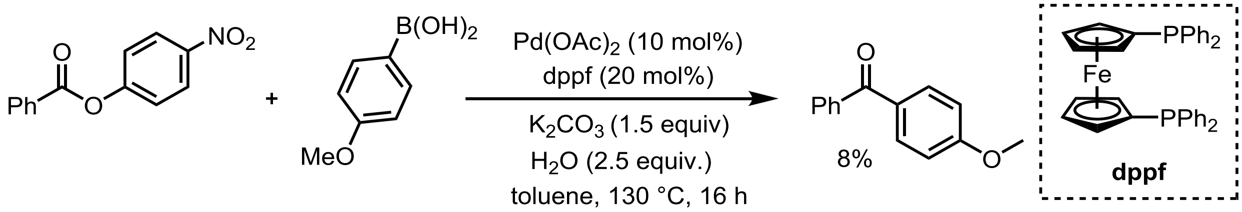
[10] This HTE part has been designed and executed by an Intern M.Sc student, Imane Yalaoui, under my mentorship.

Scheme 2.4. HTE approach towards the discovery of Suzuki-Miyaura coupling



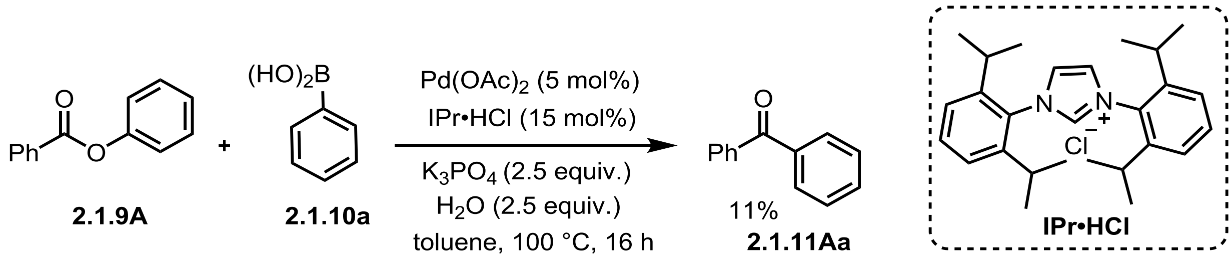
From this screening, an initial hit has been found (**Scheme 2.5**). In this discovered reaction, 4-nitrophenyl benzoate reacted with 4-methoxy-phenylboronic acid to give the corresponding ketone product in the presence of Pd(OAc)$_2$ as the catalyst and dppf as the ligand.

Scheme 2.5. Initial hit of Suzuki-Miyaura cross-coupling reaction.



This pathway of activating the C(acyl)–O bond while maintaining the carbonyl was assessed to be a potentially interesting discovery. However, it is important to note that the para-nitro group, which represents an very electron withdrawing functionality, significantly weakens the C(acyl)–O bond. This was anticipated to make the substrate more prone to oxidative addition, but also more prone to side reactions such as hydrolysis. Moving towards less activated ester electrophiles, traditional optimization was executed on a simple phenyl ester. By changing temperature, solvent, ligand and base, a reasonable yield of ketone **2.1.11Aa** was observed starting from commercially available phenyl benzoate (**Scheme 2.6**). The use of an NHC ligand was found to be critical.

Scheme 2.6. Suzuki-Miyaura coupling using simple phenyl ester after a preliminary optimization



After this promising starting point (entry 1 in the table below),[11] the transformation of phenyl benzoate and phenylboronic acid to benzophenone using palladium catalysts was chosen for further study. A portion of the extensive optimization is outlined in **Table 2.1**. Using 5 mol% $Pd(OAc)_2$, 1.5 equiv K_3PO_4, and 2.5 equiv H_2O in THF at 100 °C for 16 hours provided no desired product when utilizing many of the most common phosphine ligands for Suzuki-Miyaura and other cross-couplings, including PPh_3 (entry 2), P*t*Bu_3 (entry 3), P(*o*-tol)$_3$ (entry 4), dppf (entry 5), SPhos (entry 6), and BINAP (entry 7). The combination of $Pd(OAc)_2$ and IPr are known to inefficiently form active Pd(0) catalyst,[12] so different Pd sources were screened. The use of $Pd_2(dba)_3$, [Pd(allyl)Cl]$_2$, or [Pd(cinnamyl)Cl]$_2$ gave only slight improvements (entries 8–10), while the use of a 1:1 ratio of metal to ligand (entry 11) provided a substantial increase to 59% yield. A control experiment using the IPr ligand in the absence of the Pd source was done with significantly low yield (entry 12). Further improvement was realized when the preformed catalyst Pd(IPr)(cinnamyl)Cl[13] was used, which gave an excellent 95% yield (entry 13). With these conditions, the catalyst loading could be decreased to 3 mol% (entry 14), the temperature could be dropped to 90 °C and the run time could be reduced to 2 hours (entry 15) without impacting on the reaction outcome.[14]

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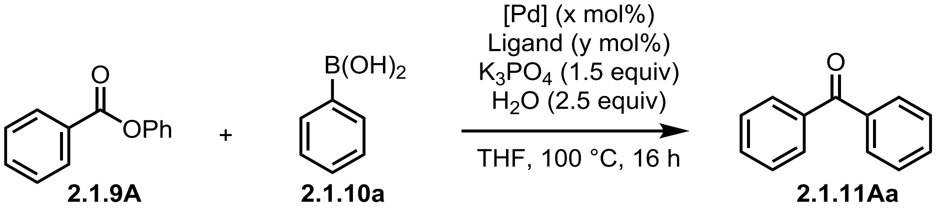
[11] After discovering this promising hit, M.Sc candidate Wanying Zhang joined the project and contributed to the optimization process that will be discussed.

[12] Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151.

[13] Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101.

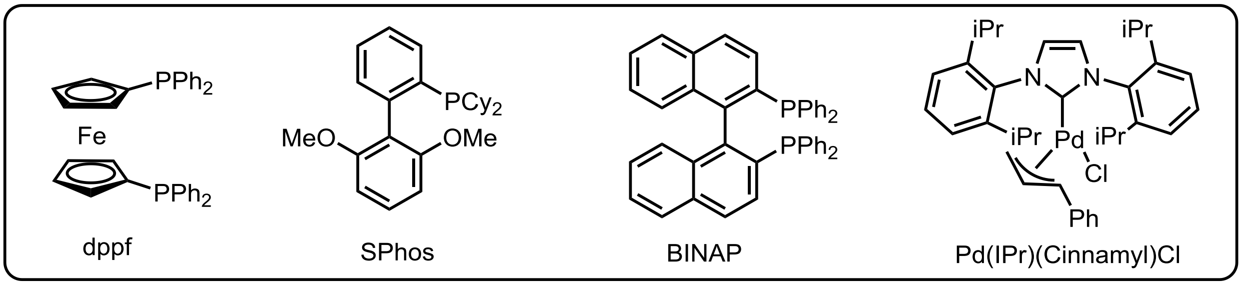
[14] The combination of a weak inorganic base, non-polar solvent, and small amount of water were necessary for obtaining high yields. In many cases, decomposition of the starting material was observed under the reaction conditions. It is thus unclear at the moment which parameters enhance the desired coupling rate and which decrease the rate of decomposition. See subsequent control experiments and optimization for further details.

Table 2.1. Optimization for Suzuki-Miyaura coupling of phenyl esters



Entry	Pd source	x	Ligand	y	Yield (%)[a]
1	$Pd(OAc)_2$	5	IPr•HCl	10	11
2	$Pd(OAc)_2$	5	PPh_3	10	<5
3	$Pd(OAc)_2$	5	$P\textit{t}Bu_3$	10	<5
4	$Pd(OAc)_2$	5	$P(\textit{o}\text{-tol})_3$	10	<5
5	$Pd(OAc)_2$	5	dppf	10	<5
6	$Pd(OAc)_2$	5	SPhos	10	<5
7	$Pd(OAc)_2$	5	BINAP	10	<5
8	$Pd_2(dba)_3$	5	IPr•HCl	10	16
9	$[Pd(allyl)Cl]_2$	5	IPr•HCl	10	19
10	$[Pd(cinnamyl)Cl]_2$	5	IPr•HCl	10	21
11	$[Pd(cinnamyl)Cl]_2$	5	IPr•HCl	5	59
12	none	-	IPr•HCl	5	<5
13	Pd(IPr)(cinnamyl)Cl	5	-	-	95
14	Pd(IPr)(cinnamyl)Cl	3	-	-	94
15	Pd(IPr)(cinnamyl)Cl	3	-	-	91[b]

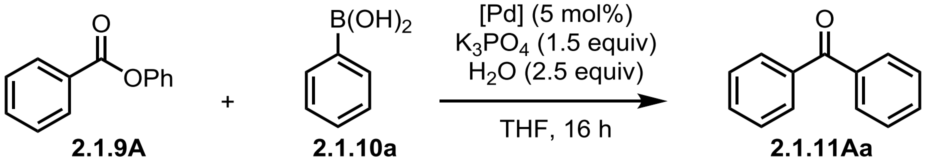
[a]Yield determined by GC with 1,3,5-trimethoxybenzene as internal standard.
[b]Reaction run for 2 hours at 90 °C. Isolated yield.



With the aim of improving the reaction conditions, we proceeded to use Nolan's procedure[13] to synthesize multiple other Pd-NHC catalysts and apply them to the discovered transformation at different reaction temperatures (**Table 2.2**). At 80 °C, Pd(SIMes)(cinnamyl)Cl (entry 2) gave a slightly lower yield than the initial Pd(IPr)(cinnamyl)Cl pre-catalyst. Using cinnamyl as the coordinating moiety seemed to perform better than the allyl species, which gave a yield of only 47% (entry 3). It was found that raising the temperature to 90 °C did improve the yield (entry 4).

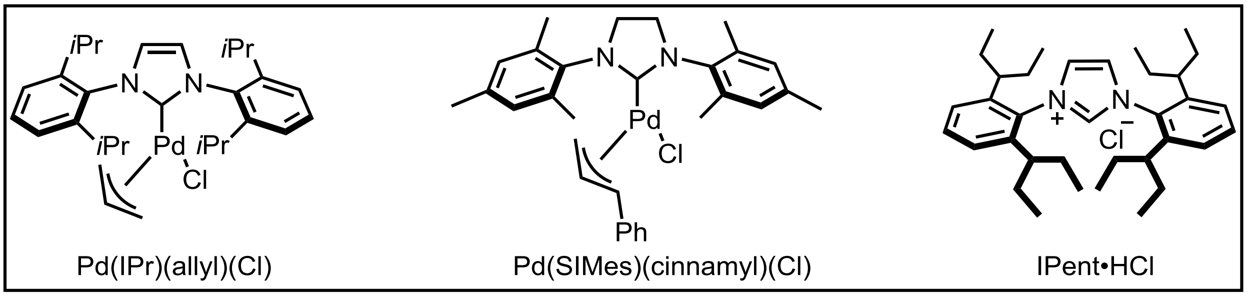
Modifying the NHC to IPent derivatives exhibited low reactivity giving a yield of less than 25% (entry 5). On the other hand, both Pd(SIMes)(cinnamyl)Cl and Pd(IPr)(cinnamyl)Cl showed promising and similar results giving 93% (entry 6) and 94% (entry 7) yields respectively at 100 °C. Based on these results, we concluded that Pd(IPr)(cinnamyl)Cl was an effective catalyst for this transformation.

Table 2.2. Catalyst and temperature screening



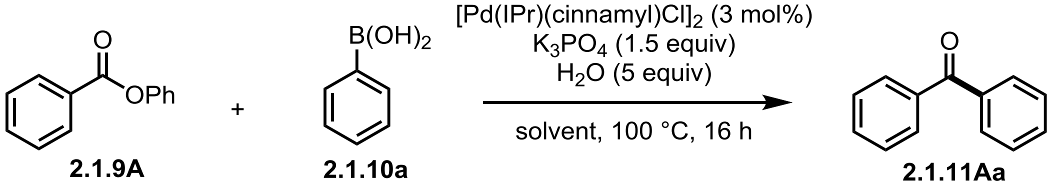
Entry	Pd source	Temperature (°C)	Yield (%)[a]
1	Pd(IPr)(cinnamyl)Cl	80	76
2	Pd(SIMes)(cinnamyl)Cl	80	74
3	Pd(IPr)(allyl)Cl	90	47
4	Pd(IPr)(cinnamyl)Cl	90	95
5	Pd(IPent)(cinnamyl)Cl	90	24[c]
6	Pd(SIMes)(cinnamyl)Cl	100	93
7	Pd(IPr)(cinnamyl)Cl	100	94[b]
8	Pd(IPr)(cinnamyl)Cl	100	95

[a] Yield determined by GC with 1,3,5-trimethoxybenzene as internal standard.
[b] Reaction with 3 mol% catalyst loading.
[c] Reaction run for 2 hours with 3 mol% catalyst loading. Isolated yield.



A variety of solvents were screened including polar, non-polar solvents and water (**Table 2.3**). There was no apparent trend in the type of solvent used. Solvents such as MeCN and DCE were not compatible, giving yields <5% (entries 1 and 2). Water, dioxane and notably toluene are more compatible giving yields of 57%, 67% and 70% respectively (entries 3-5). THF remains the optimal solvent of choice giving up to 94% yield (entry 6).

Table 2.3. Solvents screen for Suzuki-Miyaura coupling



Entry	Solvent	Yield (%)[a]
1	MeCN	trace
2	DCE	trace
3	Water	57
4	dioxane	67
5	toluene	70
6	THF	94

[a]Yield determined by GC with 1,3,5-trimethoxybenzene as internal standard.

Although the general catalytic cycle of the Suzuki-Miyaura reaction is well established, the nuances of the transmetalation step are still not completely understood. It is in this phase of the catalytic cycle that the base has a profound role on coupling. For a general Suzuki-Miyaura reaction, the addition of bases that generate hydroxide greatly increases the rate of transmetalation between organoboron reagents and metal halides.[15] This phenomenon has been explained via two mechanistic pathways (**Scheme 2.7**).[16] Path A consists of the exchange of X (a halogen or triflate) in the Pd^{II} **2.1.12** complex formed after oxidative addition with a nucleophilic species, which can be the basic anion of the base used in the Suzuki-Miyaura reaction or the hydroxide anion present in the solution, forming the corresponding intermediate **2.1.14**. In this case, the base must have significant nucleophilicity to displace the X group acting as the leaving group.

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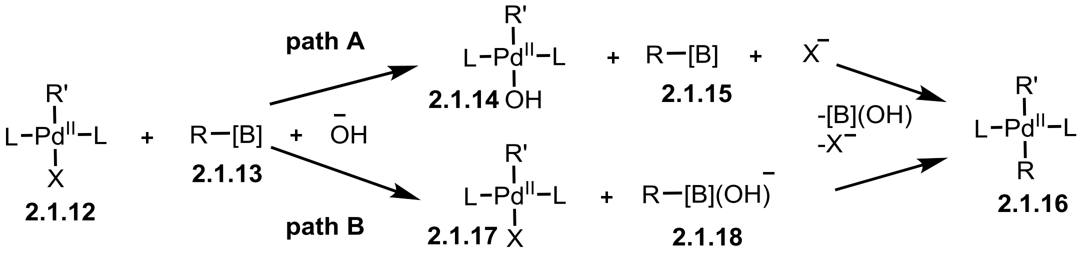
[15] (a) Brown, H. C.; Verbrugge, C.; Snyder, C. H. *J. Am. Chem. Soc*. **1961**, *83*, 1001; (b) Brown, H. C.; Snyder, C. H. *J. Am. Chem. Soc*. **1961**, *83*, 1002; (c) Larock, R. C. *J. Organomet. Chem*. **1974**, *72*, 35.

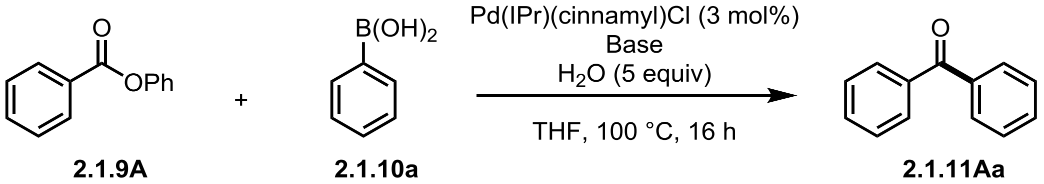
[16] Lima, C. F. R. A. C.; Rodrigues, A. S. M. C.; Silva, V. L. M.; Silva, A. M. S.; Santos, L. M. N. B. F. *ChemCatChem*. **2014**, *6*, 1291.

Scheme 2.7. Role of the base in possible pathways during transmetalation



This intermediate **2.1.14** then proceeds to react with the boronic acid **2.1.15** through transmetalation to give **2.1.16**. Path B suggests the formation of a quaternary boron species **2.1.18** with the base, which can be associated with faster ligand exchanges during transmetalation. Keeping this in mind several bases typically used in these cross-coupling reactions were screened (**Table 2.4**). K_2HPO_4 and K_2CO_3 gave moderate to high yields of 60% and 88% respectively (entries 1 and 2). Use of *t*BuOK, Cs_2CO_3, and Et_3N gave poor yields from the 10-20% range (entries 3, 4, 5). K_3PO_4 was employed with different quantities. Moreover, we concluded that the amount of this base was relevant to the experimental conditions (entries 6-8) and 1.5 equivalents (entry 7) were necessary to achieve almost quantitative yield. The preference of K_3PO_4 over the other bases could be due differences such as solubility and particle size.

Table 2.4. Base screen for Suzuki-Miyaura coupling of esters



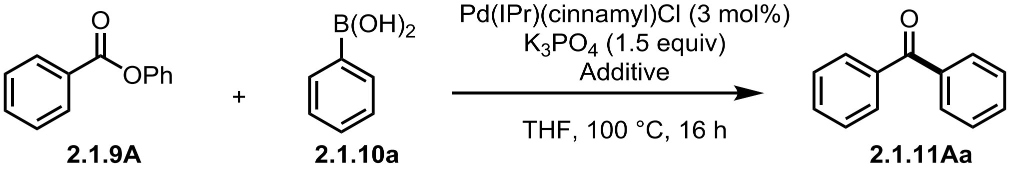
Entry	Base	Equivalents	Yield (%)[a]
1	K_2HPO_4	1.5	60
2	K_2CO_3	1.5	88
3	*t*BuOK	1.5	10
4	Cs_2CO_3	1.5	26
5	Et_3N	1.5	7
6	K_3PO_4	1	75
7	K_3PO_4	1.5	94
8	K_3PO_4	2	77
9	No base	N/A	<5

[a] Yield determined by GC with 1,3,5-trimethoxybenzene as internal standard.

The water in this reaction could potentially have several different roles. Therefore, the amount of water as an additive was screened (**Table 2.5**, entries 1-3). In a general Suzuki-Miyaura cross-coupling reaction, the role of the water is to aid in the dissolution of the base and formation of hydroxide, aiding in the formation of the boronate from boronic acid or to form the active palladium hydroxide after oxidative addition.[17] A control experiment was done to verify the necessity of water and the yield was only 60% in the absence of water as an additive (entry 1).

For this transformation, we found that 2.5 equivalents of water were enough (entries 2-4) to increase yield to 94% (entry 1). Various other additives were added in attempt to improve reaction yields. The use of DMAP significantly decreased the yield to less than 30% yield (entry 5). Salt additives such as KF and LiCl (entries 6 and 7), which are commonly used as additives for Suzuki-Miyaura cross-coupling reaction,[18] were also tested. In this reaction, these were less efficient than water as additive.

Table 2.5. Additive screen for Suzuki-Miyaura coupling of esters



Entry	Additive	Equivalents	Yield (%)[a]
1	No additive	N/A	60
2	Water	2.5	94
3	Water	5	93
4	Water	20	64
5	DMAP[b]	30 mol%	28
6	KF[b]	30 mol%	71
7	LiCl[b]	30 mol%	76

[a]Yield determined by GC with 1,3,5-trimethoxybenzene as internal standard.
[b]Reaction with 5 equiv of water.

In order to explore a variety of substrates using the optimized reaction conditions, different organoboron as well as esters were studied (**Table 2.6**). Using electron-withdrawing groups on the aryl side of the ester afforded excellent yields of the benzophenone product (entries 1 and 2).

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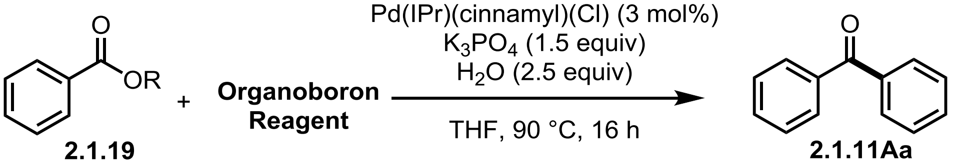
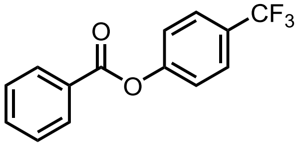
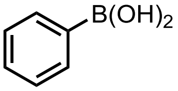
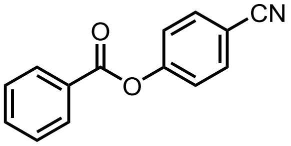
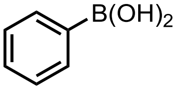
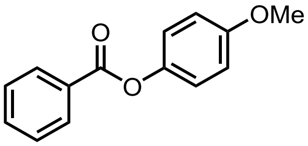
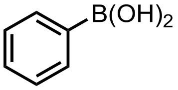
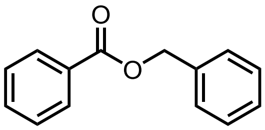
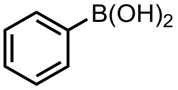
[17] Soomro, S. S.; Röhlich, C.; Köhler, K. *Adv. Synth. Catal*. **2011**, *353*, 767.

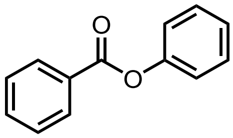
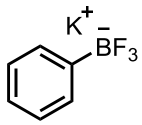
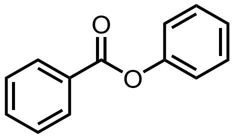
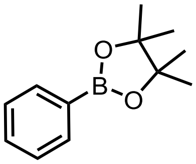
[18] (a) Bernhardt, F.; Trotzki, R.; Szuppa, T.; Stolle, A.; Ondruschka, B., *Beilstein J. Org. Chem*. **2010**, *6*, 7; (b) Boruah, P. R.; Koiri, M. J.; Bora, U.; Sarma, D., *Tetrahedron Lett*. **2014**, *55*, 2423.

The presence of an electron-donating group on the ester (entry 3) slightly dropped the product yield. Exploring more challenging C(acyl)–O activation, benzyl benzoate was employed (entry 4). A complete shutdown of the reaction and quantitative recovery of the starting material was observed. Testing the efficiency of the discovered methodology with other organoboron entities, potassium phenyltrifluoroborate (entry 5) and phenylboronic acid pinacol ester (entry 6) were used. The optimized reaction conditions were not successful with these types of nucleophilic coupling partners and low yields were observed.

Table 2.6. Substrate and boronic acid screen



Entry	Ester	Organoboron	Yield (%)[a]
1			90
2			99
3			80
4			0

5			25
6			13

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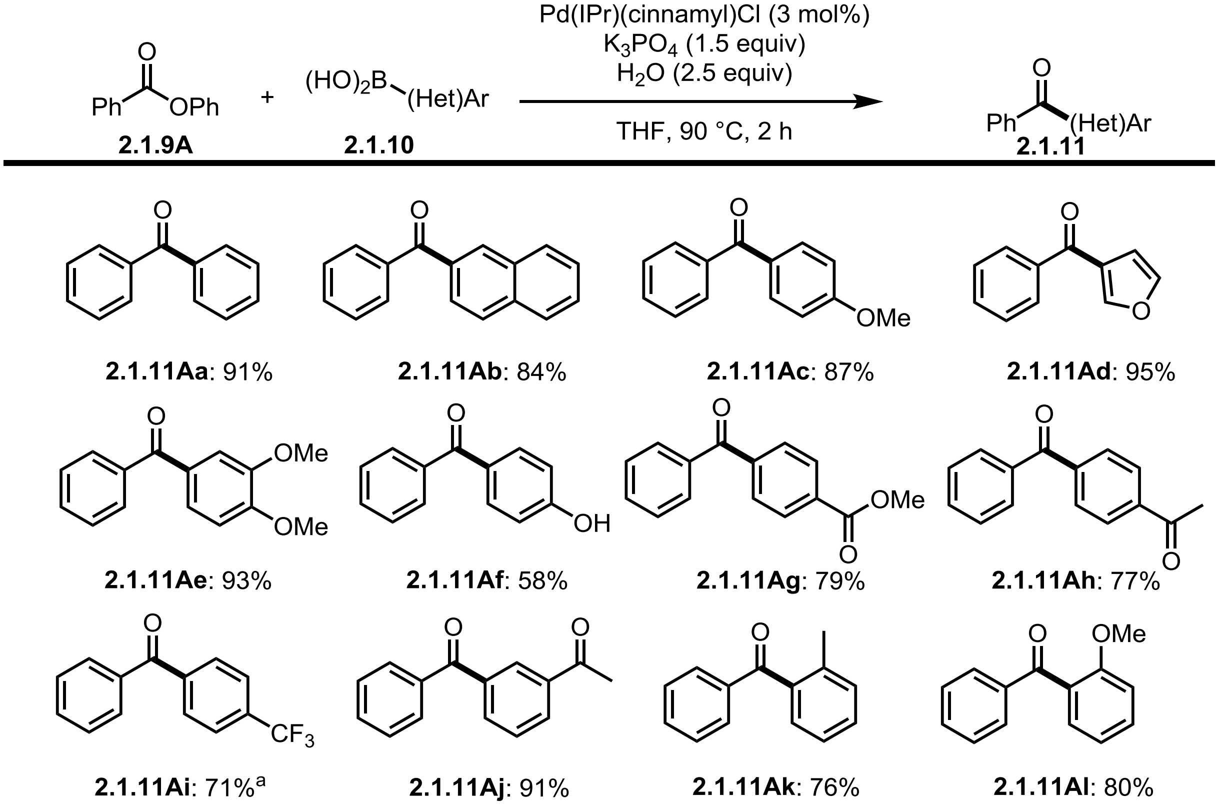
[a]Yield determined by GC with 1,3,5-trimethoxybenzene as internal standard.

2.1.3.2 Reaction scope

Using 3 mol% Pd(IPr)(cinnamyl)Cl, 1.5 equiv K_3PO_4, and 2.5 equiv H_2O in THF at 90 °C for 2 hours as the optimal reaction conditions, we next turned our attention towards the reaction scope. Using phenyl benzoate **2.1.9A**, a variety of boronic acids were used in the coupling (**Table 2.7**). Beyond the synthesis of the parent benzophenone **2.1.11Aa** in 91% yield, products arising from the coupling of electron-neutral (**2.1.11Ab**) and electron-rich (**2.1.11Ac**-**2.1.11Ae**) boronic acids were prepared in good yield. The use of an unprotected phenol-containing boronic acid was also tolerated, providing **2.1.11Af** in 58% yield. Products derived from electron-deficient (**2.1.11Ag**-**2.1.11Aj**) and sterically hindered (**2.1.11Ak** and **2.1.11Al**) boronic acids generally provided lower yields, though still above 70%. The use of a methyl ester-containing boronic acid was notable, as it showed selective cleavage of the phenyl benzoate ester bond to provide **2.1.11Ag** in 79% yield.

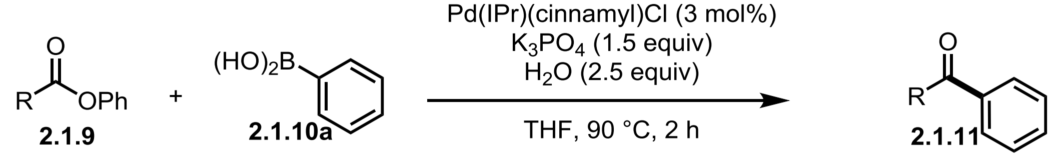
Table 2.7. Boronic acids scope of Pd-catalyzed Suzuki-Miyaura cross-coupling

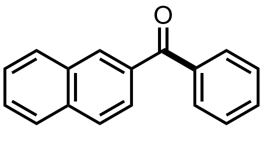


[a] 5 mol% of Pd(IPr)(cinammyl)Cl used instead of 3 mol%. Reaction stirred for 16 hours.

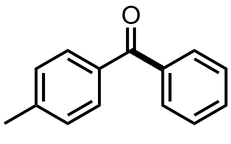
Satisfied with the breadth of organoboron species that could be utilized, we next sought to explore a variety of ester starting materials (**Table 2.8**). Several relatively electron-neutral ketones (**2.1.11Ba**–**2.1.11Da**) were prepared in good yields. Electron-rich **2.1.11Ea**, electron-poor **2.1.11Fa**, and furyl-containing **2.1.11Ga** could all be prepared in similarly good yields. These products are identical in structure to **2.1.11Ac**, **2.1.11Ai**, and **2.1.11Ad (Table 2.8)**, respectively, as are **2.1.11Ab** and **2.1.11Ba**, but with the functionality placed on the ester starting material rather than the boronic acid.

Table 2.8. Esters scope of Pd-catalyzed Suzuki-Miyaura cross-coupling

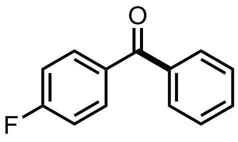




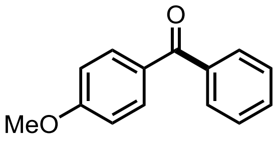
2.1.11Ba: 81%



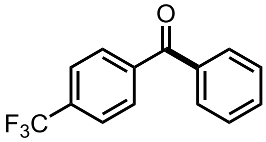
2.1.11Ca: 93%



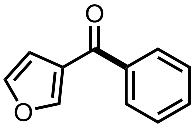
2.1.11Da: 94%



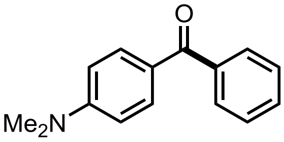
2.1.11Ea: 85%



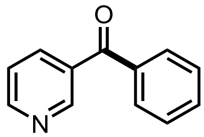
2.1.11Fa: 87%



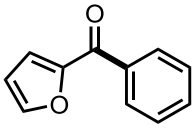
2.1.11Ga: 81%



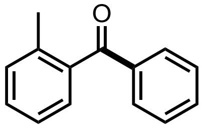
2.1.11Ha: 60%



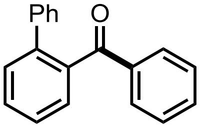
2.1.11Ia: 83%



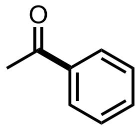
2.1.11Ja: 92%



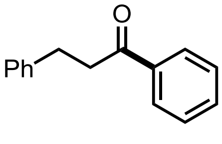
2.1.11Ka: 75%



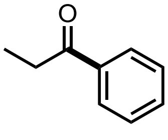
2.1.11La: 56%[a]



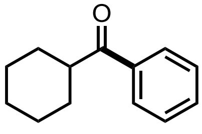
2.1.11Ma: 91%



2.1.11Na: 66%



2.1.11Oa: 74%

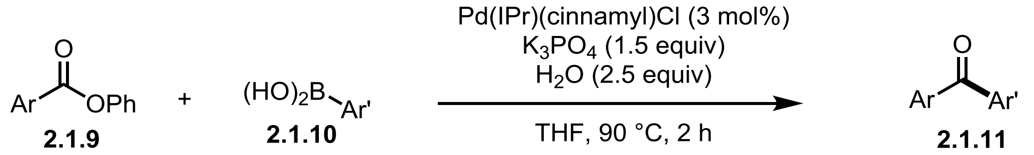


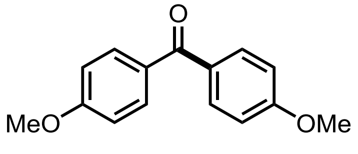
2.1.11Pa: 53%[a]

[a] Reaction run for 16 hours at 100 °C in dioxane

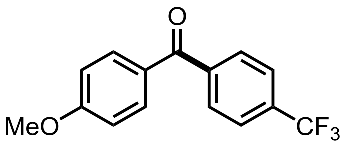
Comparing yields of these identical products prepared using different starting materials illustrates that the outcome of the reaction is more sensitive to the electronics of the boronic acid than the starting ester. While efficient reactions can be obtained with an electron-donating group on either coupling partner, an electron-withdrawing CF_3 group only provides high yield when on the ester (**2.1.11Fa**, 87%), but not on the boronic acid (**2.1.11Ai**, 71% with increased catalyst loading and reaction time). Ketones derived from highly electron-rich (**2.1.11Ha**), heterocyclic (**2.1.11Ia**, **2.1.11Ja**) and sterically hindered (**2.1.11Ka**, **2.1.11La**) esters could also be prepared. Alkyl aryl ketones **2.1.11Ma-2.1.11Oa** could be prepared from aliphatic esters, though yields decreased with increased bulk of the electrophiles. Attempts to use 2,6-disubstituted benzoic acid derivatives and aliphatic α-tertiary acids were unsuccessful, furthering this point. Nonetheless, these examples are notable since the use of alkyl halides and arylboronic acids to make alkyl aryl ketones via carbonylative coupling is rare.[19] Finally, having both components (**Table 2.9**) contain an electron-donating group (**2.1.11Ec**), an electron- rich and electron-withdrawing group (**2.1.11Ei**, **2.1.11Fc**), or electron-withdrawing groups (**2.1.11Fi**) were all tolerated, with the best yields arising from the CF_3-containing ester and OMe-containing boronic acid.

Table 2.9. Influence of varying electronics on both coupling partners

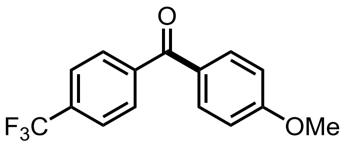




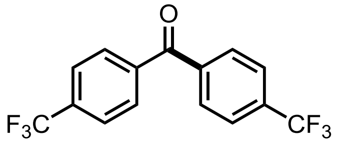
2.1.11Ec 79%



2.1.11Ei 30%



2.1.11Fc 97%



2.1.11Fi 63%

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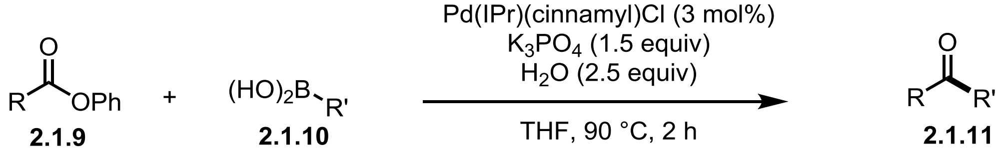
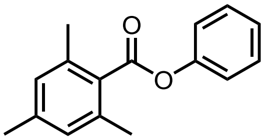
[19] Some notable exceptions include when fluorinated alkyl halides, α-halo sulfoxides, or benzyl chlorides are used. (a) Shimizu, R.; Fuchikami, T. *Tetrahedron Lett.* **1996**, *37*, 8405. (b) Shimizu, R., Fuchikami, T. *Tetrahedron Lett.* **2001**, *42*, 6891. (c) Medio-Simón, M.; Mollar, C.; Rodriguez, N.; Asensio, G. *Org. Lett.* **2005**, *7*, 4669. (d) Wu, X.-F.; Neumann, H.; Beller, M. *Adv. Synth. Catal.* **2011**, *353*, 788.

Despite the relatively broad range of substrates that could be tolerated in this Suzuki-Miyaura coupling reaction, several limitations were encountered during the scope development (**Table 2.10**). The use of sterically hindered, aliphatic **2.1.9S** and aromatic **2.1.9Q**, esters failed and recovery of the starting material has been observed. In addition, coupling partners bearing a sulfur atom (**2.1.9R** and **2.1.10n**) were not successful and quantitative starting materials recovery was detected. A significant degradation of the starting materials occurred by subjecting the Michael acceptor ester substrate **2.1.9T** or the boronic acid bearing the aldehyde functionality **2.1.10m**. Similar to most Suzuki-Miyaura cross coupling reactions, challenging aliphatic boronic acids **2.1.10o** and **2.1.10p** were not successful.[20]

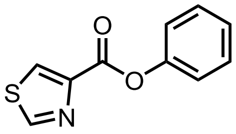
Table 2.10. Unsuccessful coupling partners in Pd-catalyzed Suzuki-Miyaura coupling



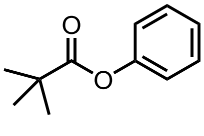
Unsuccessful esters[a]



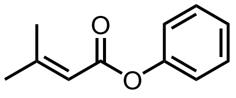
2.1.9Q



2.1.9R

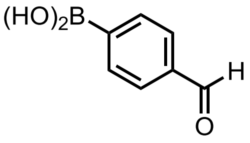


2.1.9S

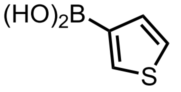


2.1.9T

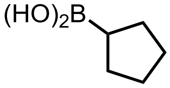
Unsuccessful boronic acids[b]



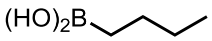
2.1.10m



2.1.10n



2.1.10o



2.1.10p

[a] Phenylboronic acid was used as nucleophilic coupling partner.
[b] Phenylbenzoate was used as electrophilic coupling partner.

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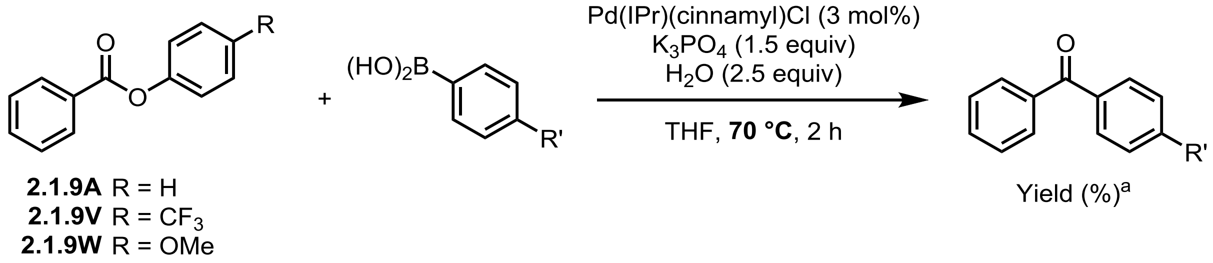
[20] Challenges with the use of alkyl boron reagents such as their reluctance to transmetalate relative to their aryl counterparts and the intermediacy of alkylmetal species that is prone to *β*–hydride elimination. For the most common classes of boron reagents used in Suzuki-Miyaura cross-coupling reaction see: Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev*. **2014**, *43*, 412.

2.1.3.3 Electronic influence

In the interest of understanding further about the electronic influence of substituents on the outcome of the reaction, the phenolic leaving group component of the ester was varied and the temperature reduced to 70 °C in order to accentuate differences in reactivity (**Table 2.11**). Under these conditions, phenyl benzoate **2.1.9A** provided the same trend observed at 90 °C with electron-rich boronic acids providing higher yields than electron-poor. Interestingly, when CF_3-containing benzoate **2.1.9V** was used as a starting material, the same products were obtained in significantly higher yields. In contrast, low yields were obtained when OMe-containing benzoate **2.1.9W** was employed. As expected, when CF_3-containing benzoate **2.1.9V** was reacted with electron-rich p-methoxy phenyl boronic acid, a very high 91% yield was obtained. This might be due to the facile oxidative addition step or the efficient transmetalation. Coupling the OMe-containing benzoate **2.1.9W** with electron deficient p-trifluoromethyl phenyl boronic acid, did not provide any product and starting material has been recovered. The drastic changes in reactivity observed with electronic variation of both the ester and boronic acid coupling partner suggests that the rate-determining step of the reaction may change depending on the choice of substrate.

Table 2.11. Electronic influence at reduced temperature



$ArB(OH)_2$ R’ =	2.1.9A R = H	2.1.9V R = CF_3	2.1.9W R = OMe
OMe	67%	91%	53%
H	40%	88%	38%
CF_3	38%	86%	0%

[a] Yield determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

2.1.3.4 Comparison of acylative coupling partners[21]

The synthesis of ketones by catalytic cross-coupling of carboxylic acid derivatives is well established with a variety of substrate, catalyst, and nucleophile combinations (see **Section 1.2.2**). Alternatively, carboxylic acids can be used directly by *in situ* derivatization to a more electrophilic intermediate.[22] It is thus important to consider the relative merits of this new method. Functional groups that are tolerant to a range of reaction conditions but can be selectively cleaved when desired are ideal in multi-step synthesis. For example, in polymer synthesis, free acid monomers are often simultaneously activated and protected as an aryl ester derivative, polymerization is carried out, and then the ester is utilized for chemoselective derivatization.[23] To compare the robustness of several acid derivatives that undergo acylative cross-coupling, a set of experiments (**Table 2.12**) were carried out with anhydride (entry 1), pyridyl ester (entry 2), twisted amide (entry 3), thioester (entry 4), and phenyl ester (entry 5) as representative acylative coupling precursors. To determine their stability to cleavage via substitution, the five substrates were dissolved together in DMF/MeOH in the presence of K_2CO_3, and consumption was monitored over time. Within 24 hours, all molecules had completely converted to the corresponding methyl ester except phenyl benzoate, which required 96 hours. To test stability in non-polar solvents, each substrate was treated with 1.1 equivalents of morpholine in toluene at 40 °C and conversion to the corresponding amide was monitored over time by GC-MS. An identical trend was observed, with the anhydride being consumed fastest and the phenyl ester being the most stable. Together, these data provide evidence that, among chosen substrates, phenyl esters are least susceptible to undesirable side reactions that may occur in multi-step synthesis.[24] It is also consistent with the catalyst requirements for coupling: While relatively simple $Pd(OAc)_2/PAr_3$ catalyst systems are sufficient for activation of these established acylative coupling partners, we found only a highly specific Pd-NHC precatalyst was able to achieve efficient C–O bond activation of phenyl esters.

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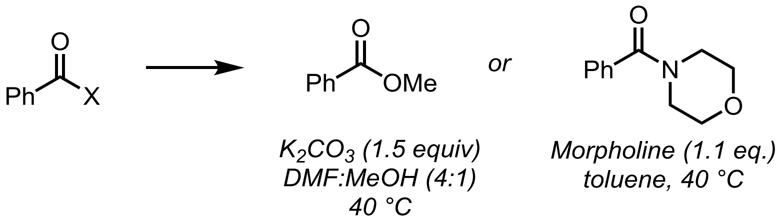
[21] This study has been performed in collaboration with former M.Sc. candidate, Wanying Zhang.

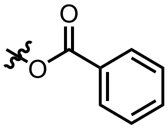
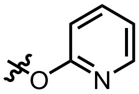
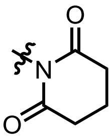
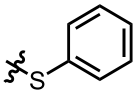
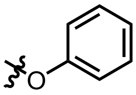
[22] (a) Pathak, A.; Rajput, C. S.; Bora, P. S.; Sharma, S. *Tetrahedron* **2013**, *54*, 2149; (b) Gooßen, L. J.; Ghosh, K.; *Eur. J. Org. Chem.* **2002**, *2002*, 3254. (c) Wang, D.; Zhang, Z. *Org. Lett.* **2003**, *5*, 4645; (d) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1333; (e) Si, S.; Wang, C.; Zhang, N.; Zou, G. *J. Org. Chem.* **2016**, 81, 4364. (f) Gooßen, L. J.; Ghosh, K. *Chem. Commun.* **2001**, 2084; (g) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, A. *Chem. Lett.* **2001**, *12*, 1242.

[23] Das, A.; Theato, P. *Chem. Rev.* **2016**, *116*, 1434.

[24] A range of thioesters of varying C–S bond strength are known to participate in cross-coupling. A more thorough study of these derivatives would be necessary to make general conclusions about the relative applicability of thioesters and aryl esters in multi-step synthesis. See: Yian, Y.; Wang, L.; Yu, H.-Z. *RSC Adv.* **2016**, *6*, 61996.

Table 2.12. Stability study of select acylative cross-coupling electrophiles[a]



Entry	X =	Stability to methanolysis	Stability to amidation
1		consumed within 10 minutes	consumed within 10 minutes
2		consumed within 1 hour	consumed within 30 min
3		consumed within 4 hours	consumed within 6 hours
4		consumed within 24 hours	trace remained after 96 hours
5		consumed within 96 hours	69% remained after 96 hours

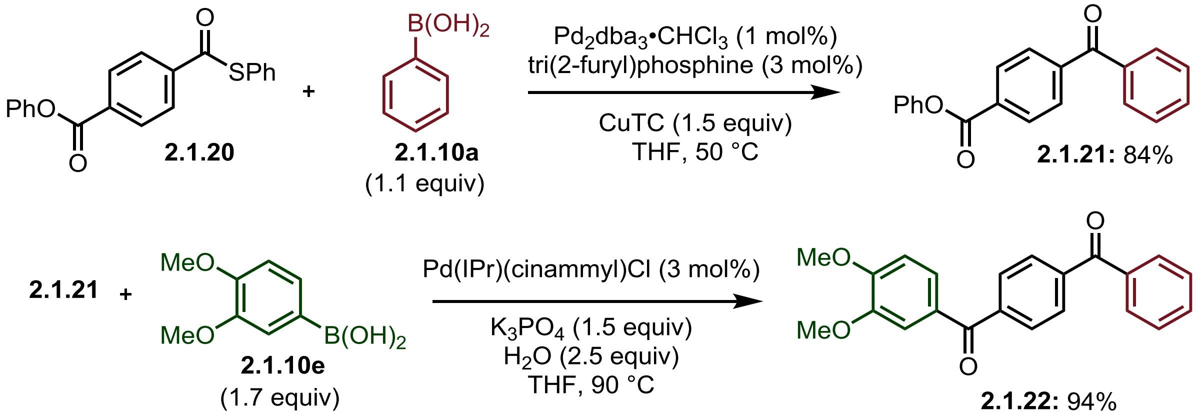
[a] GC samples were performed at regular intervals to track rate of degradation of each component.

2.1.3.5 Advantages of using aryl esters

Chemoselectivity study in the cross-coupling of multifunctional substrates

Given these greatly differing reactivities of the studied acid derivatives, competition experiments were run to determine if selective coupling reactions could be performed on multi-functional substrates. Using a Pd/phosphine system with copper(I) thiophene-2-carboxylate (CuTC) activation (Liebeskind–Srogl coupling),[25] bifunctional substrate **2.1.20** could be coupled first via selective C–S bond cleavage to provide **2.1.21** in 84% yield, followed by C–O cleavage to prepare **2.1.22** in 94% yield (**Scheme 2.8**).

Scheme 2.8. Selective C–S bond cleavage in the presence of phenyl ester



Similarly, coupling of twisted amide **2.1.23** using conditions developed by Szostak and co-workers[26] was also completely selective (**Scheme 2.9**). This substrate coupled exclusively via C–N bond cleavage, providing **2.1.24** in 80% yield, which in turn couples via C–O cleavage to provide polyketone **2.1.25** in 91% yield. Attempts to selectively first couple the phenyl ester, using our discovered reaction conditions while leaving the thioester or **2.1.20** or twisted amide of **2.1.23** intact were unsuccessful.

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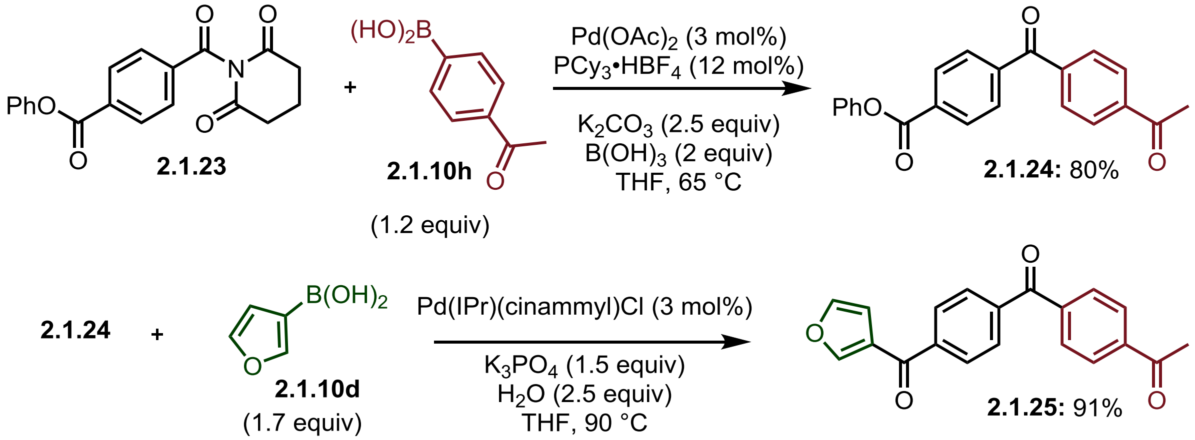
[25] Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

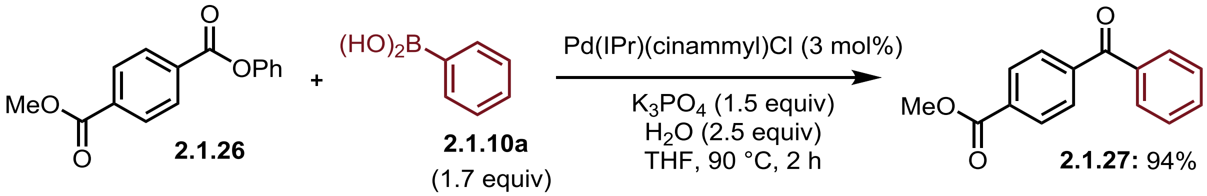
[26] Meng, G.; Szostak, M. *Org. Biomol. Chem.* **2016**, *14*, 5690.

Scheme 2.9. Selective C–N bond cleavage in the presence of phenyl ester



Next, bis-ester **2.1.26** was subjected to the cross-coupling reaction conditions to determine if C–O bond cleavage would occur at an aryl ester in the presence of a methyl ester (**Scheme 2.10**). Indeed, selective coupling occurred, providing ketone **2.1.27** in 94% yield with no evidence of reactivity of the methyl ester.

Scheme 2.10. Selective C–O bond activation of phenyl ester



Finally, **2.1.28**, bearing an aryl chloride and phenyl ester, was studied (**Scheme 2.11**). Using a slow addition strategy developed in our lab,[27] chemoselective Kumada-Corriu coupling could be performed to provide **2.1.30** in 79% yield, followed by acylative Suzuki-Miyaura to give **2.1.31** in 81% yield. The selectivity of both the Pd catalyst and the Grignard reagent react at the C–Cl bond of **2.1.28** demonstrates that the ester functionality can tolerate even harsh reaction conditions.

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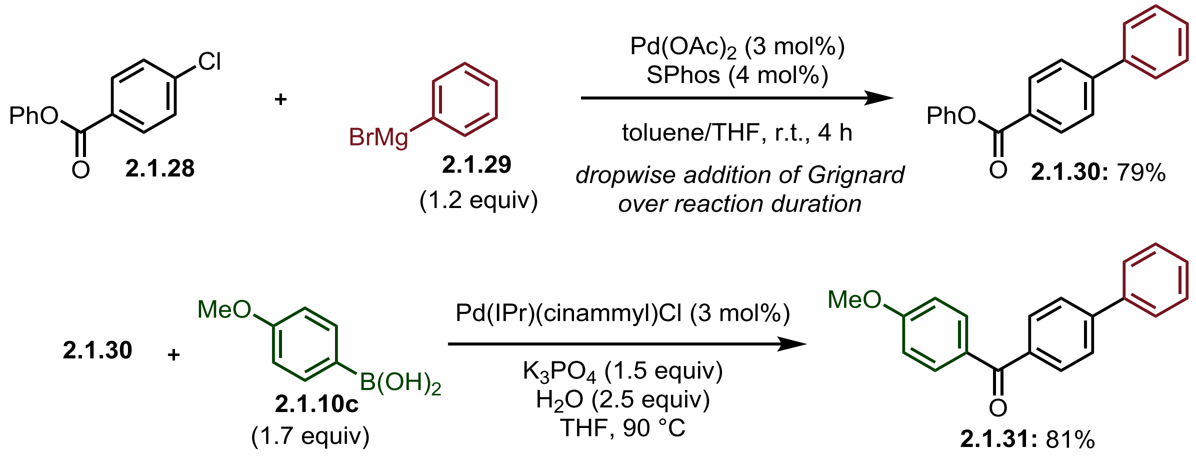
[27] Hua, X.; Masson-Makdissi, J.; Sullivan, R. J.; Newman, S. G. *Org. Lett.* **2016**, *18*, 5312.

Scheme 2.11. Selective C–Cl bond cleavage via Kumada-Corriu coupling in the presence of phenyl ester



Unique aspects of using aryl esters

The common occurrence of esters as both starting materials and products in many reactions gives them another distinct advantage over alternative acylative coupling partners. Aryl esters can be obtained from redox-neutral esterification of carboxylic acids **2.1.32**,[28] or oxidative coupling of phenol with aldehydes **2.1.33**[29] or alcohols **2.1.34**[30] (**Scheme 2.12**). Alternatively, aryl esters can be obtained from the corresponding aryl ketones **2.1.35** via Baeyer-Villiger oxidation if the R group has a lower migratory aptitude than the phenyl ring.[31]

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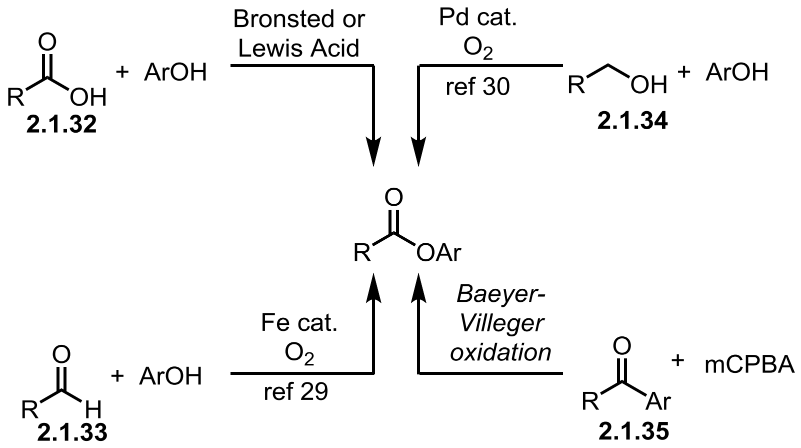
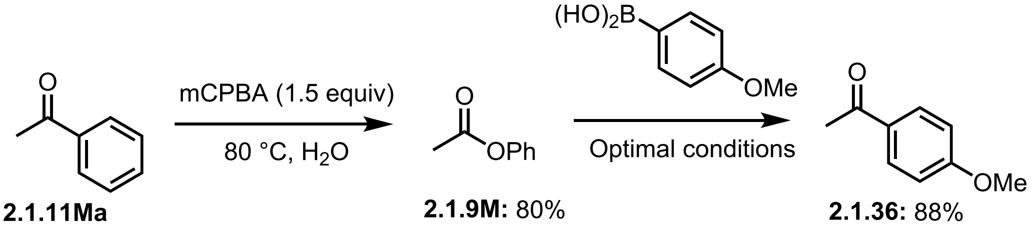
[28] Bader, A. R.; Kontowicz, A. D. *J. Am. Chem. Soc.* **1953**, *75*, 5416.
[29] Reddy, R. S.; Rosa, J. N.; Veiros, L. F.; Caddick, S.; Gois, P. M. P. *Org. Biomol. Chem.* **2011**, *9*, 3126.
[30] Luo, F.; Pan, C.; Cheng, J.; Chen, F. *Tetrahedron* **2011**, *67*, 5878.
[31] Raap, J.; Nieuwenhuis, S.; Creemers, A.; Hexspoor, S.; Kragl, U.; Lugtenburg, *J. Eur. J. Org. Chem*. **1999**, *10*, 2609.

Scheme 2.12. Aryl ester synthesis from diverse starting materials



These diverse methods provide many unique possibilities for synthetic applications. For instance, treament of acetophenone with mCPBA provides phenyl ester in 80% yield (**Scheme 2.13**). Subsequent cross-coupling, using our optimal reaction conditions, with 4-methoxyphenylboronic acid then provides ketone in 88% yield, representing an unusual two step ‘aryl exchange’ process.

Scheme 2.13. Baeyer-Villiger oxidation with subsequent phenyl ester activation



Towards the goal of decreasing waste in acylative coupling procedures, esterification of benzoic acid was carried out with catalytic Sc(OTf)$_3$ under neat conditions,[32] providing phenyl benzoate **2.1.9A** in 81% yield with water as the only by-product (**Scheme 2.14**). In the subsequent coupling, 85% of phenol could be recovered, which enables efficient recycling for an overall atom economical process.

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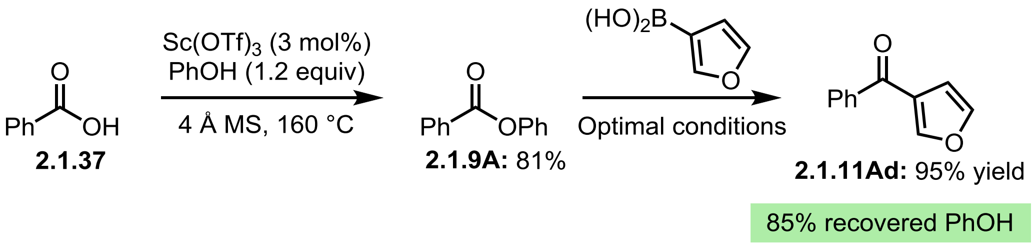
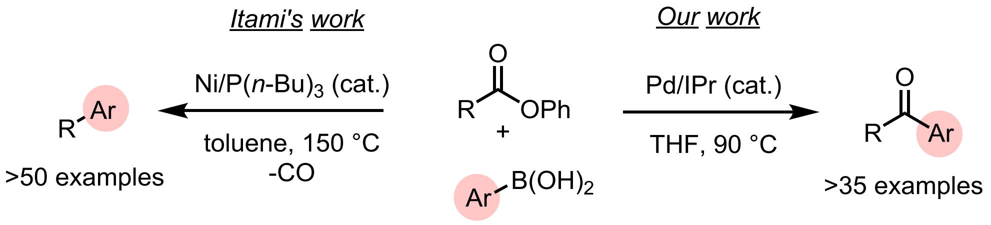
[32] Paetzold, J.; Gooßen, L. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1237.

Scheme 2.14. Atom economic process via recycling of the activating phenoxide group



Finally, the ability to form ketone-containing products by aryl ester cross-coupling is highly complementary to the high yielding decarbonylative couplings developed by Itami and co-workers,[7] allowing highly efficient and selective formation of biaryls (**Scheme 2.15**). The ability to convert one starting material into two different product classes by careful selection provides a powerful opportunity for diversification of interesting molecular scaffolds. To the best of our knowledge, only twisted amides have been reported as being able to access both of these reaction modes.[33, 26]

Scheme 2.15. Itami's decarbonylative coupling versus our work: catalyst-controlled selectivity



2.1.3.6 Mechanistic studies

An unusual divergence in selectivity is seen in the cross-coupling of carboxylic acid derivatives. Use of highly activated species such as acid chlorides and anhydrides generally provides ketone products. In contrast, recent literature on the cross-coupling of esters has deviated from this trend, demonstrating C(aryl)–O bond cleavage or C(acyl)–O cleavage with decarbonylation. Thorough mechanistic studies[34] have been done on these reactions, demonstrating the challenges

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[33] Meng, G.; Szostak, M. *Org. Lett.* **2015**, *17*, 4364.

[34] (a) Lu, Q.; Yu, H.; Fu, Y. *J. Am. Chem. Soc*. **2014**, *136*, 8252; (b) Li, Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815; (c) Muto, K.; Yamaguchi, J.; Lei, A.; Itami, K. *J. Am. Chem. Soc.* **2013**, *135*, 16384.

in forming ketones from esters via cross-coupling. The success of the current method is thus curious, and we desired to further understand the mechanism and the key factors that control the divergent behavior of different catalysts towards the coupling of esters. Using phenyl benzoate as the model substrate, density functional theory (DFT) calculations were carried out towards this goal.[35]

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[35] DFT calculations were performed by the Houk lab at the University of California, Los Angeles. Further details are freely available and could be found in the supporting information of our manuscript (**DOI:** 10.1021/jacs.6b12329).

The free energy profile of the productive pathway is shown in (**Figure 2.1**). Starting from the substrate-coordinated complex, **Int2.1.1**, the C(acyl)−O cleavage occurs through a three-centered transition state **TS2.1.1** to give the Pd(II) intermediate **Int2.1.2**. Subsequent ligand exchange with phenylboronate leads to Pd(II)-boronate intermediate **Int2.1.3**, which then undergoes the transmetalation via **TS2.1.2** to produce intermediate **Int2.1.4**. This contrasts the work on the analogous decarbonylative Suzuki-Miyaura coupling of aryl esters, which are performed under anhydrous conditions and require cluster formation of the oxidative addition complex with carbonate base prior to transmetalation.[7] Notably, The subsequent Csp^2–Csp^2 reductive elimination via **TS2.1.3** is facile, and the product-coordinated complex, **Int2.1.6**, eventually releases the product and regenerates intermediate **Int2.1.1** for the next catalytic cycle. The rate-limiting step of the whole catalytic cycle is the C(acyl)–O cleavage step via **TS2.1.1**, with a 23.3 kcal/mol barrier. Consistent with the high electronic sensitivity observed (**Table 2.11**), the barrier for transmetalation is only 1.1 kcal/mol smaller than the oxidative addition, and may thus become rate-limiting when using esters that undergo more facile oxidative addition, or nucleophiles that are less effective for transmetalation.

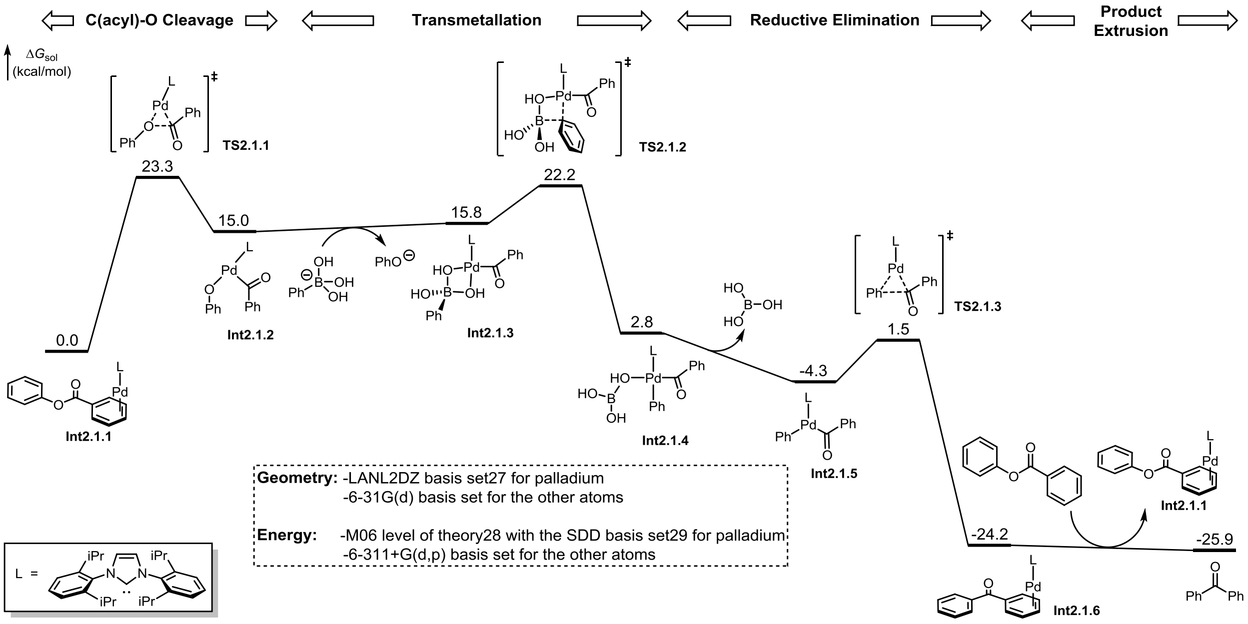

Figure 2.1. Gibbs free energy profile of the Pd-catalyzed Suzuki-Miyaura coupling reaction of phenyl benzoate[36]

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[36] “Reprinted with permission from [Ben Halima, T.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.; Houk, K.; Newman, S. *J. Am. Chem. Soc.* **2017**, *139*, 1311.]. Copyright [2017] American Chemical Society”

Based on the working mechanism, the chemoselectivity of the C–O bond cleavage step was also investigated (**Figure 2.2**). Previous theoretical study on this cleavage with a Ni/PCy$_3$ catalyst showed that the distortion of substrate controls the barrier if both C–O bonds are cleaved through similar three-centered transition states.[37] In the present system, the palladium catalyst cleaves both C(acyl)–O and C(aryl)–O bonds through three-centered transition states.[38] Consistent with experiment, **TS2.1.1**, which leads to the C(acyl)-O bond cleavage, is 15.0 kcal/mol more favorable than the competing C(aryl)–O cleavage transition state.

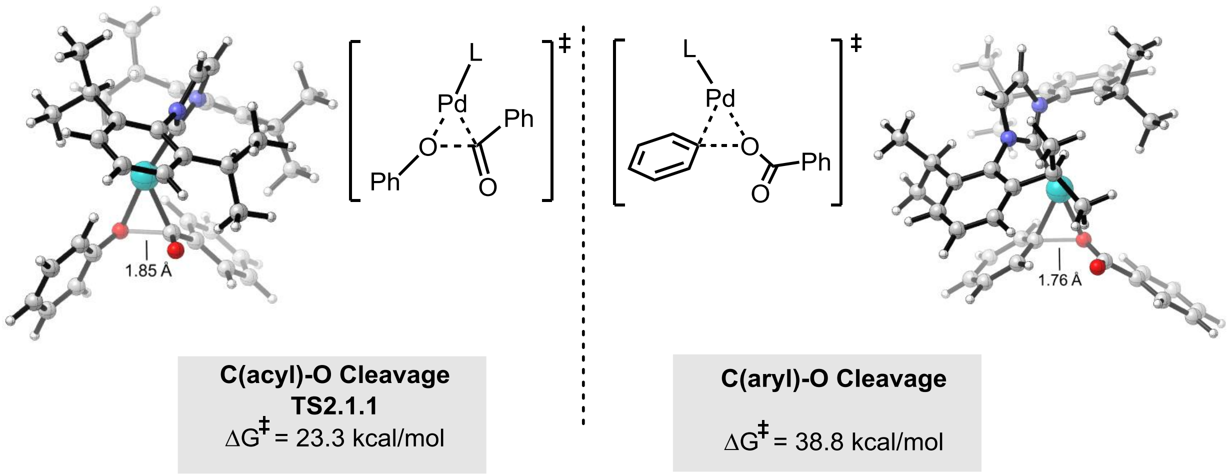

Figure 2.2. Optimized structures and free energies of competing C–O bond cleaving transition states relative to Int2.1.1.

In addition, the potential decarbonylation pathway in comparison with the productive carbonyl-retention pathway has been studied. Previous computational studies with Ni/PBu$_3$ found the acyl intermediate to undergo decarbonylation with an 8 kcal/mol barrier. In contrast, a 23.2 kcal/mol barrier was calculated with the Pd/NHC system, which is much higher as compared to the 5.8 kcal/mol barrier for direct reductive elimination. The exceptional bulkiness of the ligand makes this step both thermodynamically and kinetically more challenging. Details are listed in the experimental section (**Section 2.3.1**).

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[37] Xu, H.; Muto, K.; Yamaguchi, J.; Zhao, C.; Itami, K.; Musaev, D. G. *J. Am. Chem.* Soc. **2014**, *136*, 14834.

[38] Extensive efforts have been conducted to locate a five-centered transition state for C(aryl)–O bond cleavage. Comparing to [(NHC)Ni] catalysts, [(NHC)Pd] catalyst has a lower binding affinity for the carbonyl oxygen of ester, making the five-centered geometry unfavorable for C(aryl)–O bond cleavage.

2.1.4 Conclusion and future work

The cleavage of relatively strong phenyl ester bonds by oxidative addition has for the first time been utilized to catalytically prepare carbonyl-containing materials with high selectivity. The use of a Pd-NHC catalyst enables this reactivity, where previous systems based on nickel catalysis have only provided selectivity for C(aryl)–O and decarbonylative C(acyl)–O coupling pathways with these substrates. Excellent yields of ketone-containing products were obtained with a broad range of ester and boronic acid starting materials. These starting materials are particularly robust in comparison to other carboxylic acid derivatives used in cross-couplings, suggesting they are applicable to the synthesis of complex molecules where chemoselectivity issues may occur. Calculations were performed to reveal the underlying mechanistic features that enable this reaction to selectively occur, illustrating unique differences in reactivity modes of Pd vs Ni. Specifically, the Pd/NHC combination allows kinetically feasible C(acyl)–O oxidative addition while preventing the 5-centered transition state that may favour C(aryl)–O cleavage. The bulky NHC then prevents decarbonylation of the acyl-Pd intermediate, allowing direct coupling. The ability to selectively obtain multiple different products based on catalyst choice is of broad applicability, and further studies are underway to extend this reaction scope beyond phenyl ester electrophiles and boronic acid nucleophiles.

Although it may take time to realize the long term impact of this work, it is important to note that this methodology highlights a novel means of reactivity using simple aryl esters. This methodology has also been a stated source of inspiration that other research groups have improved upon.[39]

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[39] (a) Dardir, A. H.; Melvin, P. R.; Davis, R. M.; Hazari, N.; Mohadjer Beromi, M. *J. Org. Chem.* **2018** , *83*, 469; (b) Li, G.; Shi, S.; Lei, P.; Szostak, M. *Adv. Synth. Catal.* **2018**, *360*, 1538.

2.2 A Cross-coupling approach to amide bond formation from phenyl esters

2.2.1 Background and research goals

The Buchwald-Hartwig amination, which promotes the coupling of an amine and organohalide that would otherwise be inert towards each other, is arguably the most impactful chemical reaction discovered in the past quarter century. This is primarily due to its usefulness in the synthesis of bioactive molecules.[40] One of the most important milestones in the evolution of this transformation has been the increase in the reaction scope to include a diverse range of electrophiles, including aryl chlorides and C–O electrophiles (See **chapter 1**).

The use of esters as electrophilic coupling partners in catalytic amination reactions has recently been explored using nickel catalysis. Chatani and co-workers reported the first example in 2010,[41] coupling alkyl amines with aryl pivalates to prepare aniline derivatives via selective cleavage of the C(aryl)–O bond in the key oxidative addition step (**Scheme 2.16A**).

Despite the prevalence of amides in bioactive molecules and the inefficiency of many of the most commonly used methods for their synthesis,[42] conversion of esters to amides is still relatively underdeveloped.[43] The use of cross-coupling to form amide bonds via C(acyl)–O bond cleavage of ester electrophiles was reported for the first time in 2016 by Garg and co-workers (**Scheme 2.16B**).[44] This Ni-catalyzed reaction required stoichiometric $Al(OtBu)_3$ and was limited to 1-substituted naphthalene derivatives, indicating that catalytic amidation has not yet reached its full potential.

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[40] Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.

[41] Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed*, 2010, **49**, 2929.

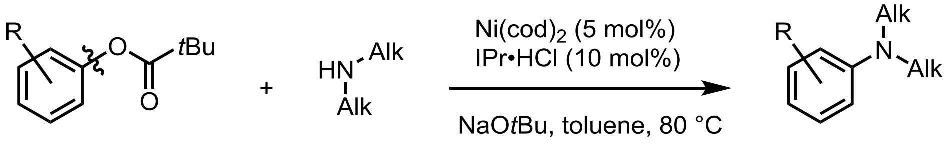
[42] Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer Jr., J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.

[43] Montalbetti, C. A. G. N.; Falque, V.; *Tetrahedron* **2005**, *61*, 10827.

[44] Hie, L.; Fine Nathel, N. F.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Garg, N. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 2810.

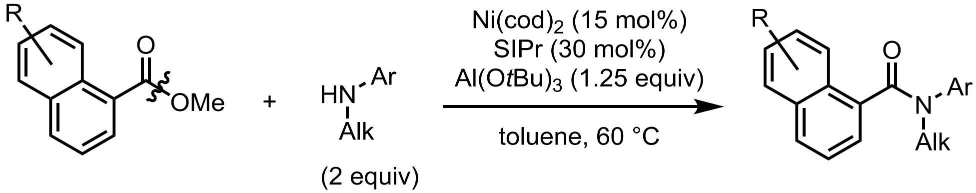
Scheme 2.16. Different reactivity modes of esters using amine nucleophiles

A. Coupling via C(aryl)–O cleavage *(Chatani and co-workers method)*



2.2.1 **2.2.2** **2.2.3**

B. Coupling via C(acyl)–O cleavage *(Garg and co-workers method)*



2.2.4 **2.2.5** **2.2.6**

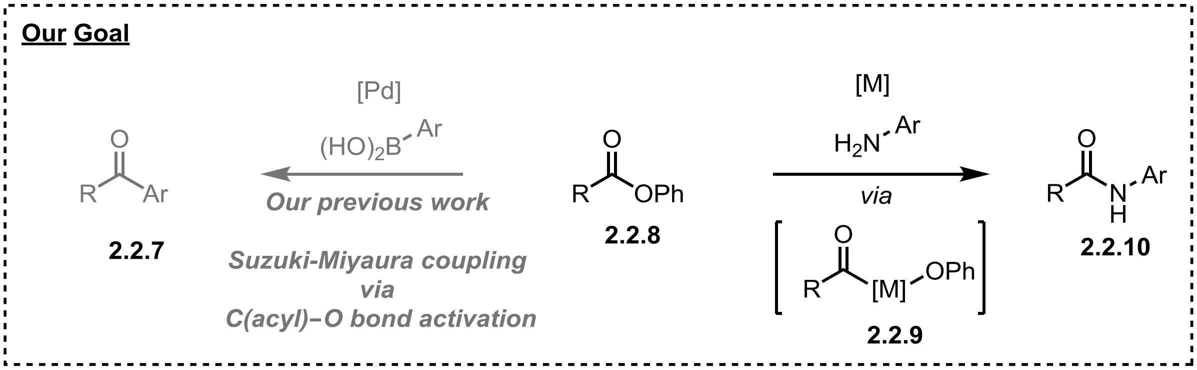
Recent contributions where Ni and Pd catalysts can oxidatively add to robust phenyl esters have been discovered. [7,8,45] These previous reports, including the work[46] disclosed in Section 2.1, go through an acyl-metal intermediate generation **2.2.9**. Given the limitations of previous methods to achieve catalytic amide bond forming reaction from ester electrophiles as well as the feasible oxidative addition into the C(acyl)–O bond of phenyl ester, we sought to explore if this species could react with nitrogen-containing nucleophiles (**Scheme 2.17**), affording expanded reactivity from esters as electrophilic coupling partners using transition metal catalysis.

---

[45] (a) Ishizu, J.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1976**, *5*, 1091; (b) Yamamoto, T.; Ishizu, J.; Kohara, T.; Komiya, S.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 3758; (c) Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 13573; (d) Guo, L.; Chatupheeraphat, A.; Rueping, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 11810; (e) Guo, L.; Rueping, M. *Chem. Eur. J.* **2016**, *22*, 16787; (f) Pu, X.; Hu, J.; Zhao, Y.; Shi, Z. *ACS Catal.* **2016**, *6*. 6692.

[46] Ben Halima, T.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Newman, S. G. *J. Am. Chem. Soc.* **2017**, *139*, 1311

Scheme 2.17. Our goal: amide bond formation via C(acyl)–O bond activation

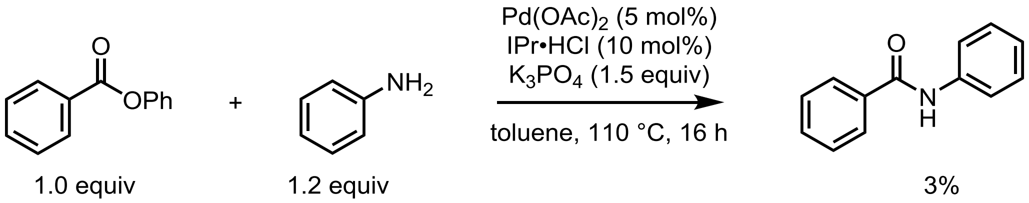


2.2.2 Results and discussion[47]

2.2.2.1 Reaction discovery and optimization

Based on the acquired knowledge on Pd-catalyzed Suzuki-Miyaura coupling, multiple reaction conditions using a selection of catalyst systems that help achieve C(acyl)–O bond activation, have been tested. For this amidation reaction, aniline has been applied as nucleophilic coupling partner and phenyl benzoate as the electrophilic partner. Initial reactivity has been observed, using Pd/IPr catalyst system (**Scheme 2.18**), and 3% of benzanilide has been generated.

Scheme 2.18. Initial hit for amide bond forming reaction



With the above result as a promising but very low yielding initial hit, the transformation of phenyl benzoate and aniline to benzanilide using palladium catalysts was chosen for further study. A portion of the extensive optimization is outlined below.

Multiple bases were screened along with different equivalents of water (**Table 2.13**). It was found that 10 equivalents of water were necessary for high conversion using K_3PO_4 as base

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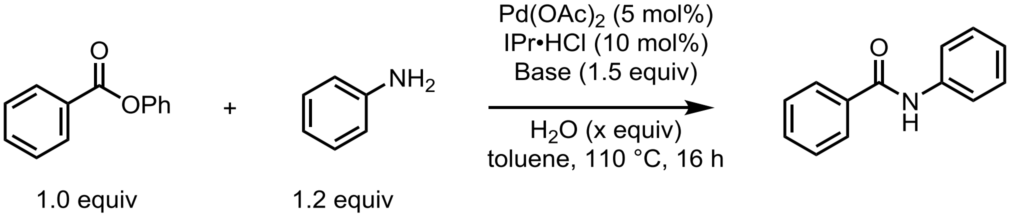
[47] The results presented herein have been published in a peer-reviewed journal: Ben Halima, T.; Vandavasi, J. K.; Shkoor, M.; Newman, S. G. A Cross-Coupling Approach to Amide Bond Formation from Esters. *ACS Catal*. **2017**, *7*, 2176.

(entries 1-3). Using water as the co-solvent provided relatively low yield (entry 4). The use of Cs_2CO_3 gave a yield of only 60% (entry 5). The highest yield was found when K_2CO_3 has been used while maintaining 10 equivalents of H_2O (entry 6)

Table 2.13. Base and water screening for catalytic amide bond formation

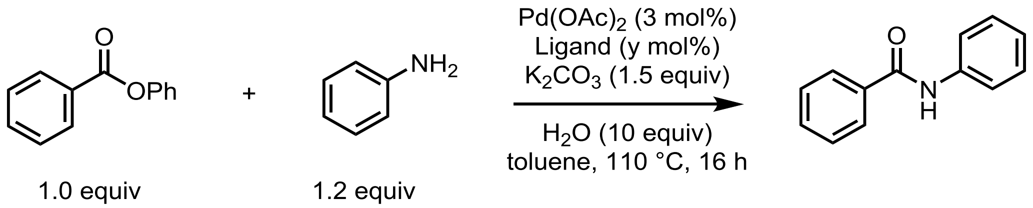


Entry	Base	(x)	Yield (%)[a]
1	K_3PO_4	-	<5
2	K_3PO_4	5 equiv	72
3	K_3PO_4	10 equiv	75
4	K_3PO_4	100 equiv	<5
5	Cs_2CO_3	10 equiv	60
6	K_2CO_3	10 equiv	80

[a] Yield determined by GC with 1,3,5-trimethoxybenzene as internal standard.

With the optimal base identified, multiple phosphine and NHC ligands were screened (**Table 2.14**). Since the preliminary results provided already high yields, catalyst loading was reduced to 3 mol% instead of 5 mol% to accentuate difference in reactivity to find better reaction conditions. Phosphine ligands proved generally ineffective for the transformation (entries 1–7). No improvement was observed when IMes·HCl was used (entry 8). The use of IPr·HCl generated a promising 37% yield at this reduced loading (entry 9). Higher conversion has been obtained with 1:1 metal to ligand ratio (entry 10). Finally, a pre-assembled NHC-ligated catalyst was particularly effective, affording almost quantitative yield (entry 11).

Table 2.14. Ligand screening for catalytic amide bond formation

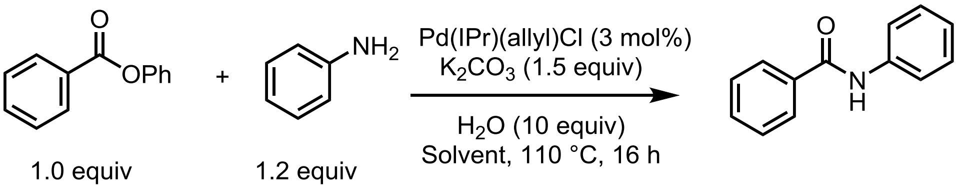


Entry	Ligand	y	Yield (%)[a]
1	PPh_3	6	<5
2	PBu_3	6	<5
3	P(*o*-tol)$_3$	6	20
4	BINAP	3	14
5	SPhos	6	12
6	dppb	3	<5
7	PCy_3•HBF_4	6	<5
8	IMes•HCl	6	<5
9	IPr•HCl	6	37
10	IPr•HCl	3	50
11	Pd(IPr)(allyl)Cl[b]	3	99

[a] Yield determined by GC with 1,3,5-trimethoxybenzene as internal standard.
[b] Pre-assembled NHC-ligated catalyst used instead of $Pd(OAc)_2$ and ligand.

Using the optimized catalyst, a short solvent screening was performed (**Table 2.15**). Toluene remained the best choice (entry 1) whereas DMF gave low yield (entry 2). Also, acetonitrile and dioxane generated moderate to good yields of 68% and 77% respectively (entries 3 and 4).

Table 2.15. Solvent screening for catalytic amide bond formation



Entry	Solvent	Yield (%)[a]
1	toluene	99
2	DMF	3
3	MeCN	68
4	dioxane	77

[a]Yield determined by GC with 1,3,5-trimethoxybenzene as internal standard.

Given the established reactivity between esters and nucleophilic aliphatic amines,[48] we thought that it was particularly important to determine the difficulty of the uncatalyzed variant of this reaction (**Table 2.16**). Using the optimized conditions without catalyst, no reactivity was observed (entry 2). N-Heterocyclic carbene (NHC) ligands have been demonstrated to act as a catalyst in the absence of metals to achieve amidation of vinyl esters.[49] For this reason IPr ligand was tested without any Pd source (entry 3), providing no detectable product. KO*t*Bu as a stronger base gave 6% yield (entry 4), while other bases (entry 5) and solvents (entry 6) were ineffective.[50] The only high yielding reactions we found were using traditional stoichiometric conditions for the direct synthesis of amides from anilines and esters. For example, pre-treatment of the aniline with the flammable organometallic reagents $AlMe_3$ (entry 7)[51] or *n*-BuLi (entry 8)[52] prior to addition of the ester gave appreciable yields. Given the prevalence of amides in complex, functional group-rich molecules, reactions with such harsh reagents are often undesirable.

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[48] Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 8460.

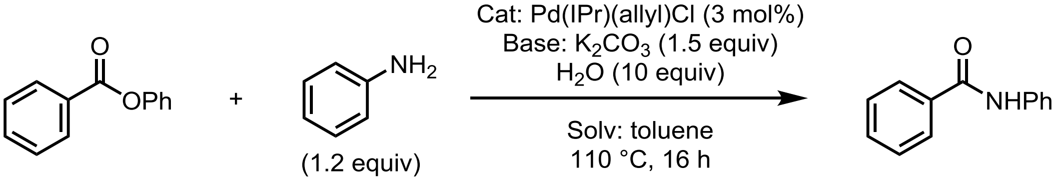
[49] (a) Guo, H.; Wang, Y.; Du, G.-F.; Dai, B.; He, L. *Tetrahedron* **2015**, *71*, 3472;. (b) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453.

[50] Starting material recovery was observed in reactions performed without strong bases or polar aprotic solvents.

[51] Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171.

[52] Deka, D. C.; Purkayastha, B.; Paul, M. *Indian J. Chem.* **2003**, *42B*, 2641.

Table 2.16. Control experiments on amidation reaction using phenyl ester



Entry	Deviation from optimal reaction conditions	Yield (%)[a]
1	No deviation	99
2	No cat.	0
3	Cat. = 3 mol% IPr (no Pd)	0
4	No cat. Base = KO*t*Bu	6
5	No cat. Base = KOH, NaOH, Cs_2CO_3, or NEt_3	trace
6	No cat. Solv = DMF, DMSO, dioxane, or DME	0
7[b]	No cat. 1 equiv $AlMe_3$, 0 °C	63
8[c]	No cat. 2 equiv BuLi, 0 °C	60

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

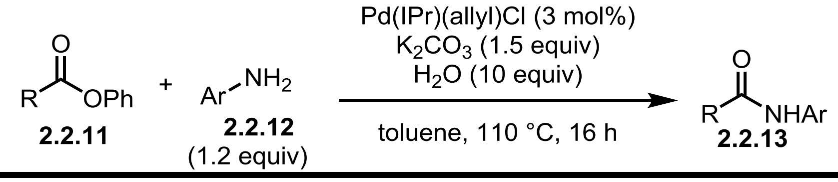
[b] Reaction performed in DCM according to ref 50.

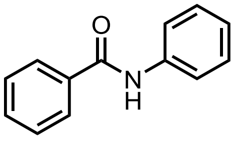
[c] Reaction performed in THF according to ref 51

2.2.2.2 Reaction scope[53]

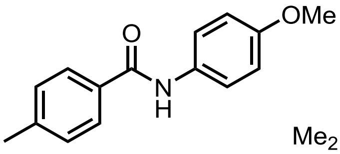
To evaluate the scope of the reaction, a diverse range of ester and aniline starting materials were explored (**Table 2.17**). The parent reaction with phenyl benzoate and aniline provided benzanilide in 91% isolated yield (**2.2.13a**). Incorporation of electron donating (**2.2.13b**–**2.2.13d**), naphthyl (**2.2.13e**, **2.2.13f**), electron-withdrawing (**2.2.13g**–**2.2.13l**) or sterically hindered (**2.2.13m**, **2.2.13n**) groups on either the nucleophilic or electrophilic coupling partners were tolerated. Chemoselectivity for phenyl esters is particularly notable (**2.2.13j**, **2.2.13k**). Various heterocyclic species could also be utilized (**2.2.13o**–**2.2.13u**). Amides bearing methyl (**2.2.13v**), primary (**2.2.13w**, **2.2.13x),** secondary (**2.2.13y**) and tertiary (**2.2.13z**) alkyl groups adjacent to the carbonyl could be obtained in good yields, demonstrating a relative insensitivity to steric hindrance. This contrasts significantly with previous catalytic reactions that feature ester bond cleavage, which generally cannot tolerate aliphatic substituents.[7,8,45] Cleavage of the C(acyl)–O bond of phenyl pivalate to provide **2.2.13z** is further interesting because the same substrate was used by Chatani and co-workers with a Ni/IPr catalyst system to provide the product of C(aryl)–O cleavage.[41] Finally, various aminophenols could be coupled (**2.2.13aa**–**2.2.13ae**). Complete chemoselectivity for amide formation over ester formation with aminophenols is particularly notable, given the precedence of ligand controlled selectivity in aminocarbonylation and alkyoxycarbonylation reactions.[54] The ability to obtain high yields regardless of the electronics of the amine nucleophile is a significant advantage of this methodology.

Table 2.17. Scope of esters and anilines coupling partners

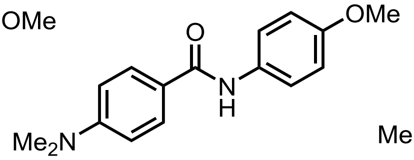




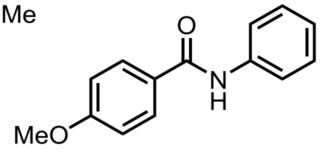
2.2.13a, 91%



2.2.13b, 95%



2.2.13c, 65%



2.2.13d, 94%

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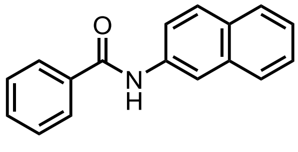
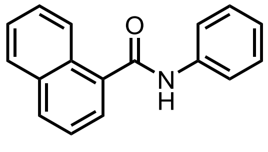
[53] Scope exploration was carried out in collaboration with postdoctoral fellow Jaya Kishore Vandavasi and visiting professor Mohanad Shkoor.

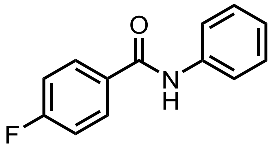
[54] (a) Xu, T.; Alper, H. *J. Am. Chem. Soc.* **2014**, *136*, 16970; (b) Xu, T.; Alper, H. *J. Am. Chem. Soc.* **2016**, *138*, 6629.



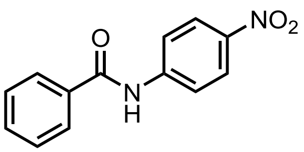
2.2.13e: 85%



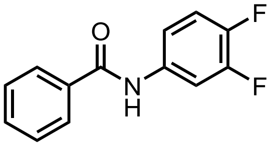
2.2.13f: 83%



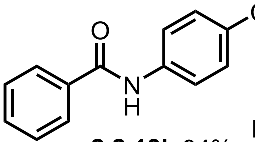
2.2.13g: 97%



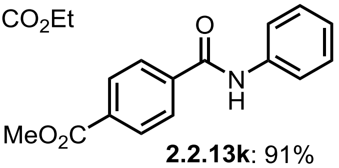
2.2.13h: 55%



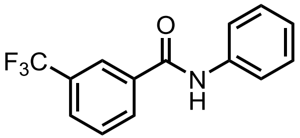
2.2.13i: 87%



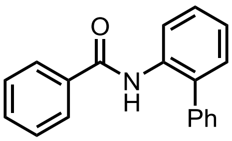
2.2.13j: 94%



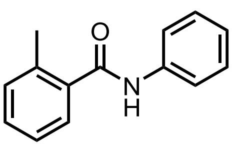
2.2.13k: 91%



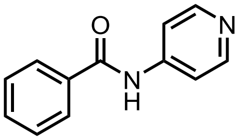
2.2.13l: 92%



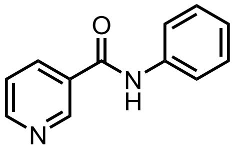
2.2.13m: 64%



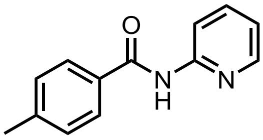
2.2.13n: 94%



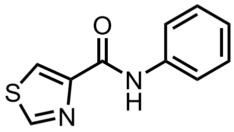
2.2.13o: 85%



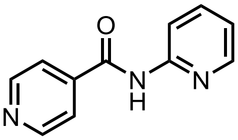
2.2.13p: 88%



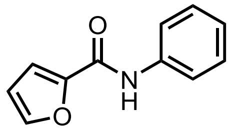
2.2.13q: 79%



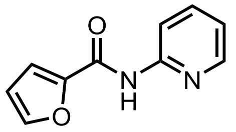
2.2.13r: 71%



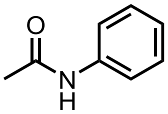
2.2.13s: 81%



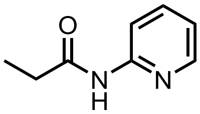
2.2.13t: 68%



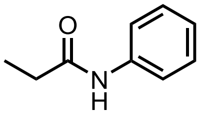
2.2.13u: 70%



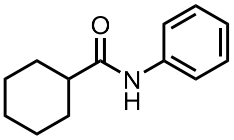
2.2.13v: 92%



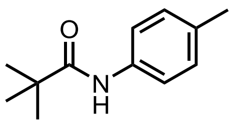
2.2.13w: 85%



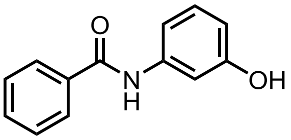
2.2.13x: 94%



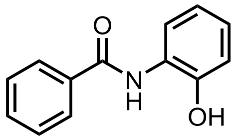
2.2.13y: 93%



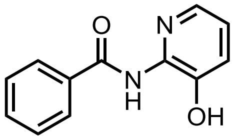
2.2.13z: 73%



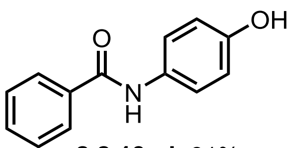
2.2.13aa: 86%



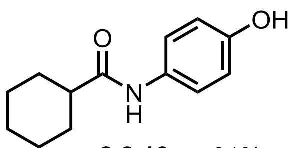
2.2.13ab: 93%



2.2.13ac: 95%



2.2.13ad: 61%

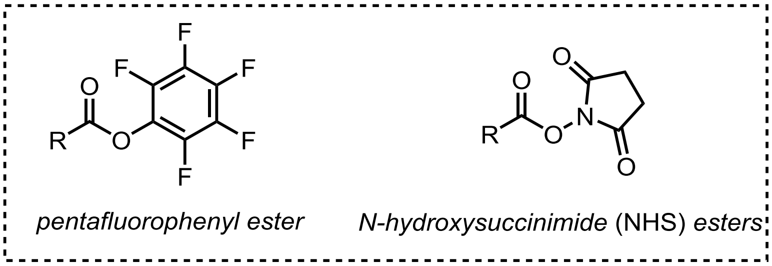


2.2.13ae: 81%

See **Section 2.3.2** for full experimental detail

2.2.2.3 Advantages of using esters as starting materials

The primary advantage of utilizing ester starting materials for amide bond formation rather than more activated derivatives such as acid chlorides or anhydrides is the enhanced stability while maintaining sufficient reactivity. For example, many pentafluorophenyl and *N*-hydroxysuccinimide-derived esters (**Figure 2.3**) are commercially available for applications in the synthesis of peptides[55] or polymers.[23,56]



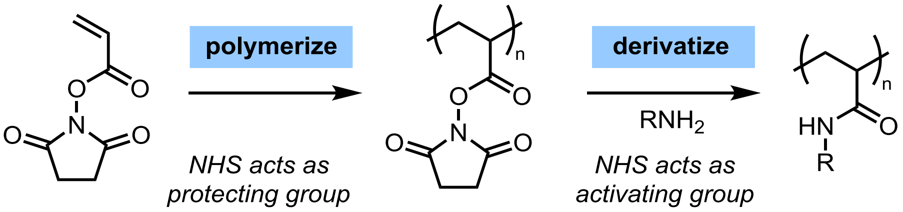
pentafluorophenyl ester

N-hydroxysuccinimide (NHS) *esters*

Figure 2.3. Common esters used in peptides and polymers syntheses

These bench-stable species are resistant to undesired side reactions that may occur with more reactive acid chlorides, while being sufficiently activated to directly react with nitrogen-centered nucleophiles to form amide bonds (**Scheme 2.19**).

Scheme 2.19. *N*-Hydroxysuccinimide (NHS) esters act as both protecting and activating groups of carboxylic acids for polymer synthesis



Alkyl amines work best in these amidations, though anilines, which react about 4 orders of magnitude slower, can also be used with these highly activated electrophiles.[57] Simple phenyl

---

[55] Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.

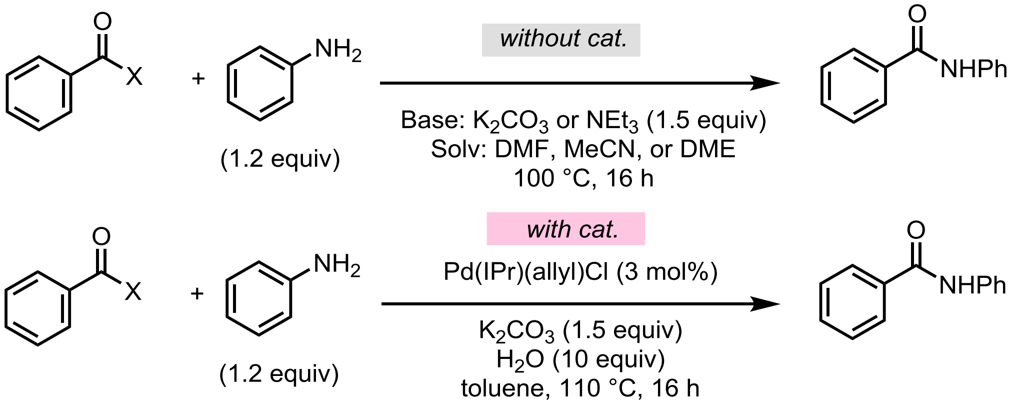
[56] (a) Pedone, E.; Li, X.; Koseva, N.; Alpar, O.; Brocchini, S. *J. Mater. Chem.* **2003**, *13*, 2825; (b) Eberhardt, M.; Mruk, R.; Zentel, R. *Eur. Polym. J.* **2005**, *41*, 1569.

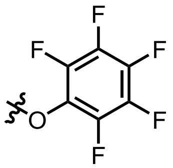
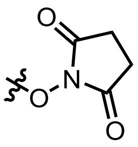
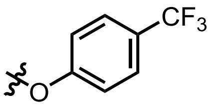
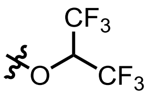
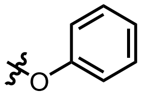
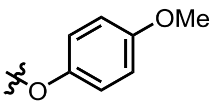
[57] (a) Cline, G. W.; Hanna, S. B. *J. Am. Chem. Soc.* **1987**, *109*, 3087; (b) Wang, G.; Yu, Q.-Y.; Wang, J.; Wang, S.; Chen, S.-Y.; Yu, X.-Q. *RSC Adv.* **2013**, *3*, 21306.

esters are considerably less electrophilic than *N*-hydroxysuccinimide or pentafluorophenyl esters, and are thus expected to be much more resistant to both desired substitution chemistry and undesired side reactions.

To get a better understanding about the practical applications of this amide bond forming reaction, we surveyed the reactivity of several esters with aniline under catalytic and non-catalytic conditions (**Table 2.18**). While activated pentafluorophenyl and *N*-hydroxy succinimide esters are known to react with aniline in the presence of mild base, non-catalytic reactions with more robust esters are rarely reported. We thus carried out a screen with a selection of solvents (DMF, MeCN, DME) and mild bases (NEt_3, K_2CO_3) at 100 °C. The yields reported below are the highest yields obtained, after performing 6 iterations of the experiment. The details regarding the other 5 combinations are provided in the experimental section of this manuscript.

Table 2.18. Evaluation of esters of varying degree of activation



X =						
pKa of X–H	5.4 (H_2O)	7.8 (H_2O) 14 (DMSO)	15.3 (DMSO)	17.2 (DMSO)	18 (DMSO)	19.1 (DMSO)
without cat.	✓ see ref 54 and ref 55	✓ see ref 54 and ref 55	~ (44%)	~ (36%)	✖ (trace)	✖ (trace)
with cat	no catalyst required	no catalyst required	✓ (94%)	✓ (65%)	✓ (99%)	✓ (74%)

Esters derived from electron-withdrawing *p*-trifluoromethylphenol and hexafluoroisopropanol[58] were found to be moderately reactive, while less electrophilic esters were essentially inert in non-catalytic conditions.[59] Since the reactivity and stability of C(acyl)–X species can be approximated by the pKa of their leaving groups, we can thus identify a point, pKa ~15(in DMSO), where catalytic substrate activation may become beneficial. Using our Pd-catalyzed conditions on substrates above this point gave substantial yield improvements in all cases. Benzanilide was formed in 94% yield from 4-trifluoromethylphenyl benzoate, 65% yield from trifluoroisopropylbenzoate, and 74% yield from 4-methoxyphenylbenzoate. The extension of efficient couplings to include these robust esters is of particular importance in multi-step chemical synthesis, where more easily hydrolyzed functional groups would not be tolerated. It also provides promising progress towards the ability to couple groups that would be typically considered protected acids, such as methyl, *t*-butyl, and benzyl esters, which often need to be deprotected prior to amidation of the free acid.[60] However, the C(acyl)–O bond of these aliphatic esters are considerably more robust, and Pd-catalyzed conditions to enable these reactions could not be found.

One of the main advantages of using pentafluorophenyl, *N*-hydroxysuccinimide, and related activated esters as starting materials for peptide synthesis is their clean reaction with amine nucleophiles with minimal epimerization of the sensitive chiral center, as can be the case when more electron-withdrawing groups are used. We were thus curious if amino acids could be directly coupled as their ester derivative (**Scheme 2.20**). Reaction of enantiopure proline-derived **2.2.14** provided anilides **2.2.15a** and **2.2.15b** in good yields. HPLC analysis showed that the stereocenter remained intact, with minimal loss of enantiopurity. The extension of this process to more diverse amino acid derivatives, particularly those bearing acidic and unreactive N–H groups, is of high importance.

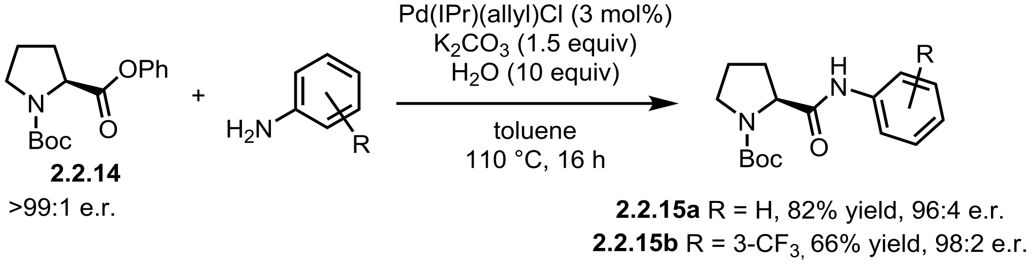
---

[58] Vatele, J.-M. *Synlett* **2015**, *26*, 2280.

[59] More nucleophilic aliphatic amines (e.g. benzyl amine) were found to react with the most robust esters studied without the need of catalyst. In contrast, very weakly nucleophilic species such as the aminopyridines showed poor reactivity even for relatively activated esters without catalyst.

[60] (a) Soria-Arteche, O.; Hernandez-Campos, A.; Yepez-Mulia, L.; Trejo-Soto, P. J.; Hernandez-Lius, F.; Gres-Molina, J.; Maldonado L. A.; Castillo, R. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6838; (b) Pan, X.; Wang, F.; Zhang, Y.; Gao, H.; Hu, Z.; Wang, S.; Zhang, J. *Bioorg. Med. Chem.* **2013**, *21*, 2527; (c) Vipilla, M. R.; Nikhar, S.; Gracia, A. P.; Cuny, G. D. *Org. Lett.* **2016**, *18*, 4726.

Scheme 2.20. Pd-catalyzed amidation reactions with enantiopure esters



2.2.2.4 Plausible mechanism

While thorough investigation is still needed to fully elucidate the mechanism of this amide bond formation, the coupling reactions of esters to form ketones and biaryls have been studied experimentally and by DFT calculations.[7,34(a,b),37,45f,46,61] From this precedent, oxidative addition of both Pd(0) and Ni(0) catalysts into C(acyl)–O bond to generate acyl–metal intermediates are both established elementary steps. Such complexes are known to react with amines to produce amides, as occurs in well-established aminocarbonylation reactions of aryl halides, either by direct attack on the carbonyl or complexation with the metal followed by reductive elimination.[62] A plausible mechanism (**Scheme 2.21**) would thus involve oxidative addition of a Pd(0)-NHC active catalyst into the ester C–O bond of the ester **2.2.11** to afford complex **2.2.16**, followed by the ligand exchange reaction with aniline providing **2.2.17**. Finally, a reductive elimination occurs to provide the corresponding product **2.2.13** and generate the active catalyst. The bulky NHC ligand is critical for donating sufficient electron density (see **Chapter 1**, **Section 1.2.1**) to the catalyst to enable oxidative addition, while preventing decarbonylation and increasing the rate of reductive elimination from Pd(II) via its steric bulk. Although it is suspected that strong bases, such as KO*t*Bu and NaO*t*Bu assist the ligand exchange step of the traditional Buchwald-Hartwig amination,[40] the necessity of K_2CO_3 and water for this reaction is not fully understood. It can be speculated, based on results obtained in previous Suzuki-Miyaura coupling conducted within our group, that these parameters might possess a profound role in the activation of the pre-assembled NHC-ligated catalyst (Pd(IPr)(allyl)Cl) or/and help on the ligand exchange step.

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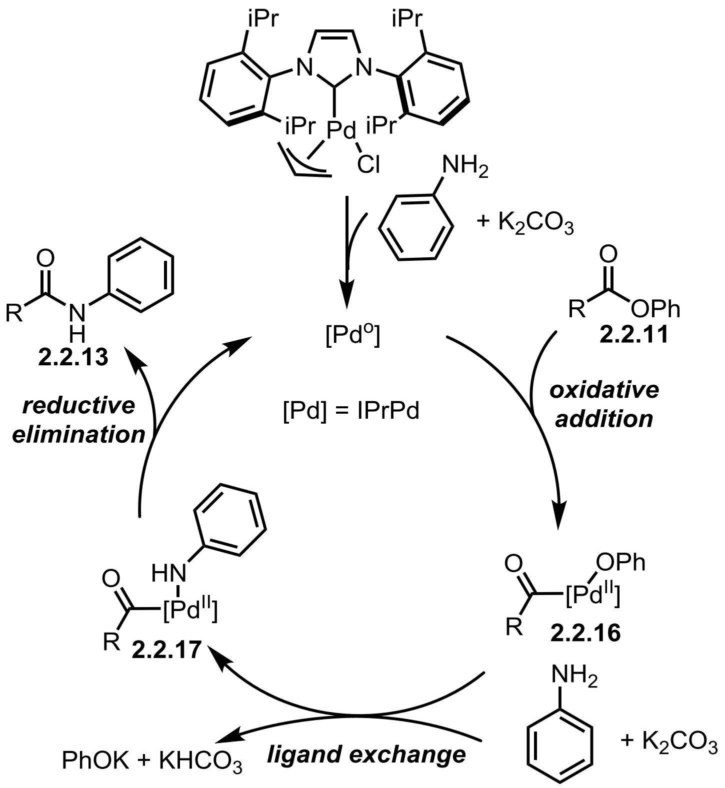
[61] Hong, X.; Liang, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 2017.

[62] (a) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327; (b) Kumar, K.; Zapf, A.; Michalik, D.; Tillack, A.; Heinrich, T.; Boettcher, H.; Arlt, M.; Beller, M. *Org. Lett.* **2004**, *6*, 7; (c) Martinelli, R.; Freckmann, D. M. M.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 4795; (d) McNulty, J.; Nair, J. J.; Robertson, A. *Org. Lett.* **2007**, *9*, 4575; (e) Fang, W.; Deng, Q.; Xu, M.; Tu, T. *Org. Lett.* **2013**, *15*, 3678; (f) Nielsen, D. U.; Taaning, R. H.; Lindhardt, A. T.; Gøgsig, T. M.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 4454; (g) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402.

Scheme 2.21. Plausible mechanism of Pd-catalyzed amide bond formation from phenyl esters



2.2.3 Conclusion

The reaction of amines with esters to form amides is of fundamental importance in organic synthesis. In non-catalytic reactions, this can occur when a highly reactive ester is used, or the nucleophile is activated by harsh stoichiometric base. The current work demonstrates that, through the use of a Pd catalyst, moderately activated aryl esters can react with a diverse range of aniline derivatives, including electron deficient aminopyridines and bifunctional aminophenols. Analysis of various ester derivatives demonstrates that this catalytic methodology pushes the boundary on the robustness of the ester starting materials that can be used for amide bond formation. Application to the synthesis of proline derivatives without destruction of stereochemical information demonstrates generality and mildness of this strategy. While our current method is not yet going to replace traditional coupling, activation of C(acyl)–O bonds through Pd catalysis is a novel strategy with a lot of potential. Further ligand and catalyst development may in the future allow cross coupling of even less activated substrates such as simple methyl esters. We thus expect our work to motivate numerous other researchers in the field to push the boundaries of C–O activation even further.

2.3 Experimental section

2.3.1 Experimental section for section 2.1: palladium-catalyzed Suzuki-Miyaura cross-coupling of aryl esters

Materials

Organic solvents were purified by rigorous degassing with nitrogen before passing through a PureSolv solvent purification system, and low water content was confirmed by Karl Fischer titration (<25 ppm for all solvents). Water was vigorously degassed for at least ten minutes prior to use. The following reagents are commercially obtained and were used as received. K_3PO_4 was obtained from Strem Chemicals. K_2CO_3 was obtained from Alfa Aesar. Cs_2CO_3, tBuOK, K_2HPO_4, NEt_3, PPh_3, P*t*Bu_3, P(*o*-tol)$_3$, and Phenol were obtained from Sigma Aldrich. Dppf, SPhos, and BINAP were obtained commercially from Combi-Blocks. Pd(OAc)$_2$, Pd_2(dba)$_3$, $PdCl_2$, and $PdCl_2$(COD) were obtained from Strem Chemicals. All boronic acids, **2.1.10a-2.1.10l,** were obtained from Combi-Blocks. *N*,*N*-dimethyl-4-aminopyridine (DMAP) was obtained from Matrix Scientific. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl) was obtained from Combi-Blocks. N-heterocyclic carbene (NHC) ligands were prepared according to the literature.[63] Pd catalysts Pd(IPr)(cinammyl)Cl, Pd(IPr)(allyl)Cl, and Pd(IMes)(cinammyl)Cl were prepared according to the literature.[64] Phenyl benzoate **2.1.9A** was obtained from Alfa Aesar. Phenyl acetate **2.1.9M** was obtained from Sigma Aldrich. The following esters were prepared according to literature: phenyl 4-(dimethylamino)benzoate **(2.1.9H)**,[65] phenyl isonicotinate **(2.1.9I)**,[8] phenyl furan-2-carboxylate **(2.1.9J)**,[66] phenyl 2-methylbenzoate **(2.1.9K)**,[67] phenyl [1,1'-biphenyl]-2-carboxylate **(2.1.9L)**,[68] phenyl 3-

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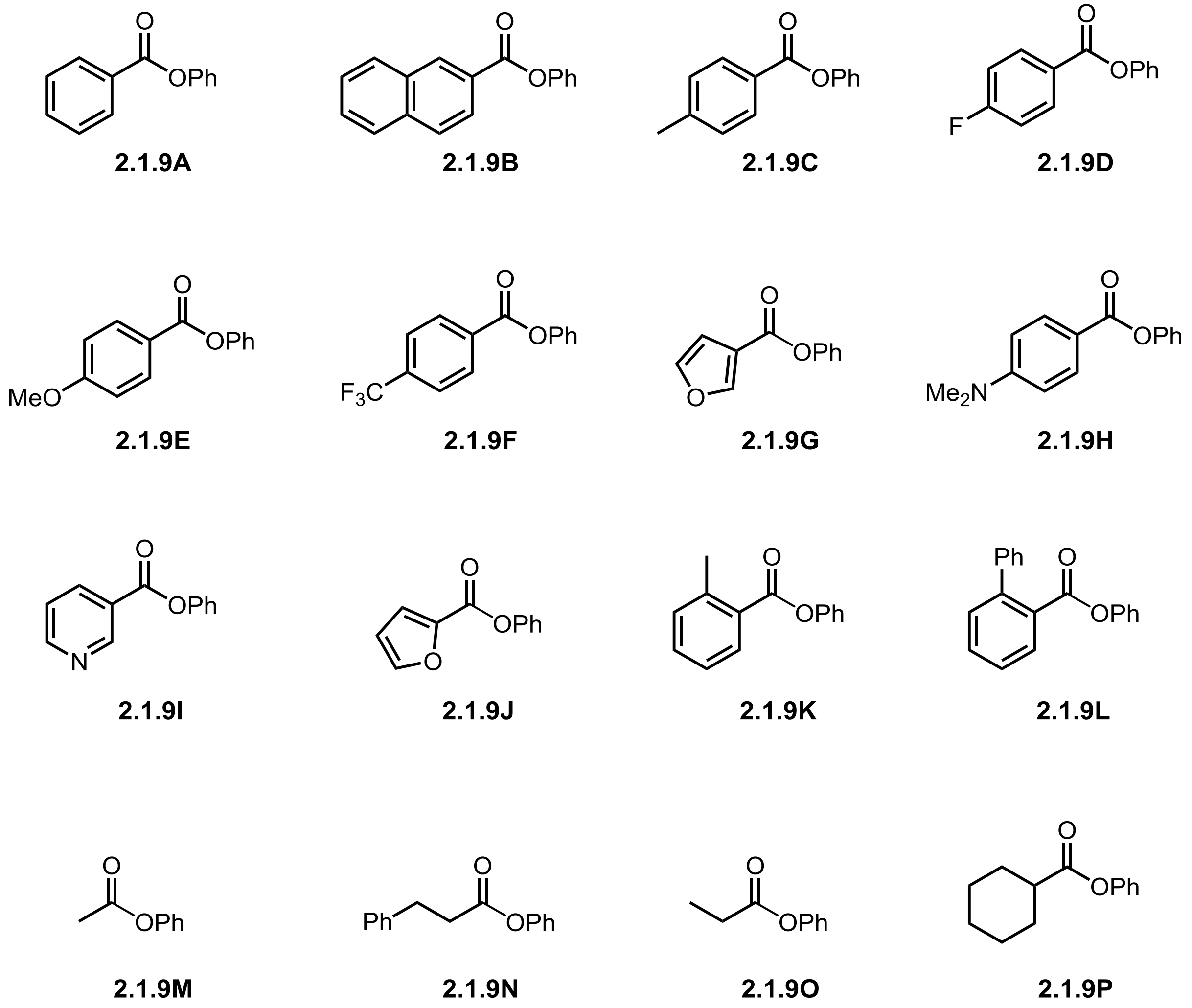
[63] Bantreil, X.; Nolan, S. P. *Nat. Protocols* **2011**, *6*, 69.
[64] Nareddy, P.; Mazet, C. *Chem. Asian J.* **2013**, *8*, 2579.
[65] Neuvonen, H.; Neuvonen, K.; Pasanen, P. *J. Org. Chem.* **2004**, *69*, 3794.
[66] Lee, C. K.; Yu, J. S.; Lee, H.-J. *J. Heterocycl. Chem.* **2002**, *39*, 1207.
[67] Engbersen, J. F. J.; Geurtsen, G.; De Bie, D. A.; Van Der Plas, H. C. *Tetrahedron Lett.* **1988**, *44*, 1795.
[68] Ueda, T.; Konishi, H.; Manabe, K. *Org. Lett.* **2012**, *14*, 3100.

phenylpropanoate **(2.1.9N)**,[69] phenyl cyclohexanecarboxylate **(2.1.9P)**,[70] 4-methoxyphenyl benzoate **(2.1.9E)**,[66] phenyl 4-chlorobenzoate (**2.1.28**).[65]



2.1.9A **2.1.9B** **2.1.9C** **2.1.9D**

2.1.9E **2.1.9F** **2.1.9G** **2.1.9H**

2.1.9I **2.1.9J** **2.1.9K** **2.1.9L**

2.1.9M **2.1.9N** **2.1.9O** **2.1.9P**

Figure 2.4. Numbering of esters

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[69] Yamazaki, J.; Watanabe, T.; Tanaka, K. *Tetrahedron: Asymmetry* **2001**, *12*, 669.

[70] Sasse, A.; Ligneau, X.; Sadek, B.; Elz, S.; Pertz, H. H.; Ganellin, C. R.; Arrang, J.-M.; Schwartz, J.-C.; Schunack, W.; Stark, H. *Arch. Pharm.* **2001**, *334*, 45.

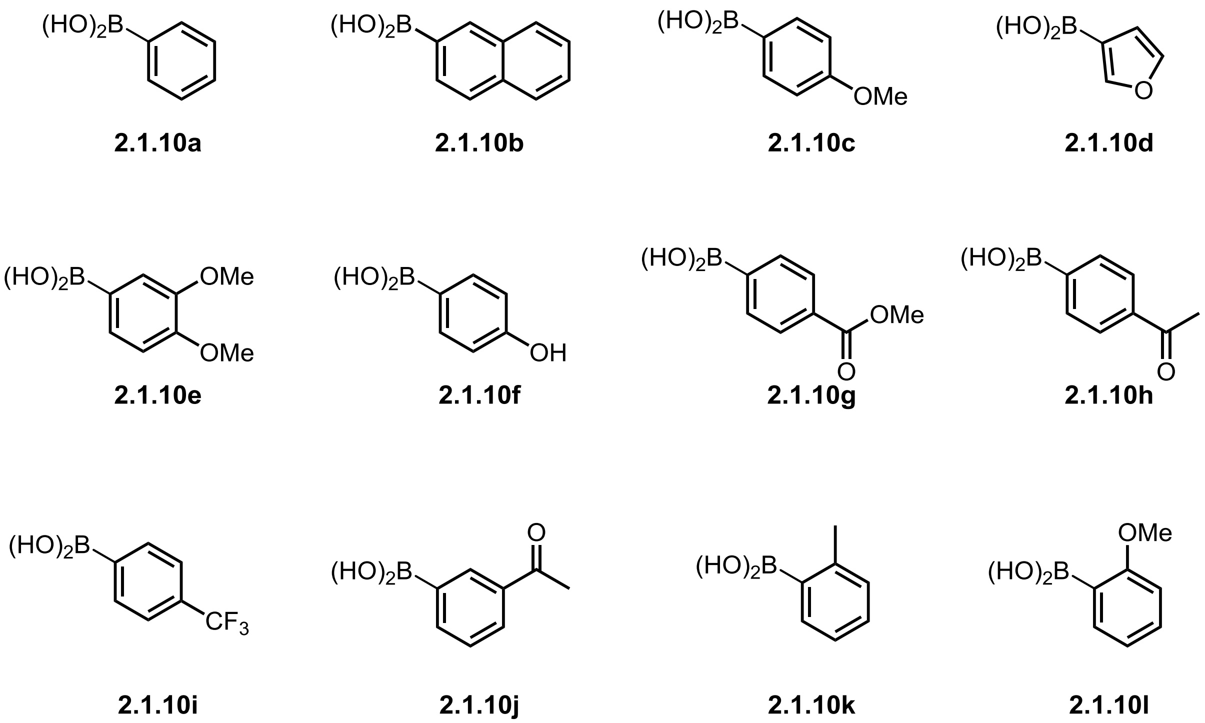
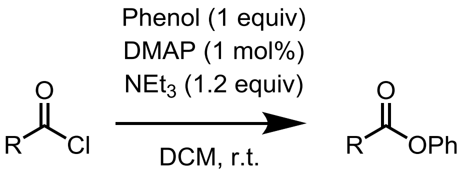


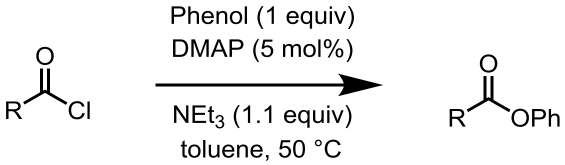
Figure 2.5. Numbering of boronic acids

<u>Synthesis of the starting materials</u>



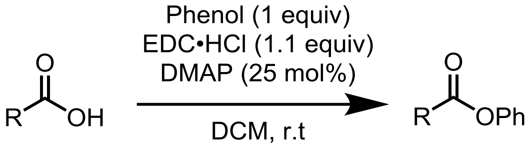
Method A

Acyl chloride was added to DCM (0.5 M), phenol (1.0 equiv), and *N*,*N*-dimethyl-4-aminopyridine (DMAP, 1 mol%) in a round bottom flask. The flask was purged with argon. After cooling the mixture to 0 °C, triethylamine (1.2 equiv) was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight. Completion of the reaction was monitored by TLC. The reaction was quenched with saturated $NaHCO_{3(aq)}$. The mixture was extracted three times with CH_2Cl_2. Subsequent washes with $NaOH_{aq}$ (1 M) were performed as necessary to remove phenol. The combined organic layers were dried over Na_2SO_4, and then filtered. The filtrate was concentrated *in vacuo*. Purification was performed by flash chromatography (hexanes: ethyl acetate) to afford the corresponding ester substrate.



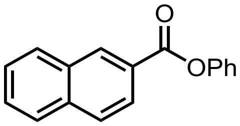
Method B

Acyl chloride was added to phenol (1.0 equiv) and *N*,*N*-dimethyl-4-aminopyridine (DMAP, 5 mol%) in a round bottom flask in toluene (0.3 M). The flask was purged with argon. Triethylamine (1.1 equiv) was added dropwise. The reaction mixture was warmed to 50 °C and stirred overnight. The reaction was monitored by TLC. After completion, the reaction was quenched with saturated $NaHCO_{3(aq)}$. The mixture was extracted three times with EtOAc. Subsequent washes with $NaOH_{(aq)}$ (1 M) were performed as necessary to remove phenol. The combined organic layers were dried over Na_2SO_4, and then filtered. The filtrate was concentrated *in vacuo*. Purification was performed by manual column chromatography to afford the corresponding ester substrate.

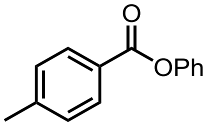


Method C

Carboxylic acid, phenol (1.0 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl, 1.1 equiv), and *N*,*N*-dimethyl-4-aminopyridine (DMAP, 25 mol%) were added to a round-bottom flask. The flask was purged with argon. DCM was added (0.5 M) to the mixture. Completion of the reaction was monitored by TLC. After stirring the mixture overnight, the reaction was quenched with saturated $NaHCO_{3(aq).}$ The mixture was extracted three times with CH_2Cl_2. Subsequent washes with $NaOH_{aq}$ (1 M) were performed as necessary to remove phenol. The combined organic layers were dried over Na_2SO_4, and then filtered. The filtrate was concentrated *in vacuo*. Purification was performed by flash chromatography to afford the corresponding ester substrate.



Phenyl 2-**naphthoate (2.1.9B)** was synthesized following method A using 2-naphthoyl chloride (760 mg, 4 mmol, 1.0 equiv), phenol (376 mg, 4 mmol, 1.0 equiv), *N*,*N*-dimethyl-4-aminopyridine (DMAP, 5 mg, 0.04 mmol, 0.01 equiv) and triethylamine (0.7 ml, 4.8 mmol, 1.2 equiv). Purification by flash chromatography (0% → 25% EtOAc in hexane) afforded **2.1.9B** as white solid (416 mg, 42% yield). Characterization data were in accordance with literature.[71] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.81 (s, 1H), 8.20 (dd, *J* = 8.61, 1.7 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.94 (dd, *J* = 11.4 Hz, 2H), 7.55-7.65 (m, 2H), 7.4-7.45 (m, 2H), 7.25-7.39 (m, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) 165.7, 151.4, 136.1, 132.8, 132.2, 129.9, 129.8, 128.7, 128.2, 127.1, 126.2, 125.8, 122.1.



***p*-Methyl benzoic acid phenyl ester (2.1.9C)** was synthesized following method B using 4-methylbenzoyl chloride (0.3 ml, 2.2 mmol, 1.0 equiv), phenol (187 mg, 2.2 mmol, 1.0 equiv), *N*,*N*-dimethyl-4-aminopyridine (DMAP, 3 mg, 0.02 mmol, 0.01 equiv) and triethylamine (0.4 ml, 2.4 mmol, 1.1 equiv). Purification by column chromatography (0% →20% EtOAc in hexane) afforded **2.1.9C** as a white solid (240 mg, 75% yield). Characterization data were in accordance with literature.[68] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.08 (d, *J* = 8.2 Hz, 2H), 7.41 (t, *J* = 9.1 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.25 (tt, *J* = 8.3, 1.0 Hz, 1H), 7.19 (ddd, *J* = 7.3, 2.0, 1.0 Hz, 2H), 2.49 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) 165.6, 151.4, 144.7, 130.5, 129.8, 129.6, 127.2, 126.1, 122.1, 22.1.

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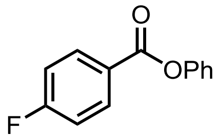
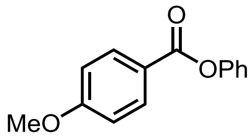
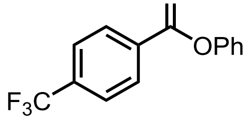
[71] Zhang, L.; Zhang, G.; Zhang, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 7472.



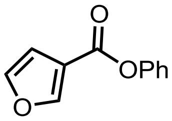
4-Fluoro-benzoic acid phenyl ester (2.1.9D) was synthesized following method B using 4-fluorobenzoyl chloride (260 mg, 2.2 mmol, 1.0 equiv), phenol (188 mg, 2.2 mmol, 1.0 equiv), *N*,*N*-dimethyl-4-aminopyridine (DMAP, 3 mg, 0.02 mmol, 0.01 equiv) and triethylamine (0.4 ml, 2.4 mmol, 1.1 equiv). Purification by column chromatography (0% → 20% EtOAc in hexane) afforded **2.1.9D** as a white solid (368 mg, 85% yield). Characterization data were in accordance with literature.[8] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.24 (m, *J* = 9.0, 5.4 Hz, 2H), 7.41 (t, *J* = 7.0 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.18 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.4 (d, *J* = 255.0 Hz), 164.5, 151.2, 133.1 (d, *J* = 9.4 Hz), 129.8, 126.3, 126.1 (d, *J* = 3.0 Hz), 122.0, 116.1 (d, *J* = 22.1 Hz).



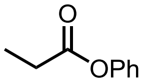
4-Methoxy-benzoic acid phenyl ester (2.1.9E) was synthesized following method B using 4-methoxybenzoyl chloride (375 mg, 2.2 mmol, 1.0 equiv), phenol (188 mg, 2.2 mmol, 1.0 equiv), *N*,*N*-dimethyl-4-aminopyridine (DMAP, 3 mg, 0.02 mmol, 0.01 equiv) and triethylamine (0.4 ml, 2.4 mmol, 1.1 equiv). Purification by column chromatography (0% → 40% EtOAc in hexane) afforded **2.1.9E** as a white solid (400 mg, 88% yield). Characterization data were in accordance with literature.[71] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.0 Hz, 2H), 7.44 (t, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 14.9 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 6.83 (t, *J* = 10.6 Hz, 2H), 3.91 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 132.6, 130.0, 126.2, 122.3, 114.3.



Phenyl 4-(trifluoromethyl)benzoate (2.1.9F) was synthesized following method A using 4-(trifluoromethyl)benzoyl chloride (834 mg, 4 mmol, 1.0 equiv), phenol (376 mg, 4 mmol, 1.0 equiv), *N*,*N*-dimethyl-4-aminopyridine (DMAP, 5 mg, 0.04 mmol, 0.01 equiv) and triethylamine (0.7 ml, 4.8 mmol, 1.2 equiv). Purification by flash chromatography (0% → 30% EtOAc in hexane) afforded **2.1.9F** as white solid (579 mg, 54% yield). Characterization data were in accordance with literature.[68] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 8.33 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.45 (t, *J* = 9.1 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 2H). **^{13}C NMR** (CDCl$_3$, 100 MHz) 164.3, 151.0, 135.6 (q, *J* = 32.7 Hz), 133.2, 130.9, 129.9, 126.6, 125.9 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.8 Hz), 121.9.



Phenyl furan-3-carboxylate (2.1.9G), was synthesized following method C using furan-3-carboxylic acid (448 mg, 4 mmol, 1.0 equiv), phenol (376 mg, 4 mmol 1.0 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl, 568 mg, 4.4 mmol, 1.1 equiv), and *N*,*N*-dimethyl-4-aminopyridine (DMAP, 122 mg, 1 mmol, 0.25 equiv). Purification by flash chromatography (0% → 30% EtOAc in hexane) afforded **2.1.9G** as clear oil (426 mg, 57% yield). Characterization data were in accordance with literature.[68] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 8.22 (d, *J* = 0.7 Hz, 1H), 7.52 (t, *J* = 1.7 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 2H), 6.90 (d, *J* = 1.9 Hz, 1H). **^{13}C NMR** (CDCl$_3$, 100 MHz) 161.4, 150.5, 148.7, 144.1, 129.5, 126.0, 121.7, 118.9, 110.1.



Phenyl propionate (2.1.9O) was synthesized following method B using propionyl chloride (0.2 ml, 2.2 mmol, 1.0 equiv), phenol (188 mg, 2.2 mmol, 1.0 equiv), *N*,*N*-dimethyl-4-aminopyridine (DMAP, 3 mg, 0.02 mmol, 0.01 equiv) and triethylamine (0.4 ml, 2.4 mmol, 1.1 equiv). Purification by column chromatography (0% → 20% EtOAc in hexane) afforded **2.1.9O** as yellowish oil. (231 mg, 70% yield). Characterization data were in accordance with literature.[72] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.39 (t, *J* = 7.1 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) 173.0, 151.0, 129.5, 125.8, 121.7, 27.9.

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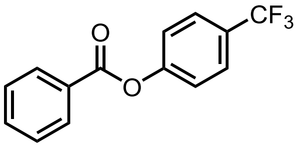
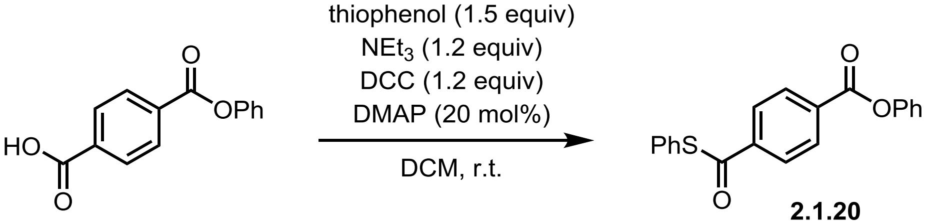
[72] Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373.



4-(Trifluoromethyl)phenyl benzoate (2.1.9V), was synthesized following method A using benzoyl chloride (464 mg, 4 mmol, 1.0 equiv), 4-(trifluoromethyl)phenol (648 mg, 4 mmol, 1.0 equiv), *N*,*N*-dimethyl-4-aminopyridine (DMAP, 5 mg, 0.04 mmol, 0.01 equiv) and triethylamine (0.7 ml, 4.8 mmol, 1.2 equiv). Purification by flash chromatography (0% → 20% EtOAc in hexane) afforded **2.1.9V** as a white solid (404 mg, 48% yield). Characterization data were in accordance with literature.[71] ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.22 (d, *J* = 7.1 Hz, 2H), 7.70-7.64 (m, 2H), 7.69 – 7.65 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H). ^{13}**C NMR** ($CDCl_3$, 100 MHz) δ 165.0, 153.8, 134.3, 130.6, 129.3, 129.1, 128.5 (q, *J* = 32.8 Hz), 127.2 (q, *J* = 3.7 Hz), 123.0 (q, *J* = 270.3 Hz), 122.6.



2.1.20

Phenyl 4-((phenylthio)carbonyl)benzoate (2.1.20). 4-(Phenoxycarbonyl)benzoic acid[73] (125 mg, 0.52 mmol, 1.0 equiv), thiophenol (64 mg, 0.62 mmol, 1.2 equiv), N,N'-Dicyclohexylcarbodiimide (DCC, 129 mg, 0.62 mmol, 1.2 equiv), and *N*,*N*-dimethyl-4-aminopyridine (DMAP, 12 mg, 0.1 mmol, 0.2 equiv) were added to a round-bottom flask and purged with argon. DCM (5 mL) was added to the mixture followed by dropwise addition of triethylamine (0.08 ml, 0.62 mmol, 1.2 equiv). Completion of the reaction was monitored by TLC. After stirring the mixture overnight, the reaction was quenched with saturated $NaHCO_{3(aq).}$ The mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and then filtered. The filtrate was concentrated *in vacuo.* Purification was performed by flash chromatography (0% → 20% EtOAc in hexane) to afford **2.1.20** as a white solid. (113 mg, 65% yield). ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 8.33 (d, *J* = 8.7 Hz, 2H), 8.16 (d, *J* = 8.7 Hz, 2H), 7.59 – 7.52 (m, 2H), 7.52 – 7.48 (m, 3H), 7.48 – 7.44 (m, 2H), 7.32 (t, *J* = 7.4 Hz,

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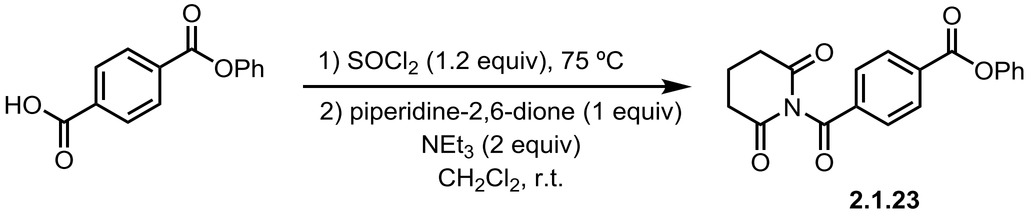
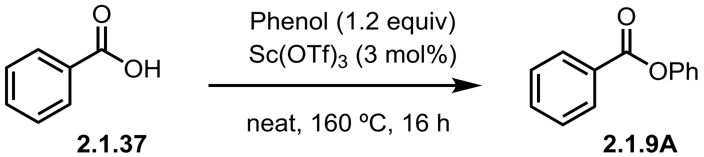
[73] Solorzano, C.; Antonietti, F.; Duranti, A.; Tontini, A.; Rivara, S.; Lodola, A.; Vacondio, F.; Tarzia, G.; Piomelli, D.; Mor, M. *J. Med. Chem.* **2010,** *53*, 5770.

1H), 7.25 (dd, *J* = 8.6, 1.1 Hz, 2H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 189.7, 164.2, 150.8, 140.5, 135.0, 133.9, 130.6, 129.9, 129.6, 129.4, 127.6, 126.8, 126.2, 121.6; **m.p**: 148-150 °C; **IR:** 1736, 1678, 1474, 1402, 1280, 1148, 1069 cm^{-1}. **Accurate mass** (EI): Theoretical: 334.0658. Found: 334.0566. Spectral Accuracy: 98.9%.



2.1.23

Phenyl 4-(2,6-dioxopiperidine-1-carbonyl)benzoate (2.1.23). An oven-dried round-bottom flask was charged with a magnetic stir bar, 4-(phenoxycarbonyl) benzoic acid[73] (201 mg, 0.8 mmol, 1.0 equiv) and SOCl$_2$ (0.3 ml, 4 mmol, 5 equiv). Reaction mixture was refluxed at 75 °C for 2 hours and then concentrated *in vacuo*. The piperidine-2,6-dione (94 mg, 0.83 mmol, 1.0 equiv), and *N*,*N*-dimethyl-4-aminopyridine (DMAP, 122 mg, 1 mmol, 0.25 equiv) were then added to reaction mixture at 0 °C under argon in DCM (5 mL) and stirred vigorously. Triethylamine (2 equiv) was added dropwise to reaction mixture and allowed to stir overnight at room temperature. After completion of reaction, reaction mixture was diluted with Et$_2$O and filtered. Organic layer was subsequently washed with HCl (1N), brine, dried and concentrated *in vacuo*. Crude product was purified by recrystallization to give **2.1.23** as a light yellow solid (149 mg, 54% yield). **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 8.31 (d, *J* = 8.7 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.46 (t, *J* = 6.9 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.26 – 7.19 (m, 2H), 2.81 (t, *J* = 6.5 Hz, 4H), 2.23 – 2.12 (m, 2H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 172.0, 171.9, 170.4, 163.9, 150.6, 135.7, 134.8, 130.8, 130.1, 129.7, 129.6, 126.6, 121.5, 32.4, 17.5; **m.p**: 159-161 °C; **IR**: 2160, 1741, 1682, 1490, 1250, 1235, 1079 cm^{-1}. **Accurate mass** (EI): Theoretical: 337.0945. Found: 337.0815. Spectral Accuracy: 94.7%.

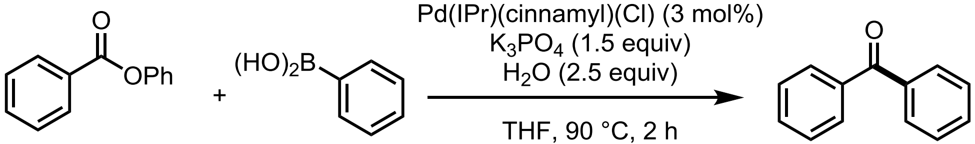


2.1.37 **2.1.9A**

Phenyl benzoate (2.1.9A) was prepared using a modified procedure.[32] An oven dried screw-capped vial was charged with a magnetic stir bar, phenol (113 mg, 1.2 mmol, 1.2 equiv), benzoic acid (122 mg, 1 mmol, 1.0 equiv), and scandium triflate (15 mg, 0.03 mmol, 0.04 equiv) and was fitted to a tube filled with powdered molecular sieves (4 Å, 100 mg). The mixture was heated to 160 ºC for 16 h. After the reaction was complete, the mixture was washed with NaOH (1N) to yield the desired phenyl benzoate **2.1.9A** as a white solid (161 mg, 81% yield)**.** Characterization data matched those previously reported**.**[65]

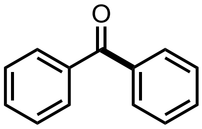
Synthesis of ketone products

Representative procedure for Suzuki-Miyaura coupling of esters

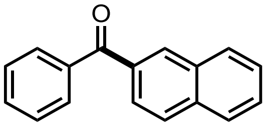


2.1.9A **2.1.10a** **2.1.11Aa**

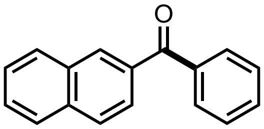
An oven dried screw-capped vial was charged with a magnetic stir bar, powdered K_3PO_4 (64 mg, 0.3 mmol, 1.5 equiv), Pd(IPr)(cinnamyl)(Cl) (3 mol%), ester **2.1.9A** (40 mg, 0.2 mmol, 1.0 equiv), and boronic acid **2.1.10a** (41 mg, 0.3 mmol, 1.7 equiv). The vial and contents were placed under vacuum and back-filled with Argon under a Schleck line three times. Fresh solvent (1 mL, 0.2 M) obtained from a solvent purification system was then added under argon. Degassed water (2.5 equiv) was subsequently added via micropipette. The vial was sealed with a PTFE-lined screw cap and stirred vigorously (700 rpm) at 90 ºC for 2 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and filtered through a plug of silica gel (10 mL of EtOAc eluent). The crude mixture was concentrated *in vacuo* and subjected to manual column chromatography. If ester starting material is present and inseparable, the reaction mixture was heated to 60 ºC in 1:1 THF : $KOH_{(aq)}$ (0.1 M). Products are numbered according to corresponding starting materials. For example, ester **2.1.9A** and boronic acid **2.1.10a** give ketone **2.1.11Aa**. Ester **2.1.9F** and boronic acid **2.1.10i** give ketone **2.1.11Fi**.



Benzophenone (2.1.11Aa) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Aa** as a white solid (34 mg, 91% yield). Characterization data matched those previously reported.[74] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.82 (d, *J* = 7.1 Hz, 4H), 7.60 (t, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 197.1, 138.0, 132.8, 130.4, 128.6.



Naphthalen-2-yl(phenyl)methanone (2.1.11Ab) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Ab** as white solid, (38 mg, 84% yield). Characterization data matched those previously reported.[74] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.29 (s, 1H), 7.97 (d, *J* = 1.2 Hz, 2H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.88 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.67 – 7.60 (m, 2H), 7.59 – 7.51 (m, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 197.1, 138.3, 135.6, 135.2, 132.7, 132.6, 132.2, 130.4, 129.8, 128.7, 128.7, 128.6, 128.2, 127.1, 126.1.



Naphthalen-2-yl(phenyl)methanone (2.1.11Ba) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to

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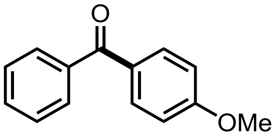
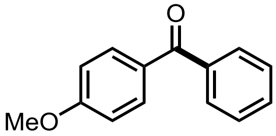
[74] Kuang, Y.; Wang, Y. *Eur. J. Org. Chem.* **2014**, *2014*, 1163.

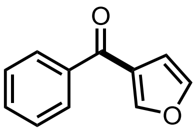
afford **2.1.11Ba** as white solid, (36 mg, 81% yield). Characterization data matched that of **2.1.11Ab**.



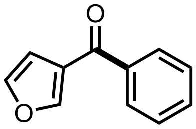
(4-Methoxyphenyl)(phenyl)methanone (2.1.11Ac) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Ac** as a white solid, (37 mg, 87% yield). Characterization data matched those previously reported.[74] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 6.9 Hz, 2H), 7.56 (t, *J* = 6.8 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 195.9, 163.6, 138.6, 132.9, 130.5, 130.5, 130.1, 128.5, 113.9, 55.8.



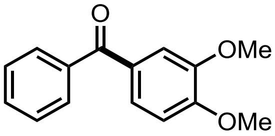
(4-Methoxyphenyl)(phenyl)methanone (2.1.11Ea) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Ea** as a white solid, (36 mg, 85% yield) Characterization data matched that of **2.111Ac**.



Furan-3-yl(phenyl)methanone (2.1.11Ad) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 15% EtOAc in hexane) afforded **2.1.11Ad** as a white solid, (32 mg, 95% yield) as well as recovered phenol (16 mg, 85% recovery). Characterization data for **2.1.11Ad** matched those previously reported.[75] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.93 (s, 1H), 7.87 (d, *J* = 7.0 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.0 Hz, 3H), 6.92 (d, *J* = 1.2 Hz, 1H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 189.8, 148.9, 144.3, 139.2, 132.8, 129.2, 128.9, 126.9, 110.6.



Furan-3-yl(phenyl)methanone (2.1.11Ga) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 15% EtOAc in hexane) afforded **2.1.11Ga** as a white solid, (26 mg, 81% yield). Characterization data matched that of **2.1.11Ad**.



(3,4-Dimethoxyphenyl)(phenyl)methanone (2.1.11Ae) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 20% EtOAc in hexane) afforded **2.1.11Ae** as a white solid, (47 mg, 93%). Characterization data matched those previously reported.[76] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.78 (d, *J* = 7.0 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.53 – 7.42 (m, 3H), 7.39 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 189.8, 148.9, 144.3, 139.2, 132.8, 129.2, 128.9, 126.9, 110.6.

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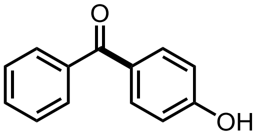
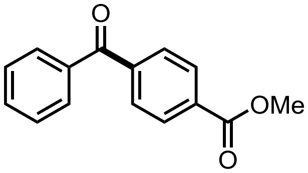
[75] Rieke, R. D.; Suh, Y.; Kim, S.-H. *Tetrahedron Lett.* **2005**, *46*, 5961.

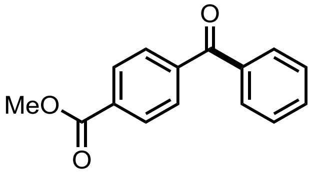
[76] Tripathi, S.; Singh, S. N.; Yadav, L. D. S. *Tetrahedron Lett.* **2015**, *56*, 4211.



(4-Hydroxyphenyl)(phenyl)methanone (2.1.11Af) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 50% EtOAc in hexane) afforded **2.1.11Af** as an off-white solid, (22 mg, 58% yield). Characterization data matched those previously reported.[77] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.78 (t, *J* = 8.7 Hz, 4H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.06 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 197.0, 161.0, 138.4, 133.4, 132.5, 130.2, 130.0, 128.6, 115.7.



Methyl 4-benzoylbenzoate (2.1.11Ag) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 20% EtOAc in hexane) afforded **2.1.11Ag** as a white solid, (37 mg, 79% yield). Characterization data matched those previously reported.[78] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.16 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.81 (d, *J* = 7.0 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 3.97 (s, *J* = 6.9 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 196.4, 166.6, 141.7, 137.3, 133.6, 133.3, 130.4, 130.1, 129.8, 128.8, 52.8.



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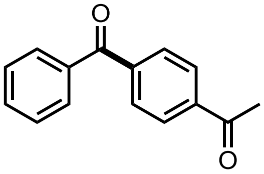
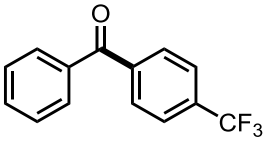
[77] Wang, G.-Z.; Li, X.-L.; Dai, J.-J.; Xu, H.-J. *J. Org. Chem.* **2014**, *79*, 7220.

[78] Li, X.; Zou, G. *Chem. Commun.* **2015**, *51*, 5089.

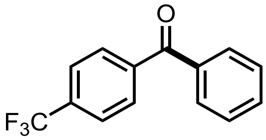
Methyl 4-benzoylbenzoate (2.1.27) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 20% EtOAc in hexane) afforded **2.1.27** as a white solid, (45 mg, 94% yield). Characterization data matched that of **2.1.11Ag**.



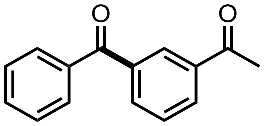
1-(4-Benzoylphenyl)ethan-1-one (2.1.11Ah) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 20% EtOAc in hexane) afforded **2.1.11Ah** as a white solid, (34 mg, 77% yield). Characterization data matched those previously reported.[77] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 8.6 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.81 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 2.68 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 197.8, 196.3, 141.7, 139.9, 137.3, 133.3, 130.4, 130.4, 128.8, 128.5, 27.2.



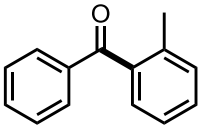
Phenyl(4-(trifluoromethyl)phenyl)methanone (2.1.11Ai) was prepared according to a modified general procedure. Pd(IPr)(cinnamyl)(Cl) (5 mol%) was used as the catalyst, and the reaction was stirred for 16 hours. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Ai** as a white solid, (32 mg, 71% yield). Characterization data matched those previously reported.[77] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.82 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 195.9, 141.1, 137.1, 133.4 (q, *J* = 32.6 Hz), 130.4, 128.9, 125.7, 125.7, 125.7 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 272.5).



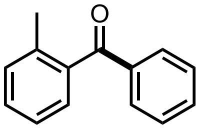
Phenyl(4-(trifluoromethyl)phenyl)methanone (2.1.11Fa) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Fa** as a white solid, (43 mg, 87% yield). Characterization data matched that of **2.1.11Ai**.



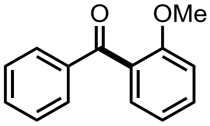
1-(3-Benzoylphenyl)ethan-1-one (2.1.11Aj) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 20% EtOAc in hexane) afforded **2.1.11Aj** as a white solid, (40 mg, 91% yield). Characterization data matched those previously reported.[76] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 8.37 (s, *J* = 1.6 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 7.0 Hz, 2H), 7.61 (q, *J* = 7.7 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 2.65 (s, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 197.6, 196.2, 138.4, 137.5, 137.3, 134.6, 133.2, 132.1, 130.4, 130.0, 129.1, 128.8, 27.1.



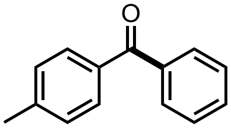
Phenyl(*o*-tolyl)methanone (2.1.11Ak) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Ak** as a colorless oil, (30 mg, 76% yield). Characterization data matched those previously reported.[76] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.82 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 8.9 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 2.35 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 199.0, 139.0, 138.1, 137.1, 133.5, 131.3, 130.6, 130.5, 128.8, 128.8, 125.5, 20.3.



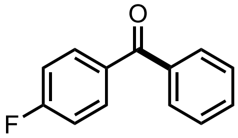
Phenyl(o-tolyl)methanone (2.1.11Ka) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Ka** as a colorless oil, (29 mg, 75% yield). Characterization data matched that of **2.1.11Ak**.



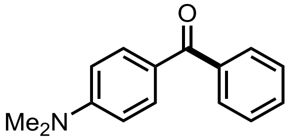
(2-Methoxyphenyl)(phenyl)methanone (2.1.11Al) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 20% EtOAc in hexane) afforded **2.1.11AI** as a white solid, (33 mg, 80% yield). Characterization data matched those previously reported.[74] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.83 (d, *J* = 7.0 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.50 – 7.43 (m, 3H), 7.37 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 3.73 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 196.8, 157.7, 138.2, 132.2, 132.2, 130.2, 129.9, 129.2, 128.5, 120.8, 111.8, 55.9.



Phenyl(*p*-tolyl)methanone (2.1.11Ca) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Ca** as a white solid, (37 mg, 93% yield). Characterization data matched those previously reported.[74] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.80 (d, *J* = 7.0 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 2.45 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 196.8, 143.6, 138.3, 135.2, 132.5, 130.6, 130.3, 129.3, 128.5, 22.0.



(4-Fluorophenyl)(phenyl)methanone (2.1.11Da) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Da** as a white solid, (37 mg, 94% yield). Characterization data matched those previously reported.[77] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.86 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.78 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 8.7 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 195.6, 165.4 (d, *J* = 260.5 Hz), 137.9, 134.2 (d, *J* = 3.1 Hz), 133.0 (d, *J* = 9.2 Hz), 130.8, 130.2, 128.7, 115.8 (d, *J* = 21.8).



(4-(Dimethylamino)phenyl)(phenyl)methanone (2.1.11Ha) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 20% EtOAc in hexane) afforded **2.1.11Ha** as a yellowish solid. (27 mg, 60% yield) . Characterization data matched those previously reported.[79] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 7.1 Hz, 2H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 2H), 6.67 (d, *J* = 8.9 Hz, 2H), 3.06 (s, 6H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 195.5, 153.6, 139.6, 133.1, 131.4, 129.8, 128.3, 125.2, 110.9, 40.4.

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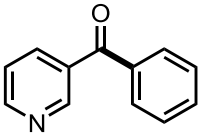
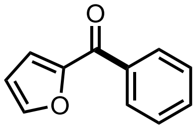
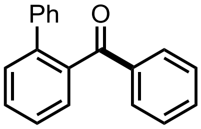
[79] Goßen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 3043.



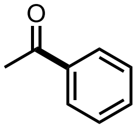
Phenyl(pyridin-3-yl)methanone (2.1.11Ia) was prepared according to the general procedure. Purification by column chromatography (gradient of 10% → 40% EtOAc in hexane) afforded **2.1.11Ia** as yellowish solid (29 mg, 83% yield). Characterization data matched those previously reported.[75] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 9.00 (d, *J* = 1.6 Hz, 1H), 8.82 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.13 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.82 (dd, *J* = 8.1, 1.0 Hz, 2H), 7.64 (t, *J* = 6.8 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.43 (dd, *J* = 8.2, 4.5 Hz, 1H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 195.2, 153.1, 151.2, 137.5, 137.0, 133.5, 130.3, 129.0, 123.7.



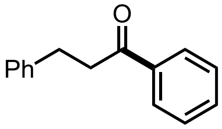
Furan-2-yl(phenyl)methanone (2.1.11Ja) was prepared according to the general procedure. Purification by column chromatography (gradient of 5% → 15% EtOAc in hexane) afforded **2.1.11Ja** as a colorless oil, (32 mg, 92% yield). Characterization data matched those previously reported.[74] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.98 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.71 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 2.9 Hz, 1H), 6.60 (dd, *J* = 3.6, 1.7 Hz, 1H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 182.9, 152.6, 147.4, 137.6, 132.9, 129.6, 128.8, 120.9, 112.5.



[1,1'-Biphenyl]-2-yl(phenyl)methanone (2.1.11La) was prepared according to the general procedure, with modifications: in dioxane at 100 °C for 16 h. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane. The material was then recrystallized in hexanes to afford **2.1.11La** as a white solid, (21 mg, 56% yield). Characterization data matched those previously reported.[80] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.65 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.59 (t, *J* = 8.2 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.30 – 7.13 (m, 7H). **^{13}C NMR** (CDCl$_3$, 100 MHz) 199.1, 141.5, 140.5, 139.3, 137.8, 133.1, 130.7, 130.4, 130.2, 129.3, 129.1, 128.6, 128.4, 127.7, 127.4.



Acetophenone (2.1.11Ma) was prepared according to the general procedure. Purification was performed by column chromatography (gradient of 5% → 15% EtOAc in hexane) afforded **2.1.11Ma** as a colorless oil, (22 mg, 91% yield). Characterization data matched those previously reported.[81] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.98-7.93 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 2.60 (s, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 198.4, 137.4, 133.4, 128.8, 128.6, 26.9.



1,3-Diphenylpropan-1-one (2.1.11Na) was prepared according to the general procedure. Purification by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Na** as a (28 mg, 66% yield). Characterization data matched those previously reported.[82] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.98 (d, *J* = 8.4, Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.35 – 7.19 (m, 5H), 3.33 (t, *J* = 7.8 Hz, 2H), 3.09 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 199.6, 141.6, 137.2, 133.4, 128.9, 128.9, 128.8, 128.4, 126.5, 40.8, 30.5.

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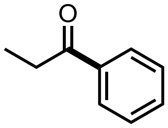
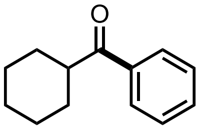
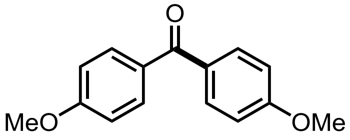
[80] Zeng, J.; Liu, K. M.; Duan, X. F. *Org. Lett.* **2013**, *15*, 5342.
[81] Das, T.; Chakraborty, A.; Sarkar, A. *Tetrahedron Lett.* **2014**, *55*, 7198.
[82] Kantam, M. L.; Kishore, R.; Yadav, J.; Sudhakar, M.; Venugopal. *Adv. Synth. Catal.* **2012**, *354*, 663.



Propiophenone (2.1.11Oa) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Oa** as a colourless liquid. (30 mg, 74% yield). Characterization data matched those previously reported.[83] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 7.1 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 2.98 (t, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 201.1, 137.3, 133.2, 128.9, 128.3, 32.1, 8.6.



Cyclohexyl(phenyl)methanone (2.1.11Pa) was prepared according to the general procedure with modifications: in dioxane at 100 °C for 16 h. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Pa** as a white solid (20 mg, 53% yield). Characterization data matched those previously reported.[74] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.95 (dd, J = 5.2, 3.4 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 3.27 (tt, J = 11.5, 3.2 Hz, 1H), 1.88 (t, J = 15.4 Hz, 4H), 1.75 (d, J = 12.5 Hz, 1H), 1.57 – 1.20 (m, 5H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 204.2, 136.7, 133.0, 128.9, 128.6, 77.7, 77.4, 77.0, 46.0, 29.8, 26.3, 26.2.



Bis(4-Methoxyphenyl)methanone (2.1.11Ec) was prepared according to the general procedure. Purification by column gradient of 5% → 30% EtOAc in hexane afforded **2.1.11Ec** as a white

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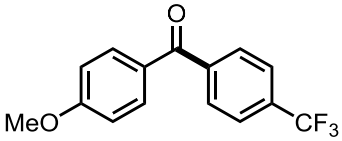
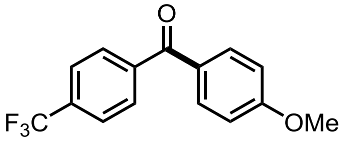
[83] Landers, B.; Berini, C.; Wang, C.; Navarro, O. *J. Org. Chem.* **2011**, *76*, 1390.

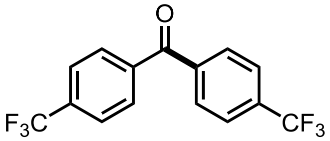
solid, (38 mg, 79% yield). Characterization data matched those previously reported.[74] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.7 Hz, 4H), 6.97 (d, *J* = 8.7 Hz, 4H), 3.89 (s, 6H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 194.8, 163.2, 132.5, 131.1, 113.8, 55.8.



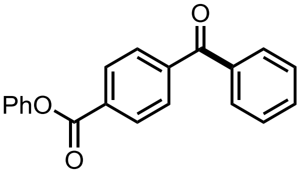
(4-Methoxyphenyl)(4-(trifluoromethyl)phenyl)methanone (2.1.11Ei) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 20% EtOAc in hexane to afford **2.1.11Ei** as a white solid, (17 mg, 30% yield). Characterization data matched those previously reported.[74] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.84 (t, *J* = 8.3 Hz, 4H), 7.75 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.91 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 194.3, 163.7, 141.5, 133.3 (q, *J* = 32.6 Hz), 132.6, 129.8, 129.4, 125.3 (q, *J* = 3.7 Hz), 122.4 (q, *J* = 274 Hz), 113.8, 55.6.



(4-Methoxyphenyl)(4-(trifluoromethyl)phenyl)methanone (2.1.11Fc) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 20% EtOAc in hexane to afford **2.1.11Fc** as a white solid (54 mg, 97% yield). Characterization data matched that of **2.1.11Ei**.



Bis(4-(Trifluoromethyl)phenyl)methanone (2.1.11Fi) was prepared according to the general procedure. Purification was performed by column chromatography. The first 5 fractions were collected using 20% DCM in hexane, followed by a gradient of 5% → 10% EtOAc in hexane to afford **2.1.11Fi** as a white solid, (40 mg, 63% yield). Characterization data matched those previously reported.[84] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.92 (d, J = 8.1 Hz, 4H), 7.79 (d, J = 8.2 Hz, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 194.7, 140.1, 134.8 (q, J = 33 Hz), 130.6, 126.0, 126.0 (q, J = 3.7 Hz), 122.5.



Phenyl 4-benzoylbenzoate (2.1.21) was prepared using Liebeskind's procedure[25] for thioester boronic acid coupling. Phenyl 4-((phenylthio)carbonyl)benzoate thiol ester **2.1.20** (67 mg, 0.2 mmol, 1.0 equiv), Cu (I) thiophene-2-carboxylate (57.2 mg, 0.3 mmol, 1.5 equiv), boronic acid (27 mg, 0.2 mmol, 1.1 equiv), $Pd_2dba_3.CHCl_3$ (2 mg, 0.002 mmol) and tris-2-furylphosphine (3 mg, 0.006 mmol) were placed in vial. The vial and contents were placed under vacuum and back-filled with argon under a Schleck line three times. THF (1 mL, 0.2 M) was then added under argon. The mixture was stirred for 18 h at 50 °C. After cooling to room temperature, Et_2O (15 mL) was added and the suspension was subsequently washed with 1 M HCl and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification was performed by column chromatography with a gradient of 10% → 30% EtOAc in hexane and followed by recrystallization to afford **2.1.21** as a white solid (51 mg, 84% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.33 (d, J = 8.6 Hz, 2H), 7.92 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 7.0 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.47 (t, J = 7.0 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.27 – 7.24 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 196.3, 164.8, 151.1, 142.3, 137.2, 133.4, 133.0, 130.5, 130.4, 130.2, 130.0, 128.9, 126.5, 121.9. **m.p.** 78-80 °C. **IR:** 3057, 3042, 1743, 1647, 1593, 1486, 1404, 1266, 1255, 1067 cm^{-1}. **Accurate mass** (EI): Theoretical: 302.0937. Found: 302.0982. Spectral Accuracy: 99.5%.

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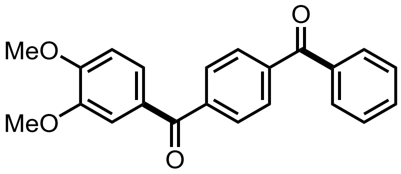
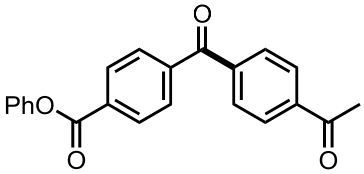
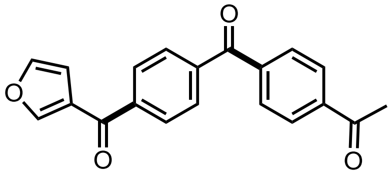
[84] Li, Y.; Lu, W.; Xue, D.; Wang, C.; Liu, Z.-T.; Xiao, J. *Synlett* **2014**, *25*, 1097.



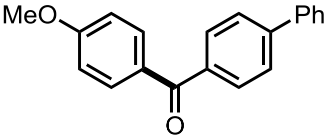
(4-Benzoylphenyl)(3,4-dimethoxyphenyl)methanone (**2.1.22**) was prepared according to the general procedure. Purification was performed by column chromatography with a gradient of 10% → 40% EtOAc in hexane to afford **2.1.22** as a beige solid (30 mg, 94% yield) **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.87-7.83 (m, 4H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.55 – 7.49 (m, 3H), 7.40 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 3.97 (d, *J* = 6.2 Hz, 6H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 196.4, 195.1, 153.8, 149.6, 141.9, 140.5, 137.4, 133.3, 130.5, 130.0, 130.0, 129.7, 128.8, 126.1, 112.3, 110.2, 56.5, 56.4, 30.0. **m.p.** 109-111°C. **IR:** 2923, 1644, 1257, 1231, 1445, 1127, 1026, 664 cm^{-1}. **Accurate mass** (EI): Theoretical: 346.1200. Found: 346.1090. Spectral Accuracy: 98.7%.



Phenyl 4-(4-acetylbenzoyl)benzoate (2.1.24) was prepared using Szostak's procedure.[33] An oven-dried vial equipped with a stir bar was charged with the phenyl 4-(2,6-dioxopiperidine-1-carbonyl)benzoate **2.1.24** (0.2 mmol, 1 equiv), potassium carbonate (0.5 mmol, 2.5 equiv), boric acid (2 equiv), (4-acetylphenyl)boronic acid (39 mg, 0.24 mmol, 1.2 equiv), $Pd(OAc)_2$ (3 mol%), and PCy_3•HBF_4 (12 mol%). The vial and contents were placed under vacuum and back-filled with argon under a Schleck line three times. Fresh THF (1 mL, 0.2 M) obtained from a solvent purification system was then added under argon. The mixture was stirred for 18 h at 65 °C. After cooling to room temperature, mixture was diluted with CH_2Cl_2, filtered and concentrated *in vacuo*. Purification was performed by column chromatography with a gradient of 10% → 40% EtOAc in hexane to afford **2.1.24** as a white solid (69 mg, 80% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.31 (d, *J* = 7.8 Hz, 2H), 8.06 (d, *J* = 7.8 Hz, 2H), 7.88 (t, *J* = 6.5 Hz, 4H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.19 (m, 3H), 2.65 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 197.4, 195.2, 164.3, 150.8, 141.1, 140.4, 140.0, 133.2, 130.2, 130.2, 130.0, 129.6, 129.0, 128.4, 127.5, 126.2, 121.6, 26.9. **m.p.** 150-152 °C; **IR:** 3041, 1732, 1683, 1650, 1251, 1070, 867, 739, 702 cm^{-1}. **Accurate mass** (EI): Theoretical: 344.1043. Found: 344.1026. Spectral Accuracy: 99.0%.



1-(4-(4-(Furan-3-carbonyl)benzoyl)phenyl)ethan-1-one (**2.1.25**) was prepared according to the general procedure with modifications: in dioxane at 110 °C for 12 h. Purification was performed by column chromatography with a gradient of 10% → 50% EtOAc in hexane, followed by recrystallization in hexanes to afford **2.1.25** as a white solid (27 mg, 91% yield) **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.09 (d, *J* = 8.3 Hz, 2H), 8.00-7.94 (m, 3H), 7.91 (dd, *J* = 8.3, 1.7 Hz, 4H), 7.56 (s, 1H), 6.95 (s, 1H), 2.69 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 197.7, 195.5, 188.9, 149.3, 144.7, 142.5, 140.9, 140.3, 130.5, 129.4, 129.0, 128.7, 127.8, 127.8, 126.8, 110.4, 27.3. **m.p.** 190-192 °C; **IR:** 3142, 3122, 1679, 1633, 1252, 1153, 860, 835, 746, 706 cm^{-1}. **Accurate mass** (EI): Theoretical: 318.0887. Found: 318.0790. Spectral Accuracy: 99.6%.



[1,1'-Biphenyl]-4-yl(4-methoxyphenyl)methanone (2.1.31) was prepared according to the general procedure. Purification was performed by column chromatography with a gradient of 5% → 30% EtOAc in hexane to afford **2.1.31** as a white solid (47 mg, 81% yield). Characterization data matched those previously reported.[85] **^{1}H NMR** ($CDCl_3$, 400 MHz) *δ* 7.94–7.83 (m, 4H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.03–6.98 (m, 2H), 3.91 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) *δ* 195.5, 163.5, 145.1, 140.4, 137.3, 132.8, 130.7, 130.6, 129.3, 128.4, 127.6, 127.2, 113.9, 55.8.

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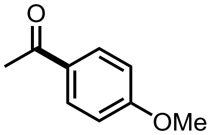
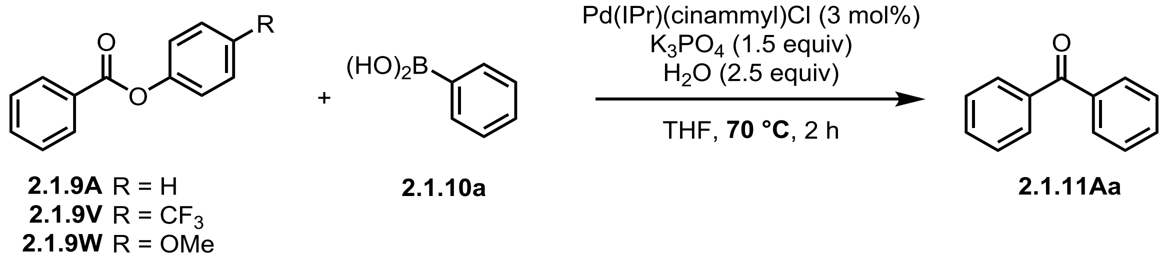
[85] Ma, J.; Hu, Z.; Li, M.; Zhao, W.; Hu, X.; Mo, W.; Hu, B.; Sun, N.; Shen, Z. *Tetrahedron Lett.* **2015**, *71*, 6733.



1-(4-Methoxyphenyl)ethan-1-one (2.1.36) was prepared according to the general procedure. Purification was performed by column chromatography with a gradient of 5% → 30% EtOAc in hexane to afford **2.1.36** as a white solid (26 mg, 88% yield). Characterization data matched those previously reported.[86] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.95 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 3.88 (s, 2H), 2.57 (s, 2H); **^{13}C NMR** (CDCl$_3$, 125 MHz) δ 197.0, 163.7, 130.8, 130.6, 113.9, 55.7, 26.6.

<u>Study of substrate and boronic acid electronics</u>



An oven dried screw-capped vial was charged with a magnetic stir bar, powdered K$_3$PO$_4$ (1.5 equiv), Pd(IPr)(cinnamyl)(Cl) (3 mol%), corresponding ester **2.1.9A, 2.1.9V** or **2.1.9W** (0.2 mmol), and boronic acid **2.1.10a** (1.2 equiv). The vial and contents were placed under vacuum and back-filled with Argon under a Schleck line three times. Fresh solvent (1 mL, 0.2 M) obtained from a solvent purification system was then added under argon. Degassed water (2.5 equiv) was subsequently added via micropipette. The vial was sealed with a PTFE-lined screw cap and stirred vigorously (700 rpm) at 70 °C for 2 h. After cooling to room temperature, internal standard, 1,3,5-timethoxybenzene (0.025 mmol) in 0.5mL THF was added. Reaction mixture was filtered through a plug of silica gel (10 mL of EtOAc eluent). The crude mixture was concentrated *in vacuo* and characterized by ^{1}H NMR. Yield determined by ^{1}H NMR.

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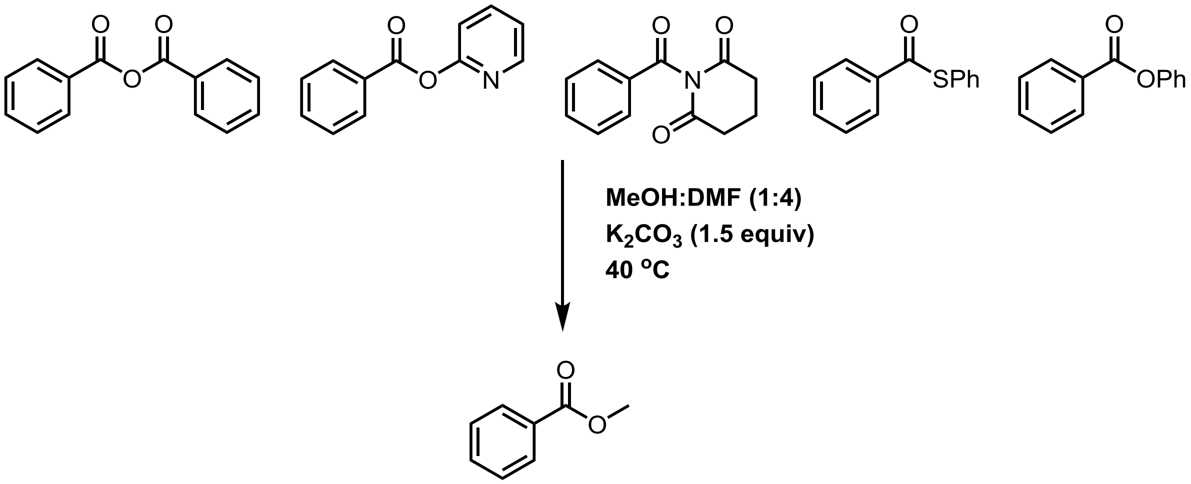
[86] Kawahara, R.; Fujita, K.-i.; Yamaguchi, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 12790.

Degradation of carboxylic acid derivatives

Degradation through methanolysis in DMF:

One screw-capped vial was charged with a magnetic stir bar, substrates (0.05 mmol each), K_2CO_3 (1.5 equiv), internal standard (1,3,5-timethoxybenzene, 0.05 mmol), and a 1:4 mixture of MeOH:DMF (2.5 mL). The solution was stirred at 40 °C until full conversion of methyl benzoate is observed and no starting material is left. GC samples were taken at regular intervals of each component. Data were calculated based on the change in ratio between the internal standard and respective substrate and normalized to 100% at time zero.

Table 2.19. Percentage of substrate remaining over time



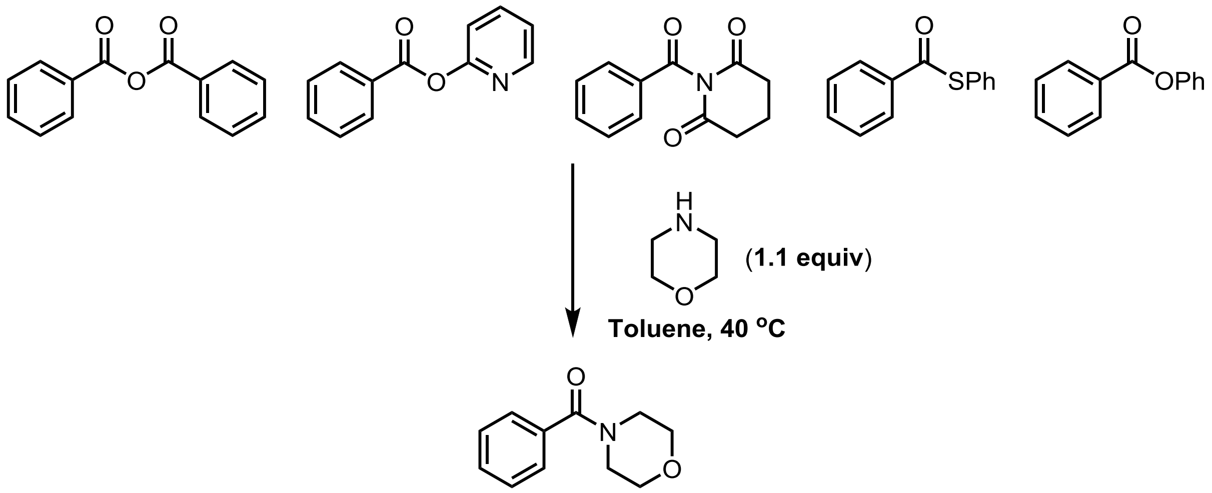
Time (hours)	Anhydride	Pyridyl ester	Twisted amide	Thioester	Phenyl ester
0	100%	100%	100%	100%	100%
0.17	0%	53%	84%	98%	97%
0.5	0%	9%	35%	67%	92%
1	0%	0%	20%	49%	83%
2	0%	0%	14%	34%	78%
4	0%	0%	0%	24%	77%
6	0%	0%	0%	19%	73%
8	0%	0%	0%	12%	67%
10	0%	0%	0%	10%	64%
24	0%	0%	0%	0%	35%
48	0%	0%	0%	0%	10%
96	0%	0%	0%	0%	0%

Degradation through amide bond formation in toluene:

Five screw-capped vials were charged with a magnetic stir bar, one substrate (0.05 mmol) internal standard (1,3,5-timethoxybenzene, 0.05 mmol) and 0.5 mL of toluene. Morpholine (1.1 equiv) was added via pipette to each and the solutions were stirred at 40 °C. GC samples taken at regular intervals to track rate of degradation of each component. Data were calculated based on the change in ratio between the internal standard and respective substrate and normalized to 100% at time zero, prior to addition of morpholine.

Five screw-capped vials were charged with a magnetic stir bar, one substrate (0.05 mmol) internal standard (1,3,5-timethoxybenzene, 0.05 mmol) and 0.5 mL of toluene. Morpholine (1.1 equiv) was added via pipette to each and the solutions were stirred at 40 °C. GC samples taken at regular intervals to track rate of degradation of each component. Data were calculated based on the change in ratio between the internal standard and respective substrate and normalized to 100% at time zero, prior to addition of morpholine.

Table 2.20. Percentage of substrate remaining over time



Time (hours)	Anhydride	Pyridyl ester	Twisted amide	Thioester	Phenyl ester
0	100%	100%	100%	100%	100%
0.17	0%	9%	90%	96%	99%
0.5	0%	0%	88%	93%	97%
1	0%	0%	76%	93%	95%
2	0%	0%	45%	92%	94%
4	0%	0%	18%	79%	94%
6	0%	0%	3%	---	---
24	0%	0%	0%	54%	91%
48	0%	0%	0%	29%	87%
96	0%	0%	0%	5%	69%

Computed catalytic cycle

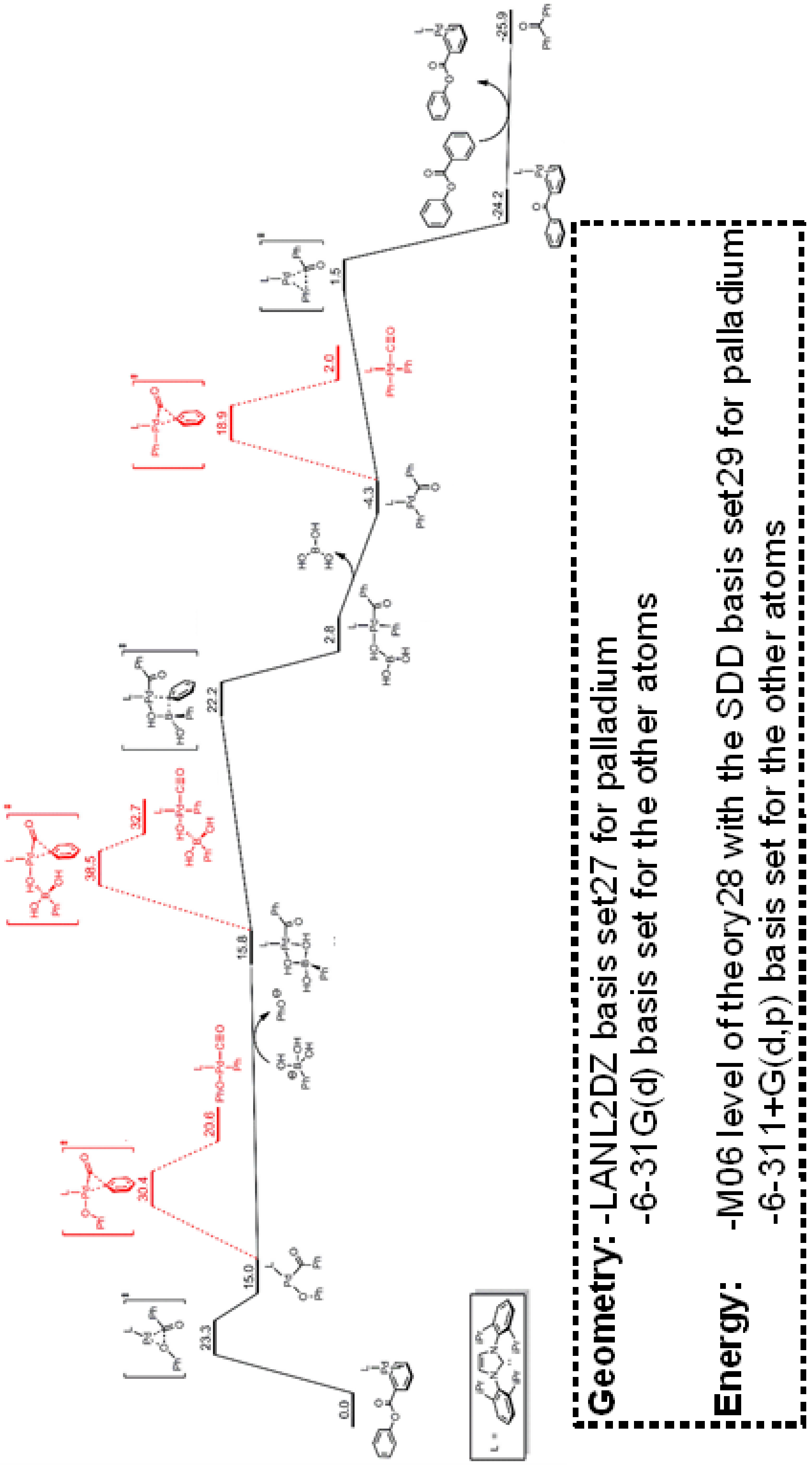


Figure 2.6. Gibbs free energy profile of the Pd-catalyzed Suzuki-Miyaura coupling reaction of phenyl benzoate with phenylboronic acid, including the possible decarbonylative pathways (labeled in red). Free energies are in kcal/mol.

2.3.2 Experimental section for section 2.2: cross-coupling approach to amide bond formation from phenyl esters

Materials

Aniline, 4-methoxyaniline, naphthylamine, 4-aminopyridine, 2-aminopyridine, 4-methylaniline, 3-aminophenol, 2-aminophenol, 2-amino-3-hydroxypyridine, 4-aminophenol, and 3-(trifluoromethyl) aniline were obtained from Sigma Aldrich. 3,4-difluoroaniline was obtained from Alfa Aesar. 4-nitroaniline was obtained from Inactive Eastman, Kodak. Ethyl 4-aminobenzoate was obtained from Fisher Scientific. 2-aminobiphenyl was obtained from Combi-Blocks. The following esters were prepared from acyl chlorides using a literature procedure:[65] phenyl 4-(dimethylamino) benzoate, phenyl 1-naphthoate, phenyl 2-methylbenzoate, methyl phenyl terephthalate, phenyl isonicotinate, phenyl 3-(trifluoromethyl)benzoate, 4-methoxyphenyl benzoate, 4-(trifluoromethyl)phenylbenzoate. The following esters were prepared from acyl chlorides according using a literature procedure:[87] phenyl 4-methylbenzoate, phenyl 4-methoxybenzoate, phenyl 4-fluorobenzoate, 1,1,1,3,3,3-hexafluoropropan-2-yl benzoate, perfluorophenyl benzoate, phenyl propionate. The following esters were prepared from carboxylic acids using a literature procedure:[88] phenyl nicotinate, phenyl thiazole-4-carboxylate, phenyl cyclohexanecarboxylate, phenyl furan-2-carboxylate, phenyl pivalate, and (*S*)-1-tert-butyl 2-phenyl pyrrolidine-1,2-dicarboxylate. For further information in the preparation of esters starting materials, see our previous work.[46]

Evaluation of non-catalytic amide bond formation (data for **Table 2.18**):

To determine which esters were sufficiently reactive to provide amide products in the absence of either a Pd catalyst or a weak base, a screening was carried out. Five esters, two bases, and three solvents were chosen for testing, totaling 30 reactions. In a multi-well screening plate, oven dried (8 x 40 mm) glass vials were each charged with a magnetic stir bar, base, and ester (0.05 mmol). Aniline (1.2 equiv) and fresh solvent (0.25 mL, 0.2 M) were then added. The vials were sealed with Teflon and silicon sheets and stirred vigorously (500 rpm) at 100 °C for 16 h. After cooling to room temperature, internal standard (1,3,5-timethoxybenzene, 0.0125 mmol in 0.25 mL THF)

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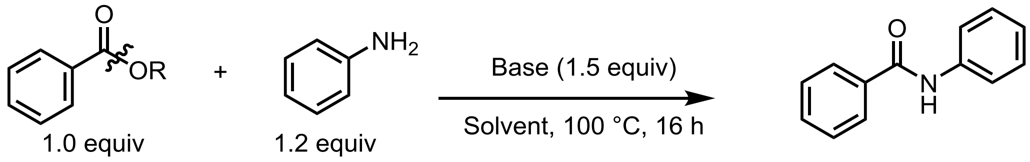
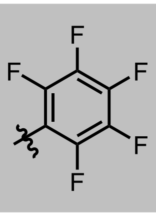
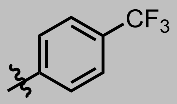
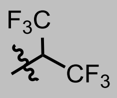
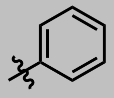
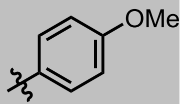
[87] Liu, Z.; Ma, Q.; Liu, Y.; Wang, Q. *Org. Lett*. **2014**, 16, 236.
[88] Kwon, E-M.; Kim, C-G.; Goh, A-R.; Park, J.; Jun, J. G. *Bull. Korean. Chem. Soc*. **2012**, 33, 1939.

was added. Reactions were diluted with ethyl acetate and filtered through plugs of silica gel (1 mL of EtOAc eluent). Yields were determined by GC using a 5 point calibration curve.

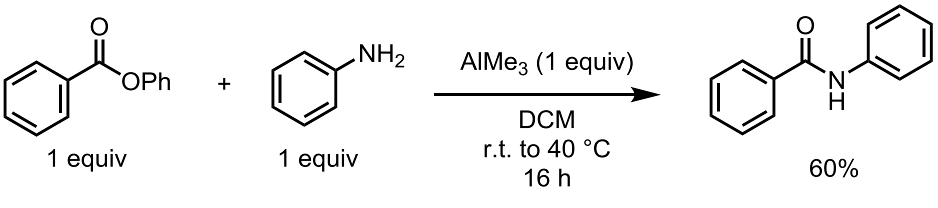
Table 2.21. Evaluation of esters of varying degree of activation in the absence of catalyst



R =					
K_2CO_3 in DMF	66%	32%	14%	2%	2%
K_2CO_3 in MeCN	36%	6%	4%	0%	2%
K_2CO_3 in DME	68%	8%	2%	8%	2%
NEt_3 in DMF	100%	0%	6%	0%	0%
NEt_3 in MeCN	92%	8%	8%	8%	2%
NEt_3 in DME	100%	44%	36%	2%	9%

<u>Amide bond formation using stoichiometric organometallic bases</u>

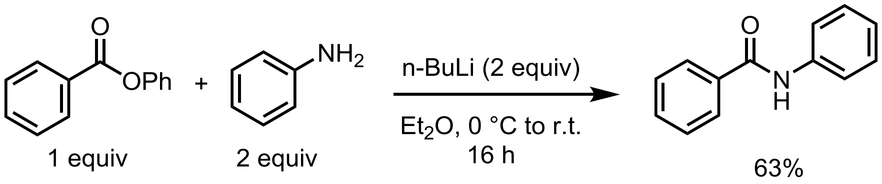
Procedure for Table 2.16, Entry 7.[51]



An oven-dried round-bottom flask was charged with a magnetic stir bar, 0.05 mL (0.1 mmol) of a 2.0 M solution of trimethylaluminum in toluene was slowly added at room temperature to a solution of 0.1 mmol of aniline in 0.25 mL of dry methylene chloride under nitrogen. The mixture was stirred at room temperature for 15 min and 0.1 mmol of phenylbenzoate was added.

The mixture was warmed at 25-40 °C under nitrogen for 16 h. After cooling to room temperature, internal standard (1,3,5-timethoxybenzene, 0.025 mmol in 0.5 mL THF) was added. The reaction was carefully quenched with dilute HCl and diluted with ethyl acetate, filtered through a plug of silica gel (10 mL of EtOAc eluent). Yield was determined by GC analysis.

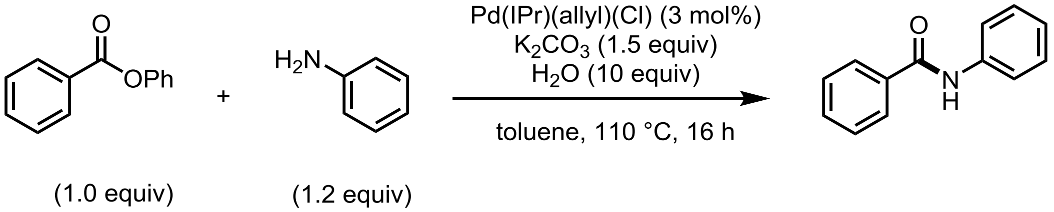
Procedure for Table 2.16, Entry 8.[52]



An oven-dried round-bottom flask was charged with a magnetic stir bar. 0.2 mmol of aniline was added to 0.2 mL of dry diethyl ether under nitrogen at 0 °C followed by addition of 0.08 mL (0.2 mmol) of n-BuLi (2.5 M in hexane). After stirring the reaction mixture for 15 min at 0 °C, 0.1 mmol of phenylbenzoate was added slowly over a period of about 10 min. Stirring at 0 °C for 2 h continued to attain room temperature and stirred for 16 h. Then internal standard (1,3,5-timethoxybenzene, 0.025 mmol in 0.5 mL THF) was added and quenched with dilute NH_4Cl. The reaction was diluted with ethyl acetate, filtered through a plug of silica gel (10 mL of EtOAc eluent). Yield was determined by GC analysis.

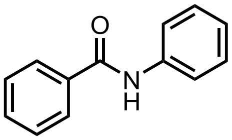
<u>Synthesis of amides</u>

General procedure for catalytic amide bond formation

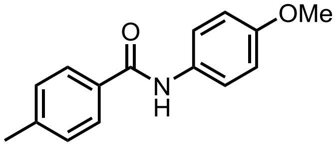


An oven dried screw-capped vial was charged with a magnetic stir bar, powdered K_2CO_3 (0.3 mmol, 1.5 equiv), Pd(IPr)(allyl)(Cl) (3 mol%), ester (0.2 mmol, 1.0 equiv), and amine (0.24

mmol, 1.2 equiv). The vial and contents were placed under vacuum and back-filled with Argon under a Schleck line three times. Dry toluene (1 mL, 0.2 M) obtained from a solvent purification system was then added under argon. Degassed water (10 equiv) was subsequently added via micropipette. The vial was sealed with a PTFE-lined screw cap and stirred vigorously (700 rpm) at 110 ^{o}C for 16 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and filtered through a plug of silica gel (10 mL of EtOAc eluent). The crude mixture was concentrated *in vacuo* and subjected to manual column chromatography.



Benzanilide (2.2.13a) was prepared according to the general procedure from aniline and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13a** as a white solid (36 mg, 91%). Characterization data matched those previously reported.[89] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.88 (d, *J* = 1.8 Hz, 3H), 7.65 (d, *J* = 7.9 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.68 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H); **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 166.1, 138.3, 135.3, 132.2, 129.4, 129.1, 127.4, 124.9, 120.6.



N-(4-Methoxyphenyl)-4-methylbenzamide (2.2.13b) was prepared according to the general procedure from 4-methoxyaniline and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13b** as a yellowish solid (46 mg, 95%). Characterization data matched those previously reported.[90] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.75-7.79 (m, 3H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 2.43 (s, 3H); **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 165.9, 156.9, 142.5, 132.5, 131.5, 129.7, 127.3, 122.4, 114.5, 55.8, 21.8.

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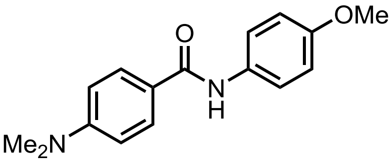
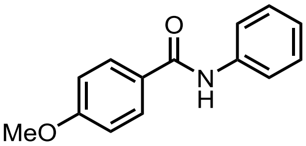
[89] Wang, Y.; Zhu, D.; Tang, L.; Wang, S.; Wang, Z. *Angew. Chem. Int. Ed*. **2011**, *50*, 8917.

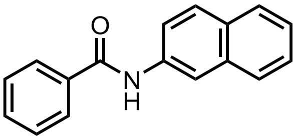
[90] Tinnis, F.; Verho, O.; Gustafson, K. P. J.; Tai, C.-W.; Backvall, J.-E. Adolfsson, H. *Chem. Eur. J.* **2014**, *20*, 5885.



4-(Dimethylamino)-N-(4-methoxyphenyl)benzamide (2.2.13c) was prepared according to the general procedure from 4-methoxyaniline and phenyl 4-(dimethylamino)benzoate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13c** as a white solid (35 mg, 65%). Characterization data matched those previously reported.[91] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76-7.80 (m, 2H), 7.71 (brs, 1H), 7.52-7.56 (m, 2H), 6.87-6.91 (m, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 3.04 (s, 6H); **^{13}C NMR (10 of 11 carbons observed)** ($CDCl_3$, 100 MHz) δ 165.8, 156.5, 152.7, 132.0, 128.9, 122.3, 114.5, 111.7, 55.8, 40.6.



4-Methoxy-N-phenylbenzamide (2.2.13d) was prepared according to the general procedure from aniline and phenyl 4-methoxybenzoate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13d** as a white solid (43 mg, 94%). Characterization data matched those previously reported.[92] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.79 (brs, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 8.1 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H).**^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.5, 162.8, 138.4, 129.4, 129.2, 127.5, 124.7, 120.5, 114.3, 55.8.



N-(Naphthalen-2-yl)benzamide (2.2.13e) was prepared according to the general procedure from 2-naphthylamine and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13e** as a brown

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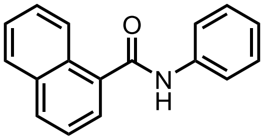
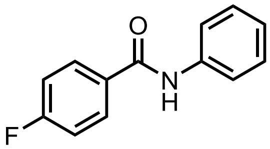
[91] Warner, P. L. U.S. Patent 3863007 A, January 28, **1975**.
[92] Luo, Q.-L.; Lv, L.; Li, Y.; Tan, J.-P.; Nan, W.; Hui, Q. *Eur. J. Org. Chem.* **2011**, *2011*, 6916.

solid (42 mg, 85%). Characterization data matched those previously reported.[93] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 8.35 (s, 1H), 8.07 (brs, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.80-7.84 (m, 3H), 7.41-7.62 (m, 6H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 166.2, 135.7, 135.3, 134.2, 132.2, 131.1, 129.2, 129.2, 128.1, 127.9, 127.4, 126.9, 125.5, 120.4, 117.4.



N-Phenyl-1-naphthamide (2.2.13f) was prepared according to the general procedure from aniline and phenyl 1-naphthoate. Purification was performed by column chromatography using a gradient of 5% → 10% EtOAc in hexane to afford **2.2.13f** as a white solid (41 mg, 83%). Characterization data matched those previously reported.[94] **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 10.58 (brs, 1H), 8.18-8.21 (m, 1H), 8.08 (d, *J* = 8.2, 1H), 8.00-8.04 (m, 1H), 7.83 (d, *J* = 7.7 Hz, 2H), 7.76 (dd, *J* = 7.0, 0.96 Hz, 1H), 7.57-7.63 (m, 3H), 7.38 (t, *J* = 8.24 Hz, 2H), 7.11-7.15 (m, 1H).**^{13}C NMR** (DMSO-d_6, 100 MHz) δ 167.3, 139.3, 134.8, 133.2, 130.1, 129.7, 128.7, 128.3, 127.0, 126.4, 125.4, 125.1, 125.1, 123.7, 119.8.



4-Fluoro-N-phenylbenzamide (2.2.13g) was prepared according to the general procedure from 4-nitro aniline and phenyl 4-fluorobenzoate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13g** as a white solid (42 mg, 97%). Characterization data matched those previously reported.[95] **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 10.23 (s, 1H), 8.02-8.06 (m, 2H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.33-7.38 (m, 3H), 7.11 (t, *J* = 7.3 Hz, 1H). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 164.4, 164.0 (d, $J_{C\text{-}F}$ = 249 Hz), 139.0, 131.37 (d, $J_{C\text{-}F}$ = 3 Hz), 130.3 (d, $J_{C\text{-}F}$ = 9 Hz), 128.6, 123.7, 120.4, 115.3 (d, $J_{C\text{-}F}$ = 22 Hz).

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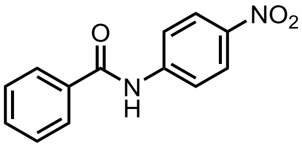
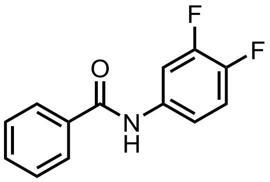
[93] Roy, S.; Sarma, M. J.; Kashyapa, B.; Phukan, P. *Chem. Commun.* **2016**, *52*, 1170.

[94] Seo, H.-A.; Cho, Y.-H.; Lee, Y.-S.; Cheon, C.-H. *J. Org. Chem.* **2015**, *80*, 11993.

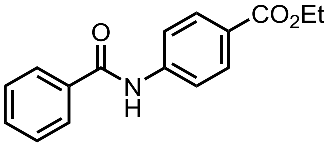
[95] (a) Deshidi, R.; Rizvi, M. A.; Shah, B. A. *RSC Adv.* **2015**, *5*, 90521; (b) Fan, W.; Yang, Y.; Lei, J.; Jiang, Q.; Zhou, W. *J. Org. Chem.* **2015**, *80*, 8782.



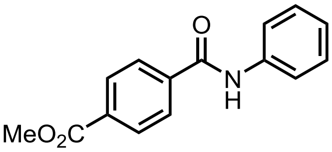
N-(4-Nitrophenyl)benzamide (2.2.13h) was prepared according to the general procedure from 4-nitro aniline and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 40% EtOAc in hexane to afford **2.2.13h** as a brown solid (27 mg, 55%). Characterization data matched those previously reported.[93] **H NMR** (DMSO-d_6, 400 MHz) δ 10.81 (brs, 1H), 8.25-8.29 (m, 2H), 8.06-8.10 (m, 2H), 7.96-8.00 (m, 2H), 7.62-7.66 (m, 1H), 7.54-7.59 (m, 2H). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 166.3, 145.5, 142.5, 134.2, 132.2, 128.5, 127.9, 124.8, 119.8.



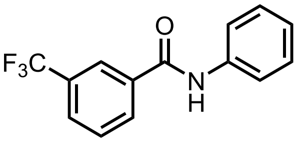
N-(3,4-Difluorophenyl)benzamide (2.2.13i) was prepared according to the general procedure from 3,4-difluoroaniline and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13i** as a light brown solid (41 mg, 87%). Characterization data matched those previously reported.[95] **H NMR** (DMSO-d_6, 400 MHz) δ 10.45 (s, 1H), 7.93-7.98 (m, 3H), 7.54-7.62 (m, 4H), 7.38-7.45 (m, 1H). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 165.7, 148.9 (dd, J_{C-F} = 241, 13 Hz), 145.5 (dd, J_{C-F} = 240, 13 Hz), 136.2 (dd, J_{C-F} = 9, 3 Hz), 134.5, 131.8, 128.5, 127.7, 117.3 (d, J_{C-F} = 17 Hz), 116.6 (dd, J_{C-F} = 6, 3 Hz), 109.2 (d, J_{C-F} = 21 Hz).



Ethyl 4-benzamidobenzoate (2.2.13j) was prepared according to the general procedure from Ethyl 4-aminobenzoate and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13j** as a white solid (51 mg, 94%). Characterization data matched those previously reported.[96] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.30 (brs, 1H), 8.01-8.04 (m, 2H), 7.85-7.87 (m, 2H), 7.74-7.77 (m, 2H), 7.52-7.56 (m, 1H), 7.43-7.47 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 166.3, 142.5, 134.9, 132.5, 131.1, 129.1, 127.4, 126.4, 119.6, 61.2, 14.7.



Methyl 4-(phenylcarbamoyl)benzoate (2.2.13k) was prepared according to the general procedure from aniline and methyl phenyl terephthalate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13k** as a white solid (47 mg, 91%). Characterization data matched those previously reported.[94] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.14 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.89 (brs, 1H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 8.3 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 3.96 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 165.2, 139.2, 137.9, 133.4, 130.4, 129.5, 127.4, 125.3, 120.6, 52.8.



N-Phenyl-3-(trifluoromethyl)benzamide (2.2.13l) was prepared according to the general procedure from aniline and phenyl 3-(trifluoromethyl)benzoate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13l** as a white solid (49 mg, 92%). Characterization data matched those previously reported.[97] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.13 (s, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.87 (brs, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.61-7.66 (m, 3H), 7.37-7.42 (m, 2H), 7.17-7.21 (m, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 164.9, 137.8, 136.1, 131.6 (q, $J_{C\text{-}F}$ = 32 Hz), 130.7, 129.9, 129.7, 129.4, 128.7 (q, $J_{C\text{-}F}$ = 4 Hz), 125.4, 124.4 (q, $J_{C\text{-}F}$ = 4 Hz), 124.0 (q, $J_{C\text{-}F}$ = 271 Hz), 120.9, 115.7.

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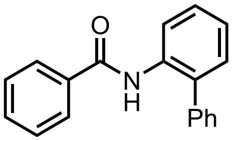
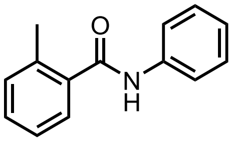
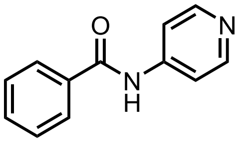
[96] Hong, G.; Wu, S.; Zhu, X.; Mao, D, Wang, L. *Tetrahedron* **2016**, *72*, 436.
[97] Sharma, R.; Vishwakarma, R. A.; Bharate, S. B. *Adv. Synth. Catal*. **2016**, *358*, 3027.



N-([1,1'-Biphenyl]-2-yl)benzamide (2.2.13m) was prepared according to the general procedure from 2-Aminobiphenyl and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13m** as a white solid (35 mg, 64%). Characterization data matched those previously reported.[98] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ = 8.55 (d, *J* = 8.0 Hz, 1H), 8.01 (brs, 1H), 7.63–7.60 (m, 2H), 7.53–7.51 (m, 2H), 7.50–7.44 (m, 5H), 7.42–7.38 (m, 2H), 7.33–7.31 (m, 1H), 7.26–7.21 (m, 1H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 165.4, 138.4, 135.2, 135.1, 132.7, 132.0, 130.3, 129.8, 129.7, 129.5, 129.1, 128.9, 128.5, 127.1, 124.7, 121.5, 115.7.



2-Methyl-N-phenylbenzamide (**2.2.13n)** was prepared according to the general procedure from aniline and phenyl 2-methylbenzoate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13n** as a white solid (40 mg, 94%). Characterization data matched those previously reported.[94] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.68 (brs, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 3H), 7.21-7.27 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 168.4, 138.3, 136.7, 136.7, 131.5, 130.5, 129.4, 126.9, 126.2, 124.8, 120.2, 20.1.



N-(Pyridin-4-yl)benzamide (2.2.13o) was prepared according to the general procedure from 4-aminopyridine and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13o** as a white solid (34 mg, 85%).

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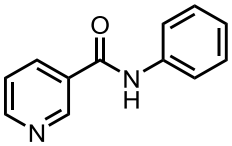
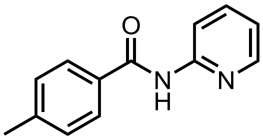
[98] Li, D.; Xu, N.; Zhanga, Y.; Wang, L. *Chem. Commun*. **2014**, *50*, 14862.

Characterization data matched those previously reported.[99] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 8.55 (d, *J* = 6.2 Hz, 2H), 8.15 (brs, 1H), 7.87-7.89 (m, 2H), 7.57-7.63 (m, 3H), 7.46-7.50 (t, *J* = 7.24 Hz, m, 2H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 166.5, 151.2, 145.4, 134.4, 132.9, 129.3, 127.5, 114.2.



N-Phenylnicotinamide (2.2.13p) was prepared according to the general procedure from aniline and phenyl nicotinate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13p** as a white solid (35 mg, 88%). Characterization data matched those previously reported.[100] **^{1}H NMR** (DMSO-*d$_6$*, 400 MHz) δ 10.51 (brs, 1H), 8.80 (dd, *J* = 1.6, 4.4 Hz, 2H), 7.86 (dd, *J* = 1.6, 4.4 Hz, 2H), 7.77 (d, *J* = 7.6 Hz, 2H), 7.35-7.40 (m, 2H), 7.12-7.16 (m, 1H). **^{13}C NMR** (DMSO-*d$_6$*, 100 MHz) δ 163.9, 150.2, 142.0, 138.6, 128.7, 124.2, 121.6, 120.5.



4-Methyl-N-(pyridin-2-yl)benzamide (2.2.13q) was prepared according to the general procedure from 2-aminopyridine and phenyl 4-methylbenzoate. Purification was performed by column chromatography using a gradient of 5% → 40% EtOAc in hexane to afford **2.2.13q** as a white solid (34 mg, 79%). Characterization data matched those previously reported.[99] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 8.79 (brs, 1H), 8.40 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 4.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.73-7.77 (m, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.04-7.07 (m, 1H), 2.42 (s, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 166.0, 152.0, 148.2, 143.2, 138.7, 131.8, 129.8, 127.6, 120.1, 114.5, 21.8.

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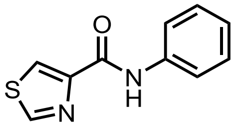
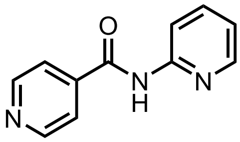
[99] Devi, E. S.; Alanthadka, A.; Tamilselvi, A.; Nagarajan, S.; Sridharana, V.; Maheswari, C. U. *Org. Biomol. Chem.* **2016**, *14*, 8228.

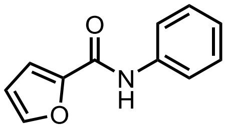
[100] Zhu, Y.-P.; Sergeyev, S.; Franck, P.; Orru, R. V. A.; Maes, B. U. W. *Org. Lett.* **2016**, *18*, 4602.



N-Phenylthiazole-4-carboxamide (**2.2.13r)** was prepared according to the general procedure from aniline and phenyl thiazole-4-carboxylate. Purification was performed by column chromatography using a gradient of 5% → 20% EtOAc in hexane to afford **2.2.13r** as a white solid (29 mg, 71%). Characterization data matched those previously reported.[101] **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 10.31 (brs, 1H), 9.26 (d, J = 2.0 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H), 7.85 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 8.3 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H).**^{13}C NMR** (DMSO- d_6, 100 MHz) δ 159.1, 155.0, 150.7, 138.5, 128.6, 125.5, 123.8, 120.4.



N-(Pyridin-2-yl)isonicotinamide (2.2.13s) was prepared according to the general procedure from 2-Aminopyridine and phenyl isonicotinate. Purification was performed by column chromatography using a gradient of 5% → 70% EtOAc in hexane to afford **2.2.13s** as a white solid (32 mg, 81%). Characterization data matched those previously reported.[102] **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 11.11 (brs, 1H), 8.76 (dd, J = 1.6, 4.4 Hz, 2H), 8.40-8.42 (m, 1H), 8.17-8.20 (m, 1H), 7.91 (dd, J = 1.6, 4.4 Hz, 2H), 7.85-7.90 (m, 1H), 7.19-7.22 (m, 1H). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 164.6, 151.7, 150.2, 148.1, 141.2, 138.3, 121.8, 120.3, 114.9.



N-Phenyl furan-2-carboxamide (2.2.13t) was prepared according to the general procedure from aniline and phenyl furan-2-carboxylate. Purification was performed by column chromatography using a gradient of 5% → 20% EtOAc in hexane to afford **2.2.13t** as a white solid (26 mg, 68%). Characterization data matched those previously reported.[95] **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 10.17 (brs, 1H), 7.92-7.93 (m, 1H), 7.75 (dd, J = 1.1, 8.5 Hz, 2H), 7.31-7.35 (m, 3H), 7.07-7.11

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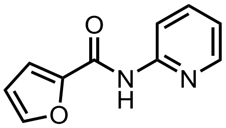
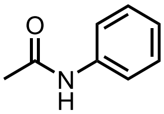
[101] Lebedeva, I. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1961**, *31*, 2618.
[102] Aakerö, C. B.; Panikkattu, S.V.; DeHaven, B.; Desper, J. *Cryst. Growth Des*. **2012**, *12*, 2579.

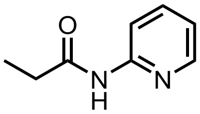
(m, 1H), 6.70 (dd, *J* = 1.7, 3.5 Hz, 1H). ^{13}**C NMR** (DMSO-d_6, 100 MHz) δ 156.2, 147.5, 145.7, 138.5, 128.6, 123.7, 120.4, 114.7, 112.1.



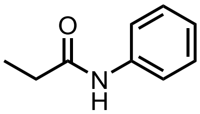
N-(Pyridin-2-yl)furan-2-carboxamide (2.2.13u) was prepared according to the general procedure from 2-aminopyridine and phenyl furan-2-carboxylate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13u** as a white solid (26 mg, 70%). Characterization data matched those previously reported.[99] ^{1}**H NMR** (DMSO-d_6, 400 MHz) δ 10.53 (brs, 1H), 8.37 (d, *J* = 3.8 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.95 (s, 1H), 7.81-7.85 (m, 1H), 7.61 (d, *J* = 3.3 Hz, 1H), 7.13-7.17 (m, 1H), 6.70 (dd, *J* = 1.6, 3.4 Hz, 1H). ^{13}**C NMR** (DMSO-d_6, 100 MHz) δ 156.5, 151.6, 148.0, 146.7, 146.5, 138.2, 119.8, 115.5, 114.5, 112.1.



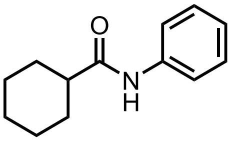
N-Phenylacetamide (2.2.13v) was prepared according to the general procedure from aniline and phenyl acetate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13v** as a white solid (25 mg, 92%). Characterization data matched those previously reported.[95] ^{1}**H NMR** (CDCl$_3$, 400 MHz) δ 7.65 (brs, 1H), 7.51 (d, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 2.16 (s, 3H). ^{13}**C NMR** (CDCl$_3$, 100 MHz) δ 168.9, 138.3, 129.3, 124.6, 120.3, 24.8.



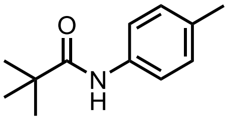
N-(Pyridin-2-yl)propionamide (2.2.13w) was prepared according to the general procedure from 2-aminopyridine and phenyl propionate. Purification was performed by column chromatography using a gradient of 5% → 40% EtOAc in hexane to afford **2.2.13w** as a white solid (26 mg, 85%). Characterization data matched those previously reported.[103] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 8.51 (brs, 1H), 8.22-8.27 (m, 2H), 7.68–7.73 (m, 1H), 7.01-7.05 (m, 1H), 2.43 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 172.9, 152.0, 147.9, 138.8, 119.9, 114.5, 31.0, 9.7.



N-Phenylpropionamide (2.2.13x) was prepared according to the general procedure from aniline and phenyl propionate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13x** as a white solid (28 mg, 94%). Characterization data matched those previously reported.[96] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.52 (d, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 3H), 7.10 (t, *J* = 7.3 Hz, 1H), 2.39 (q, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 172.5, 138.3, 129.3, 124.5, 120.2, 31.0, 10.0.



N-Phenylcyclohexanecarboxamide (2.2.13y) was prepared according to the general procedure from aniline and phenyl cyclohexanecarboxylate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13y** as a white solid (38 mg, 93%). Characterization data matched those previously reported.[96] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 7.54 (d, *J* = 7.9 Hz, 2H), 7.35 (brs, 1H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 2.24-2.27 (m, 1H), 1.94-1.97 (brd, 2H), 1.83 (brd, 2H), 1.71 (brs, 1H), 1.50-1.59 (m, 2H), 1.20-1.35 (m, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ 174.8, 138.4, 129.3, 124.4, 120.1, 46.9, 30.0, 26.0.



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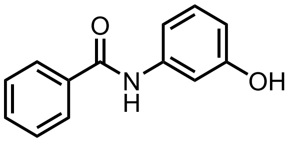
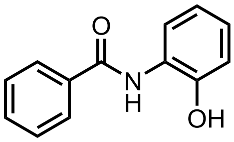
[103] Liu, J.; Xie, Y.; Zeng, W.; Lin, D.; Deng, Y.; Lu, X. *J. Org. Chem*. **2015**, *80*, 4618.

N-(*p*-Tolyl)pivalamide (2.2.13z) was prepared according to the general procedure from 4-methylaniline and p-tolyl pivalate. Purification was performed by column chromatography using a gradient of 5% → 30% EtOAc in hexane to afford **2.2.13z** as a colorless solid (28 mg, 73%). Characterization data matched those previously reported.[104] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39-7.42 (m, 2H), 7.23 (brs, 1H), 7.12 (d, *J* = 2.9 Hz, 2H), 2.31 (s, 3H), 1.31 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 176.8, 135.8, 134.1, 129.8, 120.4, 39.9, 28.0, 21.2.



N-(3-Hydroxyphenyl)benzamide (2.2.13aa) was prepared according to the general procedure from 3-aminophenol and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13aa** as a white solid (37 mg, 86%). Characterization data matched those previously reported.[105] **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 10.11 (s, 1H), 9.40 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.50-7.60 (m, 3H), 7.36 (s, 1H), 7.10-7.17 (m, 2H), 6.50 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ 165.5, 157.5, 140.2, 135.1, 131.4, 129.2, 128.3, 127.6, 111.1, 110.8, 107.5.



N-(2-Hydroxyphenyl)benzamide (2.2.13ab) was prepared according to the general procedure from 2-aminophenol and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13ab** as a pale red solid (40 mg, 93%). Characterization data matched those previously reported.[106] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.64 (s, 1H), 8.24 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.28 (s, *J* = 7.1 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.1 Hz,

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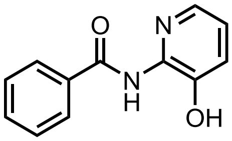
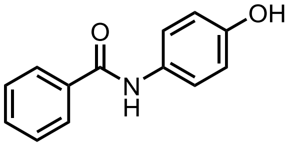
[104] Zhang, X.: Yu, X.; Feng, X.; Yamamoto, Y.; Almansour, A. I.; Arumugam, N.; Kumar, R. S.; Bao, M. *Chem. Asian J.* **2016**, 3241.
[105] Horikawa, R.; Fujimoto, C.; Yazaki, R.; Ohshima, T. *Chem. Eur. J.* **2016**, *22*, 12278.
[106] Hernandez-Olmos, V.; Abdelrahman, A.; El-Tayeb, A.; Freudendahl, D.; Weinhausen, S.; Müller, C. E. *J. Med. Chem*. **2012**, *55*, 9576.

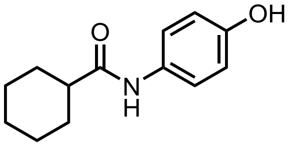
1H), 6.92 (t, *J* = 7.4 Hz, 1H).^{13}**C NMR** (CDCl$_3$, 100 MHz) δ 167.5, 149.1, 133.6, 132.9, 129.3, 127.7, 127.6, 126.0, 122.7, 121.0, 120.2.



N-(3-Hydroxypyridin-2-yl)benzamide (2.2.13ac) was prepared according to the general procedure from 2-amino-3-hydroxypyridine and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13ac** as a light yellow solid (41 mg, 95%). Characterization data matched those previously reported.[107] ^{1}**H NMR** (CDCl$_3$, 400 MHz) δ 10.50 (brs, 1H), 9.34 (brs, 1H), 7.98-8.00 (m, 2H), 7.82 (d, *J* = 3.8 Hz, 1H), 7.60-7.64 (m, 1H), 7.49-7.54 (m, 2H), 7.40 (dd, *J* = 1.4, 8.1 Hz, 1H), 7.12 (dd, *J* = 4.6, 8.6 Hz, 1H). ^{13}**C NMR** (CDCl$_3$, 100 MHz) δ 168.2, 145.2, 140.2, 139.2, 133.4, 132.6, 129.3, 128.6, 128.1, 123.2.



N-(4-Hydroxyphenyl)benzamide (2.2.13ad) was prepared according to the general procedure from 4-aminophenol and phenyl benzoate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13ad** as a pale yellow solid (26 mg, 61%). Characterization data matched those previously reported.[105] ^{1}**H NMR** (DMSO-*d*$_6$, 400 MHz) δ 10.01 (s, 1H), 9.24 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.48-7.58 (m, 5H), 6.73-6.75 (m, 2H). ^{13}**C NMR** (DMSO-*d*$_6$, 100 MHz) δ 164.9, 153.7, 135.2, 131.2, 130.7, 128.3, 127.5, 122.2, 114.9.



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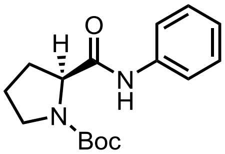
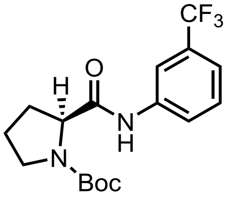
[107] Mobinikhaledi, A.; Foroughifar, N.; Fallah, M. *Phosphorus, Sulfur, and Silicon,* **2006**, *181*, 717.

N-(4-Hydroxyphenyl)cyclohexanecarboxamide (2.2.13ae) was prepared according to the general procedure from 4-aminophenol and phenyl cyclohexanecarboxylate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.13ae** as a light yellow solid (36 mg, 81%). Characterization data matched those previously reported.[108] **^{1}H NMR** (DMSO-d_6, 400 MHz) δ 9.50 (s, 1H), 9.10 (s, 1H), 7.33-7.37 (m, 2H), 6.63-6.67 (m, 2H), 2.21-2.28 (m, 1H), 1.73-1.75 (m, 4H), 1.64 (br, 1H), 1.33–1.43 (m, 2H), 1.14-1.26 (m, 3H).**^{13}C NMR** (DMSO-d_6, 100 MHz) δ 173.5, 153.0, 131.2, 120.8, 114.9, 44.7, 29.2, 25.4, 25.3.



(S)-Tert-butyl 2-(phenylcarbamoyl)pyrrolidine-1-carboxylate (2.2.15a) was prepared according to the general procedure from aniline and (S)-1-tert-butyl 2-phenyl pyrrolidine-1,2-dicarboxylate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.15a** as a light white solid (48 mg, 82%). Characterization data matched those previously reported.[109] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 9.49 (brs, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.09 (s, 1H), 4.48 (s, 1H), 3.44 (s, 2H), 2.57 (s, 1H), 2.01-1.89 (m, 3H), 1.50 (s, 9H). **^{13}C NMR** (CDCl$_3$, 150 MHz) δ 169.7, 156.7, 138.4, 128.9, 123.8, 119.6, 80.9, 60.5, 47.2, 28.4, 26.9, 24.6.



(R)-Tert-butyl-2-((3-(trifluoromethyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate (2.2.15b) was prepared according to the general procedure from 3-(trifluoromethyl)aniline and

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[108] Cho, J.; Rho, H. S.; Joo, Y. H.; Ahn, S. M.; Won, D. H.; Shin, S. S.; Park, Y-H.; Suh, K-D.; Park, S. N.; *Bull. Korean Chem. Soc*. **2012**, *33*, 1333.

[109] Zhou, G-C.; Weng, Z.; Shao, X.; Liu, F.; Nie, X.; Liu, J.; Wang, D.; Wang, C.; Guo, K. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 6549.

(S)-1-tert-butyl 2-phenyl pyrrolidine-1,2-dicarboxylate. Purification was performed by column chromatography using a gradient of 5% → 50% EtOAc in hexane to afford **2.2.15b** as a light yellow solid (47 mg, 66%). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.85 (brs, 1H), 7.89 (s, 1H), 7.58 (s, 1H), 7.39-7.29 (m, 2H), 4.51 (s, 1H), 3.52-3.34 (m, 2H), 2.49 (s, 1H), 2.02 (s, 1H), 1.97-1.93 (m, 2H), 1.51 (s, 9H). **^{13}C NMR** ($CDCl_3$, 150 MHz) *Peak broadening due to rotamers and C–F coupling prevented full characterization. A list of observable peaks is given.* δ 170.3, 156.6, 139.0, 131.3, 129.5, 129.3, 123.9 (q, $J_{C\text{-}F}$ = 271 Hz), 122.4, 120.2, 116.2, 81.1, 60.5, 47.3, 29.7, 28.4, 27.3, 24.6. $[\alpha]_D^{24}$ = -143.3 (c= 0.00006, CH_2Cl_2). IR (neat): 3287, 3105, 2973, 2930, 2881, 1701, 1669, 1599, 1411, 1337, 1130, 1114, 1068, 808, 701, 659 cm^{-1}. Accurate mass (EI): m/z calculated for $C_{17}H_{21}N_2O_3F_3$: 358.1499, found 358.1239 (spectral accuracy = 97.87%). m. p.: 186-188 ^{o}C.

Chapter 3

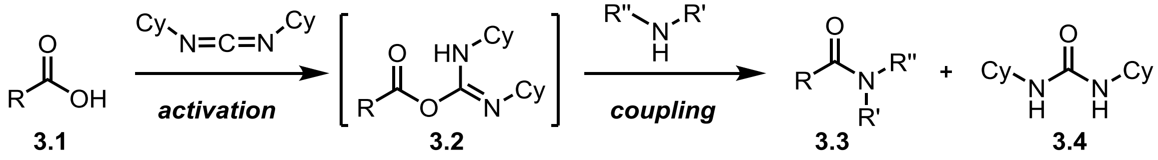
3 Nickel-catalyzed amide bond formation from methyl esters

3.1 Introduction

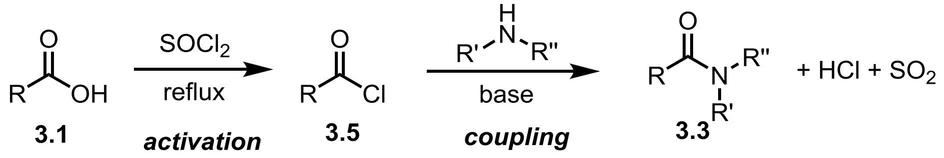
Amide bond formation is the most commonly performed chemical reaction according to a recent data analysis of the chemical patent literature.[1] The vast majority of traditional methods enabling this transformation rely on stoichiometric activation of carboxylic acids.[1] For example, the transformation of an acid to an O-acylisourea **3.2** via carbodiimide-mediated coupling (**Scheme 3.1**, route A)[2] or to an acid chloride (**Scheme 3.1,** route B) both provide sufficient activation to allow direct attack of an amine nucleophile.[3] While frequently used, these methods are not atom economic and tend to generate significant stoichiometric waste.

Scheme 3.1. Traditional methods to access amide bond from carboxylic acids

Route A: Amide bond formation via carbodiimide-mediated coupling



Route B: Amide bond formation after activation to acyl chloride via the Schotten-Baumann reaction



In the past 20 years, much progress has been made by studying new pathways to activate carboxylic acids for amidation.[4] In contrast, simple esters are rarely used to directly make amide bonds using amines. Traditional methods rely on the deprotonation of the amine with aggressive

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[1] Brown, D. G.; Boström, J. *J. Med. Chem*. **2016**, *59*, 4443.

[2] Sheehan, J. C. Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067.

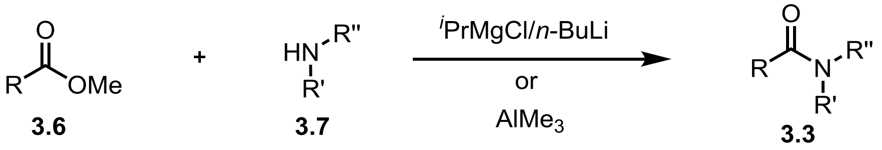
[3] (a) Schotten, C. *Ber. Dtsch. Chem. Ges*. **1884**, *17*, 2544; (b) Baumann, E. *Ber. Dtsch. Chem. Ges*. **1886**, *19*, 3218.

[4] (a) Pattabiraman, V. R., Bode, J. W. *Nature* **2011**, *480*, 471; (b) Lundberg, H., Tinnis, F., Selander, N. Adolfsson, H. *Chem. Soc. Rev*. **2014**, *43*, 2714; (c) de Figueiredo, R. M.; Suppo, J.-S.; Campagne, J.-M.. *Chem. Rev*. **2016**, *116*, 12029.

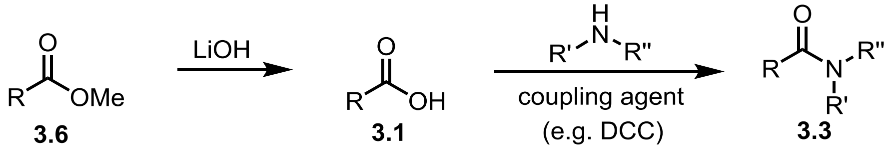
organometallic reagents,[5] such as $AlMe_3$, or with harsh stoichiometric bases[6] (**Scheme 3.2**, path A). This route suffers from limited functional group tolerance which might narrow synthetic applications in the context of complex scaffolds. Another common route to access the amide bond from unactivated esters is to hydrolyze[7] them first to the corresponding carboxylic acid (**Scheme 3.2**, path B). Then, an activation and coupling with the corresponding amine is required (as **Scheme 3.1**).

Scheme 3.2. Traditional route to access amides from unactivated methyl esters

Pathway A: Use of a strong base/aggressive organometallic reagents



Pathway B: Hydrolysis/ activation and coupling



Given the ubiquity of amide bond in important organic scaffolds, attempts to access this functionality were successfully achieved from various starting materials. Among these, oxidative amidation of alcohols[8] and aldehydes[9] with amines, NHC-catalyzed amide bond formation from α'-hydroxyenones,[10] aminocarbonylation from alkynes[11] and alkenes,[12] and using nitriles[13] as

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[5] (a) Basha, A.; Lipton, M.; Weinreb, M. S. M. *Tetrahedron Lett*. **1977**, *18*, 4171; (b) Muñoz, J. de M.; Alcázar, J.; de la Hoz, A., Díaz-Ortiz, Á.; de Diego, S.-A. A. *Green Chem*. **2012**, *14*, 1335; (c) Wang, W. B.; Roskamp, E. J. *J. Org. Chem*. **1992**, *57*, 6101.

[6] (a)Vrijdag, J. L.; Delgado, F.; Alonso, N.; De Borggraeve, W. M.; Pérez-Macias, N.; Alcázar, J. *Chem. Commun.* **2014**, *50*, 15094; (b) Kim, B. R.; Lee, H.-G.; Kang, S.-B.; Sung, G. H.; Kim, J.-J.; Park, J. K.; Lee, S.-G.; Yoon, Y.-J. *Synthesis* **2012**, *44*, 42.

[7] Dayal, B.; Salen, G.; Toom, B; Tint, G. S; Sheffer, S; Padia, J. *Steroids* **1990**, *55*, 233.

[8] (a) Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Tuan, D. T.; Johannes, C. W.; Chen, A. *Tetrahedron Lett*. **2013**, *54*, 4922; (b) Bantreil, X.; Kanfar, N.; Gehin, N.; Golliard, E.; Ohlmann, P.; Martinez, J.; Lamaty, F. *Tetrahedron* **2014**, *70*, 5093.

[9] (a) Tamaru, Y.; Yamada, Y.; Yoshida, Z.-i. *Synthesis* **1983**, *1983*, 474; (b) Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 13064; (c) Ding, Y.; Zhang, X.; Zhang, D.; Chen, Y.; Wu, Z.; Wang, P.; Xue, W.; Song, B.; Yang, S. *Tetrahedron Lett*. **2015**, *56*, 831.

[10] Chiang, P.-C.; Kim, Y.; Bode, J. W. *Chem. Commun*. **2009**, 4566.

[11] Chinchilla, R.; Na´jera, C. *Chem. Rev*. **2014**, *114*, 1783.

carboxylic acid surrogates have all been employed. Despite the presence of multiple routes with several alternative disconnections to access amides in the literature, carboxylic acid/ester activation has thus far remained the most direct/simple pathway to generate this functionality due to the high abundancy of these simple reactants.

While some milder catalytic reactions have recently been developed, issues with epimerizable stereocenters, acid or base sensitive functional groups, the need for excess reactants, or difficulties using relatively weak nucleophiles such as anilines prevent general utility.[14] These limitations are unfortunate, because carboxylic acids are frequently protected as the corresponding methyl or ethyl ester while transformations are carried out elsewhere on a molecule prior to deprotection and subsequent coupling. Moreover, to synthesize the antidepressant agent **3.11** (**Scheme 3.3**), medicinal chemists hydrolyzed initially the methyl ester functionality to the corresponding carboxylic acid.[15] Then, they applied a CDI coupling using pyrrolidine as nucleophile.

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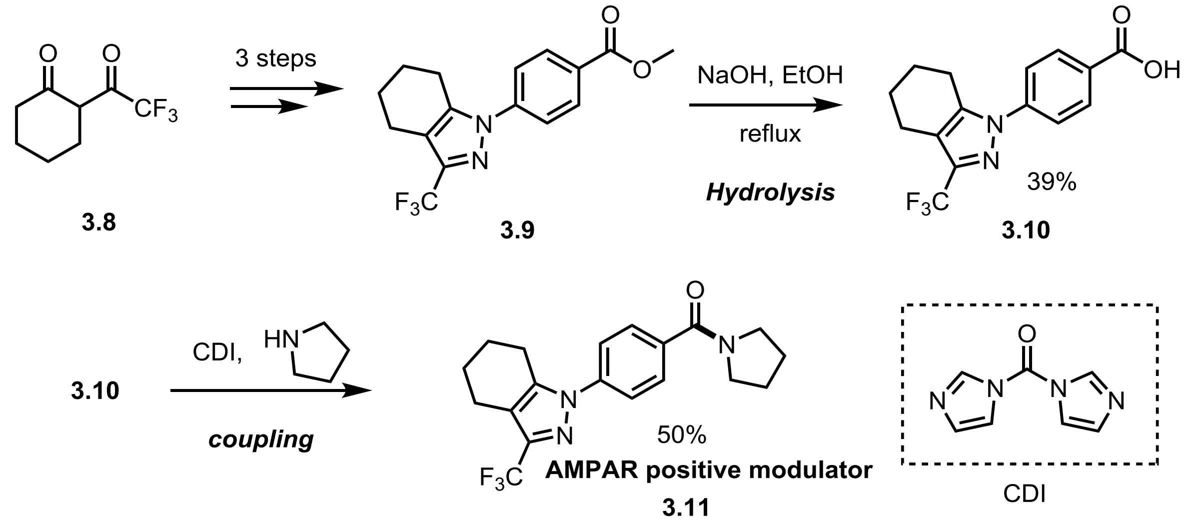
[12] Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev*. **2011**, *40*, 3405.

[13] (a) Gue´rinot, A.; Reymond, S.; Cossy, J. *Eur. J. Org. Chem*. **2012**, 19; (b) Jefferies, L. R.; Cook, S. P. *Tetrahedron* **2014**, *70*, 4204; (c) Kukushkin, V.; Pombeiro, A. *Inorg. Chim. Acta* **2005**, *358*, 1; (d) Ramo´n, R. S.; Marion, N.; Nolan, S. P. *Chem. - Eur. J*. **2009**, *15*, 8695.

[14] (a) Tsuji, J.; Yamamoto, H. *J. Am. Chem. Soc*. **2016**, *138*, 14218. (b) Caldwell, N.; Jamieson, C.; Simpson, I.; Watson, A. J. B. *Chem. Commun*. **2015**, *51*, 9495. (c) Morimoto, H.; Fujiwawa, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. *Org. Lett*. **2014**, *16*, 2018; (d) Gnanaprakasam, B., Milstein, D. *J. Am. Chem. Soc*. **2011**, *133*, 1682; (e) Movassaghi, M.; Schmidt, M. A. *Org. Lett*. **2005**, *7*, 2453. (f) Sabot, C.; Kumar, K. A.; Meunier, S.; Mioskowski, C. A *Tetrahedron Lett*. **2007**, *48*, 3863. (g) Han, C., Lee, J. P., Lobkovsky, E., Porco Jr., J. A. *J. Am. Chem. Soc*. **2005**, *127*, 10039.

[15] Ward, S. E.; Harries, M.; Aldegheri, L.; Austin, N. E.; Ballantine, S.; Ballini, E.; Bradley, D. M.; Bax, B. D.; Clarke, B. P.; Harris, A. J.; Harrison, S. A.; Melarange, R. A.; Mookherjee, C.; Mosley, J.; Dal Negro, G.; Oliosi, B.; Smith, K. J.; Thewlis, K. M.; Woollard, P. M.; Yusaf, S. P. *J. Med. Chem*. **2011**, *54*, 78.

Scheme 3.3. Literature route to couple methyl esters



The above example represents one among others[16] where synthetic chemists need to use one additional step (hydrolysis) before applying mild but wasteful coupling, affording amide bonds. Thus, developing efficient methodologies that allow direct amidation from abundant esters has the potential to resolve these synthetic issues.

Due to the importance of amide bonds and all the issues associated with forming this functional group, a roundtable event held by the ACS Green Chemistry Institute recognized the development of more atom economical methods for amide bond formation as the top priority for researchers developing new reactions.[17]

3.2 Research goals

Over the past 20 years in organic synthesis, one very important trend has seen researchers attempt to activate increasingly strong bonds. Moreover, the use of transition metal catalysts to activate strong C–O bonds by oxidative addition has been identified as a viable pathway for ester derivatization, which is unique from traditional acid/base strategies.[18]

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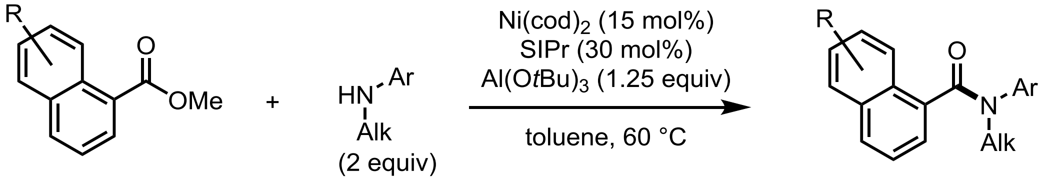
[16] Brullo, C.; Ricciarelli, R.; Prickaerts, J.; Arancio, O.; Massa, M.; Rotolo, C.; Romussi, A.; Rebosio, C.; Marengo, B.; Pronzato, M.A.; van Hagen, B.T.J.; van Goethem, N.P.; D'Ursi, P.; Orro, A.; Milanesi, L.; Guariento, S.; Cichero, E.; Fossa, P.; Fedele, E.; Bruno, O. *Eur. J. Med. Chem.* **2016**, *124*, 82.

[17] Constable, D. J. C.; Dunn, P. J.; Hayler, J. D; Humphrey, G. R.; Leazer Jr., J. L.; Lunderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem* **2007**, *9*, 411.

[18] Takise, R., Muto, K., Yamaguchi J. *Chem. Soc. Rev.* **2017**, 46, 5864.

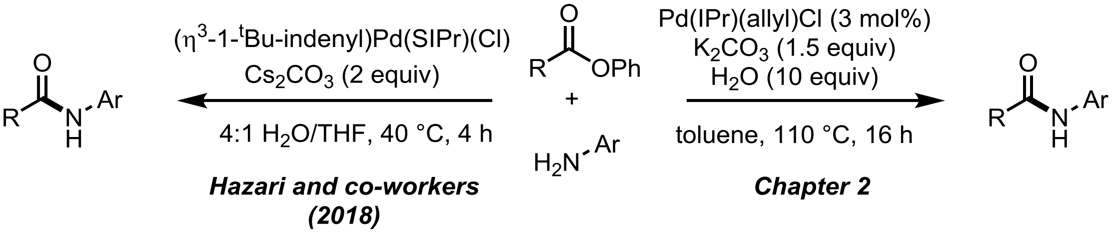
In 2016, the use of methyl esters to generate amides in a catalytic manner was explored by Garg and co-workers (**Scheme 3.4**).[19] However, the necessity of using stoichiometric Al(O*t*Bu)$_3$ and the limited substrate scope minimize wide applicability (see **Chapter 1**, **section 1.3.2**).

Scheme 3.4. Ni-catalyzed amidation of methyl naphthoates via C(acyl)–O bond cleavage



Most recently, our group[20] and the Hazari lab[21] disclosed novel reactivity, activating phenyl esters to access important amide bonds (**Scheme 3.5**). While conceptually interesting, these phenol-derived substrates are considerably activated relative to abundant methyl and ethyl esters and do not represent a major practical advance over traditional methods proceeding by stoichiometric ester activation.

Scheme 3.5. Catalytic methods to access amide bond from phenyl esters



The development of coupling reactions using unactivated and abundant methyl/ethyl esters is needed in order to make this strategy practical. Herein we sought to determine if an efficient catalytic method that overcomes previous limitations could be achieved (**Scheme 3.6**).

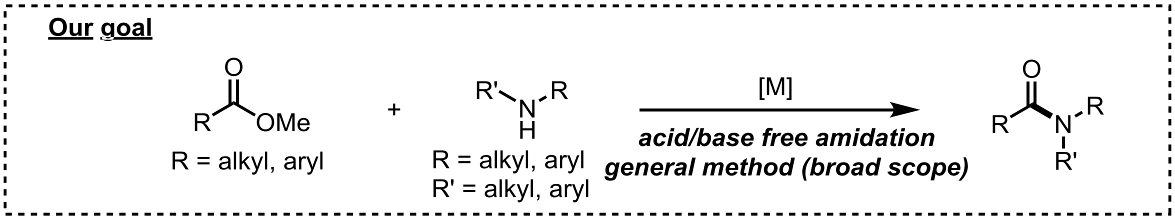
---

[19] Hie, L.; Fine Nathel, N. F.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Garg, N. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 2810.

[20] Ben Halima, T.; Vandavasi, J. K.; Shkoor, M.; Newman, S. G. *ACS Catal.* **2017**, *7*, 2176.

[21] Dardir, A. H.; Melvin, P. R.; Davis, R. M.; Hazari, N.; Mohadjer Beromi, M. *J. Org. Chem.* **2018** , *83*, 469.

Scheme 3.6. Research goal: general method enabling amide bond formation from abundant methyl esters



3.3 Results and discussion[22]

3.3.1 Reaction discovery

Given the recent abundance of catalytic reactions that proceed via cleavage of the C–O bond of esters developed by the Newman lab and others,[18] it was proposed that this strategy might be applicable to the direct reaction of amines and esters without the need for stoichiometric activating agents. For this project, a HTE approach was taken, for which details are provided in the experimental section (**Section 3.5.3**). We began by investigating the reaction of methyl benzoate with a selection of metals, ligands, and nucleophiles that had proven effective in previous catalytic coupling reactions that require cleavage of strong C–O bonds.[19,20,23] While the first several hundred reactions did not afford product, promising results arose when using Ni(cod)$_2$ as the catalyst, aniline as a nucleophile, and IMes·HCl as the ligand (**Scheme 3.7**). Moreover, traces of the desired product were observed using other NHC ligands such as SIPr·HCl and IPent·HCl.

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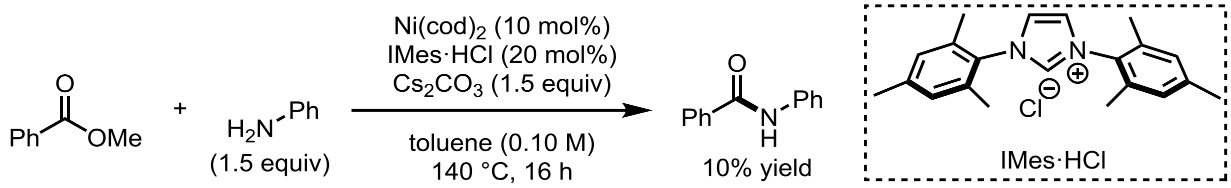
[22] The results presented herein have been published in a peer-reviewed journal: Ben Halima, T.; Masson-Makdissi, J.; Newman, S. G. *Angew. Chem., Int. Ed.* **2018**, *57*, 12925.

[23] (a) Ben Halima, T.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.; Houk, K.; Newman, S. *J. Am. Chem. Soc.* **2017**, *139*, 1311; (b) Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 13573; (c) Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508; (d) LaBerge, N. A., Love, J. A. *Eur. J. Org. Chem.* **2015**, 2015, 5546; (e) Pu, X.; Hu, J.; Zhao, Y.; Shi, Z. *ACS Catal.* **2016**, *6*, 6692; (f) Takise, R.; Isshiki, R.; Muto, K.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2017**, *139*, 3340.

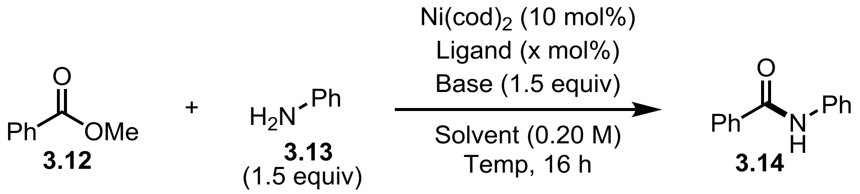
Scheme 3.7. Promising hit for amide bond formation using methyl ester



3.3.2 Reaction optimization

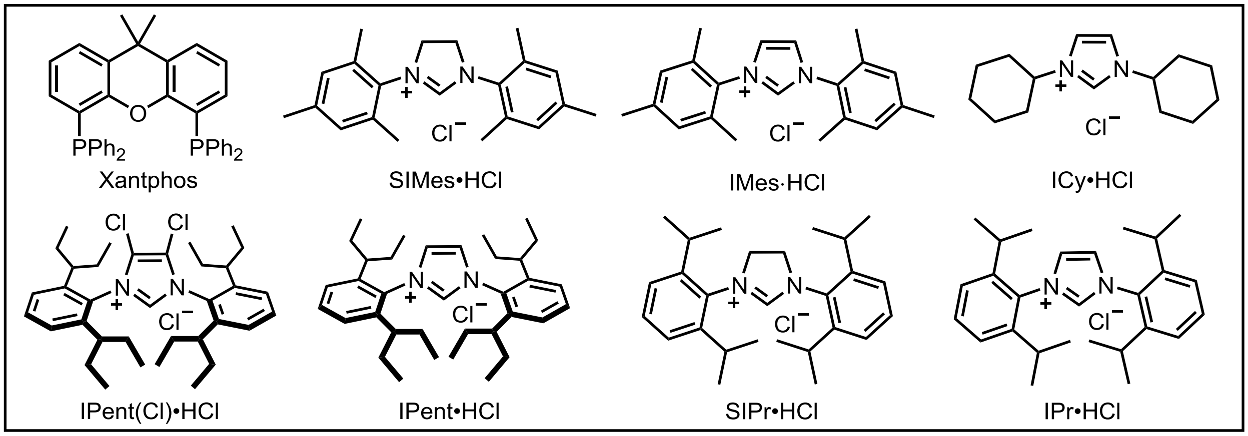
With a preliminary hit identified (entry 1 in the table below), targeted reaction screening was carried out. The transformation of methyl benzoate and aniline to benzanilide using nickel catalysts was chosen as the test reaction. A section of the optimization experiments with varied temperature, solvent, ligand, catalyst loading, and metal to ligand ratio are outlined in **Table 3.1**. Using 10 mol% Ni(cod)$_2$ in toluene at 140 °C for 16 hours provided no desired product when utilizing many of the most common phosphine ligands for cross-coupling reactions, including P(*n*-Bu)$_3$ (entry 2), Xantphos (entry 3), P(*o*-tol)$_3$ (entry 4), and DavePhos (entry 5). Also, only a trace of the desired product was detected when PCy$_3$ (entry 6) was employed. Due to the multiple hits observed during the discovery process using N-heterocyclic carbenes as ligands (see experimental section), several NHCs were screened using K_3PO_4 as base. No improvement compared to (entry 1) was observed when any of SIMes•HCl, SIPr•HCl, or ICy•HCl were used (entries 7-9). Using IMes·HCl with K_3PO_4 provided a slight improvement (entry 10), while the use of IPent(Cl)•HCl and IPent•HCl provided a substantial increase to 56% and 68% yield respectively (entry 11 and 12). Further improvement was seen when IPr•HCl was used (entry 13). The use of dioxane instead of toluene afforded lower yield using the same ligand (entry 14), and the use of DMF gave only a trace of the corresponding product (entry 15). With the deprotonated version of the ligand of choice (free IPr), the base could be removed without major effect on the reaction outcome (entry 16). In addition, a trend was observed (entries 16-18) by increasing the ligand loading from 10 mol% to 20 mol%, giving yields of 54% to 90% respectively. With these conditions, another short solvent screen was performed (entries 19 and 20) and low yield was afforded both with m-xylene or DMSO. The temperature was dropped to 110 °C and only 31% yield was obtained (entry 21). Finally, 1.2 equivalents of aniline could be used without significant loss in the reaction yield (entry 22).

Table 3.1. Select optimization data for the coupling of methyl benzoate and aniline



Entry	Ligand	x	Base	Solvent	Temp (°C)	Yield (%)
1	IMes•HCl	20	Cs_2CO_3	toluene	140	10
2	P(n-Bu)$_3$	40	none	toluene	140	0
3	Xantphos	20	none	toluene	140	0
4	P(o-tol)$_3$	20	none	toluene	140	0
5	DavePhos	20	none	toluene	140	0
6	PCy$_3$	40	none	toluene	140	trace
7	SIMes•HCl	20	K_3PO_4	toluene	140	2
8	SIPr•HCl	20	K_3PO_4	toluene	140	10
9	ICy•HCl	20	K_3PO_4	toluene	140	10
10	IMes•HCl	20	K_3PO_4	toluene	140	23
11	IPent(Cl)•HCl	20	K_3PO_4	toluene	140	56
12	IPent•HCl	20	K_3PO_4	toluene	140	68
13	IPr•HCl	20	K_3PO_4	toluene	140	78
14	IPr•HCl	20	K_3PO_4	dioxane	140	50
15	IPr•HCl	20	K_3PO_4	DMF	140	4
16	IPr	10	none	toluene	140	54
17	IPr	15	none	toluene	140	85
18	IPr	20	none	toluene	140	90
19	IPr	20	none	m-xylene	140	32
20	IPr	20	none	DMSO	140	0
21	IPr	20	none	toluene	110	31
22	IPr	20	none	toluene	140	86[a]

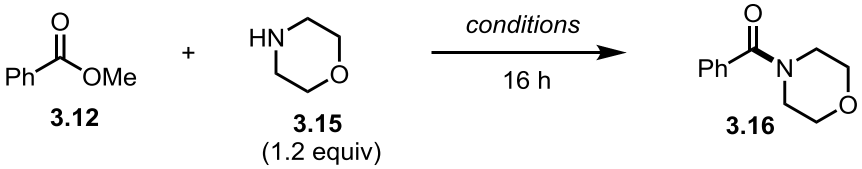
[a] Reaction run with 1.2 equiv of aniline.



3.3.3 Control experiments

To confirm that the Ni catalyst is necessary for the reaction to proceed, a range of control experiments were performed. Since background reactivity between esters and amines, if it exists, is more prone to be observed with morpholine rather than aniline, these control experiments were studied between methyl benzoate and morpholine (**Table 3.2**). The optimized reaction conditions with 10 mol% Ni(cod)$_2$ and 20 mol% IPr in toluene (0.20 M) provided amide **3.16** in 92% yield (entry 1). No product was observed when the reaction was run with no catalytic additives (entry 2), just Ni(cod)$_2$ (entry 3), or just IPr (entry 4), confirming the reaction is indeed enabled by the Ni/NHC catalyst system. To further assess the difficulty of performing this reaction by simple thermal or base-mediated conditions, the transformation was run in the absence of catalyst at elevated temperatures with *o*-xylene (entry 5) or DMSO (entry 6). No trace of product was observed. Similarly, the reaction was executed in the presence of excess K_3PO_4 (entry 7) and KO*t*Bu (entries 8 and 9), both providing no formation of **3.16**. Alternative ligands such as PBu$_3$ (entry 10), DavePhos (entry 11), and P(*o*-tol)$_3$ (entry 12) instead of IPr were ineffective. High recovery of starting material was observed in each reaction except when KO*t*Bu was used, wherein decomposition of the starting ester occurred.

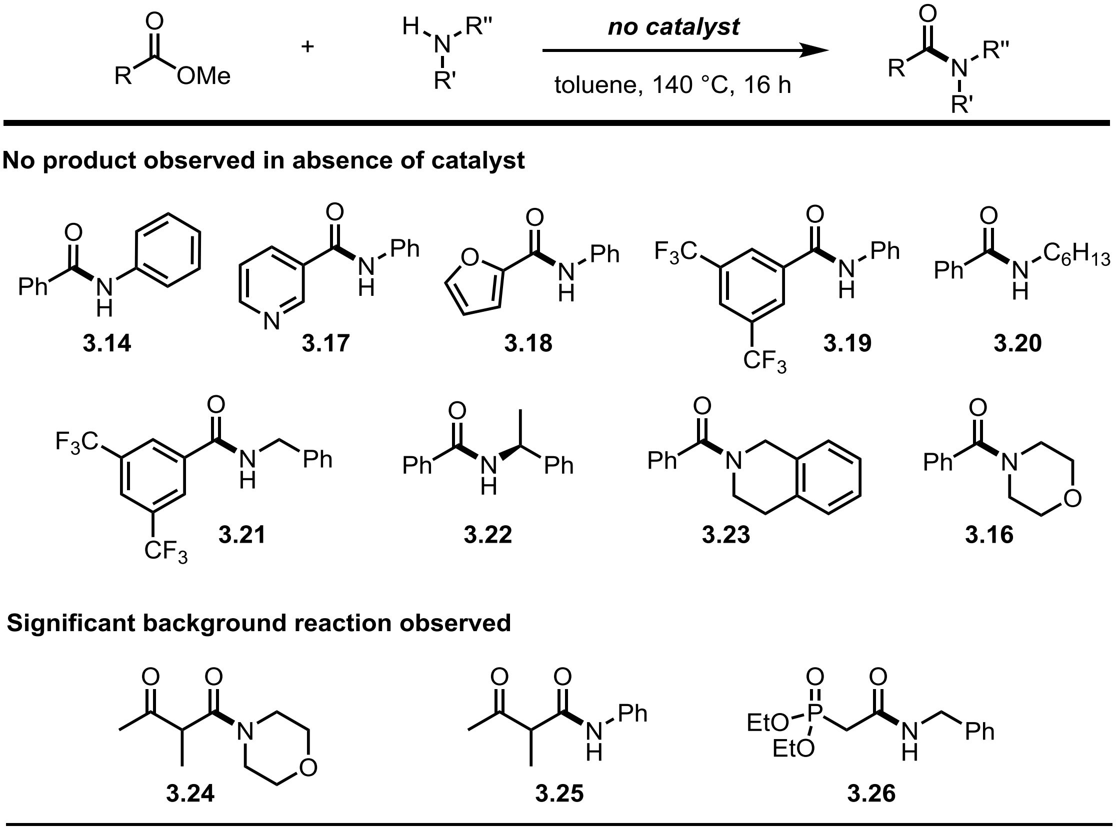
Table 3.2. Control experiments performed in the absence of the Ni/IPr catalyst system



Entry	Additives	Solvent (0.20 M)	Temp (°C)	Yield of 3.16 (%)
1	‘optimized’ catalyst	toluene	140	92
2	none	toluene	140	0
3	Ni(cod)$_2$ (10 mol%)	toluene	140	0
4	IPr (20 mol%)	toluene	140	0
5	none	*o*-xylene	170	0
6	none	DMSO	170	0
7	K_3PO_4 (1.5 equiv)	toluene	140	0
8	KO*t*Bu (1.5 equiv)	toluene	140	0
9	KO*t*Bu (1.5 equiv)	DMSO	140	0
10	PBu$_3$	toluene	140	0
11	DavePhos,	toluene	140	0
12	P(*o*-tol)$_3$	toluene	140	0

To determine if there was any significant background reactivity when varying the properties of the two coupling components, a second set of control experiments were carried out. A selection of esters and amines was treated with the ‘standard’ reaction conditions in the absence of catalyst (**Table 3.3**). In most cases, no product formation was observed, confirming that a catalyst system is critical for most amide bond formations under these conditions. More specifically, no product was detected using aniline as nucleophilic coupling partner (**3.14**, **3.17**, **3.18**, and **3.19**), primary and secondary alkyl amines (**3.20**-**3.22**), or cyclic amines (**3.23** and **3.16**). However, for specific esters bearing a ketone of phosphonate group in the β-position, product was observed in the absence of catalyst (**3.24**-**3.26**). This family of electrophiles, bearing an electron withdrawing group, adds to the class of reactions where a catalyst is not required for amide bond formation. Thus, these activated substrates were not further investigated with Ni catalysis.

Table 3.3. Substrate scope in the absence of catalysts



3.3.4 Reaction scope[24]

Using 10 mol% Ni(cod)$_2$ and 20 mol% of IPr in toluene at 140 °C for 16 hours as the optimal reaction conditions with this catalyst confirmed to be highly effective at enabling direct amide bond formation (**Table 3.4**). Using simple methyl benzoate, amides derived from secondary aliphatic amines (**3.16**, **3.23**, and **3.27-3.30**) and primary aliphatic amines (**3.20**, **3.22**, and **3.31-3.34**) could all be synthesized in good yields. Most importantly, non-nucleophilic aniline derivatives, which typically require pre-treatment with aggressive base prior to reaction with esters, could be used without any modification of the reaction conditions (**3.14** and **3.35-3.39**). On the top of this, even anilines bearing bulky (**3.35** and **3.37**) or electron-withdrawing substituents (**3.36**) were tolerated. Furthermore, ethyl benzoate could also be used to make benzanilide **3.14**, demonstrating that the reaction is not limited to methyl esters. Finally,

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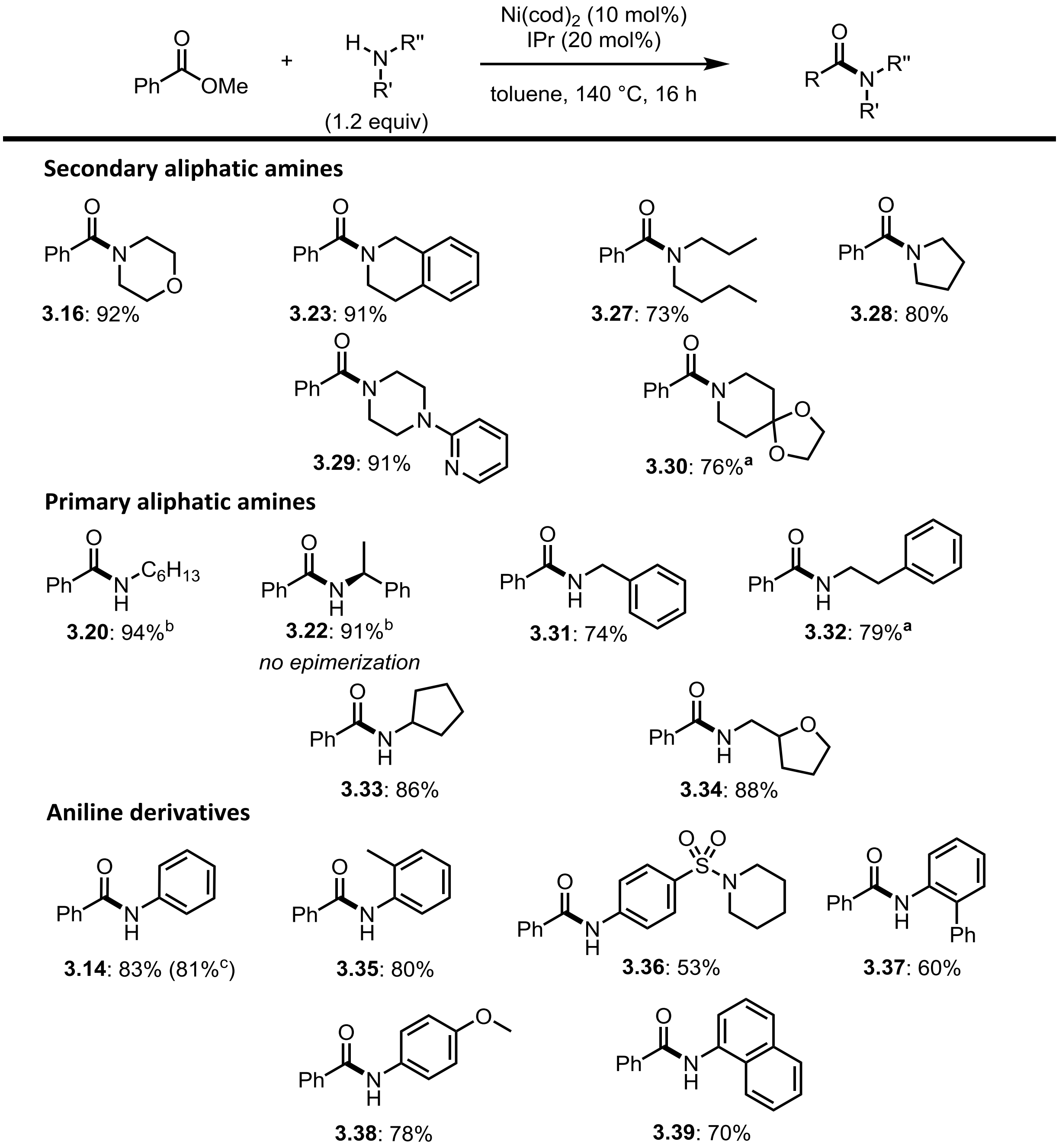
[24] This work was performed in collaboration with former M.Sc. candidate Jeanne Masson-Makdissi

stereochemical information remained intact (**3.22**) under these reactions conditions when using an α-chiral amine nucleophile.

Table 3.4. Scope of amines in Ni-catalyzed amidation



[a] dioxane instead of toluene. [b] 150 °C instead of 140 °C. [c] Et ester used instead of Me ester.

The reaction was also performed with a variety of ester coupling partners in order to prepare morpholine-derived amides with aromatic (**3.40**–**3.43**) and heteroaromatic (**3.44**–**3.52**) rings (**Table 3.5**). Fenfuram (**3.53**) could also be made, albeit in moderate yield, providing a potentially valuable route to this agrochemical that is industrially prepared by stoichiometric activation of the aniline with aluminum.[25] An α,β-unsaturated amide (**3.54**) was prepared without any competitive Michael addition occurring. While primary aliphatic ester starting materials were used to provide good yields with morpholine as a nucleophile (**3.55** and **3.56**), more hindered esters were problematic (**3.57**). Fortunately, aniline proved to be an effective nucleophile (**3.58**–**3.61**) for this substrate class. Finally, no epimerization was observed (**3.58** and **3.59**) when using enantiopure esters with epimerizable α-chiral stereocenters.

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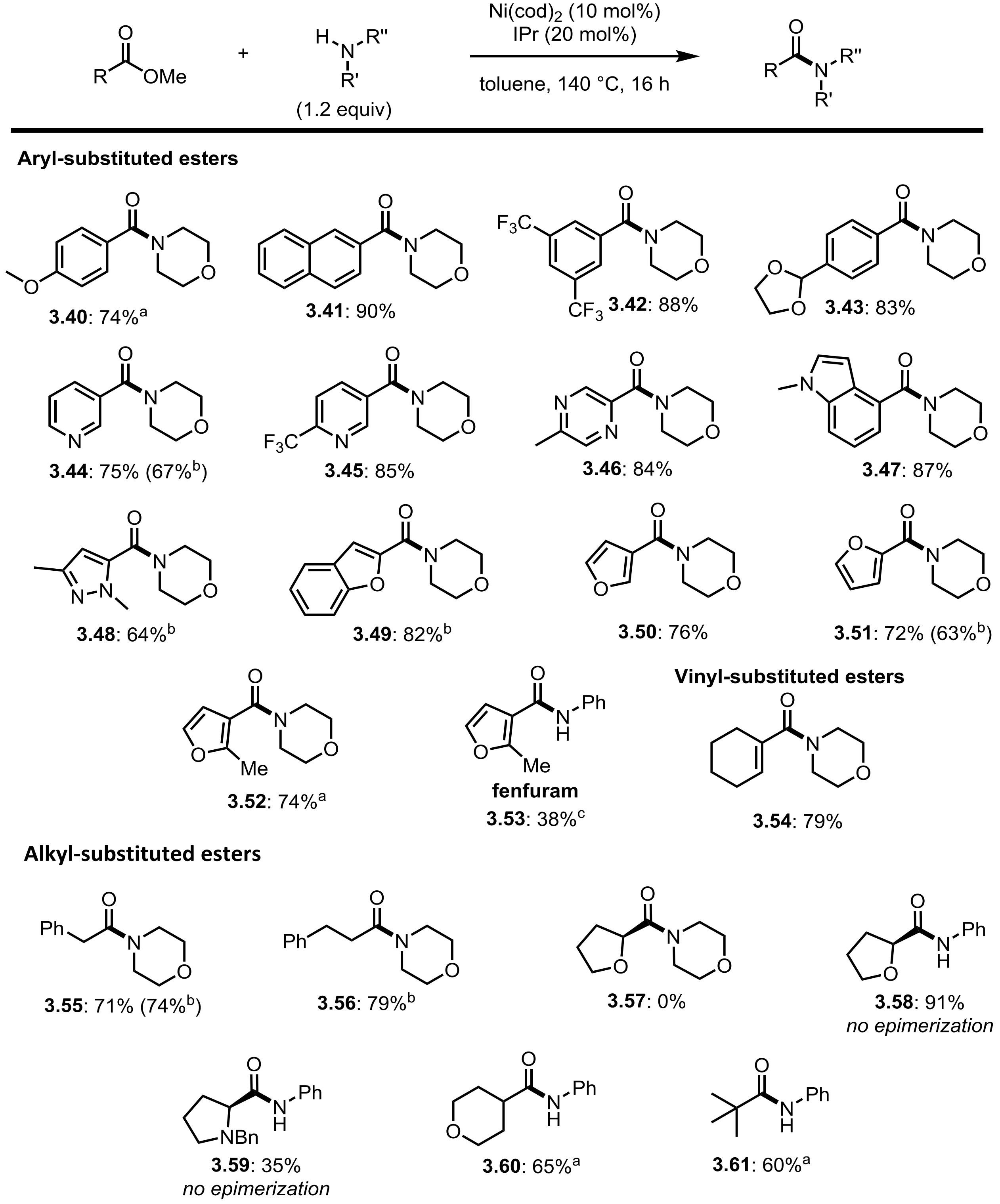
[25] Braunling, H.; Deinhammer, W.; Haberle, N.; Kaufmann, R. Process for the Manufacture of a Furancarboxylic Acid Anilide. U.S. Patent 4,187,237, February 5, 1980.

Table 3.5. Scope of esters in Ni-catalyzed amidation



Aryl-substituted esters

3.40: 74%[a]
3.41: 90%
3.42: 88%
3.43: 83%
3.44: 75% (67%[b])
3.45: 85%
3.46: 84%
3.47: 87%
3.48: 64%[b]
3.49: 82%[b]
3.50: 76%
3.51: 72% (63%[b])
3.52: 74%[a]
fenfuram
3.53: 38%[c]

Vinyl-substituted esters

3.54: 79%

Alkyl-substituted esters

3.55: 71% (74%[b])
3.56: 79%[b]
3.57: 0%
3.58: 91%
no epimerization
3.59: 35%
no epimerization
3.60: 65%[a]
3.61: 60%[a]

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[a] 150 °C instead of 140 °C. [b] Et ester used instead of Me ester. [c] concentration is 1 M instead of 0.2 M.

Overall, the observed tolerance towards weakly nucleophilic anilines, hindered nucleophiles, diverse heterocycles, acid-sensitive acetals, and a range of substitution-patterns on both coupling partners highlights the strength of this pathway for ester activation, particularly in contrast to acid- or base-mediated transformations.

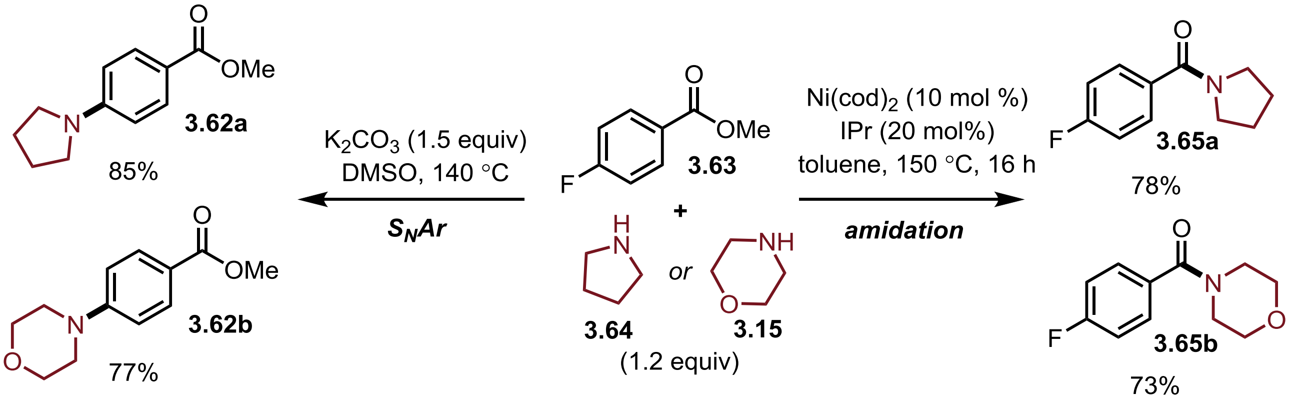
3.3.5 Applications

To further evaluate the advantages of the Ni-catalyzed amidation protocol, synthetic applications were carried out.

Orthogonal reactivity

The orthogonality of using a metal to activate esters was investigated via reactions with methyl 4-fluorobenzoate **3.63** (**Scheme 3.8**). This electrophilic coupling partner was a suitable substrate under our coupling conditions, providing product **3.65** via C(acyl)–O bond activation. On the other hand, with a base, a polar solvent, and no catalyst added, this substrate undergoes S_NAr reaction instead of amidation. This orthogonal reactivity is interesting and highlights the power of catalysis to tune the reactivity in such a way new disconnections, previously inaccessible, are now available.

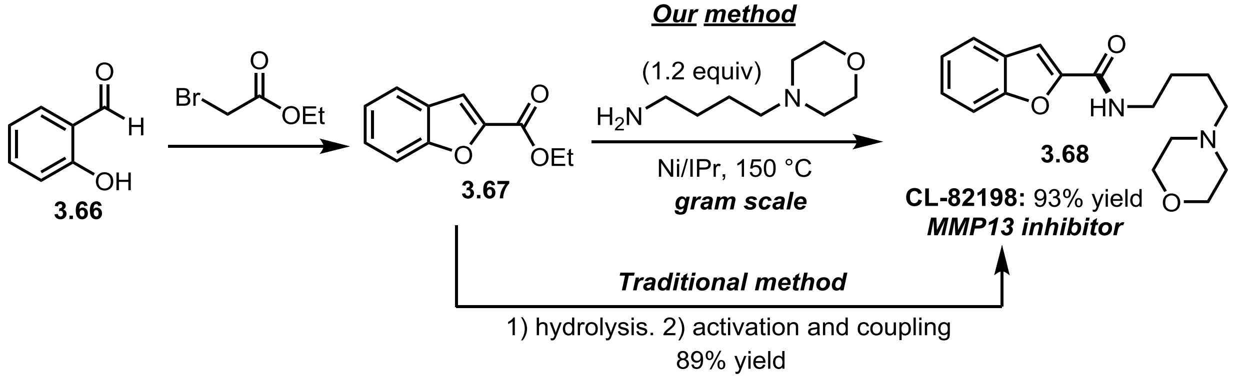
Scheme 3.8. S_NAr versus Ni-catalyzed amidation using methyl para-fluorobenzoate



Step-economy in the synthesis of bioactive molecules

One common route for the synthesis of amide-containing drugs or other bioactive molecules is to hydrolyze the corresponding ester and then couple with an amine via a stoichiometric activating agent (see **Section 3.1**). While widely used, this route is neither atom-economical nor step-economical. Our Ni-catalyzed amidation reaction allows the conversion of methyl or ethyl esters directly into amides in one step. This methodology significantly minimizes waste by generating volatile methanol or ethanol as the only stoichiometric by-product. Some attempts at utilizing our amidation protocol for the synthesis of bioactive molecules are provided. For example, benzofuran ester **3.67** can be directly converted into over 1 gram of the commercially available MMP13 inhibitor **CL-82198** (**Scheme 3.9**), avoiding the wasteful EDC-mediated couplings used to make analogous amides.[26]

Scheme 3.9. Ni-catalyzed amidation from ethyl ester of CL-82198



Similarly, lead AMPAR positive modulator **3.11** (**Scheme 3.10**) was made in the literature[15] after an initial hydrolysis and then a second step using CDI-activation and coupling (see **Section 3.1**, **Scheme 3.3**). Using our recently discovered Ni-catalyzed amide bond forming reaction, we subjected the ester **3.9** to our reaction conditions affording **3.11** in 87% yield in one step. This represents a clear advantage of using our method over multi-step routes.

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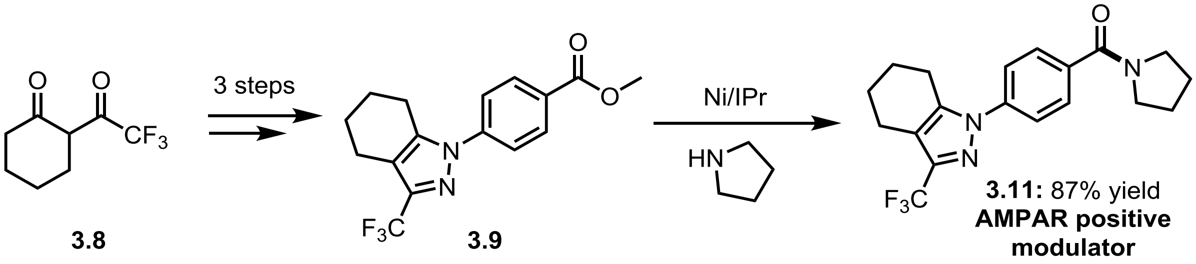
[26] Chen, J. M.; Nelson, F. C.; Levin, J. I.; Mobilio, D.; Moy, F. J.; Nilakantan, R.; Zask, A.; Powers, R. *J. Am. Chem. Soc.* **2000**, *122,* 9648.

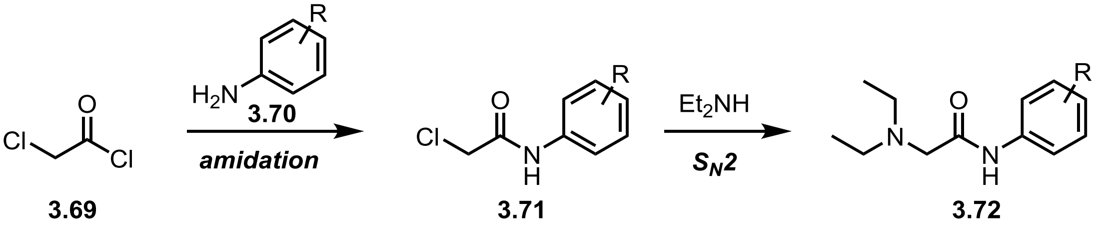
Scheme 3.10. The application of Ni-catalyzed amidation in the synthesis of AMPAR positive modulator



Alternative disconnections[27]

The use of esters rather than carboxylic acids or acid chlorides as coupling partners also enables useful synthetic disconnections for medicinal chemistry. For example, lidocaine derivatives are usually synthesized in two steps (**Scheme 3.11**). Chloroacetyl chloride **3.69** is first reacted with the aniline derivative **3.70** to form amide **3.71**. Then, this amide is reacted with diethyl amine to afford the lidocaine derivative **3.72**.

Scheme 3.11. Traditional route to synthesize lidocaine derivatives



An alternative disconnection approach could be envisioned with methyl chloroacetate used to first substitute at the α-carbon and then diversify the amide component by Ni-catalyzed coupling (**Table 3.6**). This strategy was used to more efficiently access lidocaine derivatives **3.72a**–**3.72c**[28] and **JM25-**1,[29] a recently discovered potential bronchospasm therapeutic.

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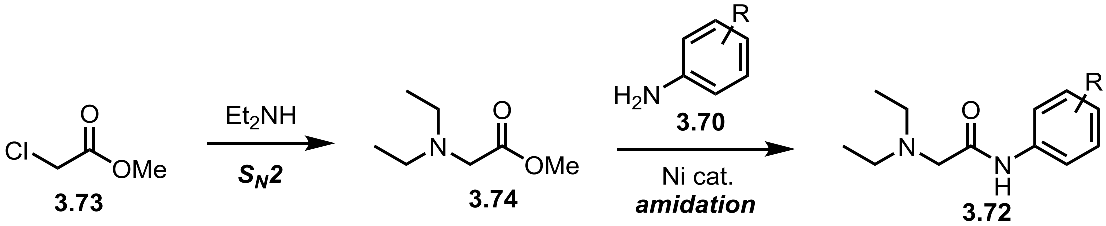
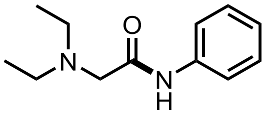
[27] This study was done in collaboration with former M.Sc. candidate Jeanne Masson-Makdissi.

[28] Costa, J. C. S.; Neves, J. S.; de Souza, M. V. N.; Siqueira, R. A.; Romeiro, N. C.; Boechat, N.; Silvab, P. M. R.; Martins, M. A. *Bioorganic Med. Chem. Lett.* **2008**, *18*, 1162.

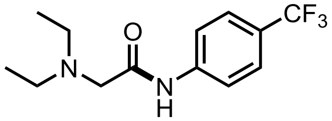
[29] Serra, M. F.; Neves, J. S.; Couto, G. C.; Cotias, A. C.; Pão, C. R *Anesthesiology* **2016**, *124*, 109.

Table 3.6. Cross-coupling approach to synthesize lidocaine derivatives

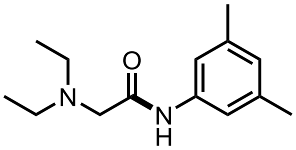




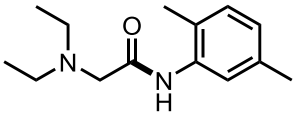
3.72a: 77% yield



3.72b: 59% yield



3.72c: 78% yield



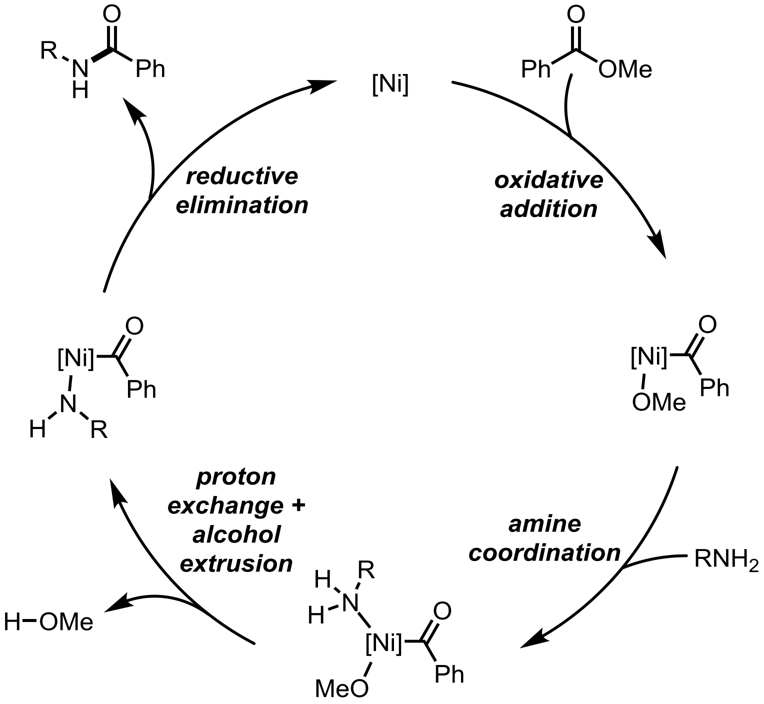
JM25-1: 54% yield
bronchospasm therapeutic

3.3.6 Mechanistic insight

Proposed mechanism

Mechanistically, the reaction likely begins via insertion of the catalyst into the strong ester C–O bond (**Scheme 3.12**) as has been previously demonstrated, primarily with activated esters.[19,23(a,c),30] Unlike more traditional Buchwald-Hartwig aminations, which require a strong external base to facilitate deprotonation of the amine nucleophile, an intramolecular proton exchange with the methoxide can occur to provide a Ni(II) amido complex that can then undergo reductive elimination. A recent DFT-study done by Hong and co-workers supported this proposed mechanism.[31]

Scheme 3.12. Plausible mechanism for Ni-catalyzed amidation



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[30] (a) Hong, X.; Liang, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 2017; (b) Lu, Q.; Yu, H.; Fu, Y. *J. Am. Chem. Soc.* **2014**, *136*, 8252; (c) Li, X.; Hong, X. *J. Organomet. Chem.* **2018**, *864*, 68.

[31] Ji, C.-L.; Xie, P.-P.; Hong, X. *Molecules* **2018**, *23*, 2681.

Reaction reversibility

Our discovered reaction (from ester to amide) is analogous to that proposed for the reverse reaction – Ni-catalyzed conversion of amides to esters – first developed by Garg, Houk, and co-workers.[32] In this pioneering work, reductive elimination (**Figure 3.1**) of a proposed acyl Ni(II) methoxide **Int3.1** was calculated to be 22.5 kcal/mol downhill with an activation energy of 7.5 kcal/mol. By the principle of microscopic reversibility, the activation energy for the oxidative addition of this Ni(0)-NHC catalyst into the C–O bond of a methyl ester can be predicted to be 30.0 kcal/mol. This study overlaps with the recent work performed by the same research groups to achieve the ester to amide transformation.[19] Also, it explains the necessity of Al(O*t*Bu)$_3$ as it is used both to help decrease the kinetic barrier and to make the reaction thermodynamically favorable (see **Chapter 1**, **Section 1.3.2**).

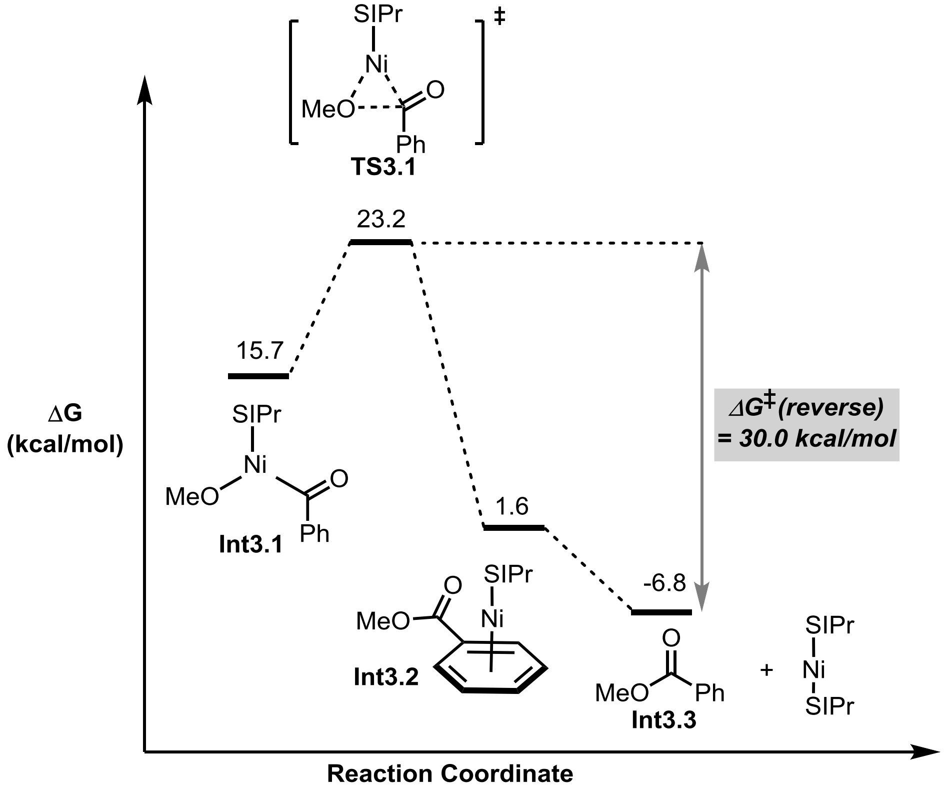

Figure 3.1. Calculated energies of the reductive elimination step done by Garg and Houk's labs[32]

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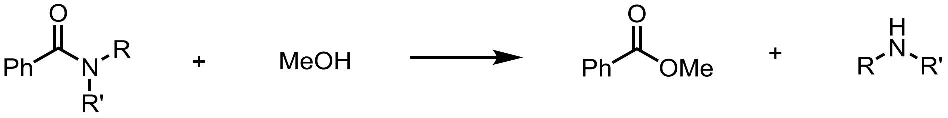
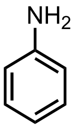
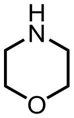
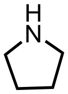
[32] Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. *Nature* **2015**, *524*, 79.

Moreover, the amide to ester transformation was calculated (**Table 3.7**) to be thermodynamically downhill with aniline (entry 1) and morpholine (entry 2) as the amine leaving groups,[32] and thermodynamically uphill with pyrrolidine (entry 3). Once again, these calculations agree with what has been reported previously to access amide bonds from esters using anilines.[19] The reaction from the ester to the amide using anilines is thermodynamically uphill; and the use of Al(O*t*Bu)$_3$ shifts the relative energies to make the reaction more thermodynamically feasible (see **Chapter 1**, **section 1.3.2**).

Table 3.7. Calculated energies from Houk and co-workers using different leaving groups



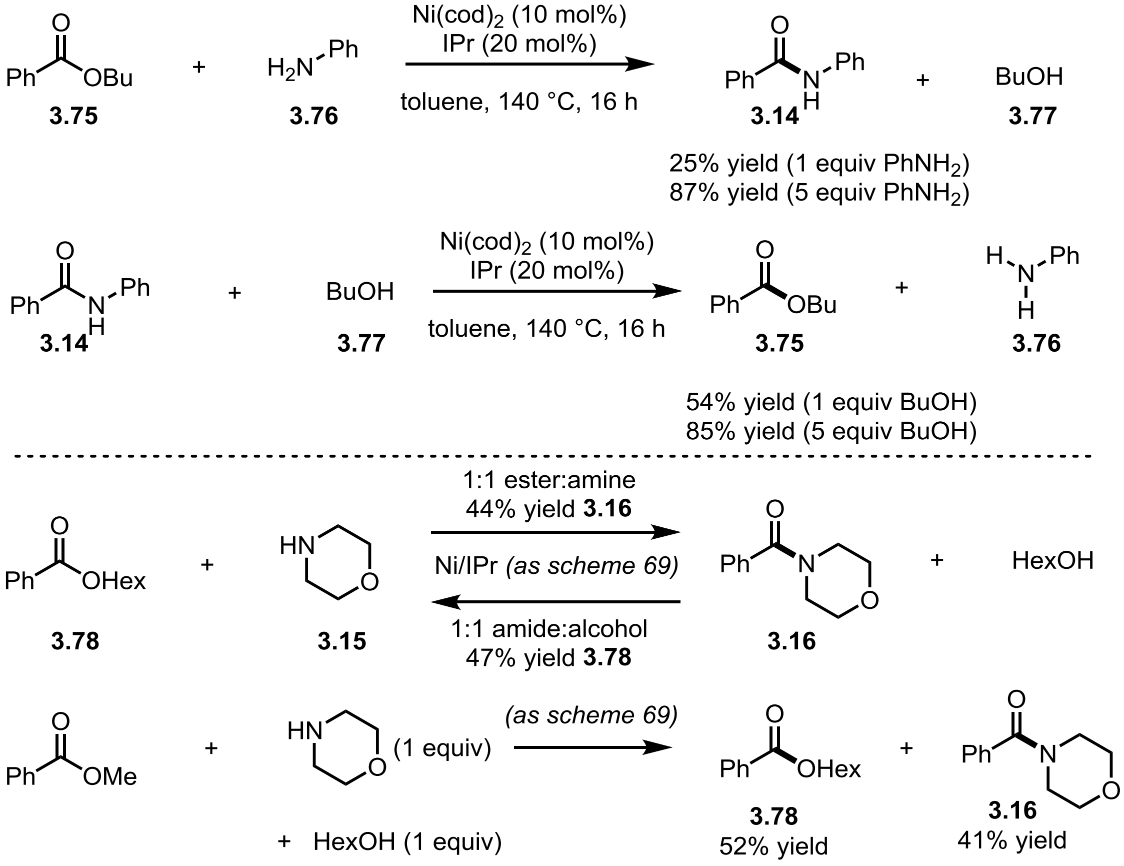
Entry	Leaving group	ΔG$_{calc}$
1		-4.3 kcal/mol
2		-1.1 kcal/mol
3		+2.4 kcal/mol

These calculations suggest that the amide bond formations discussed above using morpholine and aniline derivatives are thermodynamically unfavorable.

Given the relatively high reaction temperature used and the low boiling point of the methanol byproduct (63 °C), a series of experiments were done with esters bearing less volatile alcohol leaving groups (**Scheme 3.13**) to better understand the origin of this success.

While the reaction of aniline with both methyl and ethyl benzoate efficiently provides benzanilide, the use of butyl benzoate gave only 25% yield. Running the reaction in reverse by treating benzanilide with 1 equivalent of butanol (BuOH) under the reaction conditions gave **3.75** in 54% yield, demonstrating that esterification is more efficient for these coupling partners. Both the amidation and esterification can be driven almost to completion when using an excess of the nucleophilic coupling component. For instance, using 5 equivalents of aniline gave 87% of **3.14** and 5 equivalents of butanol provided 85% of **3.75**. Next, the use of morpholine was tested with hexyl benzoate **3.78** (**Scheme 3.13**). Running this reaction in the forward direction provided amide **3.16** in 44% yield. Operating in reverse by treating amide **3.16** with one equivalent of hexanol (HexOH) gave ester **3.78** in 47% yield. Lastly, a competition experiment between methyl benzoate, morpholine, and hexanol gave a mixture of the ester and amide products in 52% and 41% yield, respectively, with trace recovery of the starting material.

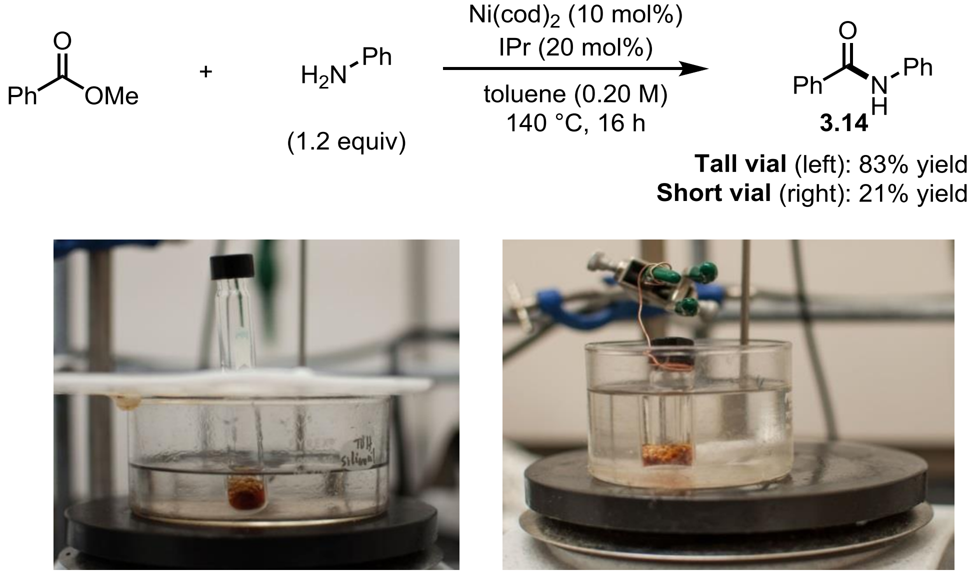
Scheme 3.13. Controlling reaction equilibrium



Together, these experiments indicate that the reaction is under equilibrium control. In agreement with calculations from the Garg and Houk groups, formation of benzanilide **3.14** is thermodynamically uphill and formation of benzoylmorpholine **3.16** is near thermoneutral. When methyl benzoate is used as a starting material, we speculate that the high reaction temperature leads to removal of the methanol by-product from the liquid phase and allows reactions to be driven forward even with near equimolar stoichiometry. These amidations and esterifications are analogous to other transformations that can be controlled by Le Chatelier's Principle. Further studies on the importance of the alcohol leaving group are provided in the experimental section.

The importance of reaction headspace

All the reactions were carried out in tall, 8 mL vials sealed with a teflon screw-cap top. The vials were partially submerged in the heating bath so that the solvent is surrounded by the high temperature oil (140 °C), but the headspace protrudes well above the oil, providing ample space for the volatile methanol to condense (**Figure 3.2**). If the reaction vessel is fully submerged in the oil bath so that no cool zone is present for the methanol to condense, the yield is reduced. Together, these experiments highlight the importance of the removal of methanol or ethanol from the liquid phase, particularly for transformations that are thermodynamically unfavored and rely on Le Chatelier's Principle to be driven to completion.



Tall vial (left): 83% yield
Short vial (right): 21% yield

Figure 3.2. Importance of the reaction headspace

3.4 Conclusion

In summary, we have developed a catalytic amide bond forming reaction from methyl esters and a range of aliphatic amine and aniline coupling partners. The reaction mechanism is proposed to proceed by a cross-coupling pathway, making it mechanistically distinct from the majority of catalytic amidations that rely on acid-mediated activation of the ester or base-mediated activation of the amine. Consequently, the reaction is highly general since it works with both aliphatic amines and anilines, tolerates diverse heterocycles and epimerizable stereocenters, and is shown to avoid side reactions with an acetal, ketal, Michael acceptor, as well as S_NAr electrophiles. We anticipate that this procedure will provide an appealing alternative to the commonly executed hydrolysis, acid chloride formation, and Schotten-Baumann sequence for accessing amides from esters, or other methods that require aggressive stoichiometric reagents. While it is remarkable that a simple and well-known Ni/NHC catalyst system can enable this transformation, relatively high catalyst loadings and reaction temperatures leave room for improvement. Further efforts in the design of tailored ligands will be needed to further establish cross-coupling as an important strategy for derivatization of common methyl esters.

3.5 Experimental section

3.5.1 Materials

Unless otherwise noted, esters, amines, and other starting materials were obtained commercially from Sigma Aldrich or Combi-Blocks. Ni(cod)$_2$ was purchased from Sigma Aldrich. IPr was made from IPr•HCl using a literature procedure.[33] Esters were used as received. Impurities in amines were found to lead to reduced yields. Newly purchased amines were used as received, while older, discolored amines were purified by either filtration over basic alumina or acid/base extraction. The following starting materials were synthesized using literature procedures: **3.79**,[34] **3.80**,[35] **3.81**,[36] **3.82**,[15] **3.83**.[37] Other starting materials were synthesized as described in Section 3.5.2 below.

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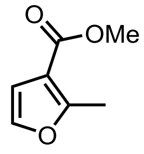
[33] Pompeo, M.; Froese, R. D. J.; Hadei, N.; Organ, M. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 11354.

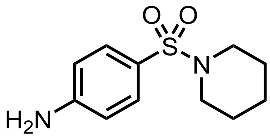
[34] Karahan, E.; Koza, G.; Balci, M *Helv. Chim. Acta* **2014**, *97*, 1487.

[35] Patel, P. R.; Ramalingan, C.; Park, Y.-T. *Bio. Med. Chem. Lett.* **2007**, *17*, 6610.

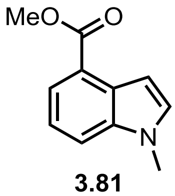
[36] Manning, D. D.; Cioffi, C. L. 5-HT3 Receptor Modulators, Methods of Making, and Use Thereof. US Patent US2009/298809 (2009).



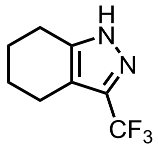
3.79



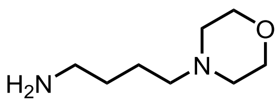
3.80



3.81

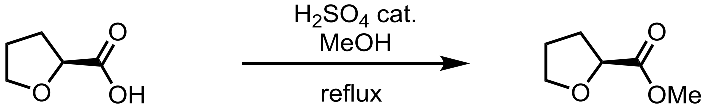


3.82



3.83

3.5.2 Synthesis of Starting Materials



3.84

(S)-Methyl tetrahydrofuran-2-carboxylate (3.84) was synthesized from a procedure adapted from the patent literature.[38] A 10 mL round-bottomed flask was equipped with a stir bar and condenser. (S)-Tetrahydro-2-furoic acid (0.4 ml, 4.00 mmol, 1.0 equiv) was added and diluted in methanol (2.0 mL). Sulfuric acid (0.02 mL, 0.22 mmol, 0.06 equiv) was then added, and the reaction mixture was refluxed at 75-80 °C overnight. After being cooled down, the mixture was diluted with water (2.0 mL). The mixture was extracted with dichloromethane (10 mL), and washed with a saturated aqueous solution of $NaHCO_3$ (2 x 10 mL), and brine (10 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The product was then purified by column chromatography (10% ether in pentane) to afford **3.84** as a colourless liquid (346 mg, 66% yield, 97.5:2.5 e.r.). Characterization data matched those previously reported.[39] **^{1}H NMR** (400 MHz, $CDCl_3$): 4.47 (dd, *J* = 8.3, 5.4 Hz, 1H), 4.04-3.99 (m, 1H), 3.94-3.89 (m, 1H), 3.75 (s, 3H), 2.29-2.20 (m, 1H), 2.07-1.86 (m, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$): 173.9, 76.8, 69.5, 52.2, 30.3, 25.4. **HPLC**: CHIRALCEL AD-H, 1.5% ^{i}PrOH in hexanes, 0.80 mL/min, 230 nm, t_{R1}(minor) = 17.4 min, t_{R2}(major) = 16.5 min.

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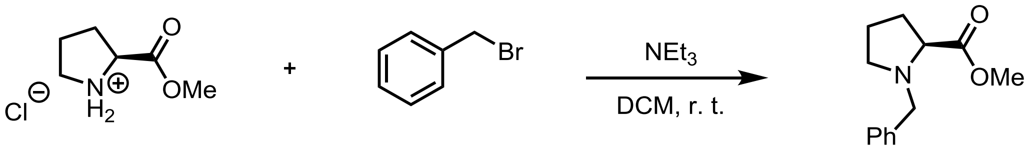
[37] Coppo, F. T., Maskell, E. S. L., Redshaw, S., Skidmore, J., Ward, R. W.; Wilson, D. M. 2-Phenyl-5-amino-1,3,4-oxadiazoles and their use as nicotinic acetylcholine receptor ligands. Patent WO2007/138033 (2007).

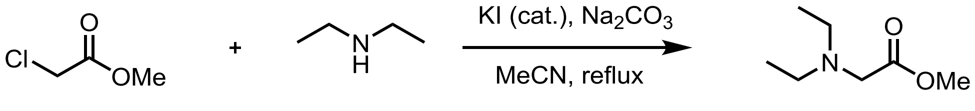
[38] Masada, S., Terao, Y.; Murata, T. Indole derivative. Patent WO2011/083804 (2011).

[39] Sebeka, M.; Holzb, J.; Börner, A.; Jähnisch, K. *Synlett* **2009**, *3*, 461.



3.85

N-Benzyl-(*S*)-proline methyl ester (3.85) was synthesized from L-proline methyl ester hydrochloride and benzyl bromide. A 50 mL round-bottomed flask was first charged with a stir bar and L-proline methyl ester hydrochloride (331 mg, 2.00 mmol, 1.0 equiv). Dichloromethane (6 mL) was then added, followed by benzyl bromide (0.3 mL, 2.4 mmol, 1.2 equiv). Triethylamine (0.6 mL, 4.4 mmol, 2.2 equiv) was added dropwise. The reaction was stirred at room temperature overnight. The solution was then diluted with DCM (10 mL), and washed with a saturated aqueous solution of sodium carbonate (2 x 10 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo*, and the crude product was purified by column chromatography (gradient 10 → 20% EtOAc in hexanes). **3.85** was obtained as a light-yellow oil (305 mg, 70%). Characterization data matched those previously reported.[40] **^{1}H NMR** (400 MHz, $CDCl_3$): 7.35-723 (m, 5H), 3.89 (d, *J* = 12.7 MHz, 1H), 3.65 (s, 3H), 3.58 (d, *J* = 12.7 Hz, 1H), 3.26 (dd, *J* = 8.9, 6.4 Hz, 1H), 3.07 (m, 1H), 2.40 (q, *J* = 8.8 Hz, 1H), 2.19-2.08 (m, 1H), 2.01-1.85 (m, 2H), 1.82-1.74 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): 174.7, 138.4, 129.4, 128.3, 127.2, 65.5, 58.9, 53.4, 51.8, 29.5, 23.1.



3.74

N,N-Diethylglycine methyl ester (3.74) was synthesized according to a procedure adapted from the literature.[41] A 300 mL round-bottomed flask was charged with a stir bar, potassium iodide (581 mg, 3.50 mmol, 1.0 equiv), and sodium bicarbonate (3240 mg, 30.6 mmol, 8.7 equiv). Acetonitrile (200 mL) was then added, followed by addition of diethylamine (3.54 mL, 34.2 mmol, 9.8 equiv). The reaction mixture was stirred at room temperature, and methyl chloroacetate (2.6 mL, 30 mmol) was added dropwise. The reaction was refluxed at 85–90°C for 4 h. After being cooled down, the crude mixture was filtered, and the solvent was evaporated *in*

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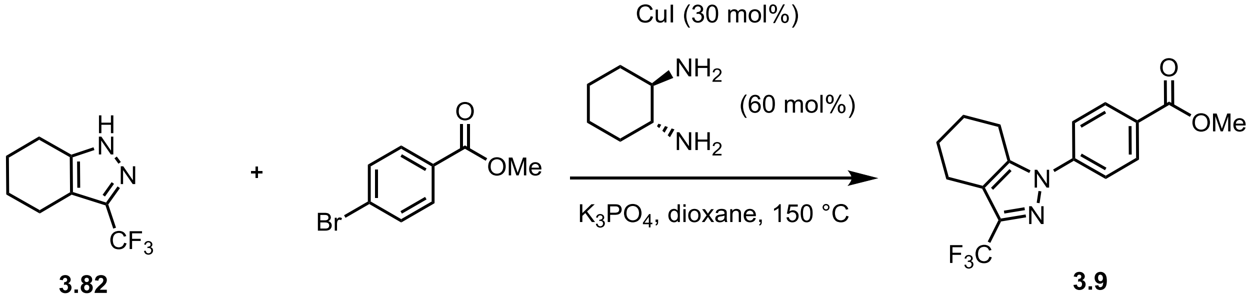
[40] Sparr, C.; Tanzer, E.-M.; Bachmann, J.; Gilmour, R. *Synthesis* **2010**, *8*, 1394.
[41] Schulze, R.; Beckhaus, H.-D.; Rüchardt, C. *J. Prakt. Chem* **1990**, *332*, 325.

vacuo. Ether (80 mL) was added, resulting in the formation of a precipitate. The mixture was filtered, and the solvent was again evaporated *in vacuo*. The crude residue was purified by column chromatography (gradient of 30% → 50% EtOAc in hexanes), yielding **3.74** as an orange oil (1.30 g, 30% yield). Characterization data matched those previously reported.[42] **^{1}H NMR** (400 MHz, $CDCl_3$): 3.71 (s, 3H), 3.32 (s, 2H), 2.64 (q, 4H), 1.06 (t, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): 172.2, 54.4, 51.7, 47.9, 12.2.



Methyl 4-[3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzoate (3.9) was synthesized according to a procedure adapted from the literature.[43] A mixture of 3-trifluoromethyl-4,5,6,7-tetrahydro-1H-indazole **3.82** (57 mg, 0.30 mmol, 1.0 equiv), methyl 4-bromobenzoate (77 mg, 0.36 mmol, 1.2 equiv), copper iodide (17 mg, 0.09 mmol, 0.3 equiv), trans-1,2-diaminocyclohexane (21 mg, 0.2 mmol, 0.6 equiv), and potassium phosphate (42 mg, 0.6 mmol, 2.0 equiv) in dioxane (1.5 ml) was stirred at 150 °C for 16 h. After being cooled down, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride. The mixture was extracted with EtOAc (3 x 2 mL) and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (gradient of 0% → 15% EtOAc in hexanes), yielding **3.9** as a white solid (89 mg, 91% yield). Characterization data matched those previously reported.[43] **^{1}H NMR** (400 MHz, $CDCl_3$): 8.15 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 3.95 (s, 3H), 2.77-2.68 (m, 4H), 1.64-1.63 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$): 166.3, 142.7, 140.6 (q, J = 36 Hz), 140.8, 130.9, 129.3, 123.0, 122.0 (q, J = 267 Hz), 117.2 (q, J = 1.5 Hz), 52.5, 24.0, 22.7, 22.2, 20.2.

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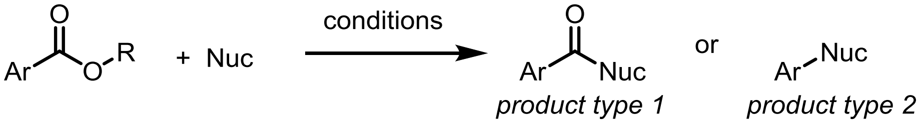
[42] Singer, S. S. *J. Org. Chem.* **1982**, *47*, 3839.
[43] Lim, D. S. W.; Lew, T. T. S.; Zhang, Y. *Org. Lett.* **2015**, *17*, 6054.

3.5.3 Reaction Discovery

Given the recent abundance of catalytic reactions that proceed via cleavage of the C–O bond of esters,[18] it was proposed that this strategy might be applicable to the direct reaction of amines and esters without the need for stoichiometric activating agents. A selection of these reactions[19,20,23] is provided to highlight the diversity of reaction components and products (**Figure 3.3a**). High throughput experimentation was used, with reaction conditions from these and other key contributions providing a starting point for selecting catalysts, solvents, and temperatures to screen. The reaction of methyl benzoate with amines and boronic acids was initially targeted. While the first several hundred reactions provided no trace of product, promising results were observed with using Ni(cod)$_2$ as a catalyst at 140 °C. The setup and results of the last and most successful 96-well plate is given in (**Figure 3.3b**) (yields approximated by GC). In all reactions, no carbonylative coupling products were observed and the starting material nearly quantitatively. The highest yield across several 96-well plates was obtained when using Ni(cod)$_2$ as the catalyst, aniline as a nucleophile, and IMes·HCl as the ligand (**Figure 3.3c**), which was reproduced for verification and accurate yield determination. The ligands used were as follows:

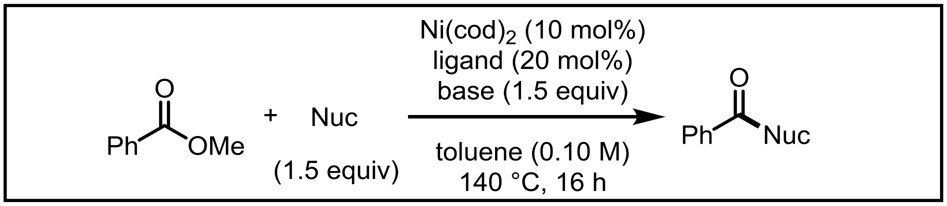
L1 : IMes·HCl
L2 : SIPr·HCl
L3 : IPent·HCl
L4 : dcype
L5 : dmpe
L6 : dcypp
L7 : PCy$_3$·HBF$_4$
L8 : dppf
L9 : 1,2-Bis[bis(pentafluorophenyl)phosphino]ethane
L10 : biphep
L11: 1,5-Bis(diphenylphosphino)pentane
L12: CyTOP 228: 1-isobutyl-2,2,6,6-tetramethyl-4-phosphorinanone

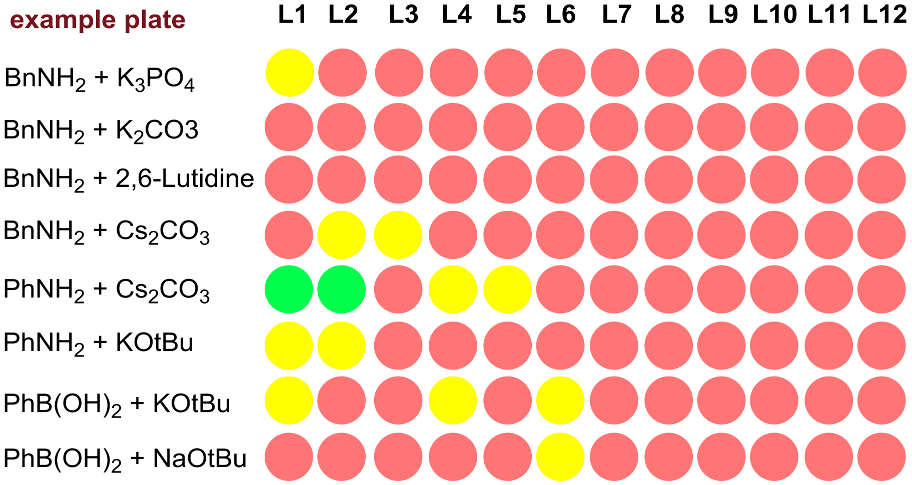
a Select literature conditions for the cross-coupling of esters



Reference	Product type	R	Nuc	Catalyst	Additives	Solvent	Temp (°C)
14	1	Ph	$ArNH_2$	Pd(IPr)(allyl)Cl	K_3PO_4, H_2O	toluene	110
17a	1	Ph	$ArB(OH)_2$	Pd(IPr)(cinnamyl)Cl	K_3PO_4, H_2O	toluene	90
17b	2	Ph	HetAr–H	Ni/dcype	K_3PO_4	dioxane	150
17c	2	Ph	$ArB(OH)_2$	Ni/PBu_3	Na_2CO_3	toluene	150
17d	2	Ph	$ArB(OH)_2$	Ni/PCy_3	Cs_2CO_3	toluene	reflux
13	1	Me	ArNHR	Ni/SIPr	Al(O*t*Bu)$_3$	toluene	60
17e	2	Ph	B_2nep_2	Ni/ICy	Na_2CO_3, NaCl	dioxane	160
17f	2	Ph	None (-CO)	Pd/dcypt	K_3PO_4	toluene	150

b Combinations of select catalysts, ligands, bases, temperatures, and solvents were screened using high throughput experimentation tools with 96 well plates





example plate	**L1**	**L2**	**L3**	**L4**	**L5**	**L6**	**L7**	**L8**	**L9**	**L10**	**L11**	**L12**
$BnNH_2$ + K_3PO_4	🟡	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
$BnNH_2$ + K_2CO3	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
$BnNH_2$ + 2,6-Lutidine	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
$BnNH_2$ + Cs_2CO_3	🔴	🟡	🟡	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
$PhNH_2$ + Cs_2CO_3	🟢	🟢	🔴	🟡	🟡	🔴	🔴	🔴	🔴	🔴	🔴	🔴
$PhNH_2$ + KOtBu	🟡	🟡	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
$PhB(OH)_2$ + KOtBu	🟡	🔴	🔴	🟡	🔴	🟡	🔴	🔴	🔴	🔴	🔴	🔴
$PhB(OH)_2$ + NaOtBu	🔴	🔴	🔴	🔴	🔴	🟡	🔴	🔴	🔴	🔴	🔴	🔴

🔴 no product observed 🟡 trace product observed (<5%) 🟢 >5% product

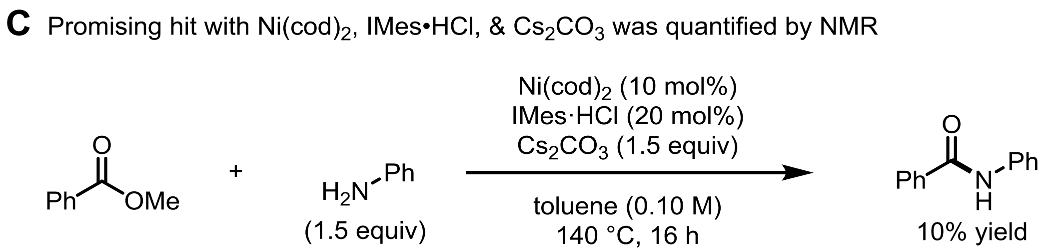
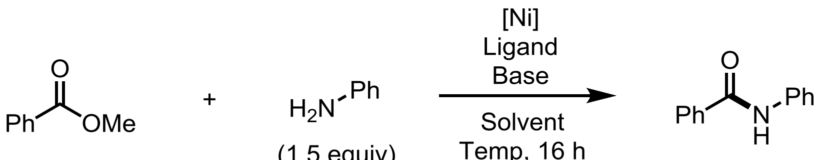


Figure 3.3. Reaction discovery via HTE using literature precedent to select the key variables to screen

3.5.4 Reaction optimization

General procedure for optimization experiments



3.14

In a glovebox, an oven dried screw-capped vial was charged with a magnetic stir bar, catalyst, ligand, and base. The solvent was then added. The reaction mixture was shaken vigorously, then methyl benzoate (0.10 mmol, 1.0 equiv) and aniline (0.15 mmol, 1.5 equiv) were subsequently added via micropipette. The vial was sealed with a Teflon-lined screw cap and shipped outside of the glovebox. The reaction was stirred vigorously (700 rpm) in a silicone oil bath heated at the specified temperature for 16 h. After cooling to room temperature 1,3,5-trimethoxybenzene was added as an internal standard. The mixture was diluted with ethyl acetate and filtered through a plug of silica gel. Yields of benzanilide **3.14** were determined by GC/FID using a 5-point calibration curve.

3.5.5 Troubleshooting

Some limitations, tips, and observations are provided below.

Limitations to the reaction scope

While the transformation proved quite general, as demonstrated in the ~50 successful examples outlined in the manuscript, certain functional groups were found to be not tolerated. The reaction of morpholine with methyl 3,5-bis(trifluoromethyl)benzoate was tested under the standard catalytic conditions with various additives (1.0 equiv). The yield in the absence of additives was 88%. Certain additives, such as phenol, nitrobenzene, and phenyl acetylene resulted in a reduction in the yield to below 20% (**Figure 3.4**, top). Many other substrates proved challenging in the reaction. For instance, attempts to couple esters with a thiazole, thiophene, oxazole, epoxide, or *ortho* substitution of methyl benzoate using both aliphatic and aryl amine nucleophiles resulted in side reactions, decomposition, or recovery of starting material (**Figure 3.4**, middle). Similarly, certain amines could not be efficiently coupled with methyl benzoate, particularly those that are highly electron-deficient or sterically hindered (**Figure 3.4**, bottom). While thermodynamically uphill reactions (e.g. methyl benzoate + aniline) are possible, these results suggest there is a limit to how unfavorable the transformation can be.

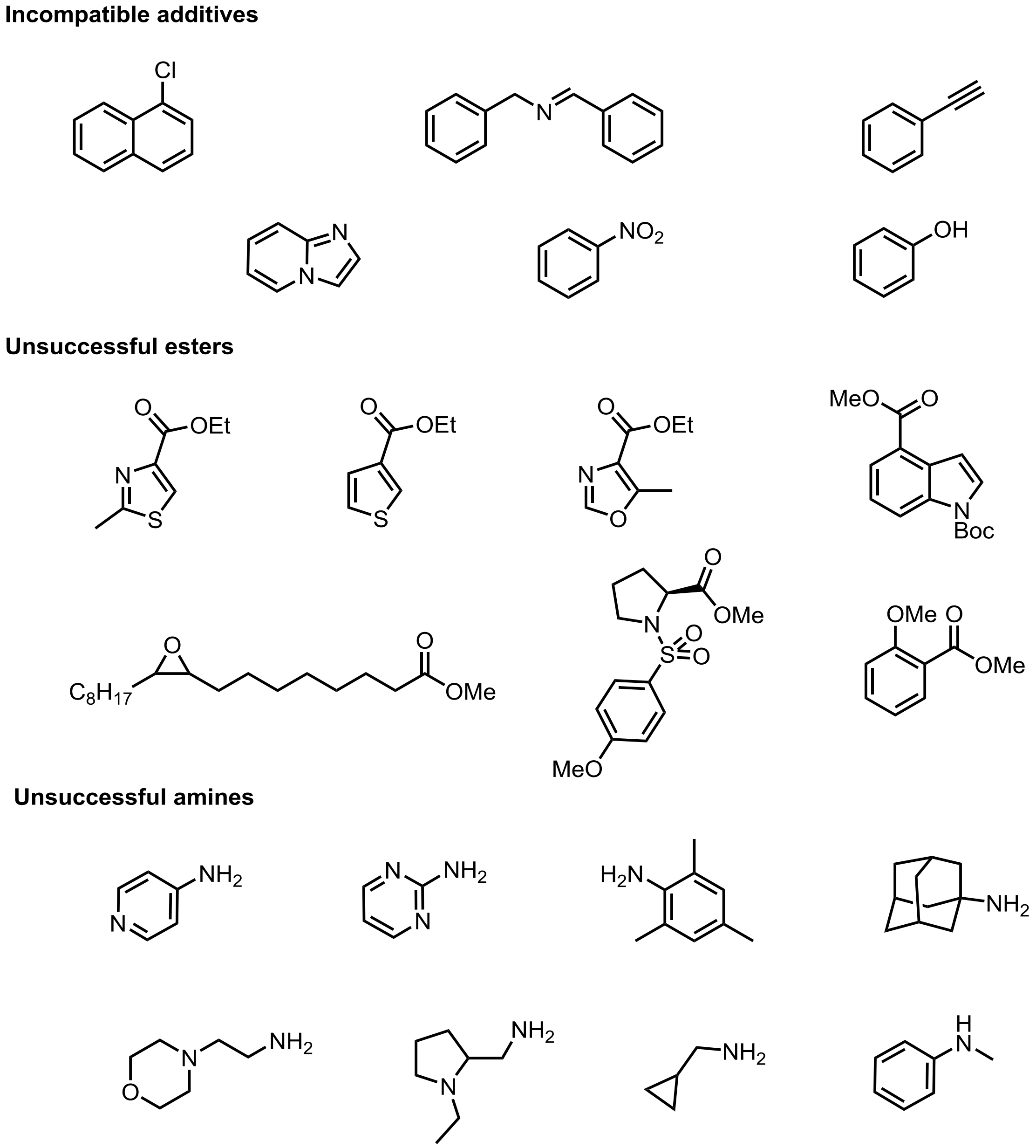
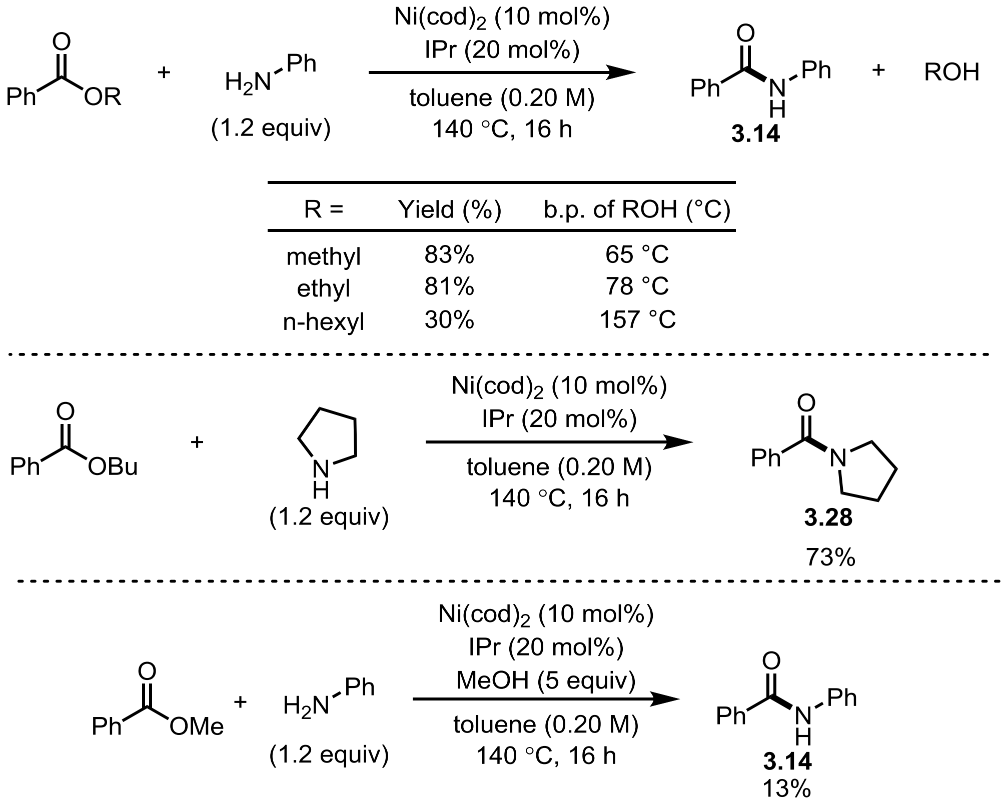


Figure 3.4. Limitations in the substrate scope

The importance of alcohol volatility

In general, the reaction proved equally effective when using both methyl and ethyl ester starting materials with aniline as a nucleophile, but diminished when using esters bearing heavier alcohol leaving groups such as hexyl benzoate (**Figure 3.5**, top). Given the modest difference in sterics between these substrates, it is likely that the higher boiling point of the heavier alcohols is responsible for reduced yields. The net reaction of an ester and aniline derivative forming a benzanilide and alcohol can be thermodynamically uphill,[19] suggesting that the removal of volatile alcohol from the reaction mixture may be critical for obtaining high yields. The negative influence of less volatile alcohol leaving groups was much less pronounced with more nucleophilic amines such as pyrrolidine (**Figure 3.5**, middle). Lastly, when the reaction was run with excess MeOH added to the vial, the yield of the benzanilide was significantly diminished (**Figure 3.5**, bottom).



R =	Yield (%)	b.p. of ROH (°C)
methyl	83%	65 °C
ethyl	81%	78 °C
n-hexyl	30%	157 °C

Figure 3.5. Influence of different alcohol leaving groups

Improving moderate yields

While the optimal described conditions proved effective for obtaining good yields of amide product in majority of cases, some notable observations were made that are important for reproducibility and improving reactions that gave unsatisfactory yields.

Air sensitivity: As is common with Ni(0) catalysis,[44] the reaction is highly sensitive to oxygen and moisture. All reactions presented were set-up in a nitrogen filled glovebox with < 1 ppm O_2 with dry, thoroughly degassed solvents. After all components were added, the vials were sealed to be air with a Teflon-lined screw cap prior to being removed from the glovebox for heating. Introduction of reagent or solvent through the septum outside of the glovebox was found to cause yields to decrease by up to 10%. Running reactions in a round bottom flask under argon have thus far lead to only moderate yields, likely due to the high air sensitivity of Ni and the challenge of excluding all O_2 on small scale.

Catalyst/ligand loading: A catalyst loading of 10 mol% is necessary to achieve good conversion in the reactions studied. Use of 5 mol% catalyst led to a decrease in yield by ~20% in select experiments. Increasing the catalyst loading to 15 or 20 mol% was sometimes found to be beneficial for particularly challenging substrates. A metal:ligand ratio of 1:2 was found to be important. Particular care must be taken when setting up small scale reactions in the glovebox, where accurately weighing these quantities can be challenging.

Starting material purity: While most experiments utilized commercially available starting materials, the purity of the amine starting materials was found to be important. For example, yields were generally above 75% with aniline as a nucleophile, provided it was recently purchased or purified. When using older, dark colored aniline, yields ranged from 20–50%. Similar observations were found with aliphatic amine nucleophiles.

Reaction time: While a 16 h reaction time was generally used throughout, it was observed that some reactions reached completion within 6 h. Moderate yielding reactions were found to benefit slightly from a longer reaction time (e.g., 40 h), but the yield typically did not increase by more than 15%.

Other comments: Other modifications that sometimes gave moderate increase in yield include increasing the reaction concentration, increasing the temperature, increasing the catalyst loading, increasing the equivalents of amine, or running the reaction in dioxane instead of toluene.

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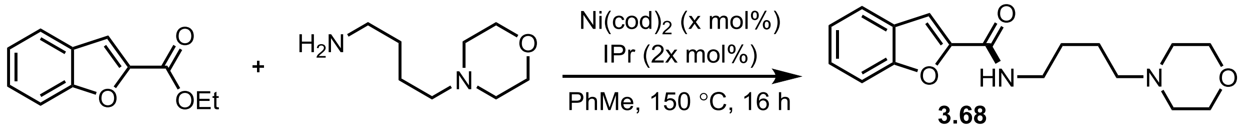
[44] Wilke, G. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 185.

Addition of freshly activated molecular sieves was observed to be modestly beneficial in some cases.

Reaction scale-up

While most experiments performed were on 0.2 mmol scale, **CL-82198** was prepared on gram scale (**Figure 3.6**). A 100 mL heavy wall pressure vessel from Chemglass (Item Number CG-1880-05) was utilized, which was partially submerged into an oil bath set at 150 °C. The reaction was run at the increased concentration of 0.4 M, and otherwise carried out identical to the small scale reactions. While a higher catalyst loading was required, this is due to the challenge of coupling these particular substrates rather than the challenge of reaction scale-up.



3.68

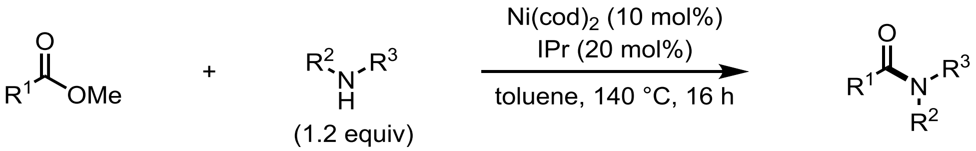
CL-82198
MMP13 inhibitor
1.03 grams prepared

Catalyst loading	Scale	Yield
10 mol%	0.2 mmol	16%
20 mol%	0.2 mmol	88%
20 mol%	3.7 mmol	93%

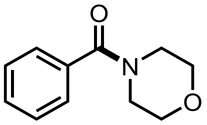
Figure 3.6. Reaction scale-up in a heavy wall pressure vessel

3.5.6 Reaction scope

General procedure for the scope of the Ni-catalyzed amidation of methyl esters



In a glovebox, an oven dried screw-capped vial was charged with a magnetic stir bar, Ni(cod)$_2$ (6 mg, 0.02 mmol, 0.1 equiv), and IPr (16 mg, 0.04 mmol, 0.2 equiv). Thoroughly degassed toluene (1.0 mL, 0.20 M) obtained from a solvent purification system was then added. The reaction mixture was shaken vigorously, and then ester (0.20 mmol, 1.0 equiv) and amine (0.24 mmol, 1.2 equiv) were subsequently added. The vial was sealed with a Teflon-lined screw cap and shipped outside of the glovebox. The reaction was stirred vigorously (700 rpm) in a silicone oil bath at 140 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride, diluted with ethyl acetate, and filtered through a plug of silica gel (10 mL of EtOAc eluent). The crude mixture was then concentrated *in vacuo* and subjected to column chromatography. When separation of the amide product from the excess amine starting material was challenging, the mixture was dissolved in EtOAc and washed with 1 M HCl $_{(aq)}$.



4-Benzoylmorpholine (3.16) was prepared according to the general procedure. Purification by column chromatography (gradient of 20% → 60% EtOAc in hexanes) afforded **3.16** as a colourless oil (35 mg, 92%). Characterization data matched those previously reported.[45] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.43-7.39 (m, 5H), 3.87-3.38 (m, 8H); **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 170.5, 135.5, 130.0, 128.7, 127.2, 67.0, 48.2, 42.7.

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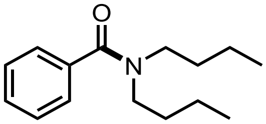
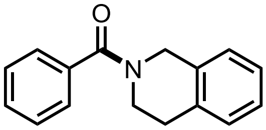
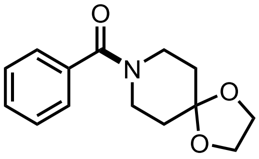
[45] Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Tuan, D. T.; Chai, C. L. L.; Chen, A. *J. Org. Chem.* **2012**, *77*, 8007.



N,N-Dibutylbenzamide (3.27) was prepared according to the general procedure. Purification by column chromatography (gradient of 20% → 30% EtOAc in hexanes) afforded **3.27** as a yellow oil (47 mg, 73%). Characterization data matched those previously reported.[46] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.39-7.33 (m, 5H), 3.49 (br, 2H), 3.19 (br, 2H), 1.76-0.78 (m, 14H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 171.8, 137.5, 129.1, 128.5, 126.6, 48.9, 44.6, 30.9, 29.8, 20.4, 19.9, 14.1, 13.7.



N-Benzoyl-1,2,3,4-tetrahydroisoquinoline (3.23) was prepared according to the general procedure. Purification by column chromatography (gradient of 10% → 60% EtOAc in hexanes) afforded **3.23** as a colourless oil (43 mg, 91%). Characterization data matched those previously reported.[47] **^{1}H NMR** (C_6D_6, 62 °C, 300 MHz): δ 7.35-7.32 (m, 2H), 7.09-7.07 (m, 3H), 6.99-6.90 (m, 2H), 6.84-6.81 (d, J = 7.4 Hz, 1H), 6.68 (br m, 1H), 4.57 (br m, 2H), 3.43 (br m, 2H), 2.45 (br m, 2H); **^{13}C NMR** (C_6D_6, 62 °C, 75 MHz): δ 170.5, 137.8, 135.2, 134.2, 129.9, 129.3, 128.8, 128.0, 127.1, 127.0, 126.9, 47.6, 43.7, 29.6.



(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)phenylmethanone (3.30) was prepared according to the general procedure with dioxane as the solvent instead of toluene. Purification by column chromatography (gradient of 20% → 60% EtOAc in hexanes) afforded **3.30** as a brown oil (38 mg, 76%). Characterization data matched those previously reported.[48] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.42-7.39 (m, 5H), 3.99 (br s, 4H), 3.86 (br s, 2H), 3.49 (br s, 2H), 1.81-1.64 (m, 4H).

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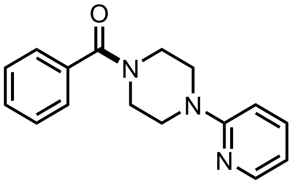
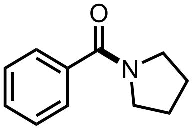
[46] Mane, R. S.; Bhanage, B. M. *J. Org. Chem.* **2016**, *81*, 1223.
[47] Gockel, S. N.; Hull, K. L. *Org. Lett.* **2015**, *17*, 3236.
[48] Narasimhulu Naidu, B.; Sorenson, M. E. HIV Integrase Inhibitors. US Patent US2007/281917, 2007.

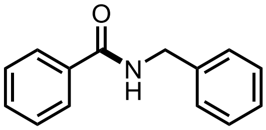
^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 170.5, 136.2, 129.7, 128.6, 126.9, 107.1, 64.6, 45.8, 40.4, 35.9, 34.9.



Phenyl(4-(pyridin-2-yl)piperazin-1-yl)methanone (3.29) was prepared according to the general procedure. Purification by column chromatography (gradient of 40% → 100% EtOAc in hexanes) afforded **3.29** as a white solid (49 mg, 91%). Characterization data matched those previously reported.[49] ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 8.21 (m, 1H), 7.53-7.49 (m, 1H), 7.46-7.43 (m, 5H), 6.69-6.66 (m, 2H), 3.90 (br s, 2H), 3.56 (br s, 6H). ^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 170.6, 159.2, 148.1, 137.8, 135.7, 130.0, 128.7, 127.2, 114.1, 107.4, 47.6, 45.6, 42.1.



N-Benzoylpyrrolidine (3.28) was prepared according to the general procedure. Purification by column chromatography (gradient of 40% → 100% EtOAc in hexanes) afforded **3.28** as a colorless oil (28 mg, 80%). Characterization data matched those previously reported.[50] ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 7.52-7.50 (m, 2H), 7.41-7.37 (m, 3H), 3.65 (t, J = 7.0 Hz, 2H), 3.42 (t, J = 6.6 Hz, 2H), 1.99-1.92 (m, 2H), 1.90-1.83 (m, 2H). ^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 169.8, 137.4, 129.8, 128.3, 127.2, 49.7, 46.3, 26.5, 24.6.



N-Benzylbenzamide (3.31) was prepared according to the general procedure. Purification by column chromatography (gradient of 10% → 40% EtOAc in hexanes) afforded **3.31** as a white

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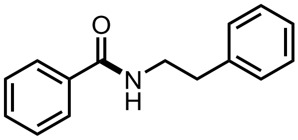
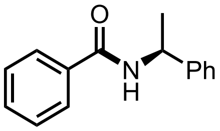
[49] Sarswat, A.; Kumar, R.; Kumar, L.; Lal, N.; Sharma, S.; Prabhakar, Y. S.; Pandey, S. K.; Lal, J.; Verma, V.; Jain, A.; Maikhuri, J. P.; Dalela, D.; Gupta, G.; Sharma, V. L. *J. Med. Chem.* **2011**, *54*, 302.

[50] Goodman, C. A.; Eagles, J. B.; Rudahindwa, L.; Hamaker, C. G.; Hitchcock, S. R. *Synth. Commun.* **2013**, *43*, 2155.

solid (31 mg, 74%). Characterization data matched those previously reported.[51] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.0 Hz, 2H), 7.37-7.28 (m, 5H), 6.53 (br s, 1H), 4.65 (d, *J* = 5.7 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.5, 138.3, 134.5, 131.8, 128.9, 128.7, 128.0, 127.7, 127.1, 44.3.



N-Phenethylbenzamide (3.32) was prepared according to a modified general procedure with 1 equivalent of phenethylamine and 1 equivalent of dibutylamine used. Purification by column chromatography (gradient of 10% → 40% EtOAc in hexanes) afforded **3.32** as a white solid (40 mg, 88%). Characterization data matched those previously reported.[52] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.70 (d, *J* = 7.1 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 6.7 Hz, 2H), 7.28-7.24 (m, 3H), 6.24 (br s, 1H), 3.73 (m, 2H), 2.95 (t, *J* = 6.7 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.6, 139.0, 134.8, 131.5, 128.9, 128.8, 128.7, 126.9, 126.7, 41.3, 35.8.



(*S*)-N-(1-Phenylethyl)benzamide (3.22) was prepared according to the general procedure, at 150 °C. Purification by column chromatography (gradient of 10% → 40% EtOAc in hexanes) afforded **3.22** as a white solid (41 mg, 91%, 99:1 e.r.). Characterization data matched those previously reported.[53] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ = 7.78 (d, *J* = 7.1 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.44-7.35 (m, 6H), 7.31-7.27 (m, 1H), 6.41 (brs, 1H), 5.39-5.32 (m, 1H), 1.62 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.7, 143.3, 134.7, 131.6, 128.9, 128.7, 127.6, 127.0, 126.4, 49.3, 21.9. **HPLC**: CHIRALCEL OD-H, 10% ^{i}PrOH in hexanes, 1.0 mL/min, 254 nm, t_{R1}(minor) = 10.5 min, t_{R2}(major) = 12.1 min.

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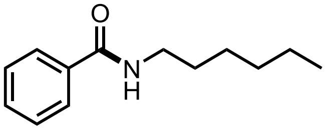
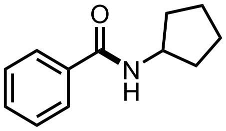
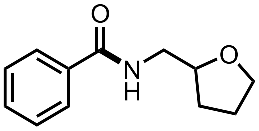
[51] Orliac, A.; Gomez Pardo, D.; Bombrun, A.; Cossy, J. *Org. Lett.* **2013**, *15*, 902.
[52] Cassani, C.; Bergonzini, G.; Wallentin, C.-J. *Org. Lett.* **2014**, *16*, 4228.
[53] Sindhuja, E.; Ramesh, R.; Balaji, S.; Liu, Y. *Organometallics* **2014**, *33*, 4269.



N-Hexylbenzamide (3.20) was prepared according to the general procedure at 150 °C. Purification by column chromatography (gradient of 10% → 40% EtOAc in hexanes) afforded **3.20** as a white solid (39 mg, 94%). Characterization data matched those previously reported.[54] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.76 (d, *J* = 7.0 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 6.33 (br s, 1H), 3.43 (q, *J* = 6.5 Hz, 2H), 1.60 (quint, *J* = 7.3 Hz, 2H), 1.41-1.26 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 167.6, 135.0, 131.4, 128.6, 127.0, 40.2, 31.6, 29.7, 26.8, 22.7, 14.1.



N-Cyclopentylbenzamide (3.33) was prepared according to the general procedure. Purification by column chromatography (gradient of 30% → 40% EtOAc in hexanes) afforded **3.33** as a white solid (33 mg, 86%). Characterization data matched those previously reported.[55] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.72 (d, *J* = 7.1 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 2H), 6.13 (br s, 1H), 4.37 (sxt, *J* = 7.0 Hz, 1H), 2.09-2.01 (m, 2H), 1.74-1.57 (m, 4H), 1.51-1.43 (m, 2H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 167.3, 135.1, 131.3, 128.6, 126.9, 51.8, 33.3, 23.9.



N-((Tetrahydrofuran-2-yl)methyl)benzamide (3.34) was prepared according to the general procedure. Purification by column chromatography (gradient of 60% → 80% EtOAc in hexanes) afforded **3.34** as a brown oil (36 mg, 88%). Characterization data matched those previously reported.[56] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.78 (d, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.1 Hz, 1H), 7.41 (m, 2H), 6.61 (s, 1H), 4.07 (qd, *J* = 7.2, 3.2 Hz, 1H), 3.88 (m, 1H), 3.77 (m, 2H), 3.34 (ddd,

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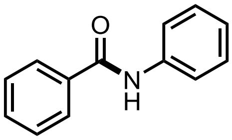
[54] Miyamura, H.; Min, H.; Soulé, J.-F.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 7564.

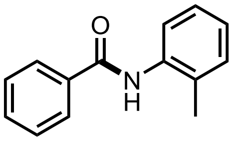
[55] Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2555.

[56] Lenstra, D. C.; Nguyen, D. C.; Mecinović, J. *Tetrahedron* **2015**, *71*, 5547.

J = 13.7, 7.4, 4.9 Hz, 1H), 2.02 (m, 1H), 1.91 (m, 2H), 1.61 (m, 1H). ^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 167.6, 134.6, 131.5, 128.6, 127.1, 77.9, 68.2, 43.7, 28.8, 26.0.



Benzanilide (3.14) was prepared according to the general procedure, starting either from methyl benzoate or ethyl benzoate. Purification by column chromatography (gradient of 10% → 40% EtOAc in hexanes) afforded **3.14** as a white solid (methyl benzoate: 33 mg, 83%; ethyl benzoate: 32 mg, 81%). Amide **3.14** synthesized from ethyl benzoate was purified by column chromatography (gradient of 5% → 35% EtOAc in hexanes) to afford a white solid (32 mg, 81%). Characterization data matched those previously reported.[57] ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 7.96 (br s, 1H), 7.88-7.86 (m, 2H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H); ^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 165.9, 138.1, 135.1, 132.0, 129.2, 128.9, 127.2, 124.7, 120.4.



N-Benzoyl-2-methylaniline (3.35) was prepared according to the general procedure. Subsequent purification by column chromatography (gradient of 5% → 30% EtOAc in hexanes) afforded **3.35** as a yellow solid (34 mg, 80%). Characterization data matched those previously reported.[58] ^{1}**H NMR** ($CDCl_3$, 400 MHz): δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.3 Hz, 2H), 7.75 (br s, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.29-7.23 (m, 2H), 7.14 (t, *J* = 6.7 Hz, 1H), 2.34 (s, 3H). ^{13}**C NMR** ($CDCl_3$, 100 MHz): δ 165.8, 135.1, 135.1, 131.9, 130.7, 129.5, 128.9, 127.2, 127.0, 125.5, 123.3, 17.9.

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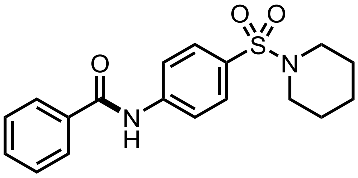
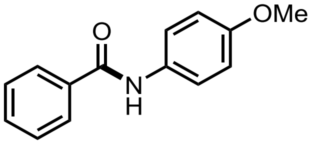
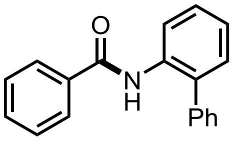
[57] Rao, Y., Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 12924.
[58] Schneider, T. L.; Halloran, K. T.; Hillner, J. A.; Conry, R. R.; Linton, B. R. *Chem. Eur. J.* **2013**, *19*, 15101.



1-(N-Benzoyl-sulfanilyl)-piperidine (3.36) was prepared according to the general procedure. Purification by column chromatography (gradient of 40% → 50% EtOAc in hexanes) afforded **3.36** as a white solid (36 mg, 53%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.11 (br s, 1H), 7.90 (d, *J* = 7.0 Hz, 2H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 2.99 (t, *J* = 5.3 Hz, 4H), 1.68-1.62 (m, 4H), 1.46-1.40 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.1, 142.0, 134.4, 132.6, 131.6, 129.1, 127.3, 119.9, 47.1, 25.3, 23.6. **IR (neat)**: 3404, 2921, 2845, 1687, 1584, 1520, 1498, 1467, 1446, 1397, 1357, 1329, 1309, 1279, 1247, 1210, 1148, 1099, 1051, 1028, 998, 927, 893, 855, 834, 817, 798, 735, 706 cm^{-1}. **HRMS** (ESI-Q-TOF): m/z calculated for $C_{18}H_{20}N_2O_3SNa$ $[M+Na]^+$: 367.1092, found 367.1086. **m.p.**: 190-192 °C.

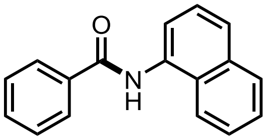


N-(*p*-Methoxyphenyl) benzamide (3.38) was prepared according to the general procedure. Purification by column chromatography (gradient of 10% → 40% EtOAc in hexanes) afforded **3.38** as a white solid (36 mg, 78%). Characterization data matched those previously reported.[43] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 7.3 Hz, 2H), 7.82 (br s, 1H), 7.56-7.53 (m, 3H), 7.48 (t, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.8, 156.8, 135.2, 131.8, 131.2, 128.9, 127.1, 122.3, 114.4, 55.7.

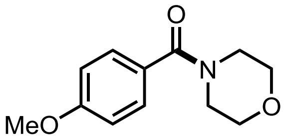


N-([1,1'-Biphenyl]-2-yl)benzamide (3.37) was prepared according to the general procedure. Purification by column chromatography (gradient of 10% → 40% EtOAc in hexanes) afforded **3.37** as a white solid (33 mg, 60%). Characterization data matched those previously reported.[32]

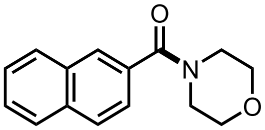
^{1}H NMR (CDCl$_3$, 400 MHz): δ = 8.55 (d, *J* = 8.0 Hz, 1H), 8.01 (br s, 1H), 7.63–7.60 (m, 2H), 7.53–7.51 (m, 2H), 7.50–7.44 (m, 5H), 7.42–7.38 (m, 2H), 7.33–7.31 (m, 1H), 7.26–7.21 (m, 1H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 165.4, 138.4, 135.2, 135.1, 132.7, 132.0, 130.3, 129.8, 129.7, 129.5, 129.1, 128.9, 128.5, 127.1, 124.71, 121.5, 115.7.



N-1-Naphthalenyl-benzamide (3.39) was prepared according to the general procedure. Purification by column chromatography (gradient of 20% → 50% EtOAc in hexanes) afforded **3.39** as a white solid (35 mg, 70%). Characterization data matched those previously reported.[59] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 8.26 (br s, 1H), 8.04-7.99 (m, 3H), 7.93-7.90 (m, 2H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.62-7.59 (m, 1H), 7.56-7.50 (m, 5H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 166.4, 135.0, 134.3, 132.5, 132.1, 129.0, 129.0, 127.6, 127.3, 126.6, 126.3, 126.2, 125.9, 121.4, 120.8.



N-(4-Methoxybenzoyl)morpholine (3.40) was prepared according to the general procedure at 150°C instead of 140°C. Purification by column chromatography (gradient of 40% → 100% EtOAc in hexanes) afforded **3.40** as a yellow liquid (33 mg, 74%). Characterization data matched those previously reported.[60] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.39 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.74-3.56 (m, 8H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 170.5, 161.0, 129.3, 127.4, 113.9, 67.0, 55.5, 48.3 (br), 44.1 (br).



Morpholino(naphthalen-2-yl)methanone (3.41) was prepared according to the general procedure. Purification by column chromatography (gradient of 20% → 60% EtOAc in hexanes)

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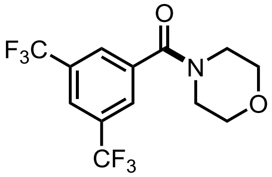
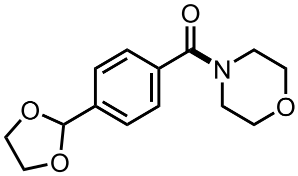
[59] Chen, M.; Li, Y.; Tang, H.; Ding, H.; Wang, K.; Yang, L.; Li, C.; Gao, M.; Lei, A. *Org. Lett.* **2017**, *19*, 3147.
[60] Tu, Y.; Yuan, L.; Wang, T.; Wang, C.; Ke, J.; Zhao, J. *J. Org. Chem.* **2017**, *82*, 4970.

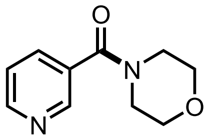
afforded **3.41** as a yellow solid (43 mg, 90%). Characterization data matched those previously reported.[60] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.92 (br s, 1H), 7.90-7.86 (m, 3H), 7.57-7.52 (m, 2H), 7.50 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.95-3.35 (m, 8H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 170.6, 133.8, 132.8, 132.7, 128.5, 128.5, 127.9, 127.3, 127.1, 126.9, 124.3, 67.0, 48.3, 42.8.



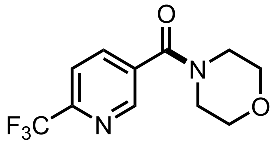
[3,5-Bis(Trifluoromethyl)phenyl]-morpholin-4-ylmethanone (3.42) was prepared according to the general procedure. Purification by column chromatography (gradient of 30% → 70% EtOAc in hexanes) afforded **3.42** as a light yellow oil (58 mg, 88%). **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.95 (s, 1H), 7.88 (s, 2H), 3.81-3.44 (m, 8H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 167.3, 137.5, 132.4 (q, *J* = 34 Hz), 127.6 (m), 124.3, 123.8 (sept, *J* = 3.7 Hz), 123.0 (q, *J* = 271 Hz), 66.8, 48.3, 42.9. **IR (neat)**: 2972, 2859, 1641, 1435, 1375, 1360, 1274, 1250, 1177, 1126, 1109, 1073, 1029, 947, 902, 849, 790, 755, 719, 705, 681 cm^{-1}. **Accurate mass (MS)**: m/z calculated for $C_{13}H_{11}F_6NO_2$: 327.0688, found 327.0676 (spectral accuracy = 99.0%).



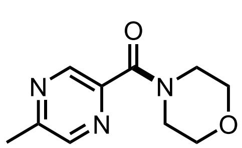
[4-(1,3-Dioxolan-2-yl)phenyl]-morpholin-4-ylmethanone (3.43) was prepared according to the general procedure. Purification by column chromatography (gradient of 80% → 100% EtOAc in hexanes) afforded **3.43** as a white solid (44 mg, 83%). **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 5.83 (s, 1H), 4.16-4.01 (m, 4H), 3.85-3.35 (m, 8H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 170.1, 139.8, 136.2, 127.3, 126.8, 103.2, 66.9, 65.5, 48.1, 42.7. **IR (neat)**: 2962, 2919, 2860, 1720, 1626, 1508, 1459, 1435, 1400, 1361, 1336, 1306, 1283, 1262, 1205, 1159, 1111, 1095, 1069, 1012, 936, 900, 841, 821, 754, 701 cm^{-1}. **Accurate mass (MS)**: m/z calculated for $C_{14}H_{17}NO_4$: 263.1152, found 263.1145 (spectral accuracy = 100%). **m.p.**: 96-98 °C.



Morpholino(pyridin-3-yl)methanone (3.44) was prepared according to the general procedure starting either from methyl nicotinate or ethyl nicotinate. Purification by column chromatography (gradient pure EtOAc → 20% MeOH in EtOAc) afforded **3.44** as a yellow liquid (methyl nicotinate: 29 mg, 75%; ethyl nicotinate: 26 mg 67%). Characterization data matched those previously reported.[61] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.69-8.66 (m, 2H), 7.77 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.38 (ddd, *J* = 8.0, 5.3, 0.8 Hz, 1H), 3.90-3.37 (m, 8H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.9, 151.1, 148.1, 135.3, 131.3, 123.7, 66.9, 48.3, 42.8.



Morpholin-4-yl-[6-(trifluoromethyl)pyridin-3-yl]methanone (3.45) was prepared according to the general procedure. Purification by column chromatography (gradient of 20% → 60% EtOAc in hexanes) afforded **3.45** as a light yellow oil (44 mg, 85%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.76 (s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 3.88-3.37 (m, 8H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.5, 149.2 (q, *J* = 35 Hz), 148.2, 136.7, 134.1, 121.2 (q, *J* = 273 Hz), 120.6, 66.8, 48.3, 42.8. **IR (neat)**: 2967, 2921, 2857, 1719, 1632, 1491, 1433, 1381, 1333, 1303, 1280, 1263, 1176, 1131, 1111, 1081, 1033, 1011, 938, 894, 858, 842, 739, 720, 661 cm^{-1}. **Accurate mass (MS)**: m/z calculated for $C_{11}H_{11}F_3N_2O_2$: 260.0737, found 260.0767 (spectral accuracy = 99.4%).



(5-Methylpyrazin-2-yl)(morpholino)methanone (3.46) was prepared according to the general procedure. Purification by column chromatography (gradient of 100% EtOAc → 20% MeOH in

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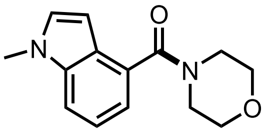
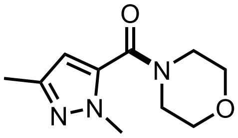
[61] Krabbe, S. W.; Chan, V. S.; Franczyk, T. S.; Shekhar, S.; Napolitano, J. G.; Presto, C. A.; Simanis, J. A. *J. Org. Chem.*, **2016**, *81*, 10688.

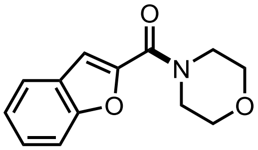
EtOAc) afforded **3.46** as a yellow oil (35 mg, 84%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.86 (d, *J* = 1.4 Hz, 1H), 8.39 (d, *J* = 1.0 Hz, 1H), 3.80 (s, 4H), 3.69 (s, 4H), 2.61 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.5, 155.3, 145.9, 145.0, 142.2, 67.1, 66.9, 47.8, 43.0, 21.8. **IR (neat)**: 2964, 2921, 2855, 1626, 1575, 1489, 1432, 1380, 1363, 1321, 1299, 1277, 1263, 1246, 1163, 1111, 1068, 1037, 1020, 937, 9078, 848, 827, 783, 729, 690 cm^{-1}. **Accurate mass (MS)**: m/z calculated for $C_{10}H_{13}N_3O_2$: 207.1002, found 207.1008 (spectral accuracy = 99.5%).



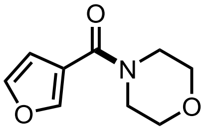
(1-Methyl-1H-indol-4-yl)(morpholino)methanone (3.47) was prepared according to the general procedure. Purification by column chromatography (gradient of 50% → 100% EtOAc in hexanes) afforded **3.47** as a white solid (43 mg, 87%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.37 (d, *J* = 8.2 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.15 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 6.49 (dd, *J* = 3.0, 0.7 Hz, 1H), 3.95-3.27 (m, 8H), 3.81 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 170.3, 136.9, 130.1, 127.7, 125.7, 121.4, 118.4, 110.7, 100.0, 67.3, 48.0, 42.8, 33.1. **IR (neat)**: 3105, 2921, 2854, 1617, 1575, 1512, 1498, 1432, 1366, 1339, 1304, 1291, 1276, 1262, 1209, 1195, 1154, 1112, 1084, 1074, 1031, 966, 925, 891, 879, 849, 825, 804, 751, 737, 711, 685 cm^{-1}. **Accurate mass (MS)**: m/z calculated for $C_{14}H_{16}N_2O_2$: 244.1179, found 244.1206 (spectral accuracy = 99.0%). **m. p.**: 152-154 °C.



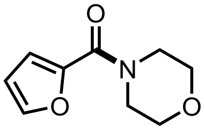
4-(2,5-Dimethyl-2H-pyrazole-3-carbonyl)-morpholine (3.48) was prepared according to the general procedure starting from the corresponding ethyl ester. Purification by column chromatography (gradient of 100% EtOAc → 20% MeOH in EtOAc) afforded **3.48** as a brown solid (27 mg, 64%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 6.07 (s, 1H), 3.90 (s, 3H), 3.70 (br s, 8H), 2.26 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.4, 147.1, 135.4, 106.3, 67.0, 48.0, 42.7, 37.9, 13.4. **IR (neat)**: 3113, 2959, 2925, 2863, 1623, 1541, 1466, 1439, 1358, 1302, 1274, 1246, 1167, 1113, 1065, 1008, 936, 890, 841, 823, 779, 751, 677, 661 cm^{-1}. **Accurate mass (MS)**: m/z calculated for $C_{10}H_{15}N_3O_2$: 209.1159, found 209.1093 (spectral accuracy = 99.6%). **m.p.**: 68–70 °C.



Benzofuran-2-yl(morpholino)methanone (3.49) was prepared according to the general procedure from the corresponding ethyl ester. Purification by column chromatography (gradient of 10% → 40% EtOAc in hexanes) afforded **3.49** as a red solid (38 mg, 82%). Characterization data matched those previously reported.[62] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.3, 1.2 Hz, 1H), 7.35 (s, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 3.98-3.82 (m, 4H), 3.79-3.78 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 159.9, 154.7, 148.9, 127.0, 126.7, 123.8, 122.4, 112.6, 112.0, 67.1, 47.2, 43.6.



3-Furanyl 4-morpholinyl methanone (3.50) was prepared according to the general procedure. Purification by column chromatography (gradient of 20% → 60% EtOAc in hexanes) afforded **3.50** as a yellow oil (28 mg, 76%). Characterization data matched those previously reported.[63] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.71 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.44 (t, *J* = 1.7 Hz, 1H), 6.55 (dd, *J* = 1.8, 0.8 Hz, 1H), 3.71 (br s, 8H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 164.0, 143.7, 143.2, 120.8, 110.2, 67.0.



2-Furanyl 4-morpholinyl methanone (3.51) was prepared according to the general procedure starting either from methyl 2-furoate or ethyl 2-furoate. Purification by column chromatography (gradient of 10% → 60% EtOAc in hexanes) afforded **3.51** as a yellow oil (methyl furoate: 26

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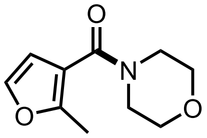
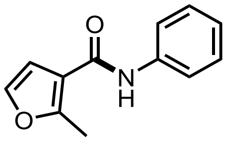
[62] Baba, H.; Moriyama, K.; Togo, H. *Synlett* **2012**, *23*, 1175.
[63] Zanatta, N.; Faoro, D.; Silva, S. C.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2014**, *45*, 5689.

mg, 72%; ethyl furoate: 23 mg, 63%). Characterization data matched those previously reported.[64] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.48 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.03 (dd, *J* = 3.4, 0.9 Hz, 1H), 6.49 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.82 (br s, 4H), 3.76-3.74 (m, 4H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 159.2, 147.9, 143.9, 116.9, 111.5, 67.1, 29.8.



4-(2-Methyl-furan-3-carbonyl)-morpholine (3.52) was prepared according to the general procedure. Purification by column chromatography (gradient of 30% → 70% EtOAc in hexanes) afforded **3.52** as a white solid (29 mg, 74%). Characterization data matched those previously reported.[65] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.25 (d, *J* = 2.0 Hz, 1H), 6.32 (d, *J* = 1.8 Hz, 1H), 3.75-3.66 (br m, 8H), 2.39 (s, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 165.5, 153.8, 140.5, 115.3, 110.2, 67.1, 47.5, 42.5, 13.1.



Fenfuram (3.53) was prepared according to the general procedure at 1.0 M concentration. Purification by column chromatography (gradient of 5% → 20% EtOAc in hexanes) afforded **3.53** as a yellow solid (15 mg, 38%). Characterization data matched those previously reported.[66] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 7.58 (dd, *J* = 8.6 Hz, 1.0 Hz, 2H), 7.43 (br s, 1H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 2.2 Hz, 1H), 7.13 (t, *J* = 7.4, 1.2 Hz, 1H), 6.55 (d, *J* = 2.2 Hz, 1H), 2.64 (s, 3H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 162.2, 158.1, 140.7, 137.9, 129.2, 124.5, 120.3, 115.9, 108.3, 13.8.

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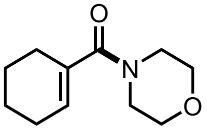
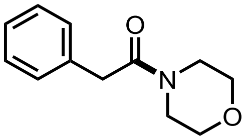
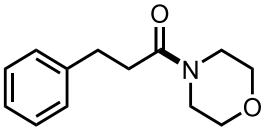
[64] Gu, J.; Fang, Z.; Liu, C.; Li, X.; Weia, P.; Guo, K. *RSC Adv.* **2016**, *6*, 72121.
[65] Maadadi, R.; Pevzner, L. M.; Petrov, M. L. *Russ. J. Gen. Chem.* **2015**, *85*, 2571.
[66] Bisagni, E.; Lhoste, J.-M.; Hung, N. C. *J. Heterocyclic Chem.* **1981**, *18*, 755.



(Cyclohex-1-enyl)(morpholin-4-yl)methanone (3.54) was prepared according to the general procedure. Purification by column chromatography (gradient of 20% → 60% EtOAc in hexanes) afforded **3.54** as a yellow oil (31 mg, 79%). Characterization data matched those previously reported.[67] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.82-5.80 (m, 1H), 3.67-3.64 (m, 4H), 3.61-3.54 (m, 4H), 2.20-2.17 (m, 2H), 2.13-2.08 (m, 2H), 1.72-1.67 (m, 2H), 1.65-1.60 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 172.0, 134.0, 128.4, 67.1, 29.8, 26.1, 24.7, 22.1, 21.7.



N-(Phenylacetyl)morpholine (3.55) was prepared according to the general procedure. Purification by column chromatography (gradient of 20% → 60% EtOAc in hexanes) afforded **3.55** as a white solid (29 mg, 71%). The yield was 74% starting from the ethyl ester. Characterization data matched those previously reported.[68] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.36-7.32 (m, 2H), 7.28-7.24 (m, 3H), 3.74 (s, 2H), 3.65 (br s, 4H), 3.50-3.43 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 169.8, 134.9, 128.9, 128.6, 127.1, 66.9, 66.6, 46.7, 42.3, 41.0.



4-(3-Phenyl-propionyl)-morpholine (3.56) was prepared according to the general procedure from the corresponding ethyl ester. Purification by column chromatography (gradient of 10% → 80% EtOAc in hexanes) afforded **3.56** as a colourless oil (35 mg, 79%). Characterization data matched those previously reported.[69] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.28 (m, 2H), 7.23-7.20 (m, 3H), 3.63 (br s, 4H), 3.51 (t, J = 4.9 Hz, 2H), 3.36 (t, J = 5.1 Hz, 2H), 2.99 (t, J = 8.2

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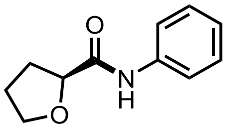
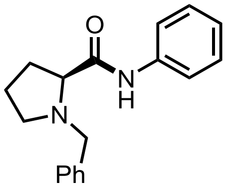
[67] Hayashi, C.; Hayashi, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 862.
[68] Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 5713.
[69] Davidsona, R. W. M.; Fuchter, M. J. *Chem. Commun.* **2016**, *52*, 11638.

Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 171.0, 141.2, 128.7, 128.6, 126.4, 67.0, 66.6, 46.1, 42.1, 34.9, 31.6.



(S)-N-Phenyloxolane-2-carboxamide (3.58) was prepared according to the general procedure starting from (S)-methyl tetrahydrofuran-2-carboxylate (**3.84**) (97.5:2.5 e.r.). Purification by column chromatography (gradient of 5% → 30% EtOAc in hexanes) afforded **3.58** as a light yellow oil (35 mg, 91%, 97:3 e.r.). Characterization data matched those previously reported.[70] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.47 (br s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 4.48 (dd, *J* = 8.4, 5.9 Hz, 1H), 4.08-3.94 (m, 2H), 2.42-2.33 (m, 1H), 2.24-2.16 (m, 1H), 2.03-1.88 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 171.4, 137.4, 129.2, 124.5, 119.7, 78.8, 69.8, 30.3, 25.7. **HPLC**: CHIRALCEL AD-H, gradient 2% to 5% ^{i}PrOH in hexanes, 1.0 mL/min, 230 nm, t_{R1}(minor) = 32.5 min, t_{R2}(major) = 38.4 min. **$[\alpha]_D^{22}$** = +7.41 (c = 0.00054 g/mL, MeCN).



(S)-1-Benzyl-N-phenylpyrrolidine-2-carboxamide (3.59) was prepared according to the general procedure. Purification by column chromatography (gradient of 10% → 30% EtOAc in hexanes) afforded **3.59** as a white solid (20 mg, 35%, >99:1 e.r.). Characterization data matched those previously reported.[71] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.47 (br s, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.39-7.26 (m, 7H), 7.11 (t, *J* = 7.5 Hz, 1H), 3.96 (d, *J* = 13.1 Hz, 1H), 3.61 (d, *J* = 12.9 Hz, 1H), 3.36 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.15 (ddd, *J* = 9.2, 6.8, 2.3 Hz, 1H), 2.48 (td, *J* = 9.8, 6.5, 1H), 2.37-2.27 (m, 1H), 2.08-2.00 (m, 1H), 1.88-1.74 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 172.9, 138.5, 137.9, 129.1, 128.8, 128.8, 127.6, 124.1, 119.4, 68.1, 60.2, 54.2, 30.9, 24.5.

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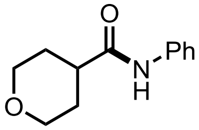
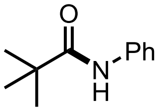
[70] Zhang, L.; Wang, W.; Wang, A.; Cui, Y.; Yang, X.; Huang, Y.; Liu, X.; Liu, W.; Son, J.-Y.; Oji, H.; Zhang, T. *Green Chem.* **2013**, *15*, 2680.
[71] Yang, H.; Xi, C.; Miao, Z.; Chen, R. *Eur. J. Org. Chem.* **2011**, 3353.

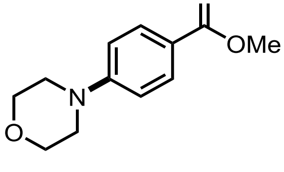
HPLC: CHIRALCEL AD-H, gradient 7% ^{i}PrOH in hexanes, 1.0 mL/min, 254 nm, t_{R1}(minor) = 7.9 min, t_{R2}(major) = 9.9 min. $[\alpha]_{D}^{22}$ = -147 (c = 0.00036 g/mL, MeCN).



Tetrahydro-pyran-4-carboxylic acid anilide (3.60) was prepared according to the general procedure at 150 °C instead of 140 °C. Purification by column chromatography (gradient of 20% → 50% EtOAc in hexanes) afforded **3.60** as a white solid (27 mg, 65%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.54-7.52 (d, *J* = 7.8 Hz, 2H), 7.38 (br s, 1H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 4.06 (d, *J* = 11.4 Hz, 2H), 3.44 (td, *J* = 11.6, 2.1 Hz, 2H), 2.54-2.46 (m. 1H), 1.98-1.82 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 172.7, 137.9, 129.2, 124.5, 120.0, 67.3, 43.4, 29.3. **IR (neat)**: 3330, 3063, 2960, 2917, 2845, 2833, 2761, 2696, 1661, 1598, 1536, 1496, 1470, 1439, 1381, 1335, 1322, 1306, 1280, 1245, 1191, 1179, 1127, 1087, 1046, 1012, 986, 964, 905, 845, 758, 731, 693, 674 cm^{-1}. **Accurate mass (MS)**: m/z calculated for $C_{12}H_{15}NO_2$: 205.1037, found 205.1097 (spectral accuracy = 98.5%). **m.p.**: 145–147 °C.



N-Pivaloylaniline (3.61) was prepared according to the general procedure at 150 °C instead of 140 °C. Purification by column chromatography (gradient of 5% → 30% EtOAc in hexanes) afforded **3.61** as a white solid (21 mg, 60%). Characterization data matched those previously reported.[72] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.34 (br s, 1H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 1.33 (s, 9H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 176.7, 138.2, 129.1, 124.3, 120.1, 39.7, 27.8.



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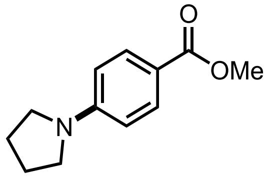
[72] Zhu, Y.-P.; Sergeyev, S.; Franck, P.; Orru, R. V. A.; Maes, B. U. W. *Org Lett.* **2016**, *18*, 4602.

Morpholin-4-yl-benzoic acid methyl ester (3.62b) was synthesized via an S_NAr reaction. An oven dried screw-capped vial was charged with a magnetic stir bar, ester **3.63** (26 µL, 0.20 mmol, 1.0 equiv), morpholine (17 µL, 0.20 mmol, 1.0 equiv), potassium carbonate (42 mg, 0.3 mmol, 1.5 equiv), and DMSO (1.0 mL). The reaction was sealed with a Teflon-lined screw cap and stirred at 140 ºC for 16 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (1 mL) and the organic phase was extracted with EtOAc. The crude mixture was concentrated *in vacuo*, and purified via flash column chromatography (gradient eluent 10 → 50% EtOAc in hexanes). Product **3.62b** was obtained as a white powder (34 mg, 77%). Characterization data matched those previously reported.[73] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.94 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 3.86 (t, *J* = 5.1 Hz, 4H), 3.29 (t, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.2, 154.3, 131.4, 120.5, 113.6, 66.7, 51.8, 47.9.



4-Pyrrolidin-1-yl-benzoic acid methyl ester (3.62a) was synthesized via S_NAr. An oven dried screw-capped vial was charged with a magnetic stir bar, ester **3.63** (26 µL, 0.20 mmol, 1.0 equiv), pyrrolidine (16.4 µL, 0.20 mmol, 1.0 equiv), potassium carbonate (42 mg, 0.30 mmol, 1.5 equiv), and DMSO (1.0 mL). The reaction was sealed with a Teflon-lined screw cap and stirred at 140 ºC for 16 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (1 mL) and the organic phase was extracted with EtOAc. The crude mixture was concentrated *in vacuo*, and purified via flash column chromatography (gradient eluent 10 → 40% EtOAc in hexanes). Product **3.62a** was obtained as a brown solid (35 mg, 85%). Characterization data matched those previously reported.[74] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.91 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.36 (t, *J* = 6.5 Hz, 4H), 2.04 (t, *J* = 6.6 Hz, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.7, 150.9, 131.4, 116.3, 110.7, 51.5, 47.6, 25.5.

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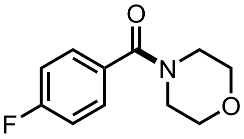
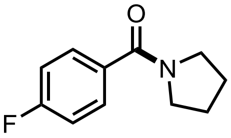
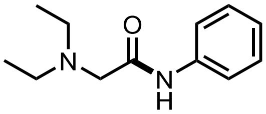
[73] Sandtorv, A. H.; Stuart, D. R. *Angew. Chem. Int. Ed.* **2016**, *55*, 15812.
[74] Noble, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 11602.



4-(4-Fluorobenzoyl) morpholine (3.65b) was prepared according to the general procedure, at 150 °C instead of 140 °C. Purification by column chromatography (gradient of 20% → 60% EtOAc in hexanes) afforded **3.65b** as a light yellow oil (30 mg, 71%). Characterization data matched those previously reported.[75] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.43 (dd, *J* = 8.6 Hz, 5.3 Hz, 2H), 7.11 (t, *J* = 8.6 Hz, 2H), 3.90-3.40 (m, 8H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 169.6, 163.6 (d, *J* = 248 Hz), 131.4 (d, *J* = 2.9 Hz), 129.6 (d, *J* = 8.8 Hz), 115.8 (d, *J* = 21.3 Hz), 67.0, 48.4, 43.1.



(4-Fluorophenyl)(pyrrolidin-1-yl) methanone (3.65a) was prepared according to the general procedure at 150 °C instead of 140 °C. Purification by column chromatography (gradient of 20% → 70% EtOAc in hexanes) afforded **3.65a** as a white solid (31 mg, 80%). Characterization data matched those previously reported.[76] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.54 (dd, *J* = 8.5 Hz, 5.5 Hz, 2H), 7.08 (t, *J* = 8.7 Hz, 2H), 3.64-3.43 (m, 4H), 1.95-1.90 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 168.8, 163.6 (d, *J* = 250 Hz), 133.4 (d, *J* = 3.7 Hz), 129.6 (d, *J* = 8.8 Hz), 115.4 (d, *J* = 22.0 Hz), 49.8, 46.4, 26.6, 24.6.



2-Diethylamino-N-phenylacetamide (3.72a) was prepared according to a modified general procedure at 145 °C for 40 h at 0.40 M. Purification by column chromatography (gradient of 40% → 100% EtOAc in hexanes) afforded **3.72a** as a yellow oil (32 mg, 77%). Characterization

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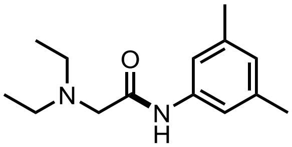
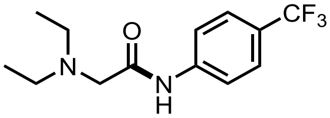
[75] Gálvez, A. O.; Schaack, C. P.; Noda, H.; Bode, J. W. *J. Am. Chem. Soc.* **2017**, *139*, 1826.
[76] Leow, D. *Org. Lett.* **2014**, *16*, 5812.

data matched those previously reported.[77] **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 9.43 (br s, 1H), 7.59 (dd, *J* = 8.5 Hz, 1.1 Hz, 2H), 7.34 (t, *J* = 8.4 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 3.16 (s, 2H), 2.66 (q, *J* = 7.1 Hz, 4H), 1.10 (t, *J* = 7.5 Hz, 6H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 170.2, 137.8, 129.1, 124.2, 119.4, 58.2, 49.0, 12.6.



2-(Diethylamino)-N-(3,5-dimethyl-phenyl)acetamide (3.72c) was prepared according to a modified general procedure at 145 °C for 40 h at 0.40 M. Purification by column chromatography (gradient of 50% EtOAC in hexanes → 10% MeOH in EtOAc) afforded **3.72c** as an orange oil (37 mg, 78%). **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 9.31 (br s, 1H), 7.22 (s, 2H), 6.76 (s, 1H), 3.14 (s, 2H), 2.65 (q, *J* = 7.3 Hz, 4H), 2.32 (s, 6H), 1.10 (t, *J* = 7.2 Hz, 6H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 170.1, 138.8, 137.7, 125.9, 117.1, 58.3, 49.0, 21.5, 12.6. **IR (neat)**: 3291, 2968, 2923, 2827, 1686, 1611, 1530, 1450, 1421, 1376, 1323, 1296, 1270, 1204, 1162, 1118, 1089, 1068, 1038, 978, 908, 888, 838, 786, 739, 688 cm^{-1}. **Accurate mass (MS)**: m/z calculated for $C_{14}H_{22}N_2O$: 234.1727, found 234.1740 (spectral accuracy = 99.0%).



2-(Diethylamino)-N-(4-trifluoromethyl-phenyl)acetamide (3.72b) was prepared according to a modified general procedure at 145 °C for 40 h at 0.40 M. Purification by column chromatography (gradient 70% → 100% EtOAc in hexanes) afforded **3.72b** as an orange solid (33 mg, 59%). **^{1}H NMR** (CDCl$_3$, 400 MHz): δ 9.62 (br s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 3.14 (s, 2H), 2.64 (q, *J* = 7.1 Hz, 4H), 1.07 (t, *J* = 7.2 Hz, 6H). **^{13}C NMR** (CDCl$_3$, 100 MHz): δ 170.7, 140.8, 126.4 (q, *J* = 3.7 Hz), 125.9 (q, *J* = 32 Hz), 124.3 (q, *J* = 270 Hz), 119.0, 58.2, 49.1, 12.6. **IR (neat)**: 3264, 2964, 2930, 2870, 2824, 1683, 1614, 1592, 1524, 1503, 1409, 1370, 1318, 1261, 1206, 1185, 1159, 1125, 1113, 1083, 1066, 1017, 996, 978, 865,

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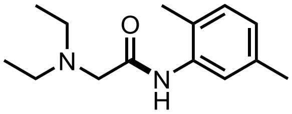
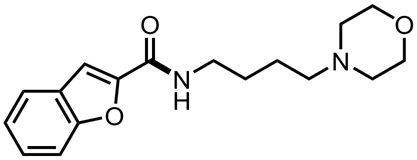
[77] Yoshimitsu, T.; Matsuda, K.; Nagaoka, H.; Tsukamoto, K.; Tanaka, T. *Org Lett.* **2007**, *9*, 5115.

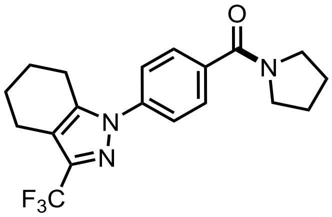
837, 785, 747, 732, 695 cm^{-1}. **HRMS** (ESI-Q-TOF): m/z calculated for $C_{13}H_{18}F_3N_2O$ [M+H]$^+$: 275.1371, found 275.1377. **m.p.**: 44-46 °C



2-(Diethylamino)-N-(2,5-dimethyl-phenyl)acetamide (JM25-1) was prepared according to a modified general procedure at 145 °C for 40 h at 0.40 M with 20 mol% catalyst loading. Purification by column chromatography (70% EtOAC in hexanes) afforded **JM25-1** as an orange oil (26 mg, 54%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.47 (br s, 1H), 8.01 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 3.19 (s, 2H), 2.67 (q, *J* = 7.1 Hz, 4H), 2.34 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 6H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 170.0, 136.8, 135.9, 130.2, 125.0, 124.0, 121.5, 58.6, 48.9, 21.4, 17.4, 12.8. **IR (neat)**: 3300, 2968, 2925, 2871, 2826, 1691, 1581, 1528, 1483, 1450, 1421, 1377, 1347, 1288, 1260, 1204, 1161, 1122, 1089, 1067, 1039, 1003, 980, 888, 803, 731, 680 cm^{-1}. **HRMS** (ESI-Q-TOF): m/z calculated for $C_{14}H_{23}N_2O$ [M+H]$^+$: 235.1810, found 235.2026.



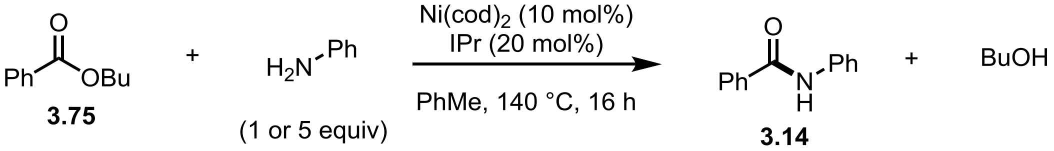
N-[4-(4-Morpholinyl)butyl]-2-benzofurancarboxamide (CL-82198) was prepared according to a modified general procedure on 3.7 mmol scale in a 100 mL heavy wall pressure vessel with 20 mol% catalyst loading at 0.4 M concentration. Purification by column chromatography (gradient of 40% → 100% EtOAc in hexanes) afforded **CL-82198** as a yellow oil (1034 mg, 93%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.67 (d, *J* = 7.8 Hz, 1H), 7.48-7.46 (m, 2H), 7.40 (td, *J* = 7.7, 1.1 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.06 (br s, 1H), 3.76 (t, *J* = 4.6 Hz, 4H), 3.51 (q, *J* = 6.5 Hz, 2H), 2.47 (m, 4H), 2.41 (t, *J* = 7.1 Hz, 2H), 1.74-1.60 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 159.0, 154.8, 149.1, 127.8, 126.9, 123.8, 122.8, 111.7, 110.4, 67.0, 58.4, 53.8, 39.3, 27.5, 24.0. **IR (neat)**: 3313, 2933, 2856, 2808, 1648, 1594, 1518, 1447, 1295, 1258, 1114, 1069, 863, 837, 667 cm^{-1}. **HRMS** (ESI-Q-TOF): m/z calculated for $C_{17}H_{22}N_2O_3Na$ [M+H]$^+$: 325.1528, found 325.1527.



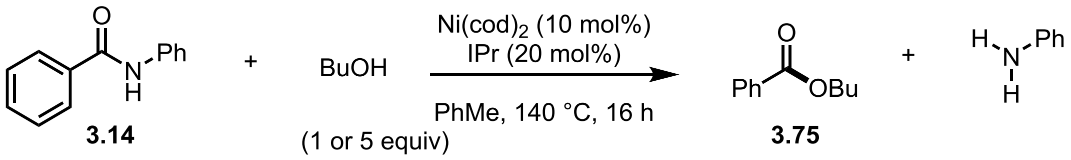
1-[4-(1-Pyrrolidinylcarbonyl)phenyl]-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole (3.11) was prepared according to the general procedure, at 150 °C instead of 140 °C. Purification by column chromatography (gradient of 60% → 100% EtOAc in hexanes) afforded **3.11** as a yellow oil (64 mg, 87%). Characterization data matched those previously reported.[15] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.62 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.53 (dt, *J* = 8.8, 2.0 Hz, 2H), 3.65 (t, *J* = 7.0 Hz, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.72-2.67 (m, 4H), 2.00-1.86 (m, 4H), 1.82 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 168.7, 140.7, 140.6 (q, *J* = 36 Hz), 140.1, 136.7, 128.3, 123.4, 122.1 (q, *J* = 268 Hz), 116.8 (q, *J* = 1.5 Hz), 49.7, 46.4, 26.5, 24.5, 23.7, 22.6, 22.2, 20.1.

3.5.7 Controlling Reaction Equilibrium

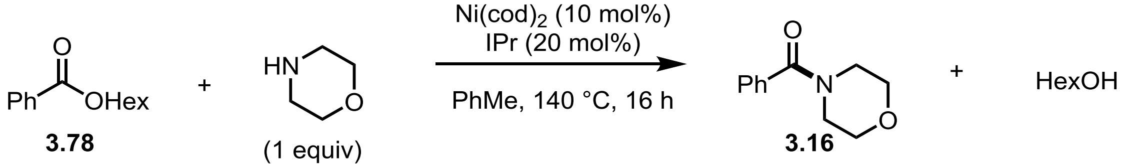
The following experiments were performed to evaluate the performance of the transformation with esters bearing less volatile alcohol leaving groups and determine if the reaction was under equilibrium control.



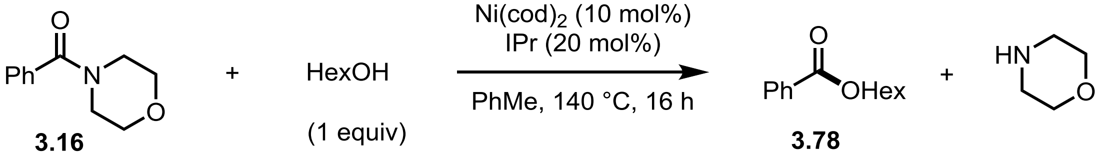
Performed according to the general procedure for optimization experiments (Section 3.5.4). The yield of **3.14** was determined by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard (7.66 ppm, 2H). A 25% yield of benzanilide was observed when using 1 equiv aniline, and an 87% yield was observed when using 5 equiv aniline.



Performed according to the general procedure for optimization experiments (Section 3.5.4). The yield of **3.75** was determined by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard (4.34 ppm, 2H). A 54% yield of butyl benzoate was observed when using 1 equiv butanol, and an 85% yield was observed when using 5 equiv butanol.

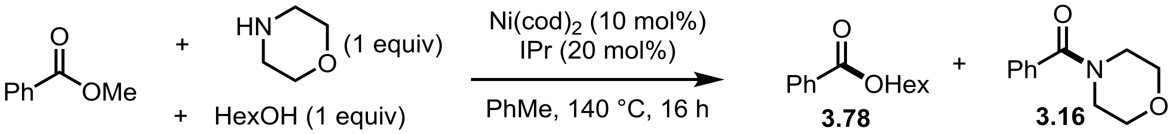


Performed according to the general procedure for optimization experiments (Section 3.5.4). The yield of **3.16** was determined by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard (7.39-7.43 ppm, 5H). A 44% yield of 4-benzoylmorpholine was observed.



Performed according to the general procedure for optimization experiments (Section 3.5.4). The yield of **3.78** was determined by ^{1}H NMR of the crude reaction mixture using 1,3,5-

trimethoxybenzene as internal standard (7.39-7.43 ppm, 5H). A 47% yield of hexyl benzoate was observed.



Performed according to the general procedure for optimization experiments (Section 3.2). The yields of **3.78** and **3.16** were determined by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard (4.33 ppm, 2H for **3.78**. 7.39-7.43 ppm, 5H for **3.16**). A 52% yield of hexyl benzoate and a 41% yield of 4-benzoylmorpholine was observed with trace recovery of methyl benzoate.

Chapter 4

4 Methyl ester activation: Exploring new reactivity using high-throughput screening experimentation

4.1 Background and research goals

High-throughput experimentation (HTE)

High-throughput experimentation is emerging in both the academic and industrial settings as a powerful tool to aid in the discovery of new reactions.[1] Moreover, HTE is also used in the optimization of known reactions,[2] along with the synthesis of complex natural products and the synthesis of highly functionalized drug leads.[3]

The role of HTE is to allow the evaluation of a large number of transformations and enable simultaneous variation of interrelated parameters via multi-well plates, rather than the more traditional one variable at a time (OVAT) screening. This has the effect of streamlining the discovery process (**Scheme 4.1**).

Within the context of this thesis, HTE refers to using contemporary tools such as multi-well plates, liquid transfer tools, multi-well filtration plate for work-up, and rapid GC-MS analysis to set up/analyze dozens of reactions in parallel and allow more comprehensive exploration of reaction space.

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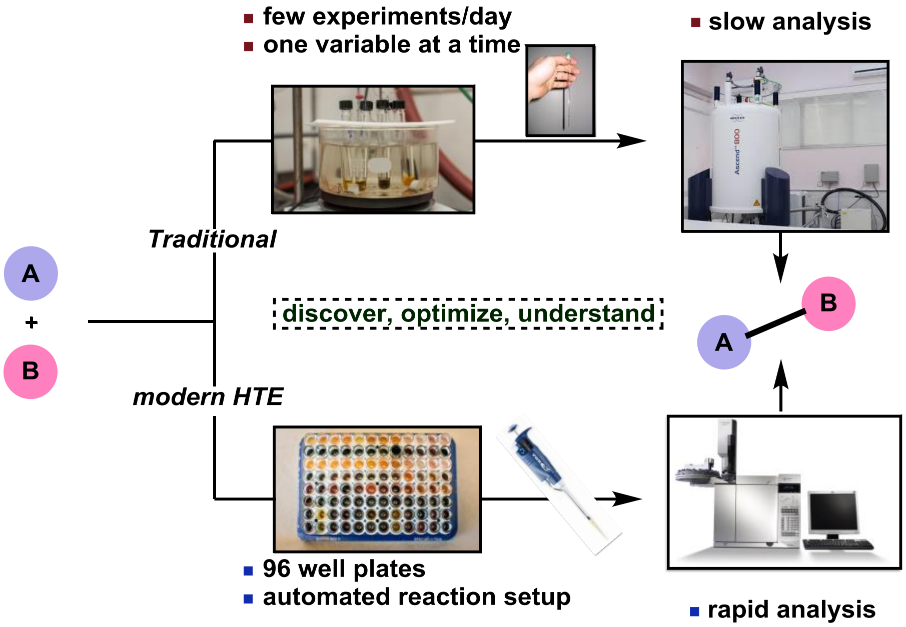
[1] (a) Collins, K. D.; Gensch, T.; Glorius, F. *Nat. Chem*. **2014**, *6*, 859; (b) Moreira, R.; Havranek, M.; Sames, D. *J. Am. Chem. Soc*. **2001**, *123*, 3927; (c) Robbins, D. W.; Hartwig, J. F. *Science* **2011**, *333*, 1423; (d) Monfette, S.; Blacquiere, J. M.; Fogg, D. E. *Organometallics* **2011**, *30*, 36.

[2] (a) Schmink, J. R.; Bellomo, A.; Berritt, S. *Aldrichim. Acta* **2013**, *46*, 71; (b) Preshlock, S. M.; Ghaffari, B.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E.; Smith, M. R. *J. Am. Chem. Soc*. **2013**, *135*, 7572.

[3] Santanilla, A. B.; Regalado, E. L.; Pereira, T.; Shevlin, M.; Bateman, K.; Campeau, L. C.; Schneeweis, J.; Berritt, S.; Shi, Z.-C.; Nantermet, P.; Liu, Y.; Helmy, R.; Welch, C. J.; Vachal, P.; Davies, I. W.; Cernak, T.; Dreher, S. D. *Science* **2015**, *347*, 49.

Scheme 4.1. HTE versus traditional tool of discovery



HTE as a tool for discovery of new cross-coupling reactions from methyl esters

In the past four years, esters were explored as electrophilic coupling partners in cross coupling chemistry (see **Chapter 1**). Methyl esters, which represent the protected version of carboxylic acids, are both abundant and robust. The activation of this functionality using Ni catalysis to generate amide bonds was initially investigated by Garg and co-workers[4] and then by our research group[5] (see **Chapter 3**). Mechanistic studies[4,6] supported the fact that the Ni catalyst inserts into the strong C(acyl)–O bond via an oxidative addition step to generate intermediate **4.2** (**Scheme 4.2**).

Given the ubiquity of methyl esters in important organic scaffolds and the relative robustness of the C(acyl)–O bond compared to other acylative electrophiles, exploring more nucleophilic coupling partners with this functional group has the potential to lead to valuable new methods (**Scheme 4.2**). With this motivation in mind, an HTE strategy was applied to help achieve this

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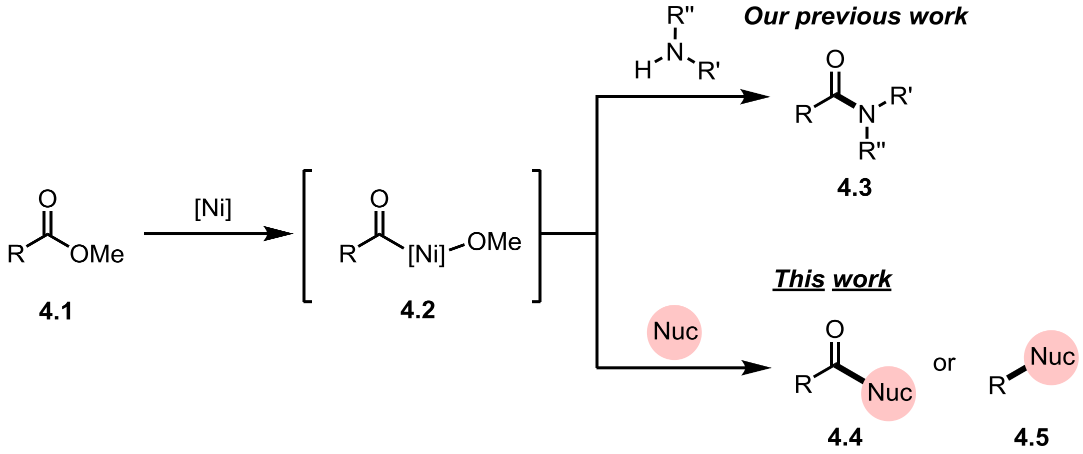
[4] Hie, L.; Fine Nathel, N. F.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Garg, N. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 2810.
[5] Ben Halima, T.; Masson-Makdissi, J.; Newman, S. G. *Angew. Chem., Int. Ed*. **2018**, *57*, 12925.
[6] Ji, C.-L.; Xie, P.-P.; Hong, X. *Molecules* **2018**, *23*, 2681.

goal, thus opening access to novel transformations from methyl ester electrophiles beyond the C–N bond formation examples that were previously discussed.

Scheme 4.2. Methyl ester activation using Ni catalysis



4.2 HTE approach to discovery

HTE represents a powerful tool to discover new chemical transformations. Moreover, certain research groups have used this technique in a serendipitous "chance discovery" manner where a large number of random chemical reactions are screened.[7] By doing so, the probability of realizing a novel discovery is increased.

For this project, however, the strategy was slightly different. More specifically, 288 reactions were carried out within twelve 24-well plates using literature precedent in combination with our knowledge on methyl ester activation to guide the experimental design.

Reaction screens were performed on the parameters predicted to be of greatest importance (**Scheme 4.3**). In total, 12 nucleophiles were used – one per plate. The reaction of each nucleophile was attempted with 2 starting materials, 3 conditions, and 4 ligands, using Ni(cod)$_2$ as catalyst. Each reaction was executed for 16 hours at 150 °C. Reactions were performed on a 30 micromole scale in 1 mL glass vials that were set up and sealed in 96-well aluminum blocks

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[7] McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114.

inside a glovebox. Stock solutions and liquid handling robotics facilitated material transfer, with analysis being performed by GC-MS.

Choice of the fixed parameters

The two reports on methyl ester activation used Ni catalysts (see **Section 4.1** and **Chapter 3**). This might be explained by the inability of Pd to oxidatively add to strong C–O bonds, suggesting that only nickel should be explored for this project (**Scheme 4.3**).

The ligand plays an important role in catalytic reactions (see **Chapter 1**, **Section 1.1.1**). For this reason, this parameter was carefully chosen. Based on the success of NHC ligands (IPr, SIPr, and L2),[4,5,8] on accessing amide bond formation from methyl ester electrophiles, IPr•HCl (L1) and L2 were chosen. Given the efficiency of ICy•HCl (L3) as ligand on methyl ester activation for unpublished work done within the Newman lab, this ligand was selected for screening. Finally, L4 was chosen due to the efficiency of this bidentate phosphine ligand on the activation of methyl esters towards transesterification reaction (**Scheme 4.3**)[9].

These Ni/L1-4 catalysts were applied to all of the twelve tested transformations in order to enhance the chances of accessing the challenging oxidative addition step. Similarly, based on our knowledge on the relatively high temperature required to achieve amide bond formation from methyl ester electrophiles presented in chapter 3, this parameter was set to 150 °C for all the screened reactions.

Choice of the rest of variables

The majority of nucleophilic coupling partners (**Scheme 4.3**) chosen for this project have been proven to be reactive in combination with other cross-coupling electrophiles. Parameters such as bases, additives and solvents were tuned in order to be as close as possible to the proposed literature conditions used for each specific nucleophile.

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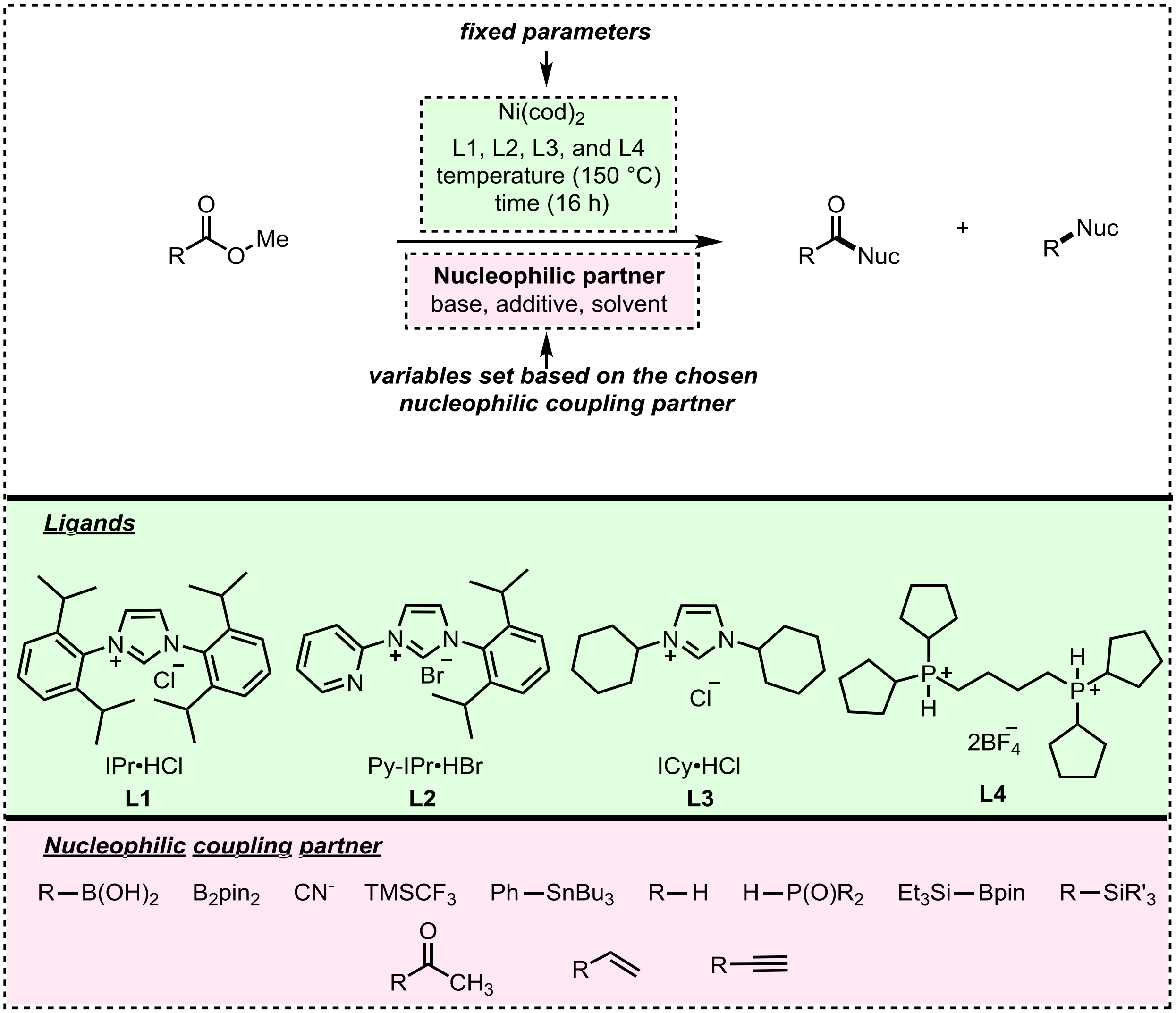
[8] For efficiency of L2 to access amide bonds from methyl esters, see recent published work done within the Newman lab: Zheng, Y.-L.; Newman, S. *ACS Catal*. **2019**, *9*, 4426.

[9] For work done within the Newman lab on Ni catalyzed transesterification of methyl esters, see: Jeanne Masson-Makdissi, M.Sc thesis, University of Ottawa, **2018**. (http://dx.doi.org/10.20381/ruor-22651)

Scheme 4.3. HTE strategy using methyl ester electrophiles



This chosen HTE approach gives substantial diversity, rationality, reflection of literature precedent, and by using this approach with multi-well plates provides a reasonable commitment of time and resources.

4.3 Results

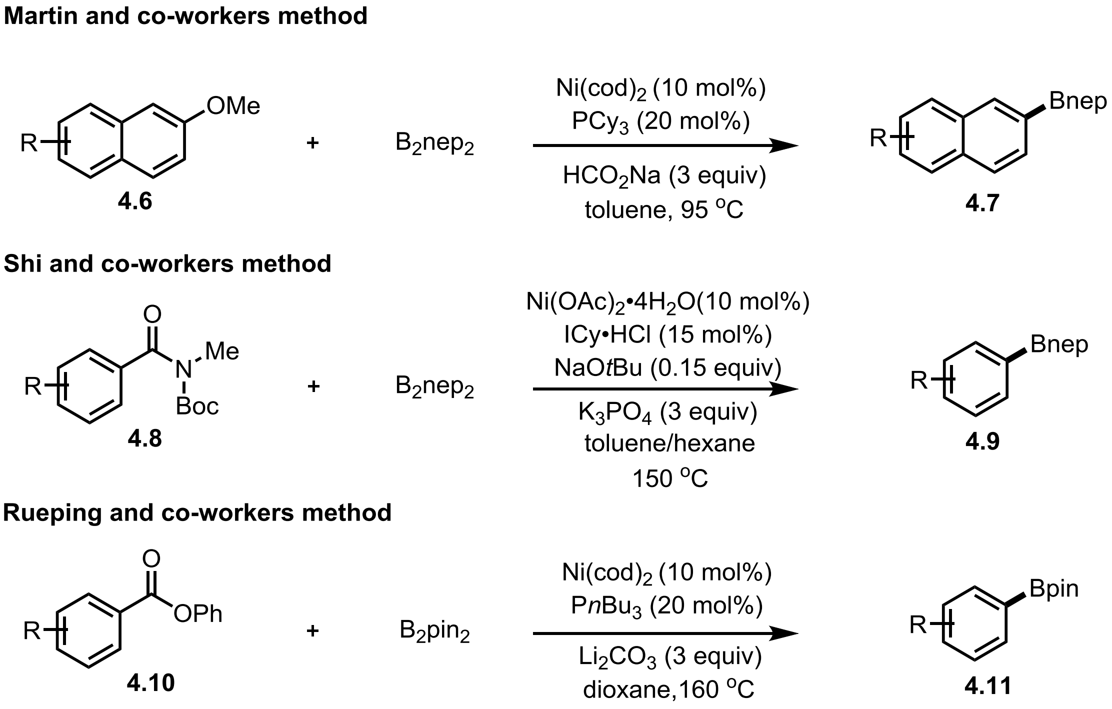
Towards searching for new productive reactions that proceed by methyl ester activation, 288 experiments were performed. In order to provide representative examples of the strategy that was followed, the design and analysis of two 24-well plates will be discussed in detail. The entireties of the data are provided in the experimental section (**Section 4.5**). These plates have been dedicated to explore the possibility that a nickel catalyzed methyl ester system could also be used in both borylation and Suzuki-Miyaura cross-coupling chemistry. In addition, preliminary optimizations for the borylation reaction as well as some scope examples for Suzuki-Miyaura coupling reaction are disclosed. Further details regarding the design of some 24-well plates that were run such as cyanation, trifluoromethylation and Stille cross coupling reactions, as well as summary of hits, are provided in the experimental section (**Section 4.5**).

4.3.1 Ni-catalyzed borylation reaction from methyl ester electrophiles

Design and analysis of the 24 well plate

Based on precedent set in borylation reactions (**Scheme 4.4**) from aryl ethers **4.6**, amides **4.8**, and phenyl esters electophiles **4.10** conducted by the Martin group,[10] Shi group,[11]and Rueping group[12], this 24-well plate (**Figure 4.1**) was executed using B_2pin_2 as a nucleophilic coupling partner, 3 bases (K_3PO_4, HCO_2Na, and Li_2CO_3), and 2 starting materials.

Scheme 4.4. Literature precedence on borylation cross-coupling reaction



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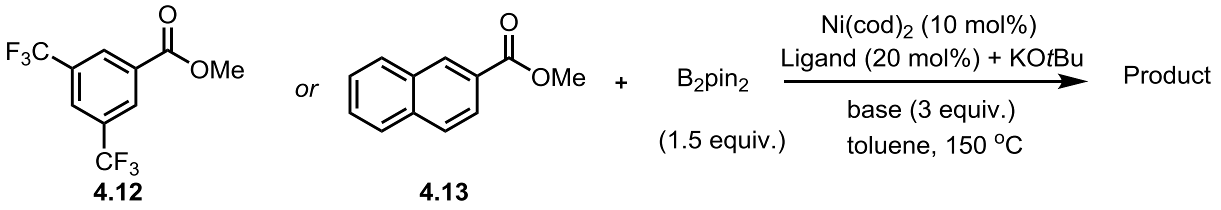
[10] Zarate, C.; Manzano, R.; Martin, R. *J. Am. Chem. Soc*. **2015**, *137*, 6754.
[11] Hu, J.; Zhao, Y.; Liu, J.; Zhang, Y.; Shi, Z. *Angew. Chem., Int. Ed*. **2016**, *55*, 8718.
[12] Guo, L.; Rueping, M. *Chem. - Eur. J*. **2016**, 22, 16787.

For the fixed parameters: Ni(cod)$_2$, and 4 ligands, were applied in toluene at 150 °C (**Figure 4.1**). The ligand and KO*t*Bu were added in equal amounts in order to ensure deprotonation of the ligand, and thus formation of the active catalyst.

The HTE results obtained after GC analysis of this 24-well plate are outlined below (**Figure 4.1**). Color coding was used: green signifies that the product was detected and red is used for unproductive reactions where either starting material recovery or degradation was obtained. While preliminary yields were approximated by GC using an internal standard, duplication of these results was preformed using singleton experiments and accurate NMR yields were obtained further in the optimization process.



	4.12	**4.12**	**4.12**	**4.13**	**4.13**	**4.13**
L1	🟥 Li_2CO_3	🟥 K_3PO_4	🟥 HCO_2Na	🟥 Li_2CO_3	🟥 K_3PO_4	🟥 HCO_2Na
L2	🟥 Li_2CO_3	🟥 K_3PO_4	🟥 HCO_2Na	🟥 Li_2CO_3	🟥 K_3PO_4	🟥 HCO_2Na
L3	🟥 Li_2CO_3	🟥 K_3PO_4	🟥 HCO_2Na	🟥 Li_2CO_3	🟥 K_3PO_4	🟩 HCO_2Na
L4	🟥 Li_2CO_3	🟥 K_3PO_4	🟥 HCO_2Na	🟥 Li_2CO_3	🟥 K_3PO_4	🟥 HCO_2Na

🟩 product observed 🟥 Starting material recovery and/or degradation

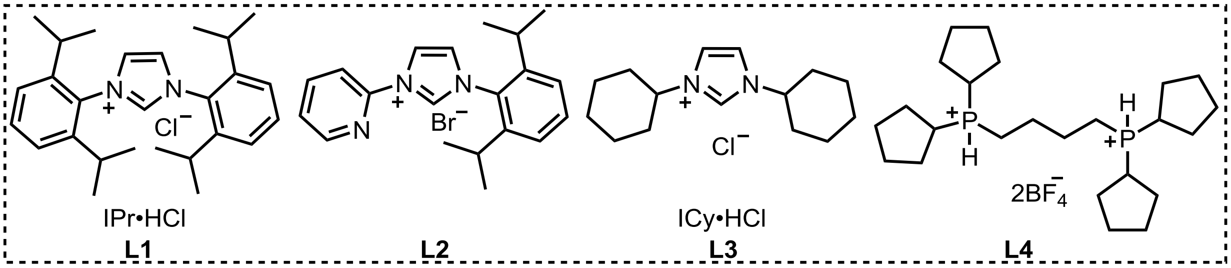
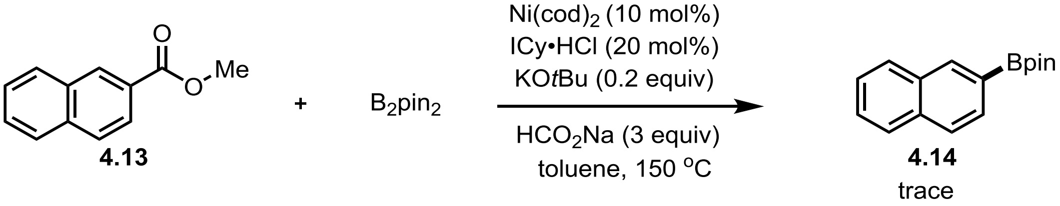


Figure 4.1. Plate design and analysis for borylation reaction

For the above 24-well plate, most reactions conducted led to a recovery of starting material. The only promising result was obtained when **4.13**, ICy•HCl (L3), B$_2$Pin$_2$, and HCO$_2$Na were used

(**Scheme 4.5**). The exact same conditions didn't afford any productive results using **4.12** bearing two electron withdrawing groups (CF_3). These two starting materials (**4.12** and **4.13**) are quite similar and by observing a hit with one and not with the other could be indicative of a false positive. Also, it might be due to the fact that the peak of product from **4.12** exists but it is under the threshold of the GC-MS sensitivity. Another reasonable explanation could be that this experiment failed with **4.12** due to the presence of EWG on the arene that hinders one of the steps of the catalytic cycle.

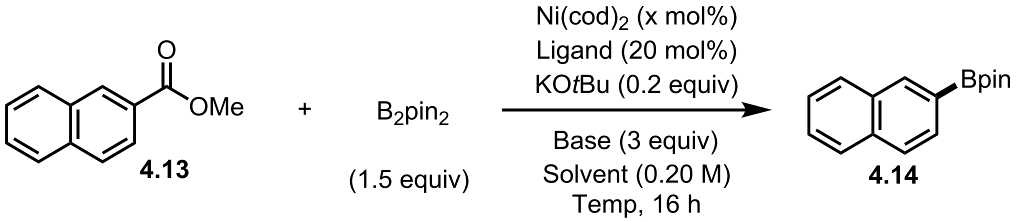
Scheme 4.5. Initial hit for borylation cross-coupling reaction from methyl ester electrophile



Preliminary optimization

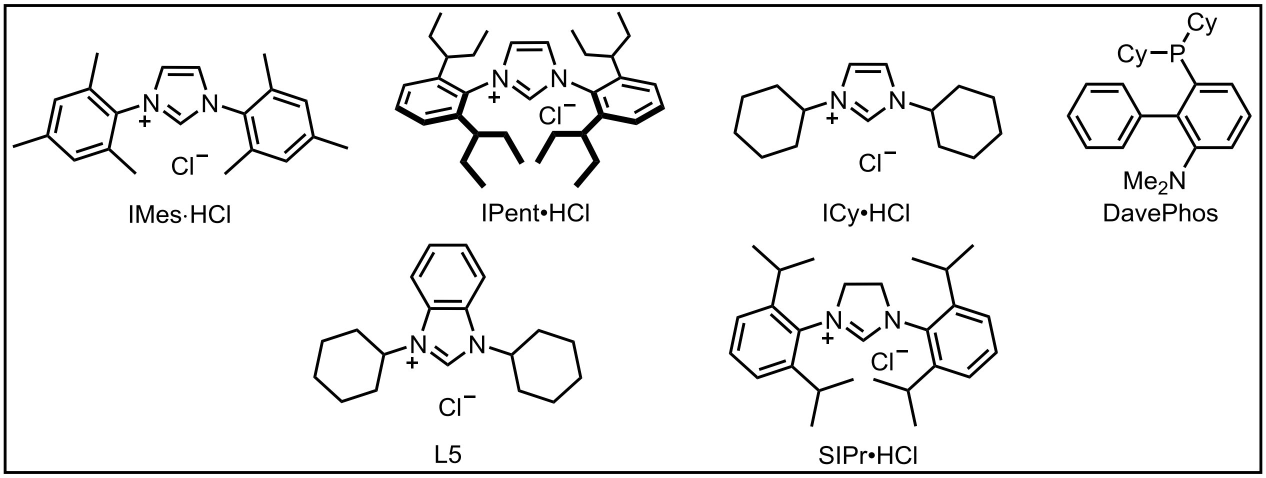
While the results for the plate were not particularly promising, the trace yield of product observed in this unprecedented reaction warranted further exploration using OVAT optimization. A selection of optimization experiments with varied bases, temperature, solvent, ligand, catalyst loading, and metal to ligand ratio are outlined in **Table 4.1**. To provide an accurate yield, the HTE result was duplicated in batch using 10 mol% $Ni(cod)_2$, 20 mol% ICy•HCl, 0.2 equiv KO*t*Bu, and 3 equiv HCO_2Na in toluene at 150 °C for 16 hours. These conditions afforded a yield of 4% (entry 1). While no desired product was detected in the absence of the Ni catalyst (entry 2), trace product was obtained in the absence of base (entry 3). In addition, no enhancement was observed when KO*t*Bu was used (entry 4). A significant improvement was seen when Li_2CO_3 was used and 36% yield was obtained (entry 5). With this identified base, different NHC ligands (entries 6-9) were performed without any increase on the reaction yield. Even though NHCs represent the only class of ligand that had success on activating methyl ester strong C(acyl)–O bond, some phosphine ligands, such as PCy_3 proved able to cleave similarly challenging C–O ether bonds (see **Chapter 1**). For this reason, a short phosphine ligand screen was attempted (entries 10-12). Unfortunately, no product was observed. Given all these failed reactions using versatile ligands, ICy•HCl was used once again at higher temperature (entry 13), with 15 mol% Ni(cod)$_2$ (entry 14), and in dioxane (entry 15). No improvement was seen in comparison with the yields obtained in entry 5. While an initiation to improve this reaction has been made, further investigation is needed to achieve significant progress.

Table 4.1 Initial optimization of the Ni-catalyzed borylation reaction



Entry	Ligand	x	Base	Solvent	Temp (°C)	Yield (%)[a]
1	ICy•HCl	10	HCO_2Na	toluene	150	4
2	ICy•HCl	none	HCO_2Na	toluene	150	0
3	ICy•HCl	10	none	toluene	150	3
4	ICy•HCl	10	KO*t*Bu	toluene	150	0
5	ICy•HCl	10	Li_2CO_3	toluene	150	36
6	SIPr•HCl	10	Li_2CO_3	toluene	150	trace
7	IPent•HCl	10	Li_2CO_3	toluene	150	0
8	L5	10	Li_2CO_3	toluene	150	trace
9	IMes•HCl	10	Li_2CO_3	toluene	150	16
10	P(*o*-tol)$_3$	10	Li_2CO_3	toluene	150	0
11	DavePhos	10	Li_2CO_3	toluene	150	0
12	PCy_3	10	Li_2CO_3	toluene	150	0
13	ICy•HCl	10	Li_2CO_3	toluene	160	15
14	ICy•HCl	15	Li_2CO_3	toluene	160	22
15	ICy•HCl	15	Li_2CO_3	dioxane	160	trace

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.



4.3.2 Ni-catalyzed Suzuki-Miyaura cross-coupling reaction from methyl esters

Design and analysis of the 24-well plate

Based on the work performed on the Suzuki-Miyaura cross coupling reaction within the groups of Love,[13] Fu,[14] and Tu[15], this 24 well plate (**Figure 4.2**) was executed using 3 bases (Cs_2CO_3, KO*t*Bu, and CsF) with electron-rich *p*-methoxy phenylboronic acid as the nucleophilic coupling partner. It is theorized that the electron rich nature of these coupling partners may help facilitate the transmetalation step. Two starting materials–**4.15** was tried in order to facilitate oxidative addition step, while **4.16** was selected for duplication purposes, to provide diversity, and to explore if product 3 could be generated after a decarbonylation step followed by β-hydride elimination. If observed, this product 3 might be an interesting result by itself even if it has nothing to do with Suzuki-Miyaura cross-coupling reaction. Once more, for the fixed parameters: $Ni(cod)_2$ and 4 ligands, were applied in dioxane at 150 °C.

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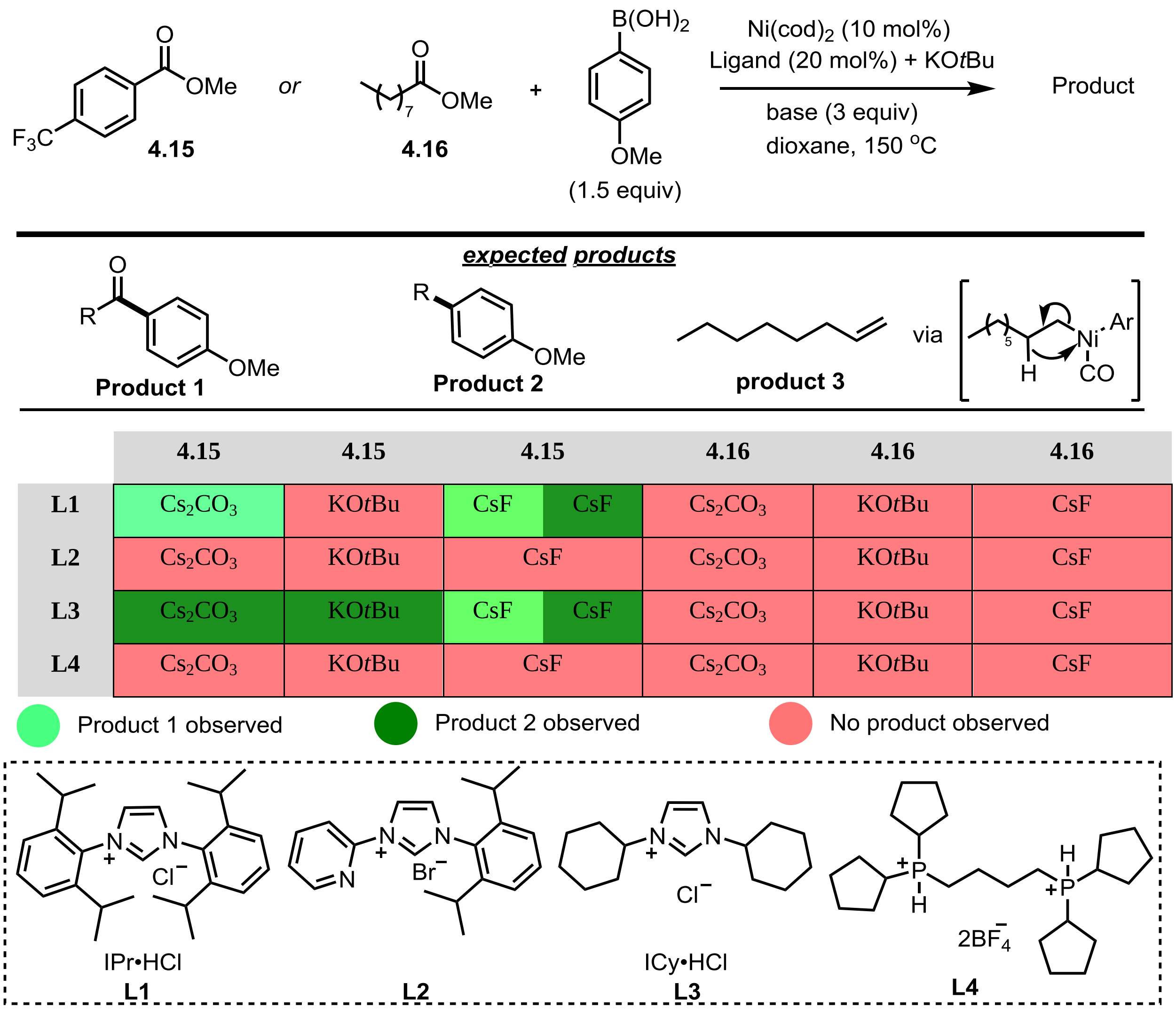
[13] LaBerge, N. A.; Love, J. A. *Eur. J. Org. Chem.* **2015**, *2015*, 5546.
[14] Saito, B.; Fu, G. C. *J. Am. Chem. Soc*. **2007**, *129*, 9602.
[15] Tu, T.; Sun, Z.; Fang, W.; Xu, M.; Zhou, Y. *Org. Lett.* **2012**, *14*, 4250.



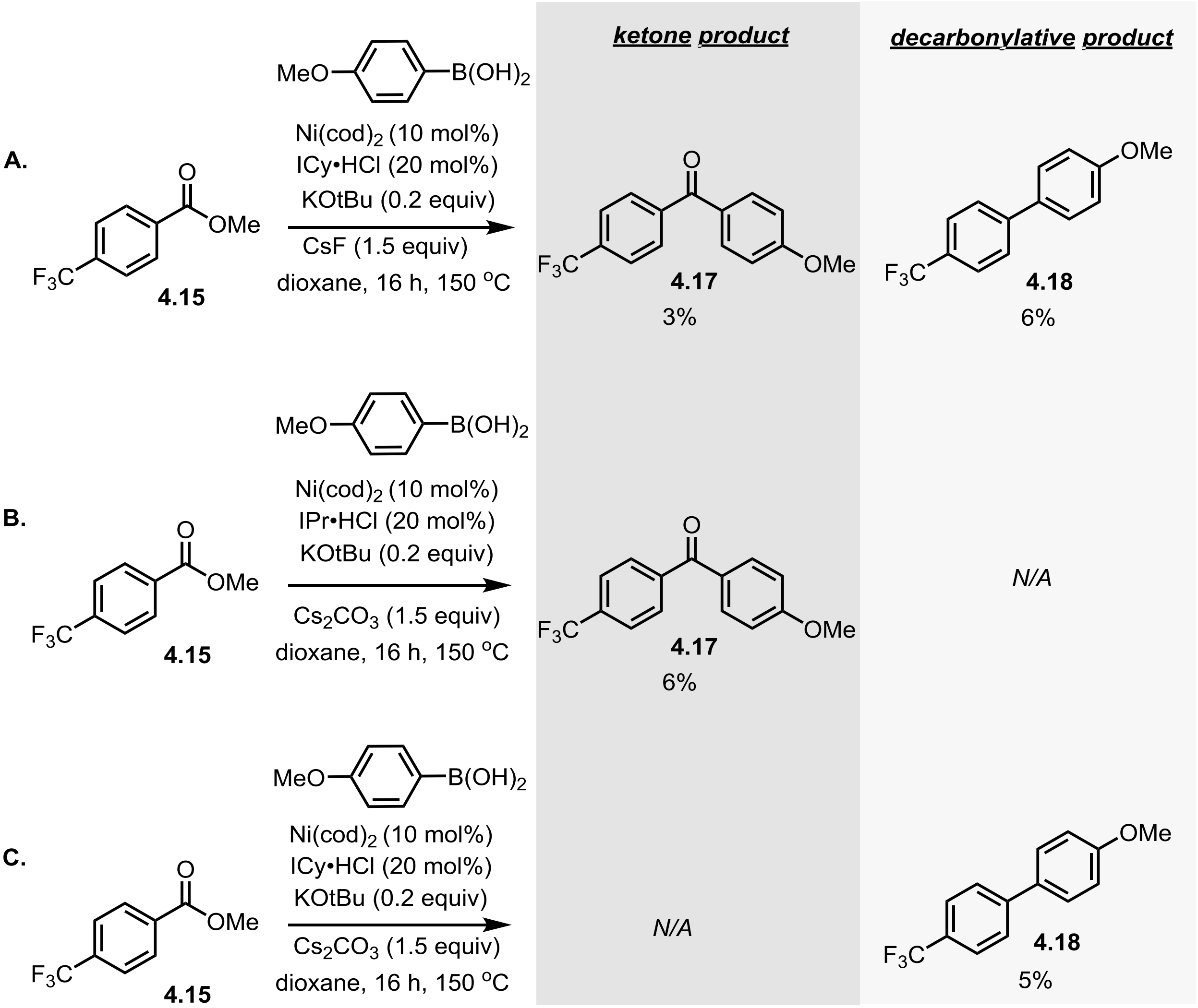
	4.15	4.15	4.15	4.16	4.16	4.16
L1	🟩 Cs_2CO_3	🟥 KO*t*Bu	🟩 CsF ▩ CsF	🟥 Cs_2CO_3	🟥 KO*t*Bu	🟥 CsF
L2	🟥 Cs_2CO_3	🟥 KO*t*Bu	🟥 CsF	🟥 Cs_2CO_3	🟥 KO*t*Bu	🟥 CsF
L3	▩ Cs_2CO_3	▩ KO*t*Bu	🟩 CsF ▩ CsF	🟥 Cs_2CO_3	🟥 KO*t*Bu	🟥 CsF
L4	🟥 Cs_2CO_3	🟥 KO*t*Bu	🟥 CsF	🟥 Cs_2CO_3	🟥 KO*t*Bu	🟥 CsF

🟩 Product 1 observed ▩ Product 2 observed 🟥 No product observed

Figure 4.2. Plate design and analysis for Suzuki-Miyaura cross-coupling reaction

For the above 24-well plate, starting material recovery and/or degradation was obtained when aliphatic ester (**4.16**) was employed. On the other hand, multiple hits were observed with ICy•HCl and IPr•HCl as ligands using **4.15**. These experiments, where a product was detected by GC-MS, were duplicated in batch and accurate NMR yields are provided below (**Scheme 4.6**). Two types of products were detected using CsF as base, the ketone and the biaryl products (**Scheme 4.6A**). Using Cs_2CO_3, IPr•HCl, and **4.15** a 6% yield of the ketone **4.17** was obtained (**Scheme 4.6B**). However, by changing the ligand to ICy•HCl, the same conditions provided the biaryl compound **4.18** in 5% yield, without the observance of any ketone product (**Scheme 4.6C**). This selectivity between decarbonylative (using ICy•HCl) versus carbonyl retentive (using IPr•HCl) couplings is both interesting and exciting. This discovery could be explained by taking into account the relative bulkiness of isopropyl groups on the IPr•HCl ligand, a feature which might prevent decarbonylation (see **Chapter 2**).

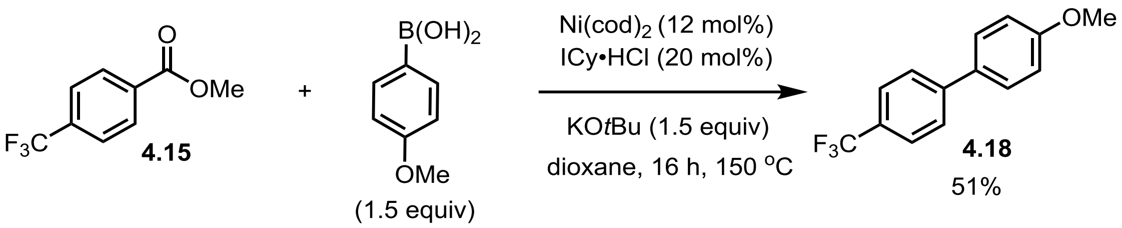
Scheme 4.6. Hits obtained for Ni-catalyzed Suzuki-Miyaura cross-coupling reaction



<u>*Optimizing conditions*</u>

Based on the interesting results described above (**Scheme 4.6**), batch reactions with varied coupling partners, temperature, solvent, ligand, catalyst loading, and metal to ligand ratio were performed to optimize this Ni-catalyzed Suzuki-Miyaura cross-coupling reaction (see experimental section :**Section 4.5**). While experiments designed in order to tune the reaction conditions towards obtaining selectively forming benzophenone derivatives (ketone product) were unsuccessful, typically affording very low yields, a promising result affording decarbonylative product was obtained when Ni(cod)$_2$, ICy•HCl, and KO*t*Bu were used in dioxane at 150 °C. These conditions allowed the selective formation of biphenyl **4.18** with a 51% isolated yield (**Scheme 4.7**).

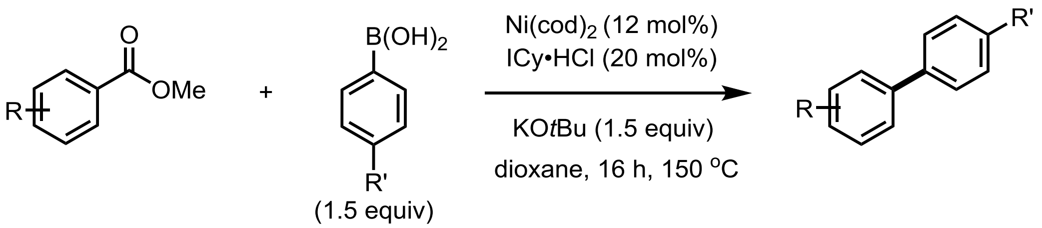
Scheme 4.7. Highest obtained yield of Ni-catalyzed Suzuki-Miyaura coupling

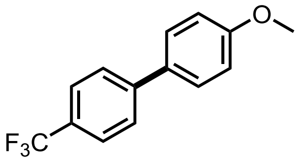


Scope examples

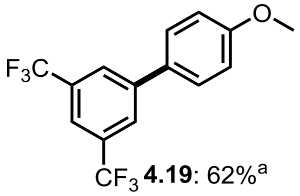
Using the aforementioned optimized conditions, attention was then turned towards the reaction scope (**Table 4.2**). Initial results indicated that the reaction proceeded to the fullest extent with a yield of 51% when the nucleophilic coupling partner contained an electron donating OMe group and the electrophilic partner contained an electron withdrawing CF$_3$ group (**4.18)**. Following this trend, it was noticed that a slight increase in the yield was obtained (**4.19**) when an additional CF$_3$ group was attached to the corresponding ester, giving a yield of 62%. Surprisingly, only a trace of the product **4.20** was afforded when the same electrophilic coupling partner was utilized using phenyl boronic acid. This appears to indicate that this reaction is not only dependent on the oxidative addition step and that other steps, such as transmetalation, might be critical. Biaryls **4.21** and **4.22** could also be made, albeit in low yield. Finally, compound (**4.23**) was prepared in moderate yield. Further details on the unsuccessful examples are provided in the experimental section.

Table 4.2. Scope of esters and boronic acid for Ni-catalyzed Suzuki-Miyaura coupling

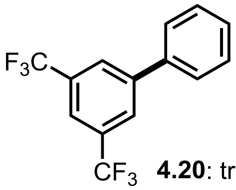




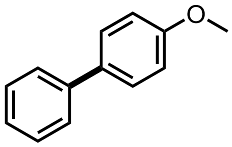
4.18: 51%



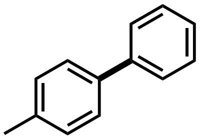
4.19: 62%[a]



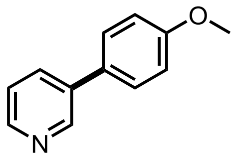
4.20: trace



4.21: 23%



4.22: 12%



4.23: 37%[b]

[a] Cs_2CO_3 + 0.4 equivalents of KO*t*Bu instead 1.5 of KO*t*Bu.

[b] ^1H NMR yield

Even though the substrate scope appeared to be limited to electrophilic coupling partners that bear electron withdrawing groups and/or to nucleophilic partners with electron donating groups, this reaction represents a promising starting point to achieve important Suzuki-Miyaura coupling from simple methyl ester electrophiles.

4.4 Conclusion and future work

In summary, different types of cross-coupling reactions using methyl esters as electrophilic coupling partner have been evaluated. A high-throughput screening technique has been applied and combination of specific ligands, known by their efficiency to activate strong C−O bonds, with literature-based conditions has been designed for the chosen transformations. Multiple promising hits were obtained and further investigation of transformation such as decarbonylative borylation and Suzuki-Miyaura couplings were accessed using ICy•HCl ligand.

Due to the time limit, only preliminary investigation for Suzuki-Miyaura and borylation reaction was performed. Initial optimizations for both transformations were problematic. Since the catalyst systems were chosen to achieve the challenging oxidative addition step, the relative low yielding for borylation and the limited substrate scope for Suzuki-Miyaura coupling might be due to other challenging steps of the catalytic cycle. As future work, these reactions might be explored further by carrying out other experiments using OVAT optimization or even with rapid HTE technique by taking into account previous successful results. As mentioned in the experimental section (**Section 4.5**), other traces of products were observed for Stille coupling and phosphorylation reaction using ICy•HCl. In total, four hits out of five were detected using this same NHC ligand. Since these hits had yet to be explored in batch, similar ligands could also be synthesized and tested to try to improve the discovered reaction conditions for each transformation. Most importantly, this ICy•HCl provided only the decarbonylative product for all reactions. The unique selectivity provided using this NHC ligand is interesting. Even though for certain transformation, such as borylation and cyanation reactions, these decarbonylative couplings were expected based on the literature precedence, the low steric bulk of ICy•HCl compared to other NHC ligands such as IPr•HCl might be tightly linked to these results.

In order to better guide the experimental design towards the improvement of current reactions conditions, collaboration with computational chemists might be beneficial. Together, further understanding the influence of the catalyst on the rate determining step might be acquired. Also, these analyses, in combination with results obtained in the laboratory, could be used to synthesize and design new catalysts that will enable optimal cross-coupling reactions from methyl ester electrophiles.

4.5 Experimental section

4.5.1 Materials

Unless otherwise noted, B_2Pin_2, esters, boronic acid, ligand and other starting materials were obtained commercially from Sigma Aldrich or Combi-Blocks. L2 ligand was synthesized using a literature procedure.[16]

4.5.2 Reaction discovery via high throughput experimentation

4.5.2.1 Method

HTE was performed using 96-well plates (four 24-well plates each) equipped with 8 × 40 mm glass vials. Ligands, bases, some nucleophilic coupling partners, and other additives were added to individual vials on the bench, provided they were air-stable solids. A magnetic stir bar was added to each vial and the plate was brought into a nitrogen-filled glovebox. Inside the glovebox, stock solutions were prepared for $Ni(cod)_2$ and the esters with the appropriate reaction solvent. Other additives, including air sensitive and/or liquid nucleophiles and bases, were similarly diluted in the appropriate solvent. These stock solutions were added into the corresponding reaction vial and any extra necessary solvent was added to give 0.25 mL volume at 0.2 M final concentration. The plate was then sealed using 2 rubber gaskets and a PTFE sheet and screwed in accordingly, removed from the glovebox and heated at desired temperature with stirring for 16 hours in an aluminum-heating block. Upon cooling, the plate was unsealed and the internal standard 1,3,5-trimethoxybenzene was added as a 0.05 M stock solution in THF by pipette. Moreover, the contents of each vial were passed through a multi-well filtration plate filled with silica gel, eluting with acetonitrile. The filtrates were diluted to an appropriate concentration and then analyzed by GC-MS. The effectiveness of each reaction was monitored by integration of the product peak relative to the internal standard. Crude ^1H NMR yields of selected reactions were taken for accuracy and to confirm the GC results.

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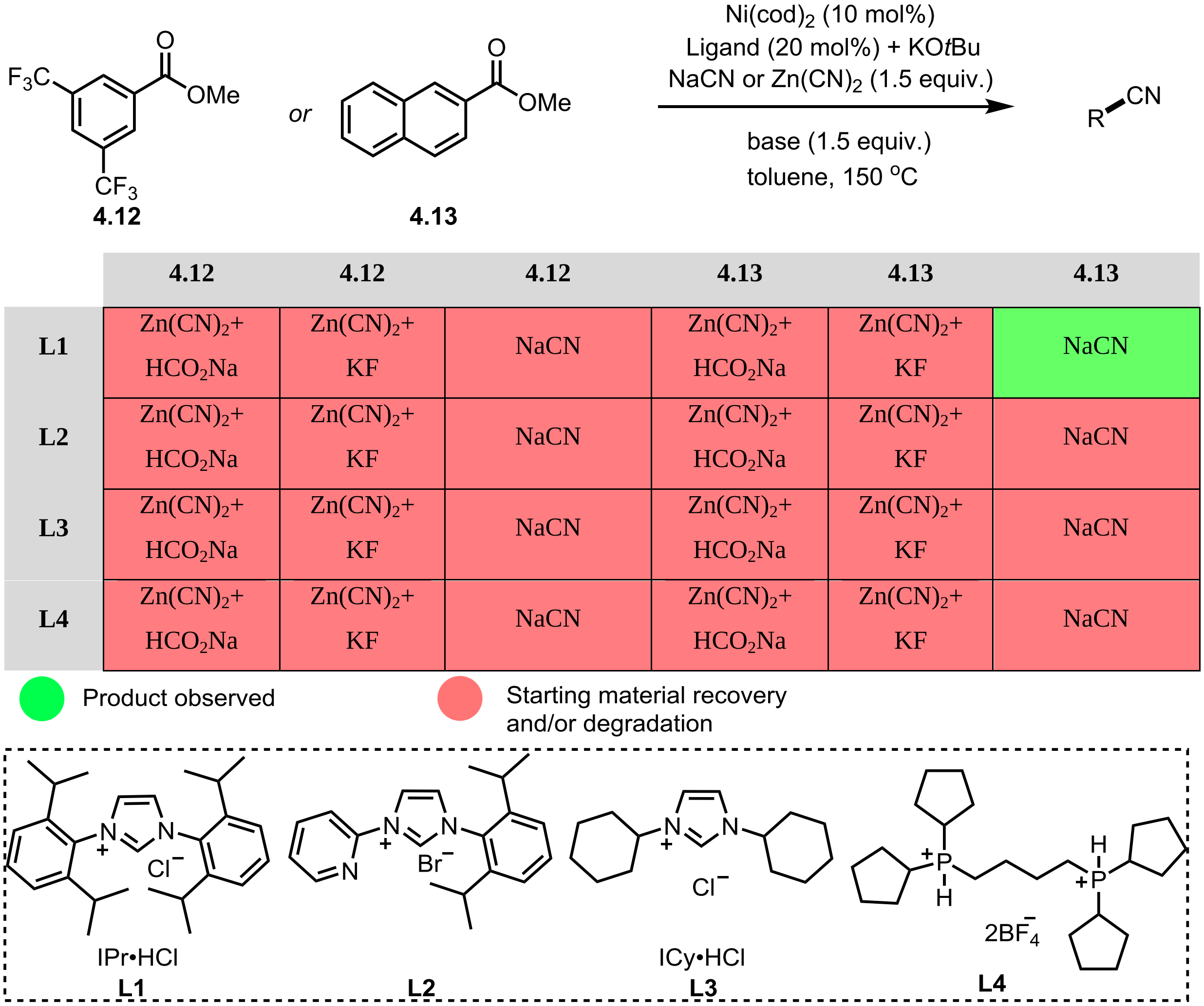
[16] Tulloch, A. A. D.; Danopoulos, A. A.; Winston, S.; Kleinhenz, S.; Eastham, G. *J. Chem. Soc., Dalton Trans*. **2000**, 4499.

4.5.2.2 HTE results of 24-well plates: analysis and design

For the HTE result described below, color coding was used: green signifies that the product was observed and red is used for unproductive reactions where either starting material recovery or degradation was obtained. While preliminary yields were approximated by GC using an internal standard, duplication of these results was preformed using batch chemistry and accurate NMR yields were obtained further in the optimization process. It is important to mention that the ligand and KO*t*Bu were added in equal amounts in order to ensure deprotonation of the ligand, and thus activation of the catalyst system. For the fixed parameters: Ni(cod)$_2$, and 4 ligands, were applied with the corresponding solvent at 150 °C

Cyanation cross-coupling reaction

Based on precedent set in cyanation reactions from phenyl esters and amide electrophiles conducted by both the Rueping group[17] and Szostak group[18], this 24-well plate was executed using $Zn(CN)_2$ and NaCN as nucleophilic coupling partners, 2 bases (HCO_2Na and KF), and 2 starting materials in toluene (**Figure 4.3**).



4.12 **4.13**

	4.12	**4.12**	**4.12**	**4.13**	**4.13**	**4.13**
L1	🟥 $Zn(CN)_2$+ HCO_2Na	🟥 $Zn(CN)_2$+ KF	🟥 NaCN	🟥 $Zn(CN)_2$+ HCO_2Na	🟥 $Zn(CN)_2$+ KF	🟩 NaCN
L2	🟥 $Zn(CN)_2$+ HCO_2Na	🟥 $Zn(CN)_2$+ KF	🟥 NaCN	🟥 $Zn(CN)_2$+ HCO_2Na	🟥 $Zn(CN)_2$+ KF	🟥 NaCN
L3	🟥 $Zn(CN)_2$+ HCO_2Na	🟥 $Zn(CN)_2$+ KF	🟥 NaCN	🟥 $Zn(CN)_2$+ HCO_2Na	🟥 $Zn(CN)_2$+ KF	🟥 NaCN
L4	🟥 $Zn(CN)_2$+ HCO_2Na	🟥 $Zn(CN)_2$+ KF	🟥 NaCN	🟥 $Zn(CN)_2$+ HCO_2Na	🟥 $Zn(CN)_2$+ KF	🟥 NaCN

🟩 Product observed

🟥 Starting material recovery and/or degradation

IPr•HCl
L1

L2

ICy•HCl
L3

L4

Figure 4.3. Plate design and analysis for cyanation reaction

For the above 24-well plate, most reactions conducted led to a recovery of starting material. The only promising result was obtained when **4.13**, IPr•HCl (L1), and NaCN were used (**Figure 4.3**).

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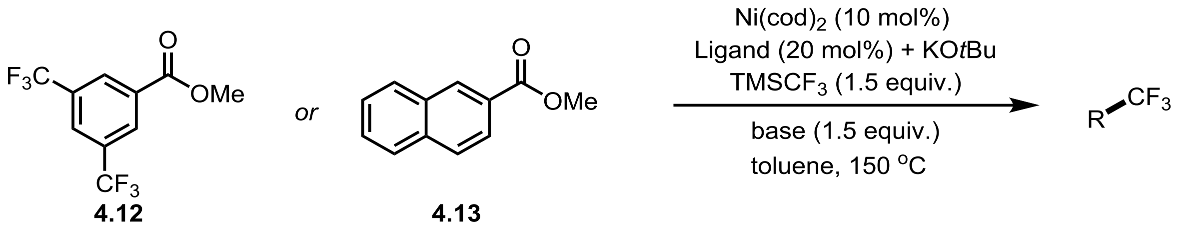
[17] Chatupheeraphat, A.; Liao, H. H.; Lee, S. C.; Rueping, M. *Org. Lett.* **2017**, *19*, 4255.

[18] Shi, S.; Szostak, M. *Org. Lett*. **2017**, *19*, 3095.

Trifluoromethylation cross-coupling reaction

Based on precedent set in trifluoromethylation reactions from carboxylic acids and aryl chlorides conducted by both the Schoenebeck group[19] and Buchwald group[20], this 24-well plate was executed using $TMSCF_3$ as nucleophilic coupling partners, 3 bases (K_3PO_4, CsF, and KF), and 2 starting materials in toluene (**Figure 4.4**). For the below 24-well plate, all reactions conducted led to a recovery of starting material.



	4.12	4.12	4.12	4.13	4.13	4.13
L1	K_3PO_4	CsF	KF	K_3PO_4	CsF	KF
L2	K_3PO_4	CsF	KF	K_3PO_4	CsF	KF
L3	K_3PO_4	CsF	KF	K_3PO_4	CsF	KF
L4	K_3PO_4	CsF	KF	K_3PO_4	CsF	KF

● Starting material recovery and/or degradation

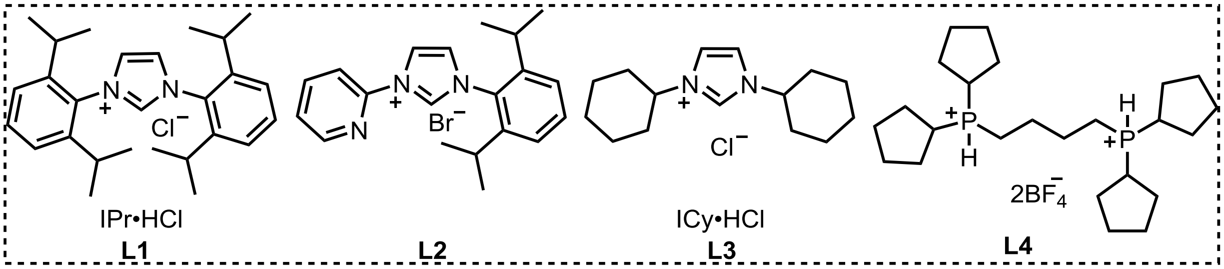


Figure 4.4. Plate design and analysis for trifluoromethylation reaction

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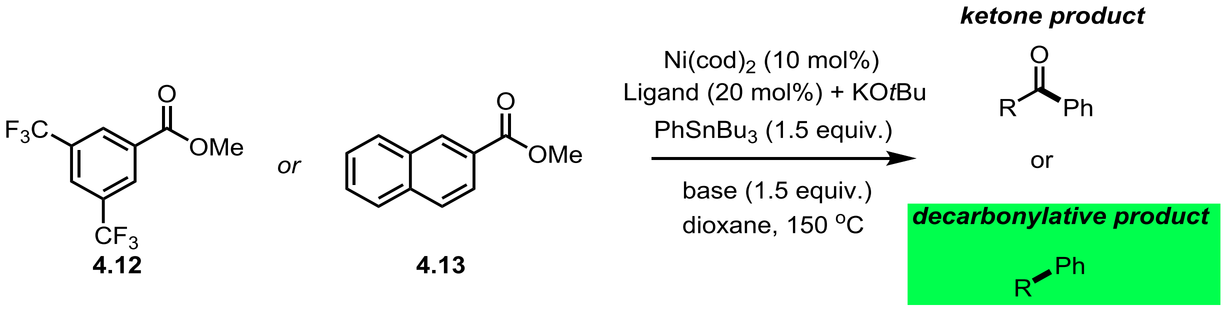
[19] Keaveney, S. T.; Schoenebeck, F. *Angew. Chem., Int. Ed.* **2018** , *57*, 4073.

[20] Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.

Stille cross-coupling reaction

Based on precedent set in Ni-catalyzed Stille cross-coupling reactions via C–N bond cleavage conducted by the Yamaguchi group[21] as well as other related work performed on similar reactions,[22] this 24-well plate was executed using phenyltributyltin as nucleophilic coupling partners, 3 bases (CsF, LiCl, and K_2CO_3), and 2 starting materials in dioxane (**Figure 4.5**).



	4.12	4.12	4.12	4.13	4.13	4.13
L1	🟩 CsF	🟥 LiCl	🟥 K_2CO_3	🟥 CsF	🟥 LiCl	🟥 K_2CO_3
L2	🟥 CsF	🟥 LiCl	🟥 K_2CO_3	🟥 CsF	🟥 LiCl	🟥 K_2CO_3
L3	🟩 CsF	🟩 LiCl	🟩 K_2CO_3	🟥 CsF	🟥 LiCl	🟥 K_2CO_3
L4	🟩 CsF	🟥 LiCl	🟥 K_2CO_3	🟥 CsF	🟥 LiCl	🟥 K_2CO_3

🟢 Product observed 🔴 Starting material recovery and/or degradation

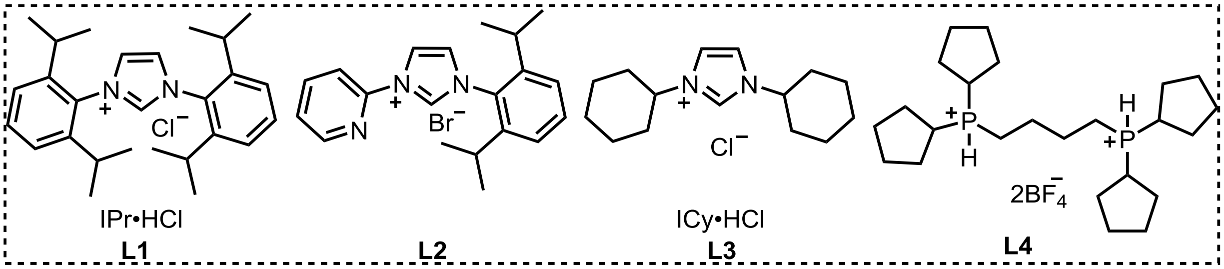


Figure 4.5. Plate design and analysis for Stille cross-coupling

For the above 24 well plate, starting material recovery and/or degradation was obtained when (**4.13**) was employed. On the other hand, multiple hits were observed with ICy•HCl, IPr•HCl,

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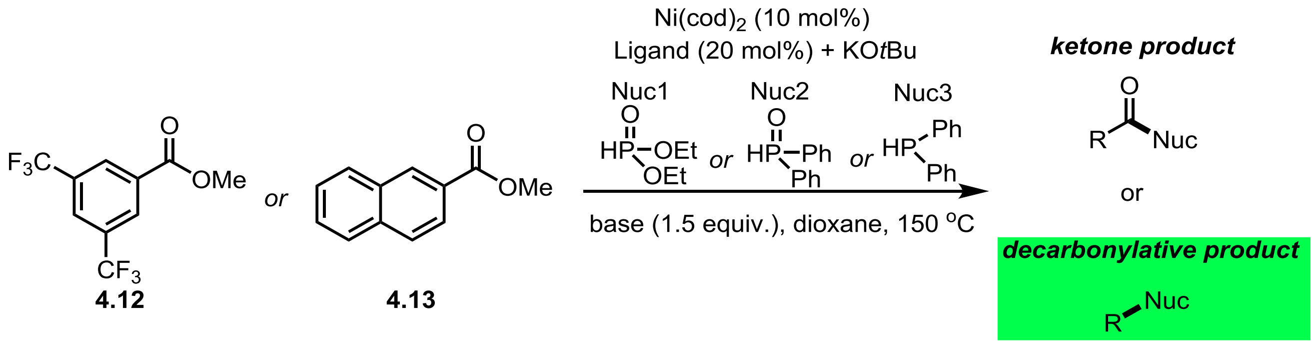
[21] Wang, D.-Y.; Kawahata, M.; Yang, Z.-K.; Miyamoto, K.; Komagawa, S.; Yamaguchi, K.; Wang, C.; Uchiyama, M. *Nat. Commun*. **2016**, *7*, 12937.

[22] (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033; (b) Del Valle, L.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem*. **1990**, *55*, 3019.

and L4 as ligands using **4.12**. For all reactions performed on this plate, biaryl product (decarbonylative product) was detected without the observance of any ketone product.

Phosphorylation cross-coupling reaction

Based on precedent set in Ni-catalyzed phosphorylation reactions conducted by the Han group[23] as well as other related work,[24] this 24-well plate was executed using 3 nucleophilic coupling partners, 3 bases (Na_2CO_3, KO*t*Bu, and K_2CO_3), and 2 starting materials in dioxane (**Figure 4.6**).



4.12 **4.13**

	4.12 + Nuc1	**4.12 + Nuc2**	**4.12 + Nuc3**	**4.13 + Nuc1**	**4.13 + Nuc2**	**4.13 + Nuc3**
L1	🟥 Na_2CO_3	🟥 KO*t*Bu	🟥 K_2CO_3	🟥 Na_2CO_3	🟥 KO*t*Bu	🟥 K_2CO_3
L2	🟥 Na_2CO_3	🟥 KO*t*Bu	🟩 K_2CO_3	🟥 Na_2CO_3	🟥 KO*t*Bu	🟥 K_2CO_3
L3	🟥 Na_2CO_3	🟥 KO*t*Bu	🟩 K_2CO_3	🟥 Na_2CO_3	🟥 KO*t*Bu	🟩 K_2CO_3
L4	🟥 Na_2CO_3	🟥 KO*t*Bu	🟩 K_2CO_3	🟥 Na_2CO_3	🟥 KO*t*Bu	🟥 K_2CO_3

🟩 Product observed

🟥 Starting material recovery and/or degradation

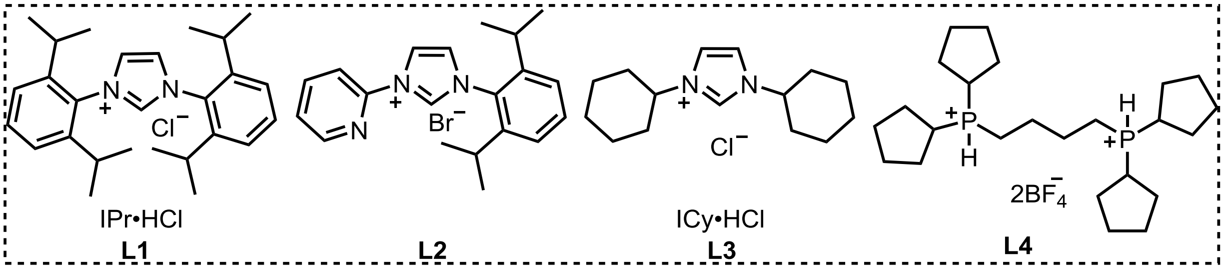


Figure 4.6. Plate design and analysis for phosphorylation cross-coupling

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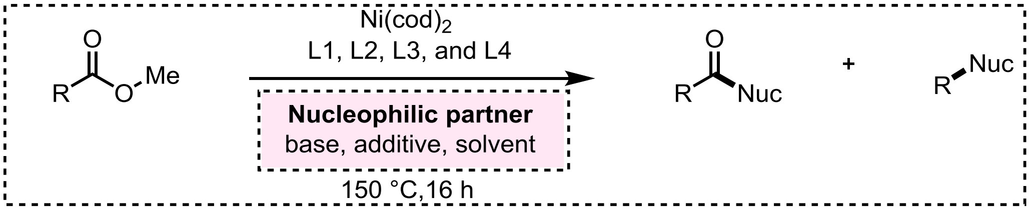
[23] (a) Yang, J.; Xiao, J.; Chen, T.; Yin, S.-F.; Han, L.-B. *Chem. Commun*. **2016**, *52*, 12233; (b) Yang, J.; Chen, T.; Han, L.-B. *J. Am. Chem. Soc*. **2015**, *137*, 1782.

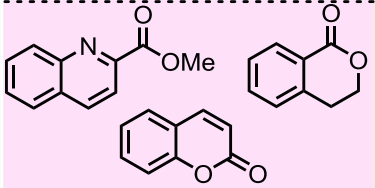
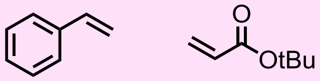
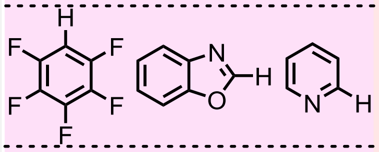
[24] (a) Liu, C.; Szostak, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 12718; (b) Shen, C.; Yang, G.; Zhang, W. *Org. Biomol. Chem.* **2012**, *10*, 3500.

For the above 24-well plate, starting material recovery and/or degradation was obtained for most reactions when (**4.13**) was employed. However, using the same starting material decarbonylative product was observed when Nuc3, K_2CO_3, and ICy•HCl was utilized. On the other hand, multiple hits were observed with L2, ICy•HCl, and L4 as ligands using **4.12**. For all reactions performed on this plate, biaryl product (decarbonylative product) was detected without the observance of any ketone product.

For the rest of the performed 24 well plates, no product was detected. Moreover, starting material recovery and/or degradation was observed. For further details on the different used variables for these transformations, see **Table 4.3**.

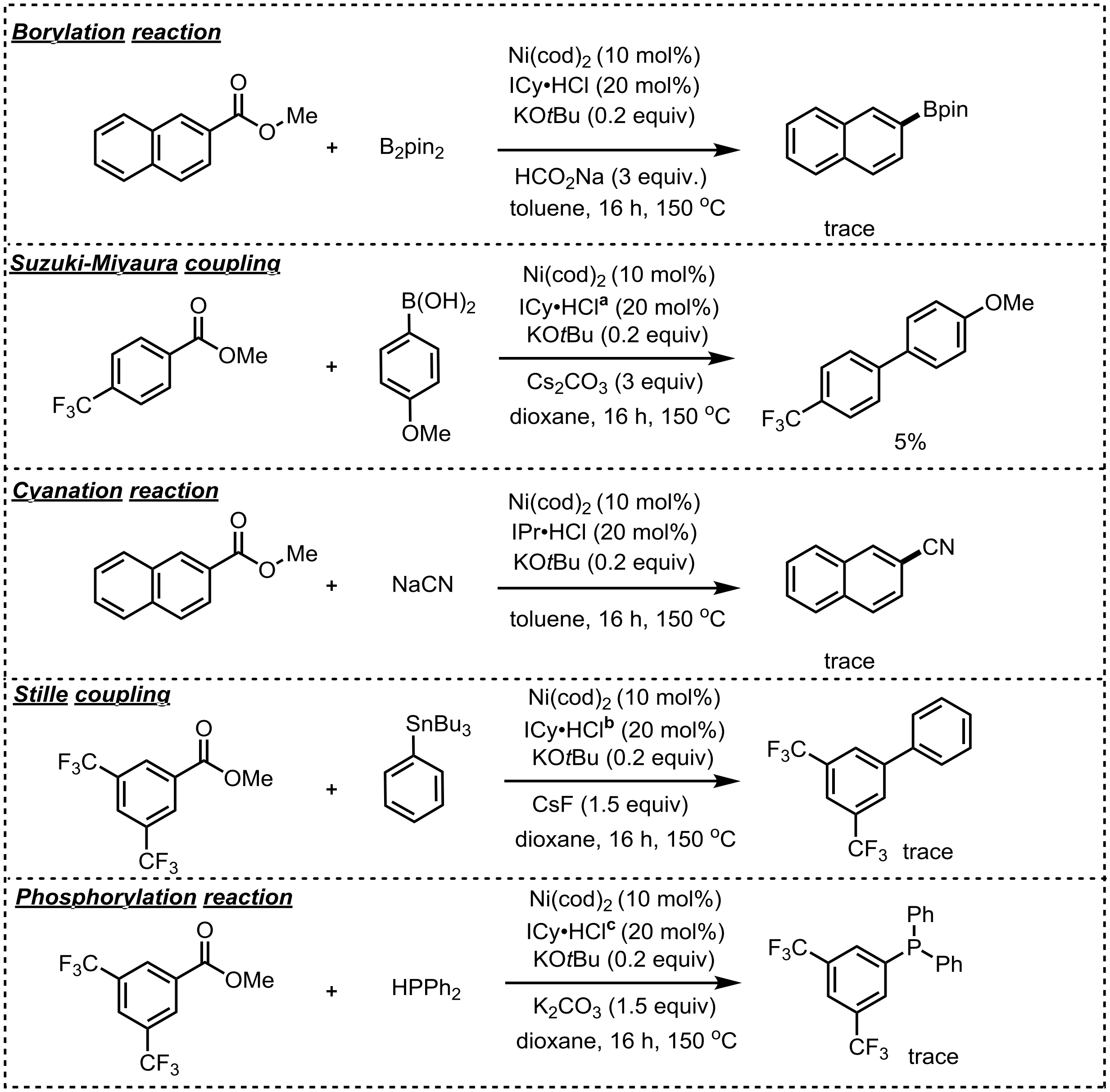
Table 4.3. Parameters used in unsuccessful 24-well plates



	Nucleophilic coupling partner	***Bases additives solvents***
Hiyama cross-coupling	$PhSi(OEt)_3$ $PhSiMe_3$ 	CsF toluene
No Nuc coupling (Intramolecular)		CsF toluene
α-arylation		K_3PO_4, CsF, KO*t*Bu toluene
Heck cross-coupling		K_3PO_4, K_2CO_3, Cy_2NMe LiCl toluene
C—H activation		K_3PO_4, K_2CO_3, KO*t*Bu toluene
Sonogashira coupling	R—≡ + CuI	NEt_3, Cs_2CO_3, KO*t*Bu DMF, toluene

Summary of the HTE result: hits from twelve 24 well plates

Scheme 4.8. Summary of productive HTE results



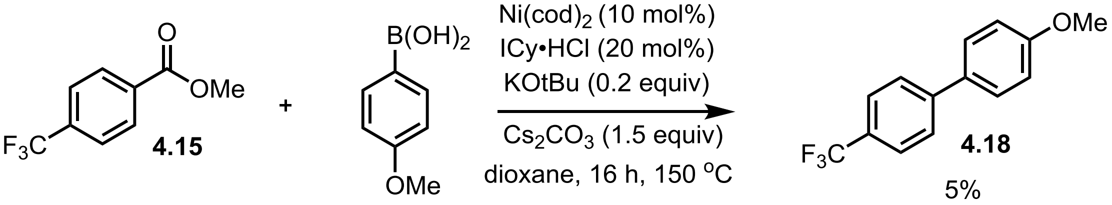
[a] The use of IPr•HCl generated a trace of the ketone product.

[b] The use of IPr•HCl and L4 generated a trace of the product.

[c] The use of L2 and L4 generated a trace of the product using K_2CO_3 as base.

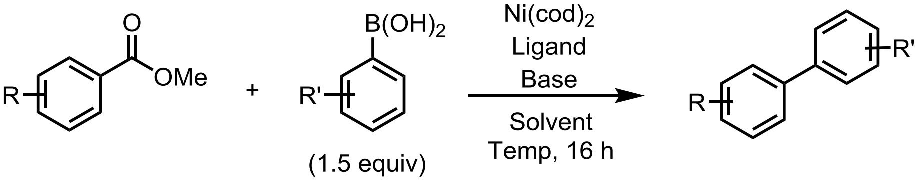
4.5.2.3 Suzuki-Miyaura cross-coupling reaction

Initial HTE result



Optimization: A selected number of experiments are outlined below:

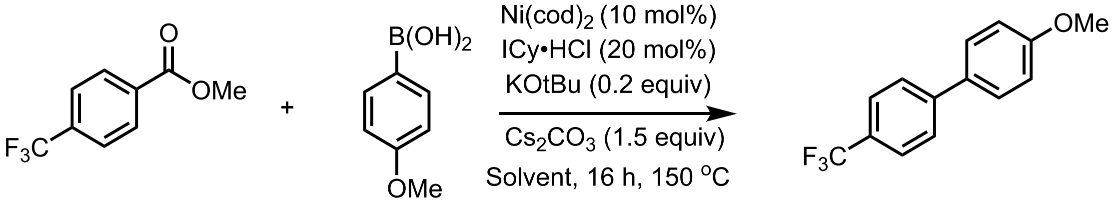
General procedure for optimization experiments



In a glovebox, an oven dried screw-capped vial was charged with a magnetic stir bar, catalyst, ligand, boronic acid, and base. Following the addition of the solvent the reaction mixture was shaken vigorously, and the corresponding ester (0.10 mmol) was subsequently added via micropipette. The vial was sealed with a Teflon-lined screw cap and shipped outside of the glovebox. The reaction was stirred vigorously (700 rpm) in a silicone oil bath heated at the specified temperature for 16 h. After cooling to room temperature 1,3,5-trimethoxybenzene was added as an internal standard from a 0.05 M stock solution in THF. The mixture was diluted with ethyl acetate and filtered through a plug of silica gel. Yields of biaryls were determined by ^{1}H NMR.

Solvents screen

Table 4.4. Solvent screen for Ni-catalyzed Suzuki-Miyaura cross-coupling reaction

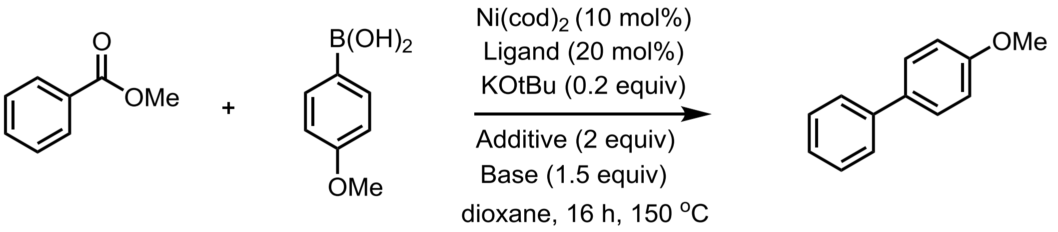


Entry	Solvent	Yield (%)[a]
1	dioxane	5
2	toluene	trace
3	DMSO	trace
4	DMF	trace
5	t-amyl alcohol	0

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

Bases, ligand, and additives screen

Table 4.5. Optimization for Suzuki-Miyaura coupling with various bases, additives, and ligands

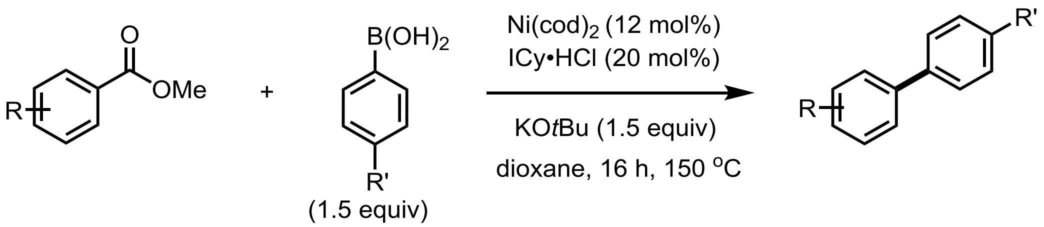


Entry	Ligand	Additive	Base	Yield (%)[a]
1	ICy•HCl	none	Cs_2CO_3	7
2	IPent•HCl	none	Cs_2CO_3	trace
3	IPent•HCl	none	KO*t*Bu	trace
4	IPent•HCl	H_2O	KO*t*Bu	trace
5	IPent•HCl	KF	KO*t*Bu	trace
6	IPent•HCl	LiCl	KO*t*Bu	trace
7	IMes•HCl	none	KO*t*Bu	trace
8	ICy•HCl	none	KO*t*Bu	25

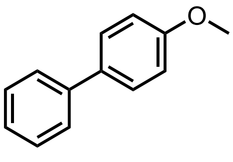
[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

Scope examples

Representative procedure for the Ni-catalyzed Suzuki-Miyaura coupling of methyl esters



In a glovebox, an oven dried screw-capped vial was charged with a magnetic stir bar, Ni(cod)$_2$ (7 mg, 0.02 mmol, 0.1 equiv), ICy•HCl (11 mg, 0.04 mmol, 0.2 equiv), KO*t*Bu (0.3 mmol, 1.5 equiv), and boronic acid (0.3 mmol, 1.5 equiv). Dioxane (1.0 mL, 0.20 M) obtained from a solvent purification system was degassed for 5 minutes and then added. The reaction mixture was shaken vigorously, and then the corresponding ester (0.20 mmol, 1.0 equiv) was subsequently added. The vial was sealed with a Teflon-lined screw cap and shipped outside of the glovebox. The reaction was stirred vigorously (700 rpm) in a silicone oil bath at 150 °C for 16 h. After cooling to room temperature, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride, diluted with ethyl acetate, and filtered through a plug of silica gel (10 mL of EtOAc eluent). The crude mixture was then concentrated *in vacuo* and subjected to column chromatography.



4-Methoxybiphenyl (**4.21**) was prepared according to the general procedure. Purification was performed by column chromatography with a gradient of 2% → 20% DCM in hexane to afford **4.21** as a white solid (8 mg, 23% yield). Characterization data matched those previously reported.[25] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.31 (t, *J* = 7.5

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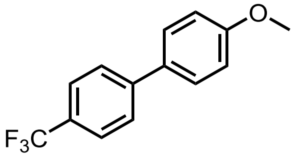
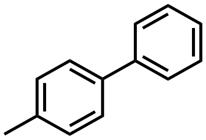
[25] Zhang, X.-Q.; Wang, Z.-X. *J. Org. Chem.* **2012**, *77*, 3658.

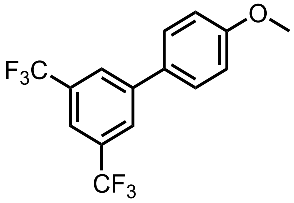
Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.58−7.52 (m, 4H); **^{13}C NMR** (CDCl$_3$) δ 55.5, 114.4, 126.8, 126.9, 128.3, 128.9, 133.9, 141.0, 159.3.



4-Methoxy-4'-(trifluoromethyl)biphenyl (**4.18**) was prepared according to the general procedure. Purification was performed by column chromatography with a gradient of 0% → 15% DCM in hexane to afford **4.18** as a white solid (26 mg, 51% yield). Characterization data matched those previously reported.[25] **^{1}H NMR** (400 MHz, CDCl$_3$) δ 3.88 (s, 3H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.67 (s, 4H); **^{13}C NMR** (CDCl$_3$) δ 55.5, 114.6, 123.1, 125.8 (q, *J* = 3.8 Hz), 126.3, 127.0, 128.5, 128.7, 129.0, 132.3, 144.5, 160.0.



4-Methylbiphenyl (**4.22**) was prepared according to the general procedure. Purification was performed by column chromatography with a gradient of 0% → 10% DCM in hexane to afford **4.22** as a white solid (4 mg, 12% yield). Characterization data matched those previously reported.[25]. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 2.40 (s, 3H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.59 (m, 2H); **^{13}C NMR** (CDCl$_3$) δ 21.3, 127.1, 127.2, 128.9, 129.6, 129.6, 137.2, 138.5, 141.3.



4-Methoxy-3′,5′ bis(trifluoromethyl) biphenyl (**4.19**) was prepared according to the general procedure. Purification was performed by column chromatography with a gradient of 0% → 15% DCM in hexane to afford **4.19** as colourless oil (40 mg, 62% yield). Characterization data matched those previously reported.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.57(d, *J* = 8.8 Hz, 2H), 7.81(s, 1H), 7.98(s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.6, 114.9, 120.3, 120.3, 120.4, 122.2, 124.9, 126.7, 126.8, 128.5, 130.8, 132.2 (q, *J* = 33 Hz), 143.0, 160.5

Unsuccessful scope examples

This first report of Suzuki-Miyaura cross-coupling reaction from methyl esters represents an important initiation towards improving the current reaction conditions. For instance, many substrates proved challenging in the reaction; For example, attempts to couple esters with a thiophene, furan, para-benzaldehyde, or *ortho/meta* substitution of methyl benzoate resulted in side reactions, decomposition, or recovery of starting material (**Figure 4.7**). Similarly, multiple boronic acids could not be efficiently coupled with methyl benzoate.

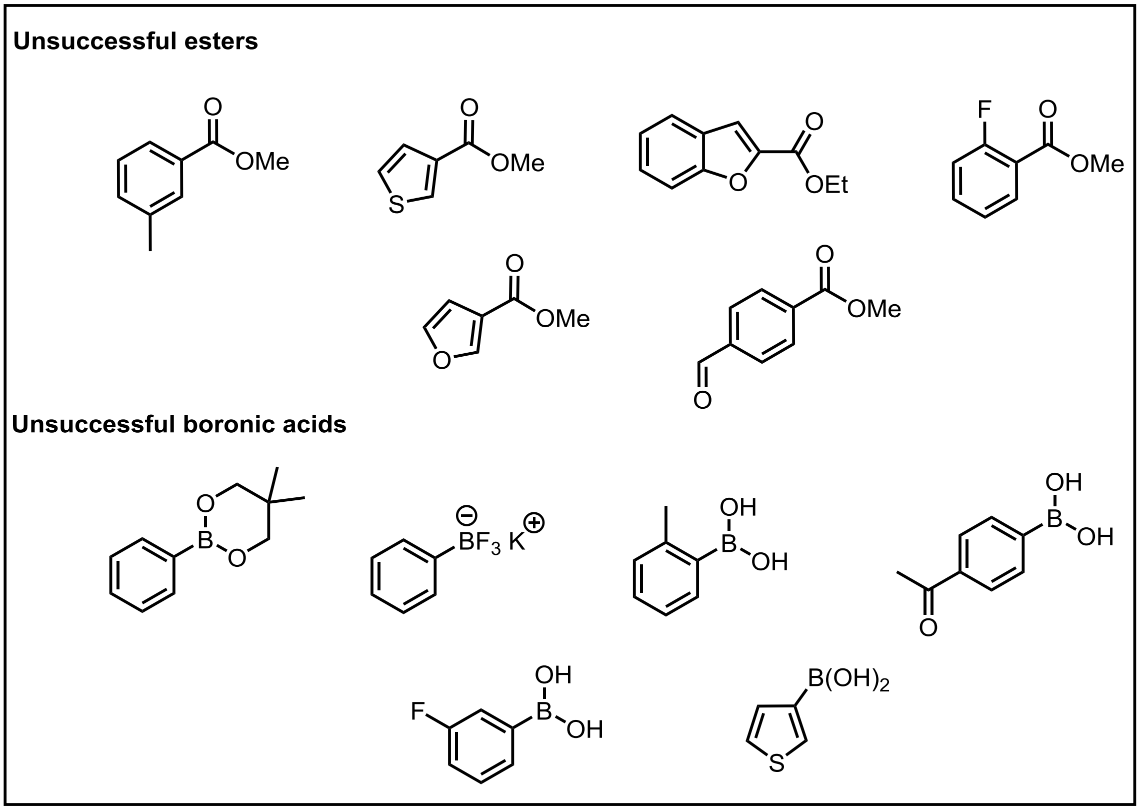


Figure 4.7. Limitations in the substrate scope

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[26] Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P.; Tseng, C.-C.; de Fraine, P.; Parr, N. J.; Scicinski, J. J. *Appl. Organomet. Chem*. **2007**, *21*, 572.

Conclusions

5 Conclusions and outlook

Three new cross-coupling methods are described in this thesis. At first, the cleavage of relatively strong C(acyl)–O bond of phenyl esters by oxidative addition was targeted (**Chapter 2**). Two discoveries were made via Pd-NHC catalysts– a Suzuki-Miyaura cross-coupling reaction and amide bond forming reaction. For the first discovery, excellent yields of ketone-containing products were obtained with a broad range of ester and boronic acid starting materials. This work represents a rare entry of Pd into the field of C–O bond activation, giving a unique reaction pathway compared to previous studies done in this field, especially compared to the decarbonylative cross-coupling using nickel catalysis where a 5-centered transition state favour the C(aryl)–O cleavage. For the second methodology, a palladium-catalyzed cross-coupling reaction between aryl esters and anilines was discovered. Similar to the Suzuki-Miyaura chemistry, the reaction proceeds via insertion of the Pd/NHC catalyst into the C(acyl)–O bond via oxidative addition. Success in applying such a strategy allowed the coupling of relatively non-nucleophilic anilines that otherwise requires stoichiometric activation with strong bases.

The development of phenyl ester activation attracted the attention of the scientific community[1] and motivated numerous other researchers to improve these discovered methods.[2] Even though conceptually interesting, phenyl esters are considerably activated relative to abundant methyl and ethyl esters and do not represent a major practical advance over traditional methods proceeding by stoichiometric ester activation. Extensive efforts were devoted to develop novel methodology from simple methyl ester electrophiles to access amide bonds (**Chapter 3**). In this work a Ni/NHC catalyst system was used to enable a diverse range of aliphatic and aromatic esters to couple with amines nucleophiles. No stoichiometric base, acid, or other activating agent is needed, providing exceptional functional group tolerance and producing only methanol as a by-product. The discovery is of both fundamental and practical importance because it is the first to demonstrate that simple, activating agent-free conditions can enable Ni to cleave the C–O bond of a simple methyl ester. Moreover, this method was successfully applied for synthesizing

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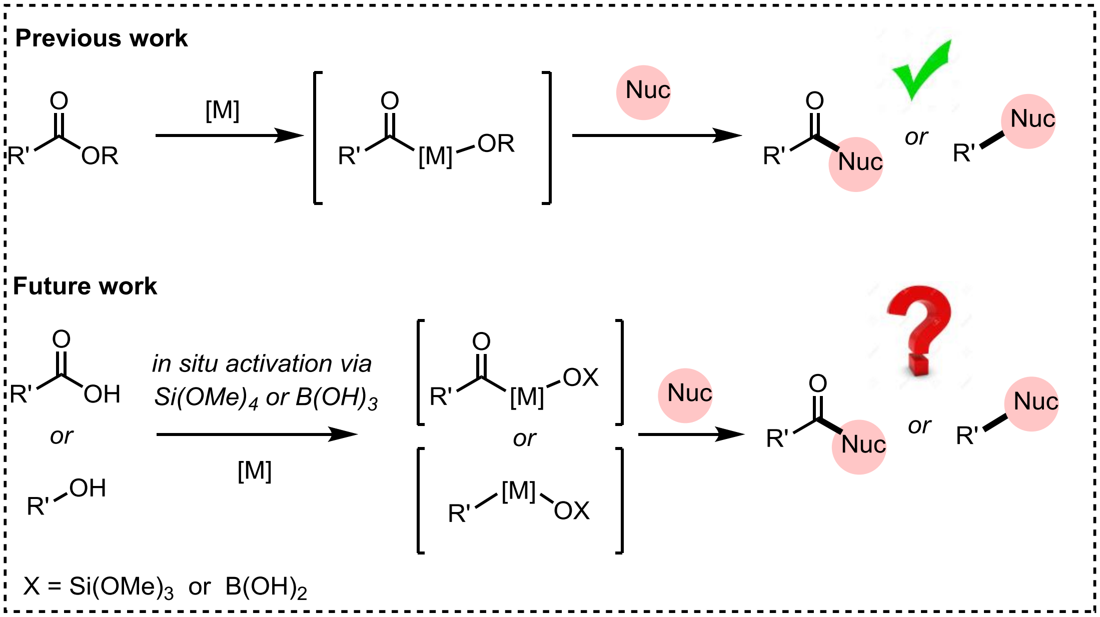
[1] This work, which has been published in J. Am. Chem. Soc. and ACS Catal. has been cited 83 and 38 times, respectively (Google Scholar, Apr 2019)

[2] (a) Dardir, A. H.; Melvin, P. R.; Davis, R. M.; Hazari, N.; Mohadjer Beromi, M. *J. Org. Chem*. **2018** , *83*, 469; (b) Li, G.; Shi, S.; Szostak, M. *Adv. Synth. Catal*. **2018**, *360*, 1538; (c) Shi, S.; Nolan, S. P.; Szostak, M. *Acc. Chem. Res*. **2018**, *51*, 2589.

amide-containing bioactive molecules. Given the ubiquity of methyl esters in important organic scaffolds and the relative robustness of the C(acyl)–O bond compared to other acylative electrophiles, this functional group was explored with other nucleophilic coupling partners using HTE technique (**Chapter 4**). Multiple promising hits were obtained using ICy•HCl - decarbonylative borylation and Suzuki-Miyaura couplings will be explored in the near future. This research, using esters as electrophilic coupling partner contributes to the well-established but still growing field of cross-coupling chemistry. By using multi-well plates rather than traditional batch screening allowed the discovery of each different projects with reasonable commitment of time and resources.

For future work, the optimization of hits obtained using HTE (**Chapter 4**) such as cyanation, phosphorylation, and Stille coupling from methyl ester as electrophilic coupling partner will be further studied. Moreover, other abundant functionalities such as carboxylic acids and alcohols might be studied as alternative electrophiles to perform different types of cross-coupling reactions (**Scheme 5.1**). These simple free-alcohol functionalities might be activated in situ with tetramethyl orthosilicate or boric acid; then an oxidative addition step will be presumably feasible into the C(acyl)–O bond and different cross coupling reactions will be achieved. The continuous use of the HTE approach might be an option of having a rapid starting point.

Scheme 5.1. Achieved versus future goals using acyl cross coupling electrophiles



6 Claims to original research

Intellectual propety

1. Newman, S. G.; Ben Halima, T.; Masson-Makdissi, J. Synthesis of Amides from Esters. **2018**. US Provisional Patent application S/N 62/624,286.

Peer Reviewed Journal Articles

3. Ben Halima, T.; Masson-Makdissi, J.; Newman, S. Nickel-Catalyzed Amide Bond Formation from Methy Esters. *Angew. Chem. Int. Ed.* **2018**, *57*, 12925.

2. Ben Halima, T.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.; Houk, K.; Newman, S. Palladium-Catalyzed Suzuki-Miyaura Coupling of Esters. *J. Am. Chem. Soc.* **2017**, *139*, 1311.

-Highlighted in Synfacts. (DOI: 10.1055/s-0036-1590050)

-Highlighted in Organic Chemistry Frontiers (DOI: 10.1039/C7QO00068E)

-Web of Science "Highly Cited Paper" (top 1% of chemistry)

1. Ben Halima, T.; Vandavasi, J. K.; Shkoor, M.; Newman, S. A Cross-Coupling Approach to Amide Bond Formation from Esters. *ACS Catalysis* **2017**, 7, 2176.

Peer Reviewed Conference Contributions

Talk

9. Centre for Catalysis Research and Innovation Technical Seminar, Ben Halima, T.; Newman, S. (**2018**) The Use of High-Throughput Screening for the Discovery of New Reactions, *Institutional.* University of Ottawa, ON., CAN.

8. 27th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry. Ben Halima, T.; Newman, S. (**2016**) Palladium-Catalyzed Cross Coupling of Esters. *Regional.* University of Waterloo**,** ON., CAN.

7. 24th Canadian Symposium on Catalysis. Ben Halima, T.; Newman, S. (**2016**) Palladium-Catalyzed Suzuki-Miyaura Coupling of Esters. *National*. University of Ottawa, ON., CAN.

Poster

6. 16th Belgian Organic Synthesis Symposium. Ben Halima, T.; Newman, S. (**2018**) Nickel-Catalyzed Amide Bond Formation from Methyl Esters. *International*. Université Libre de Bruxelles (ULB), Brussels, Belgium.

5. 27th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry. Ben Halima, T.; Newman, S. (**2017**) A Cross-Coupling Approach to Amide Bond Formation from Esters. *Regional*. McGill University, QC., CAN.

4. Networking event 2017. Ben Halima, T.; Newman, S.G. (**2017**) Sustainable Chemical Synthesis in Batch and Flow. *Institutional*. University of Ottawa, ON., CAN.

3. OCCI Day Symposium. Ben Halima, T.; Newman, S.G. (**2017**) A Cross-Coupling Approach to Amide Bond Formation from Esters. *Institutional.* University of Ottawa, ON., CAN

2. 100th Canadian Chemistry Conference and Exhibition. Ben Halima, T.; Newman, S.G. (**2017**) A Cross-Coupling Approach to Amide Bond Formation from Esters. *National*. Metro Toronto Convention Center, Toronto, ON., CAN.

1. Ontario and Canada Research Chairs Symposium. Ben Halima, T.; Newman, S.G. (**2015**) Sustainable Chemical Synthesis in Batch and Flow. *Provincial*. Metro Toronto Convention Center, Toronto, ON., CAN.

General experimental details

7 General experimental details

Unless otherwise indicated, reactions were conducted under an atmosphere of argon in 5 mL screw-capped vials that were oven dried (120 °C). Column chromatography was either done manually using Silicycle F60 40-63 µm silica gel, or using a Combiflash Rf+ automated chromatography system with commercially available RediSep Rf normal-phase Silica Flash columns (35-70 µm). Analytical thin layer chromatography (TLC) was conducted with aluminum-backed EMD Millipore Silica Gel 60 F_{254} pre-coated plates. Visualization of developed plates was performed under UV light (254 nm) and/or using $KMnO_4$ or ceric ammonium molybdate (CAM) stain.

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer. ^1H NMR spectra were internally referenced to the residual solvent signal (e.g. $CDCl_3$ = 7.27 ppm). ^{13}C NMR spectra were internally referenced to the residual solvent signal (e.g. $CDCl_3$ = 77.36 ppm). ^{19}F specra were unreferenced. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration. NMR yields for optimization studies were obtained by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

GC yields for optimization studies were obtained via a 5 point calibration curve using FID analysis on an Agilent Technologies 7890B GC with 30 m x 0.25 mm HP-5 column. IR spectra were recorded on Agilent Cary 630 FTIR spectrometer and are reported in terms of frequency absorption (cm^{-1}). Melting point ranges were determined on a Mel-Temp 1101D Melting Point Apparatus. Accurate mass data (EI) obtained from an Agilent 5977A GC/MSD using MassWorks 4.0 from CERNO bioscience.[1]

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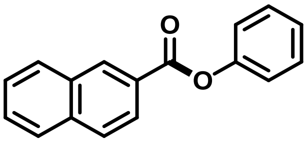
[1] Wang, Y.; Gu, M. *Anal. Chem.* **2010**, *82*, 7055.

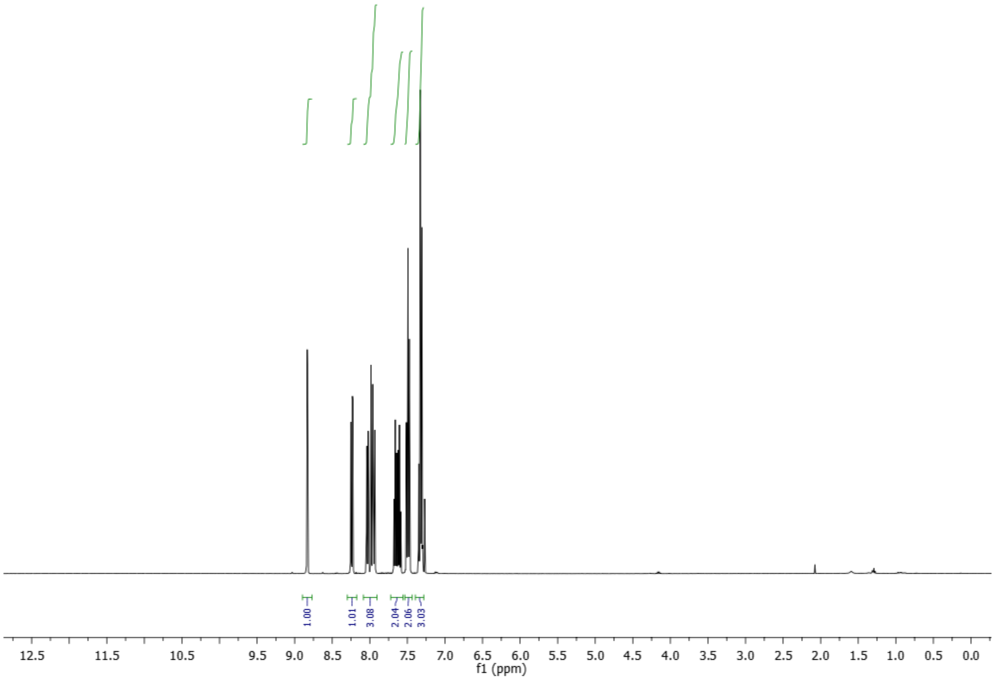
Appendices

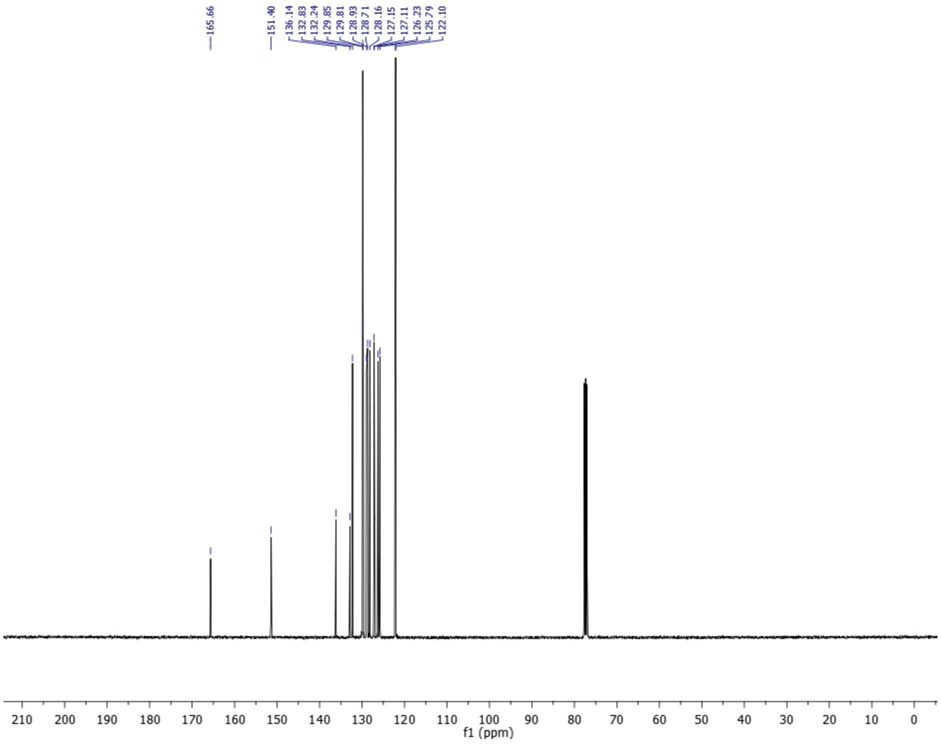
8 Appendices

8.1 Appendix1 : ^{1}H, ^{13}C NMR spectra and HPLC traces from Chapter 2

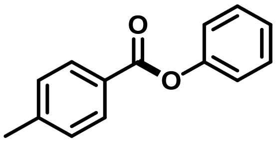
Phenyl 2-naphthoate (**2.1.9B**). $CDCl_3$, 400MHz:

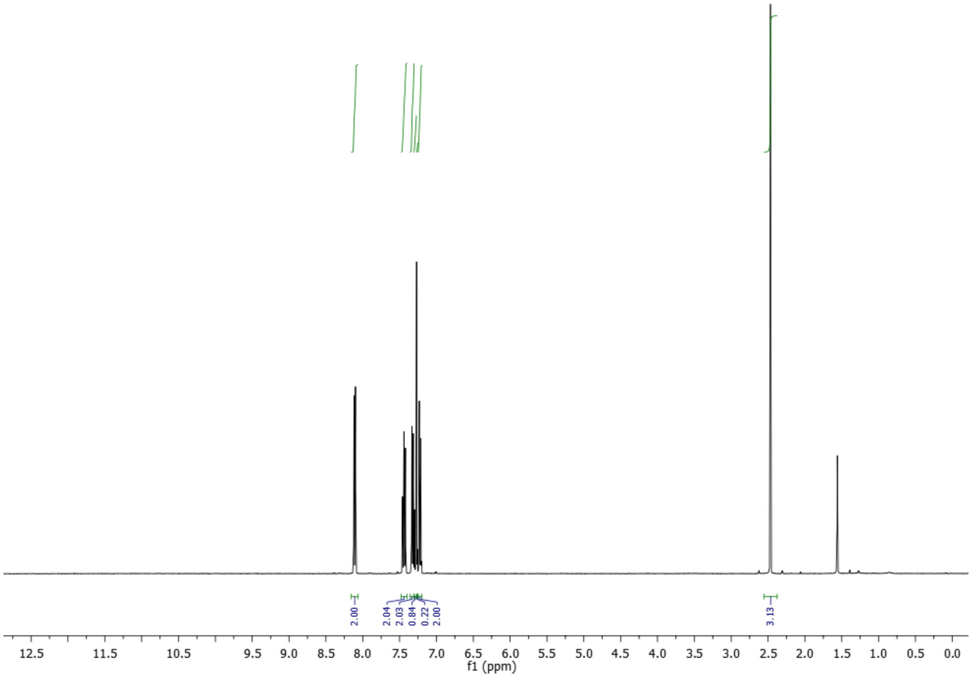


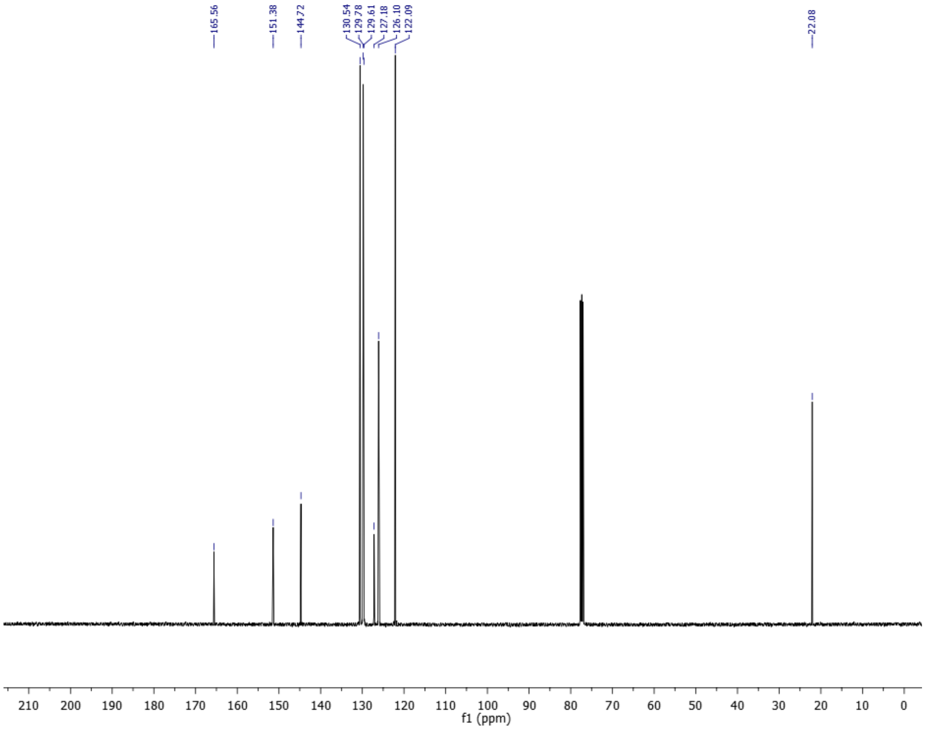




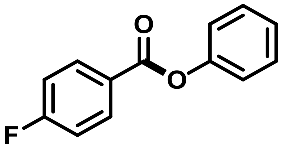
p-Methyl benzoic acid phenyl ester (**2.1.9C**). CDCl$_3$, 400MHz:

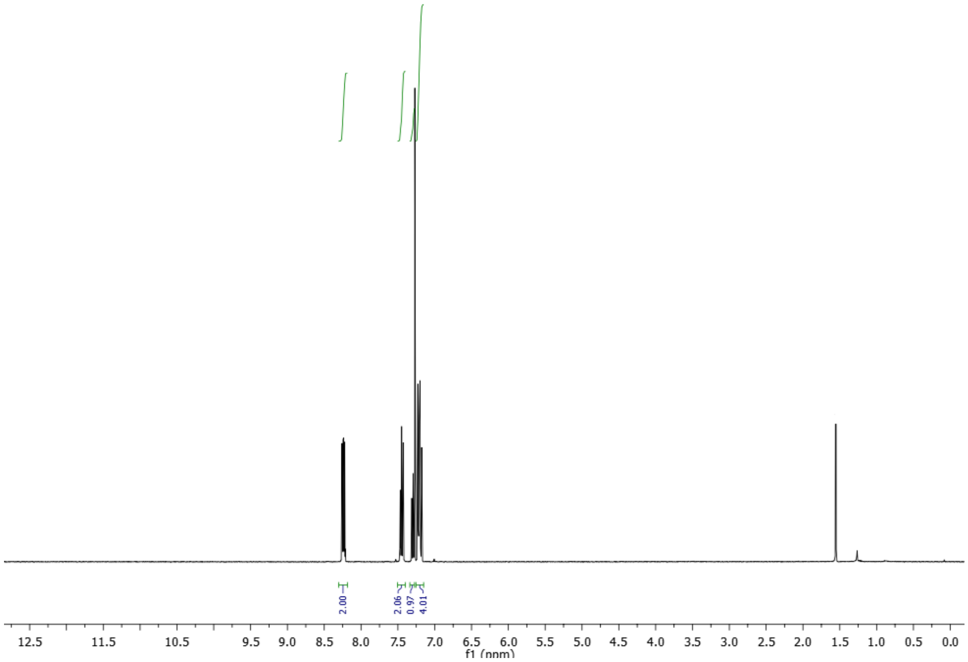


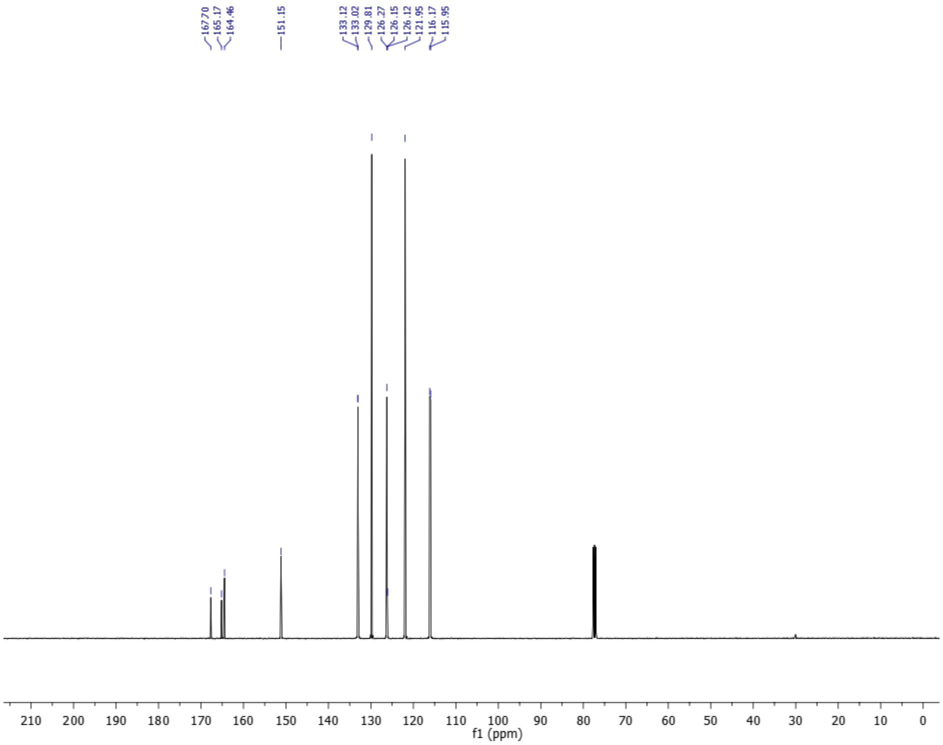




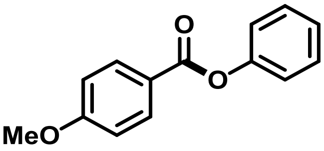
4-Fluoro-benzoic acid phenyl ester (**2.1.9D**). $CDCl_3$, 400 MHz:

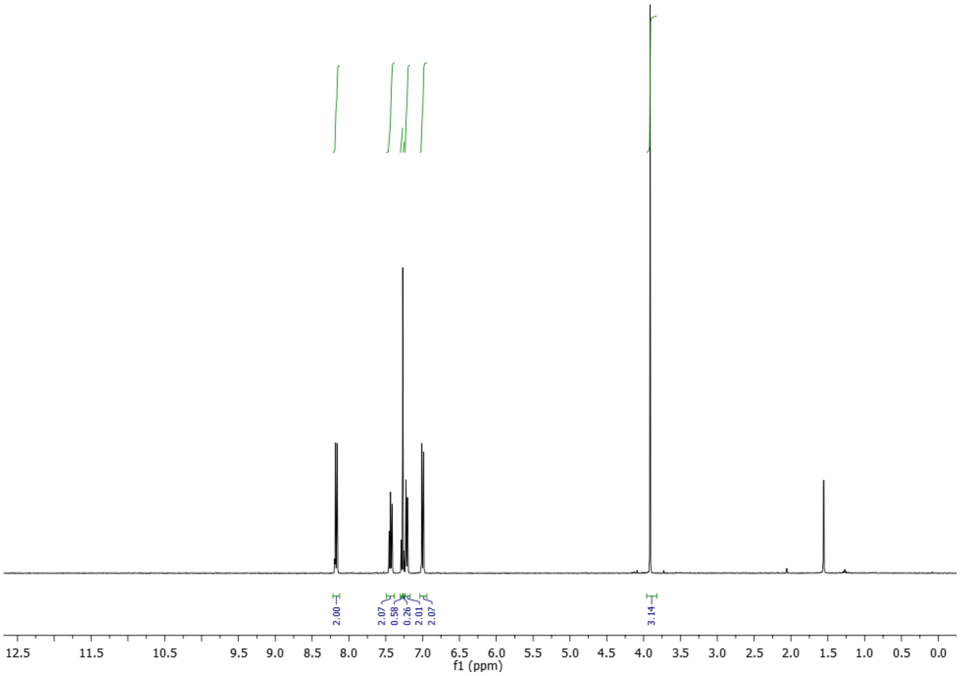


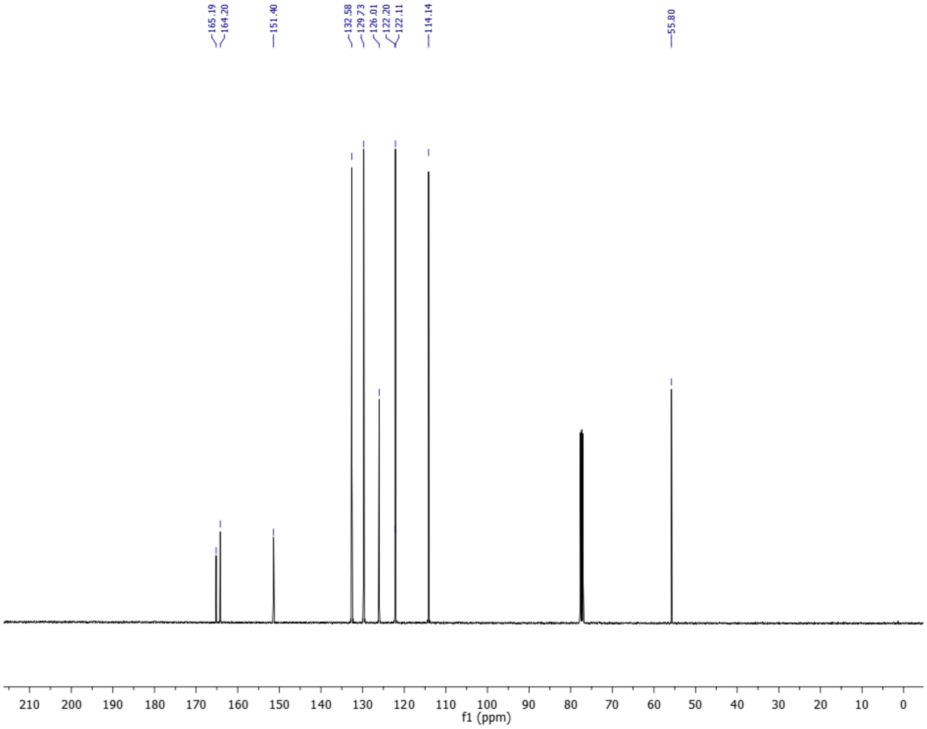




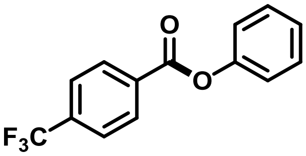
4-Methoxy-benzoic acid phenyl ester **(2.1.9E).** CDCl$_3$, 400 MHz:

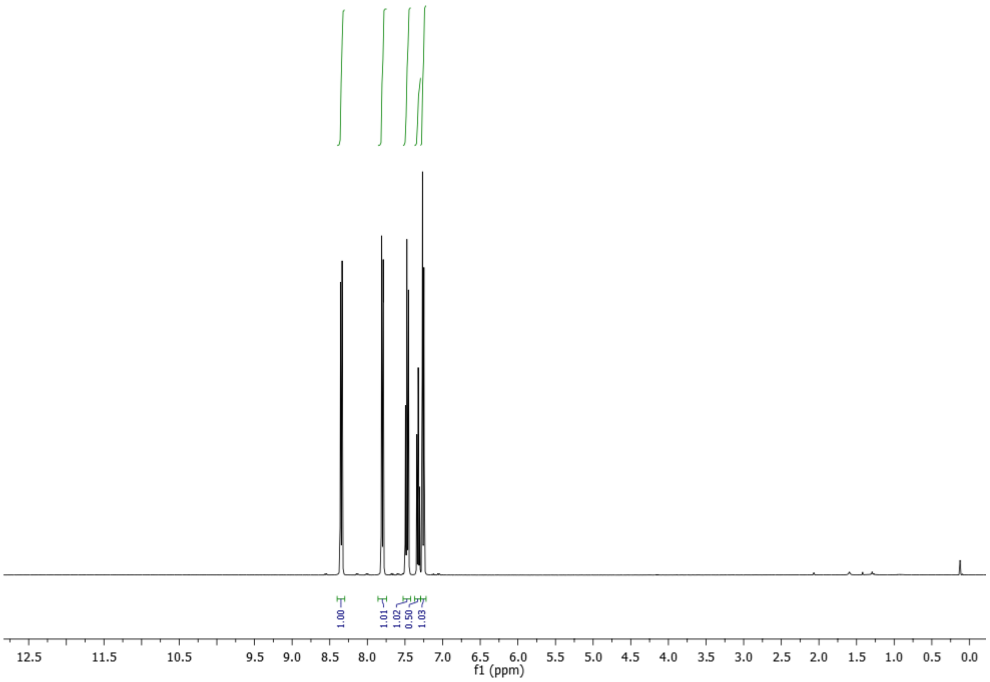


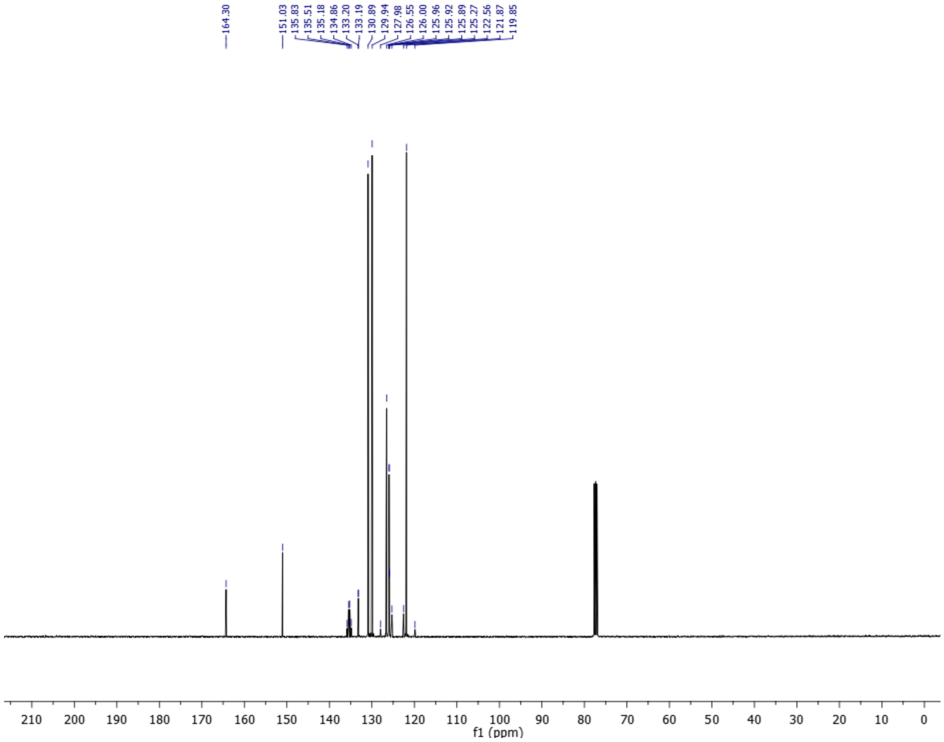


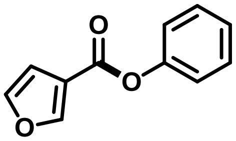


Phenyl 4-(trifluoromethyl) benzoate (**2.1.9F**). $CDCl_3$, 400 MHz:

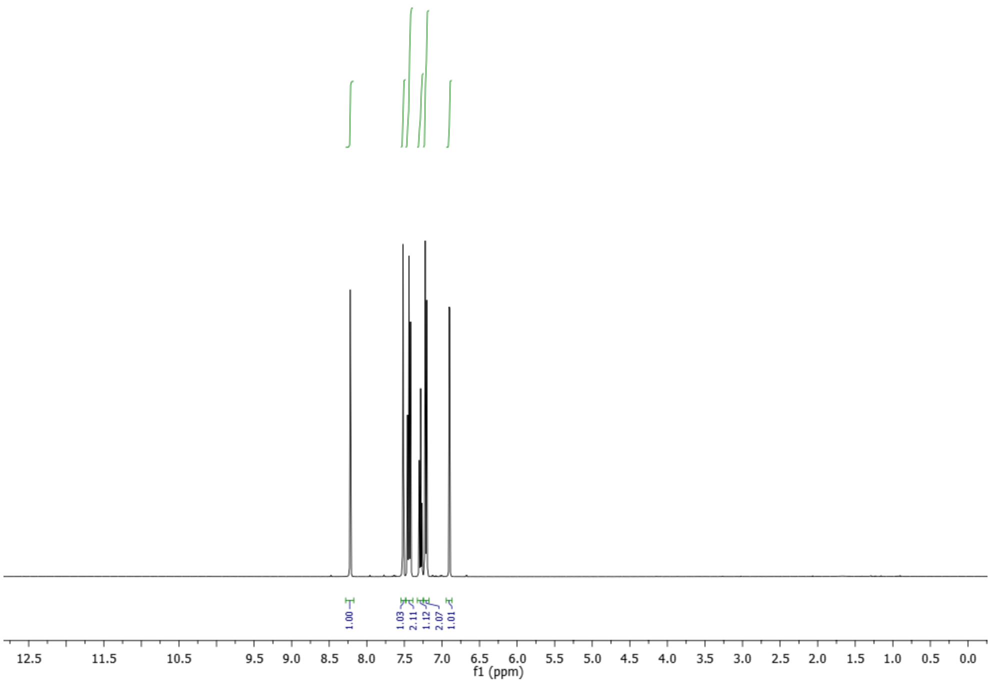


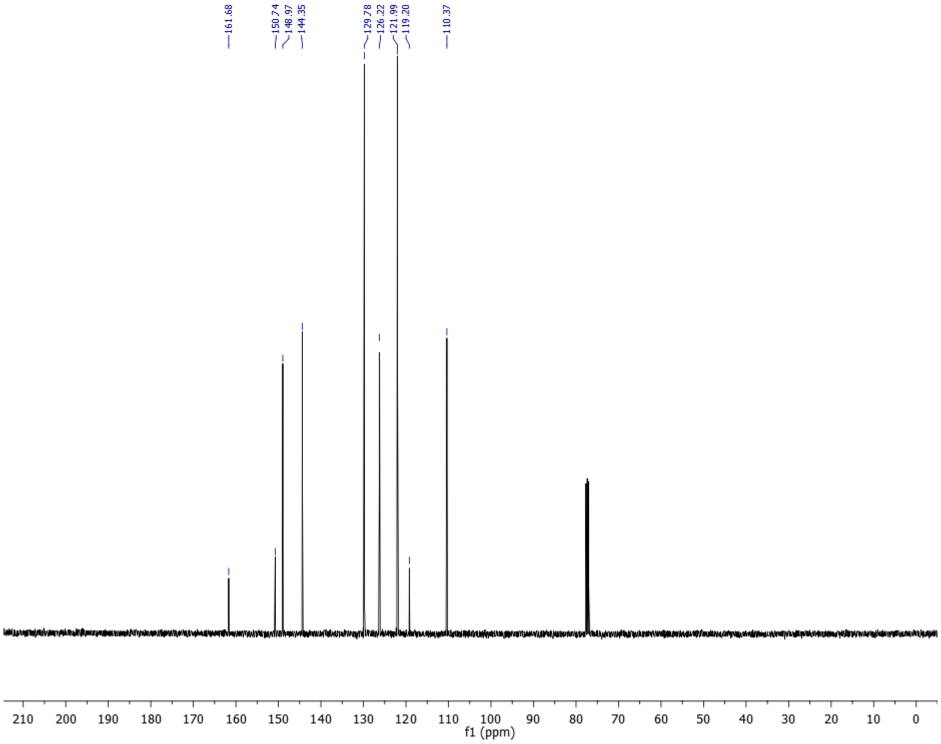




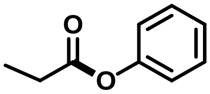


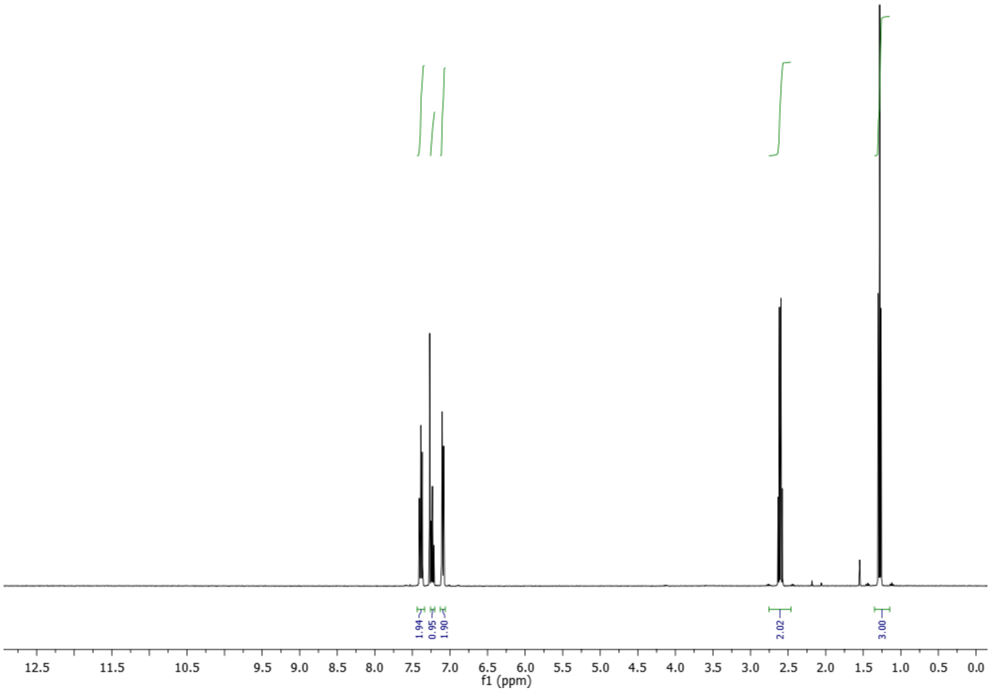
Phenyl furan-3-carboxylate **(2.1.9G).** CDCl$_3$, 400 MHz:

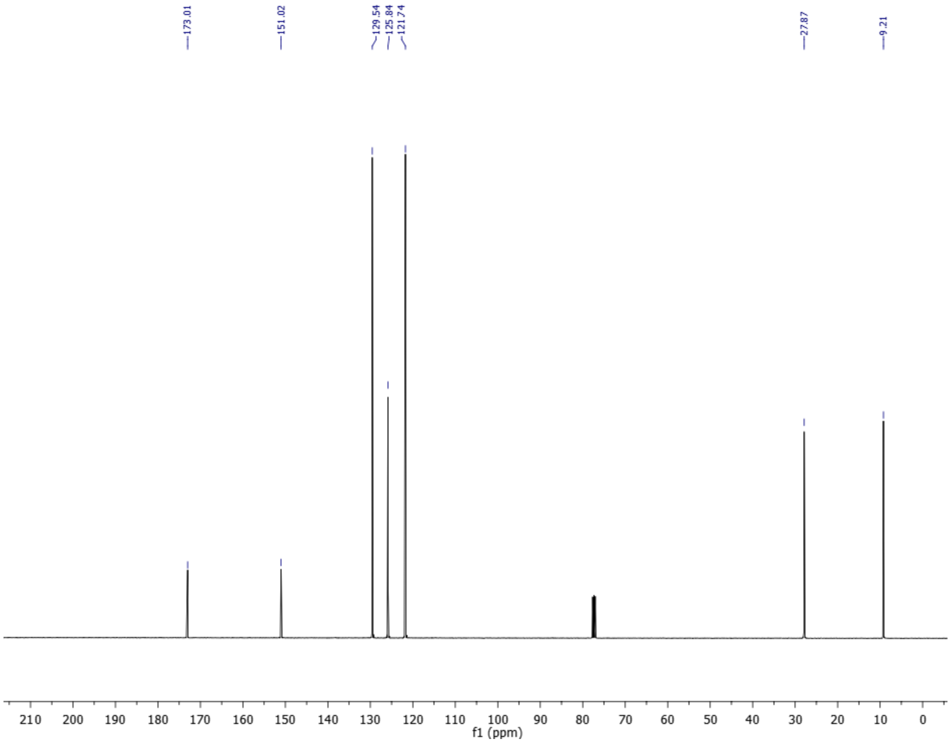




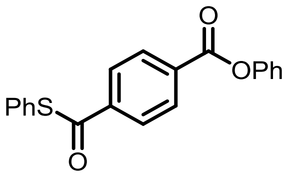
Phenyl propionate **(2.1.9O).** CDCl$_3$, 400 MHz:

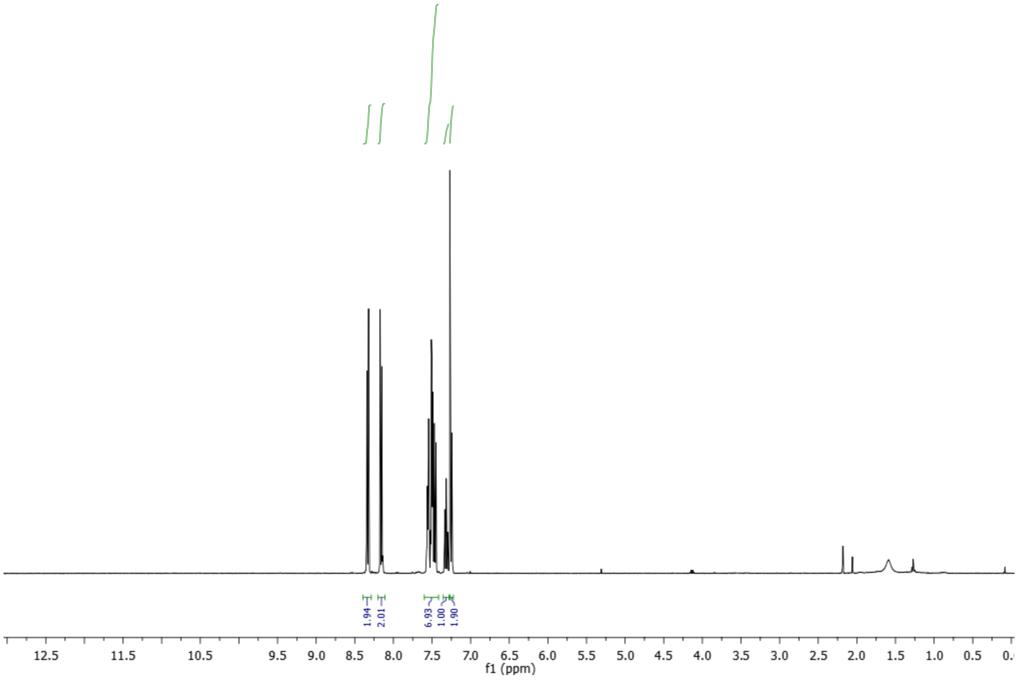


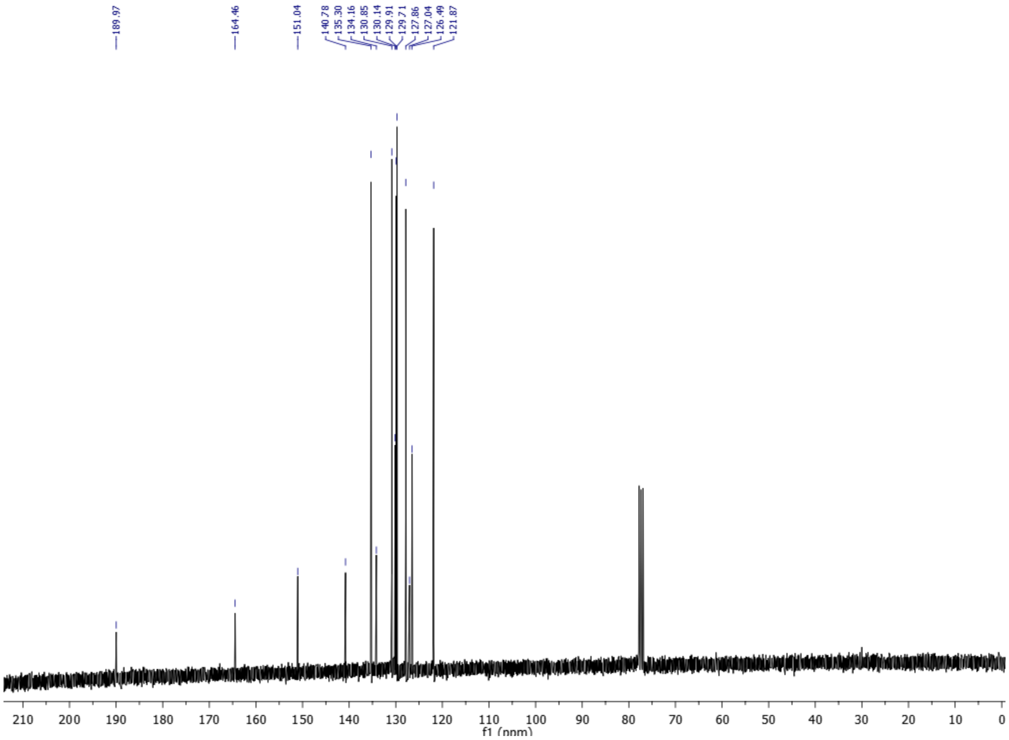




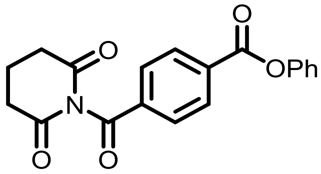
Phenyl 4-((phenylthio) carbonyl) benzoate (**2.1.20**). $CDCl_3$, 400 MHz:

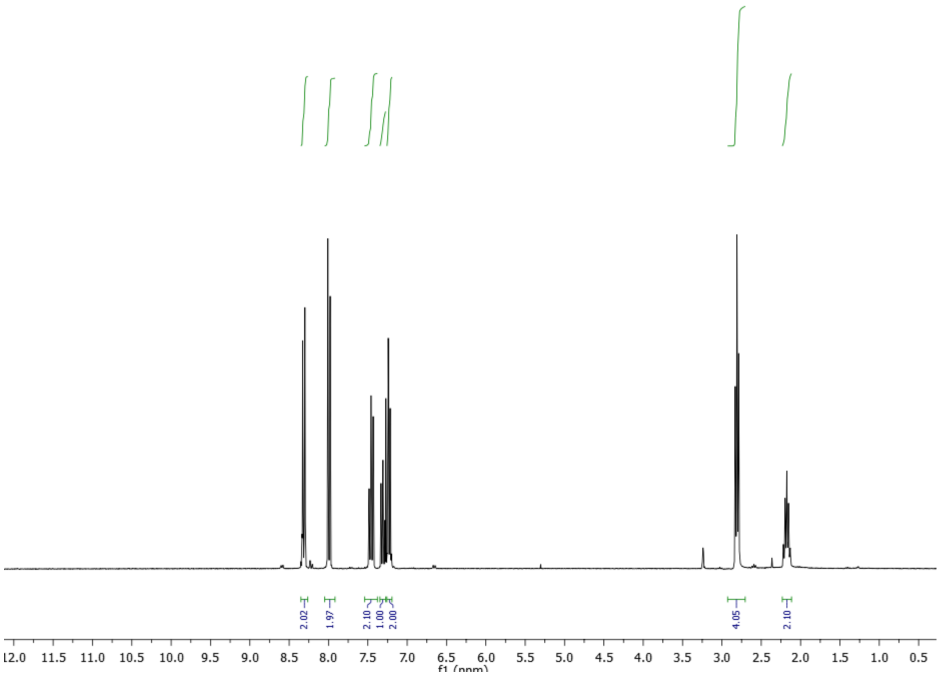


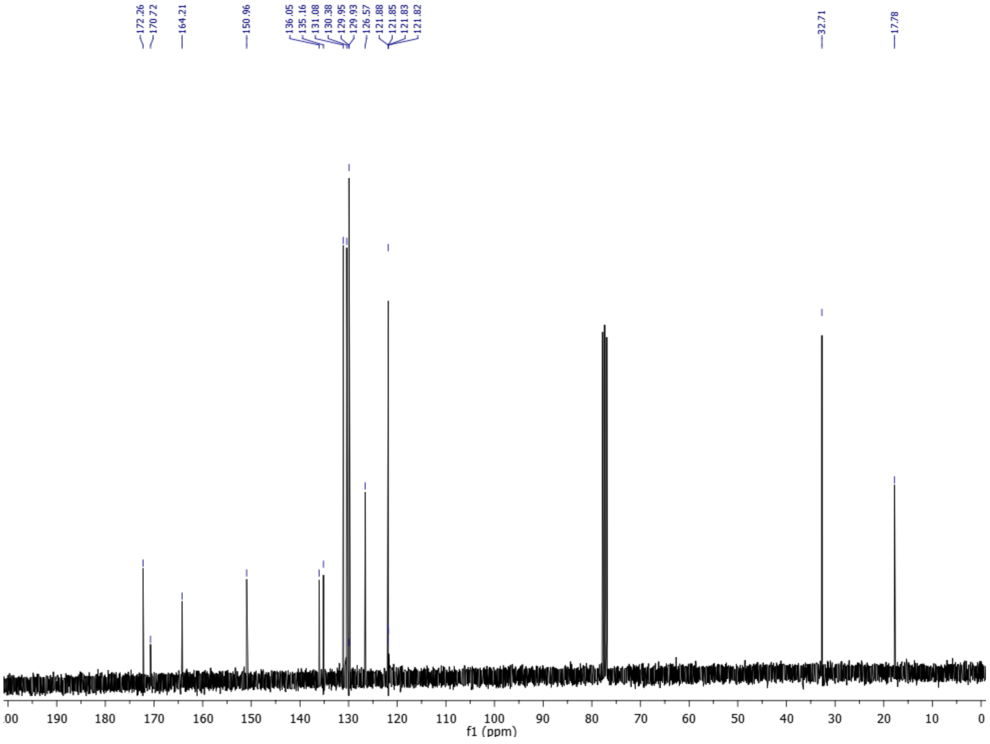




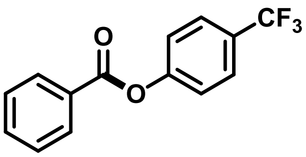
Phenyl 4-(2,6-dioxopiperidine-1-carbonyl)benzoate (**2.1.23**). $CDCl_3$, 400 MHz:

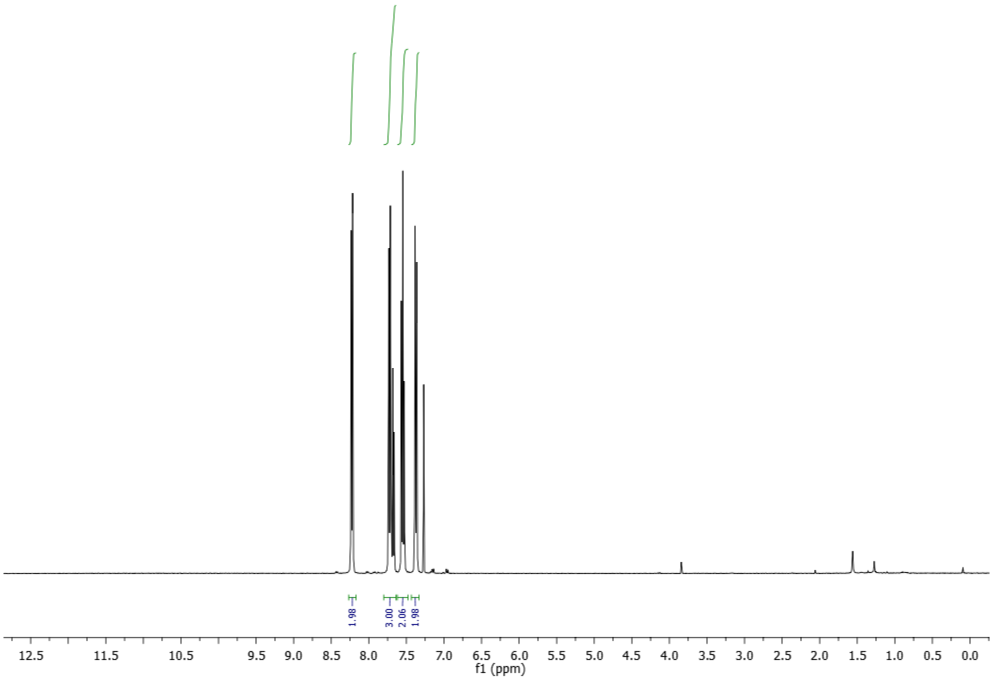


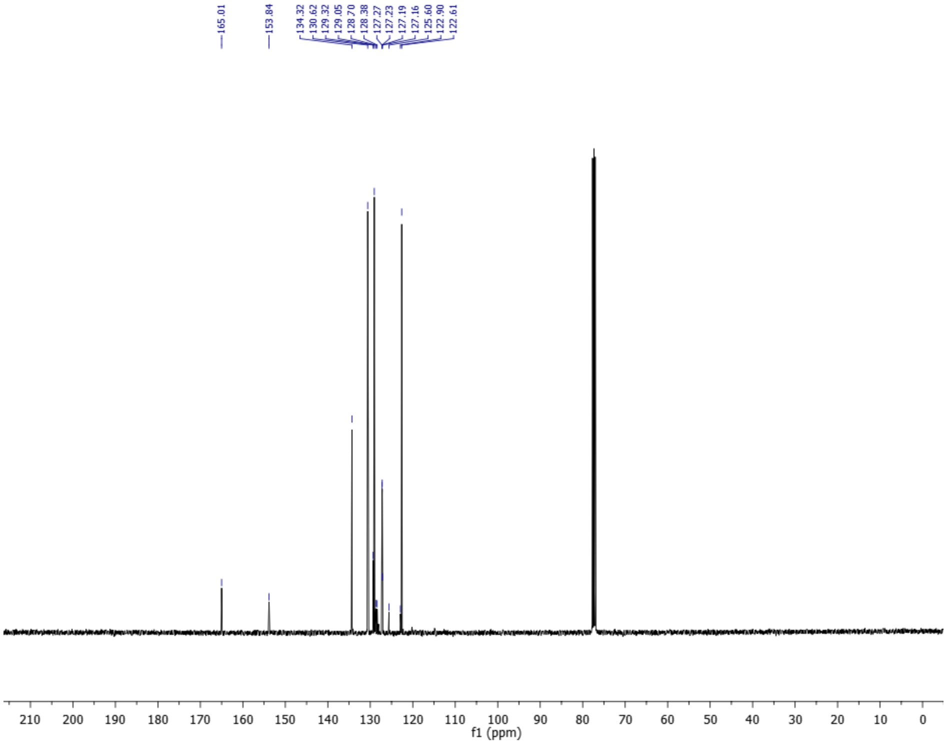




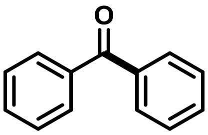
4-Trifluoromethyl) phenyl benzoate **(2.1.9V).** CDCl$_3$, 400 MHz:

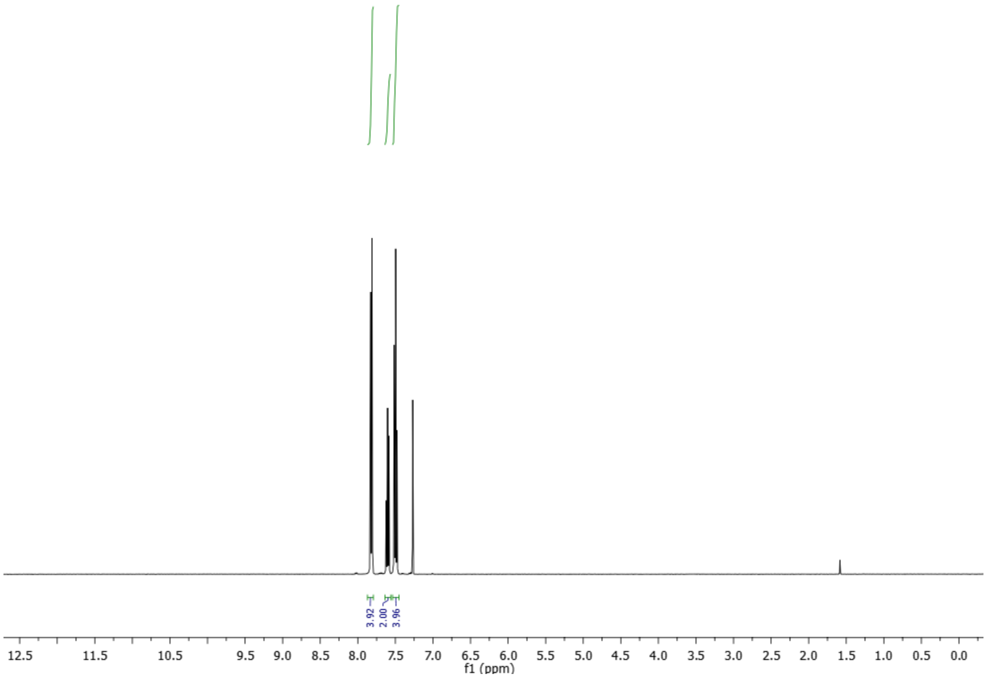


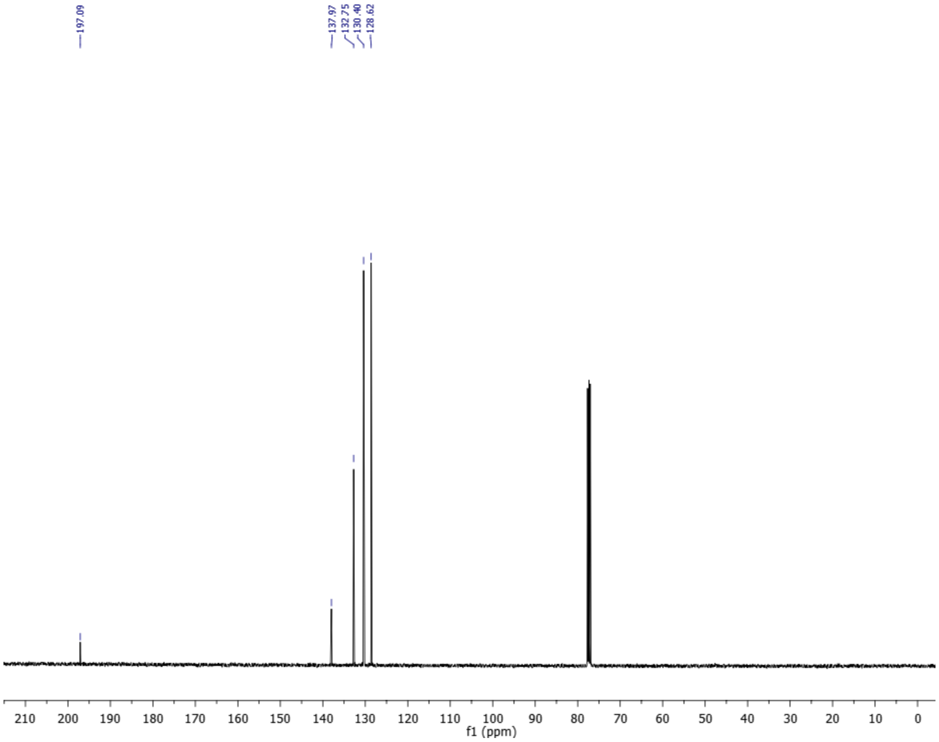




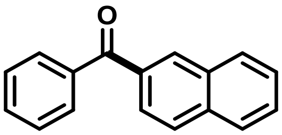
Benzophenone (**2.1.11Aa**). $CDCl_3$, 400 MHz:

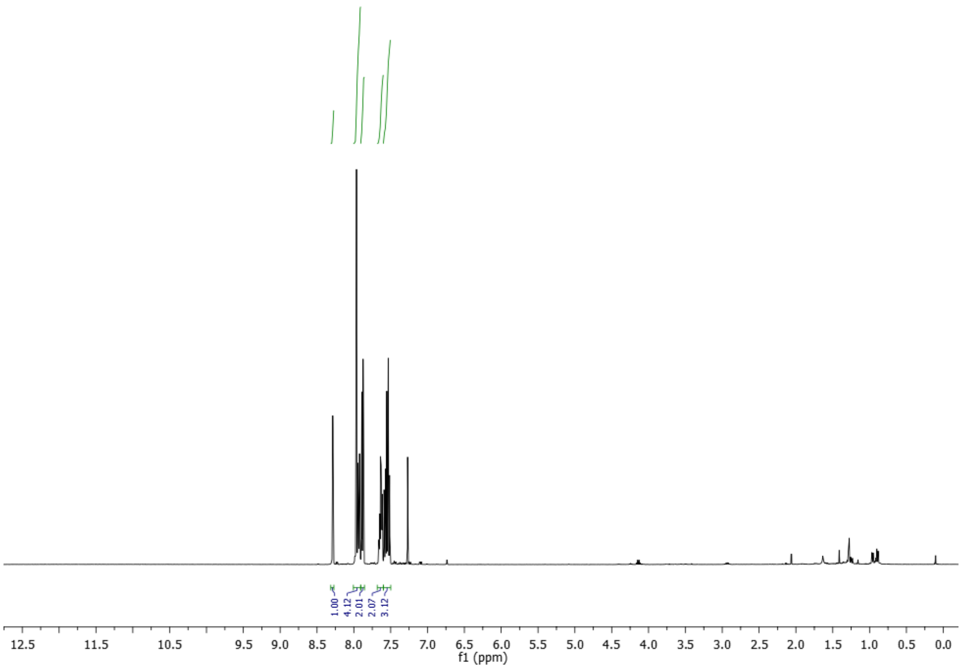


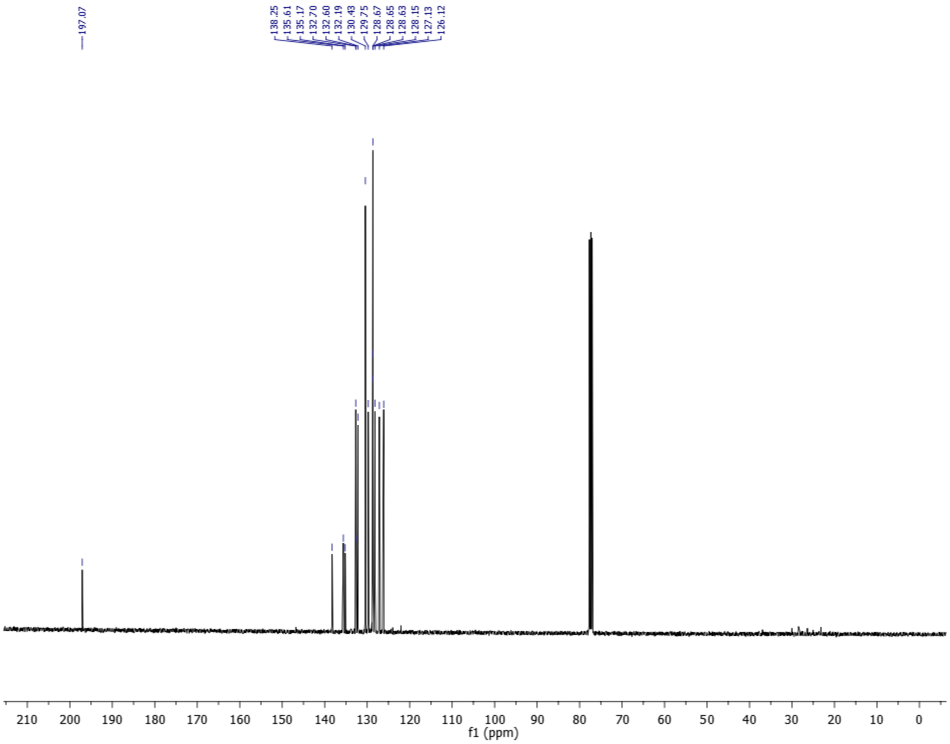




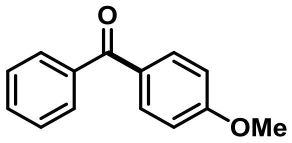
Naphthalen-2-yl(phenyl) methanone (**2.1.11Ab**). $CDCl_3$, 400 MHz:

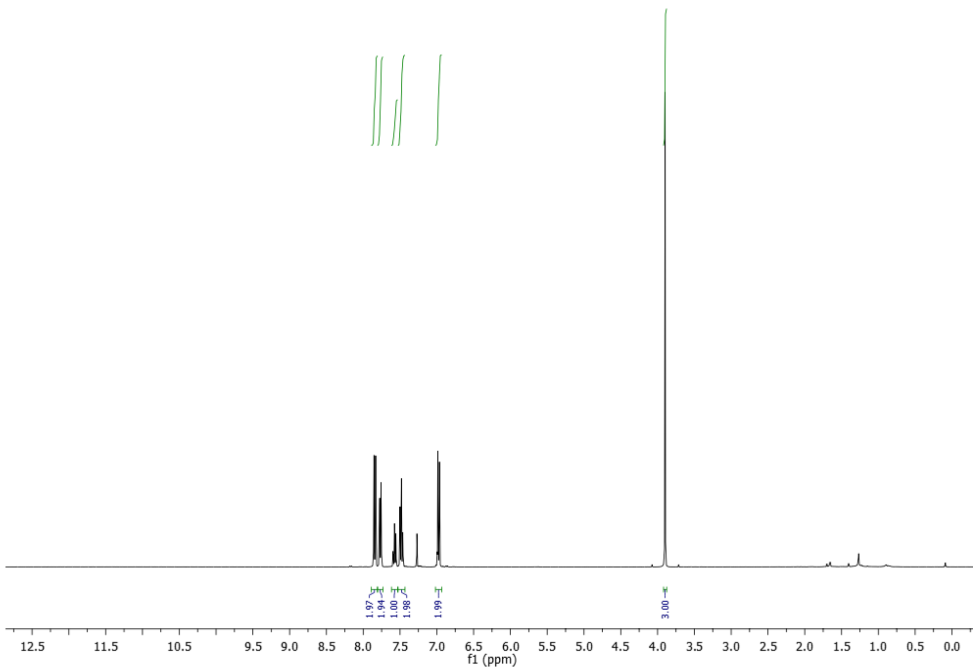


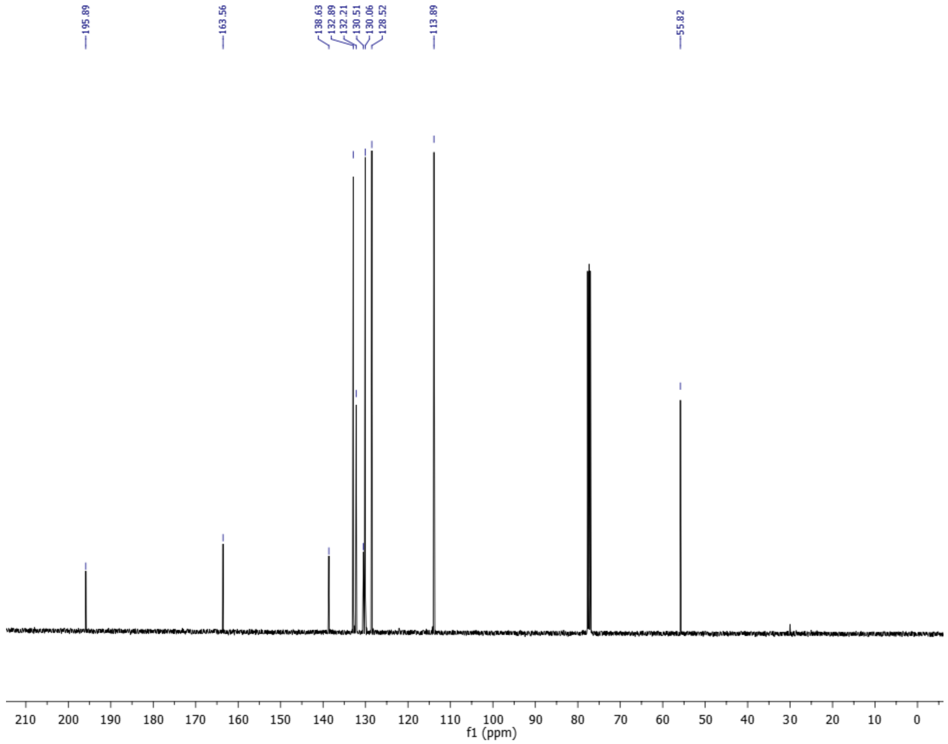




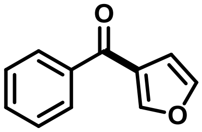
4-Methoxyphenyl-(phenyl) methanone (**2.1.11Ac**). $CDCl_3$, 400 MHz:

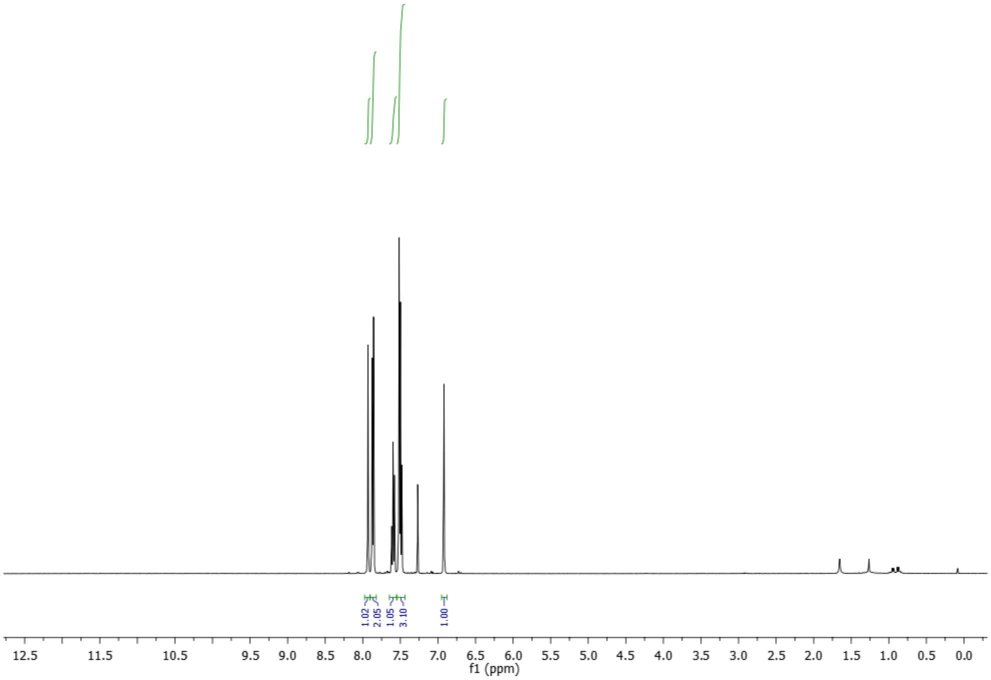


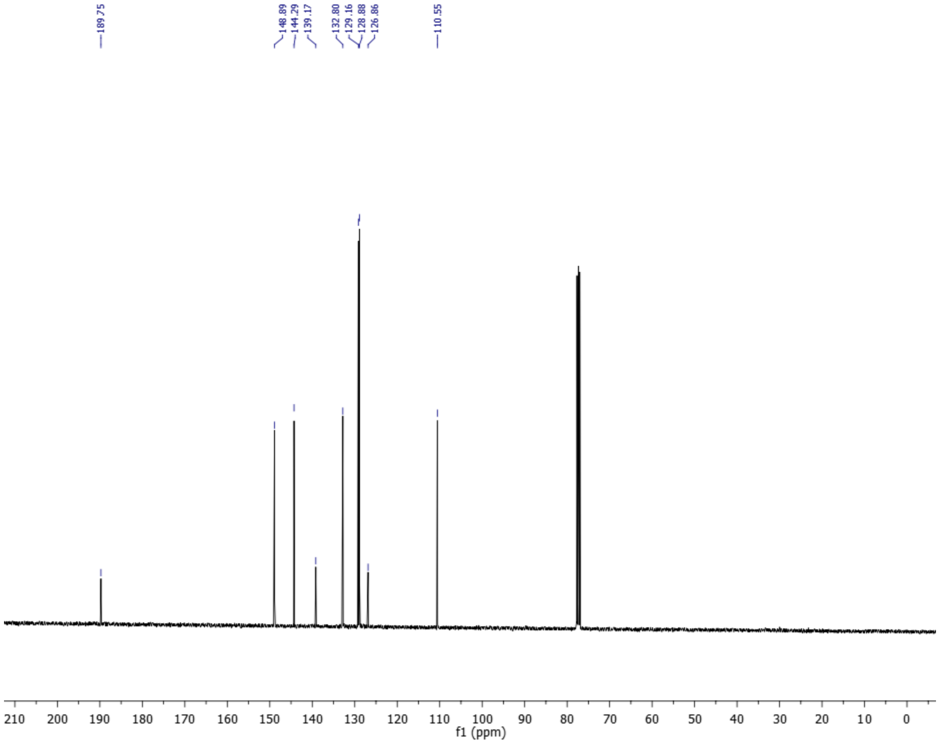


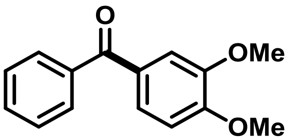


Furan-2-yl(phenyl)methanone (**2.1.11Ad**). $CDCl_3$, 400 MHz:

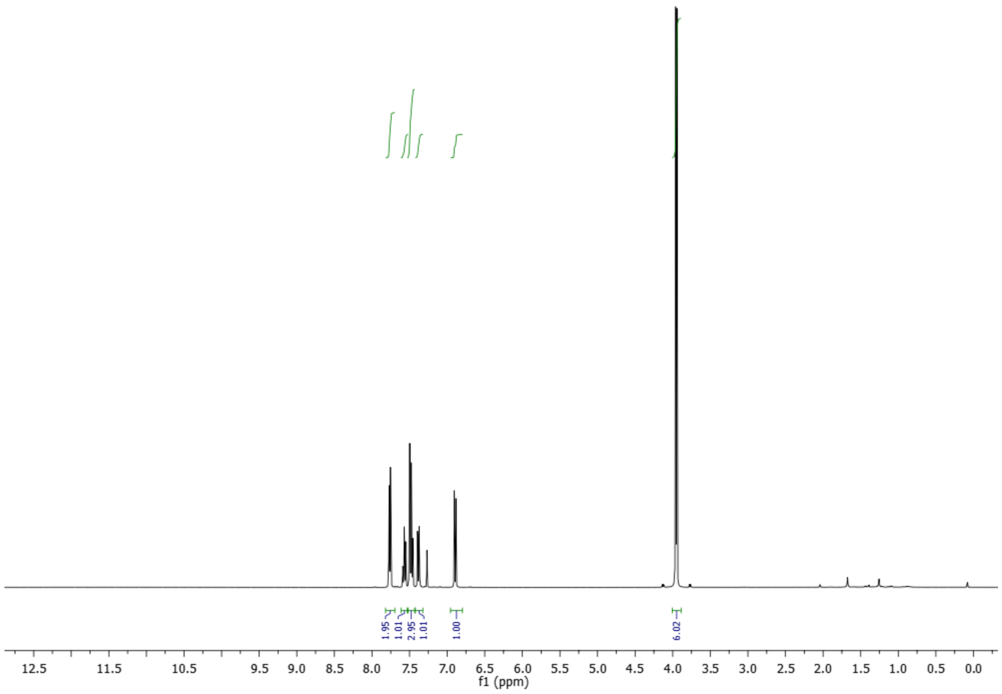


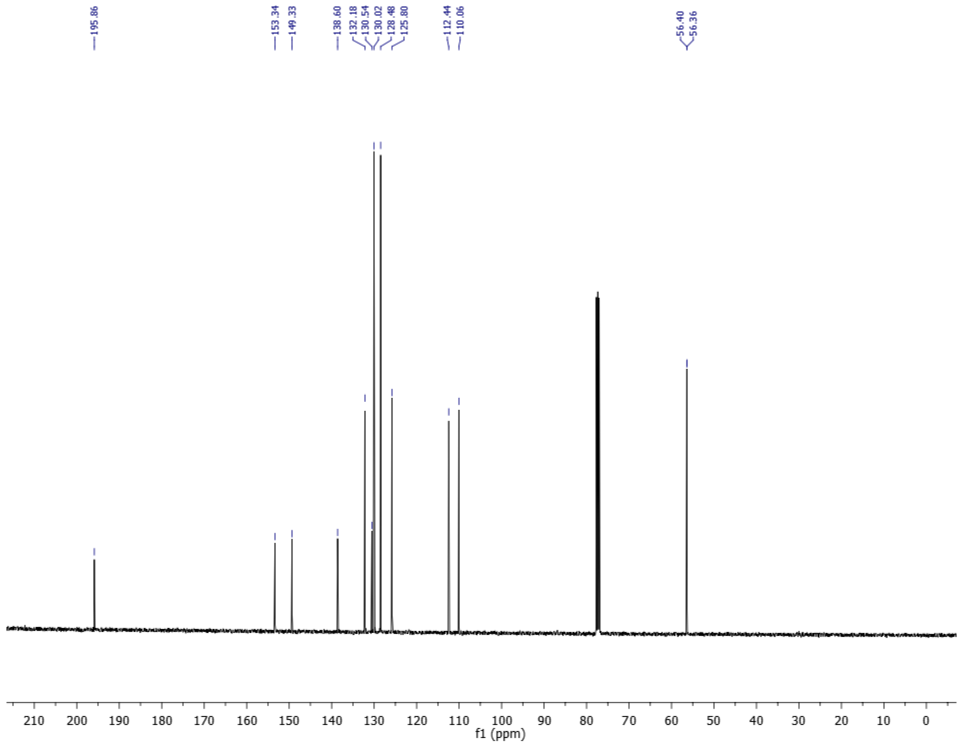




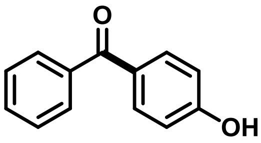


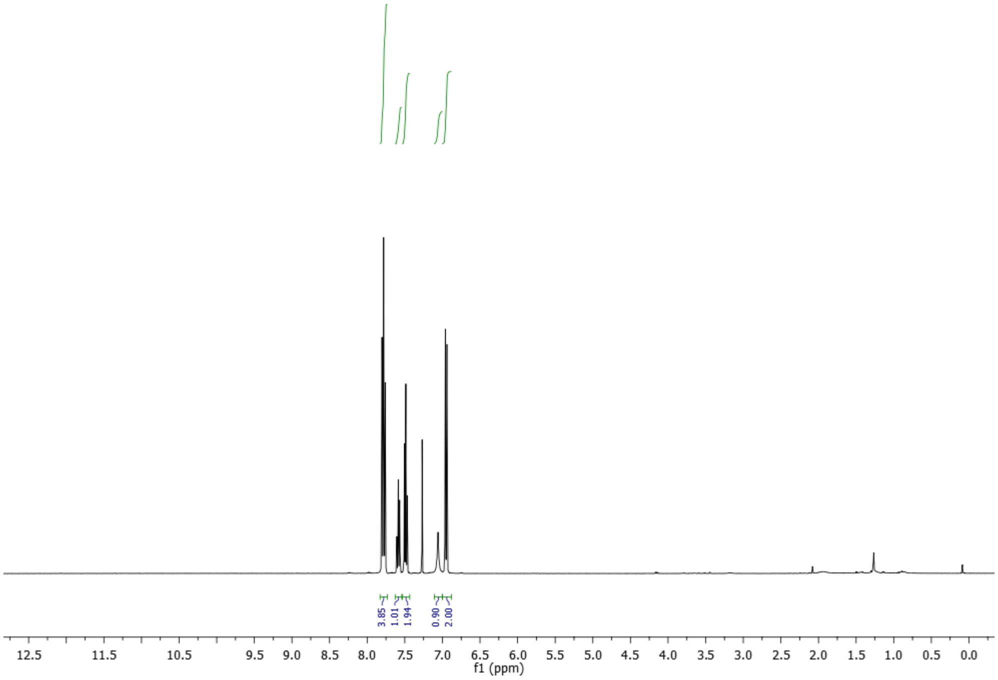
3,4-Dimethoxy benzophenone (**2.1.11Ae**). $CDCl_3$, 400 MHz:

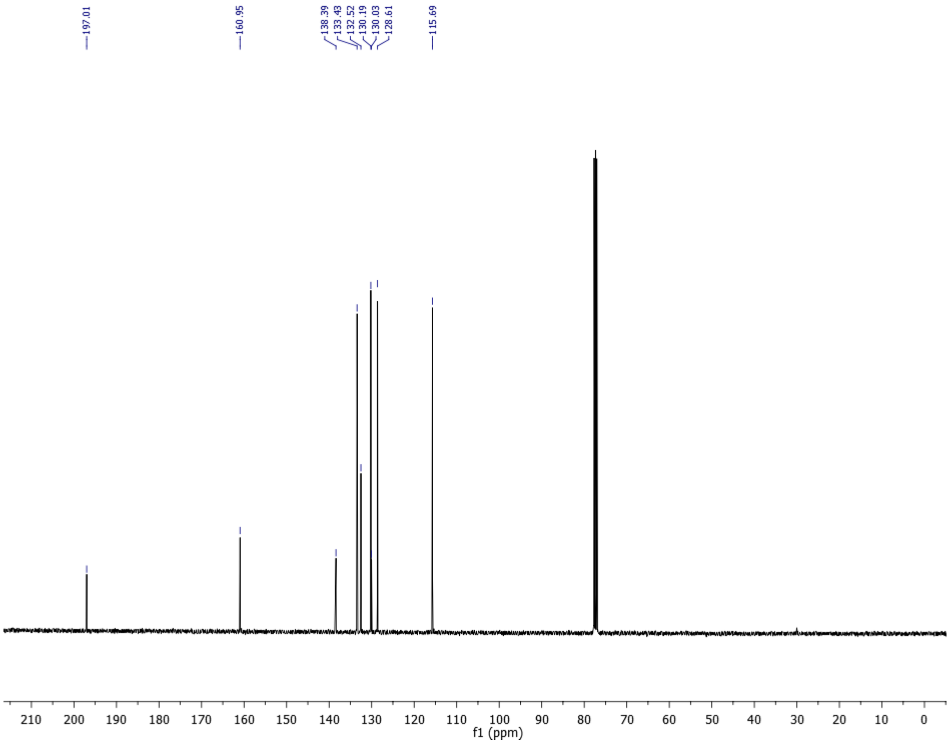


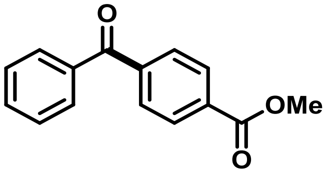


4-Hydroxy-benzophenone (**2.1.11Af**). $CDCl_3$, 400 MHz:

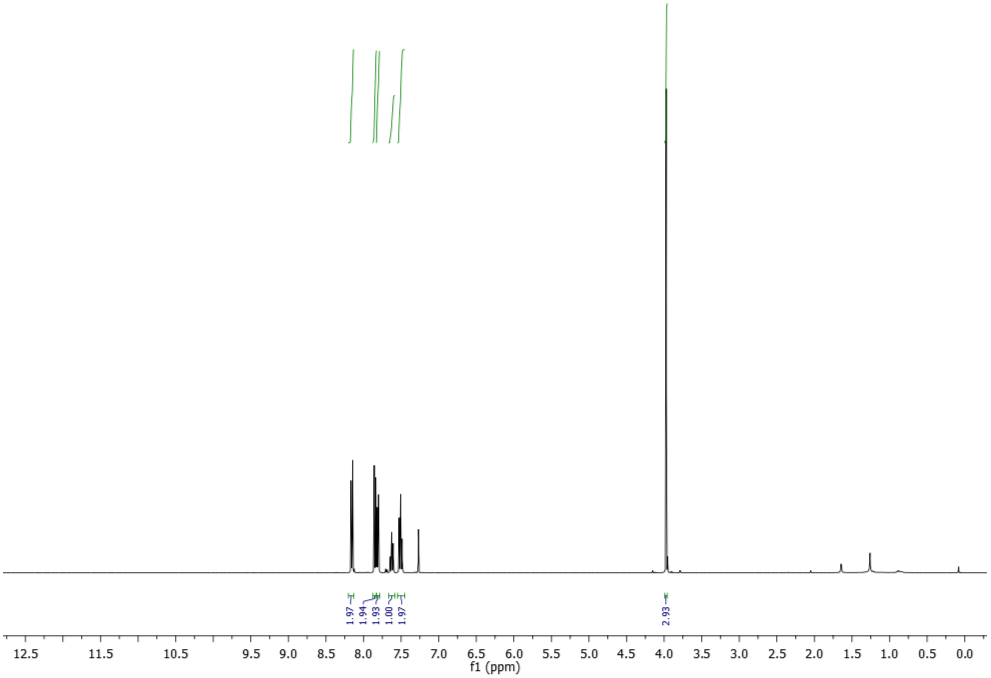


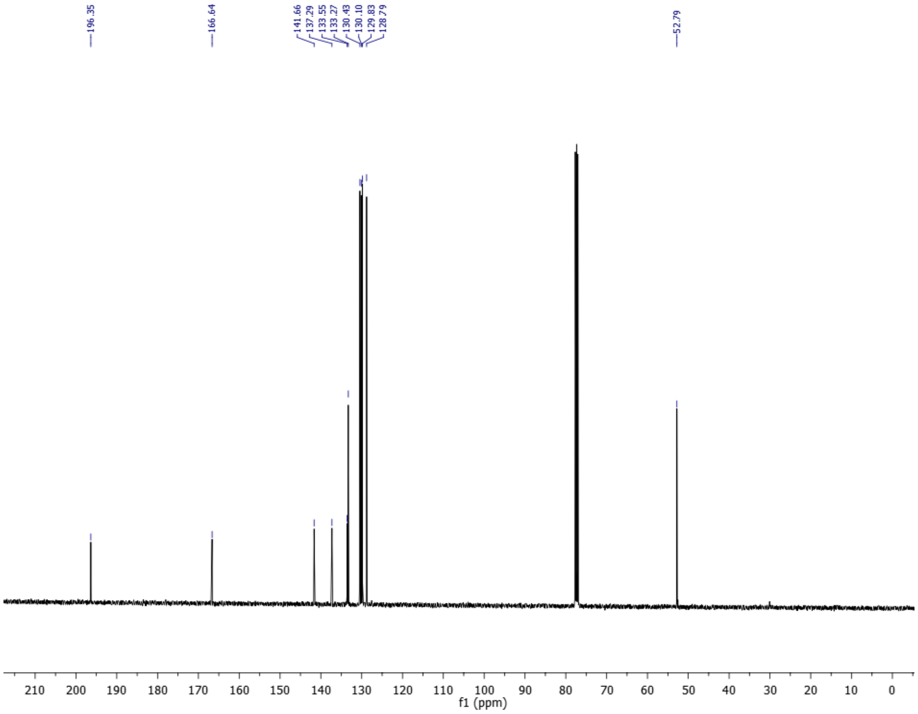


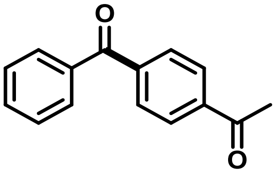




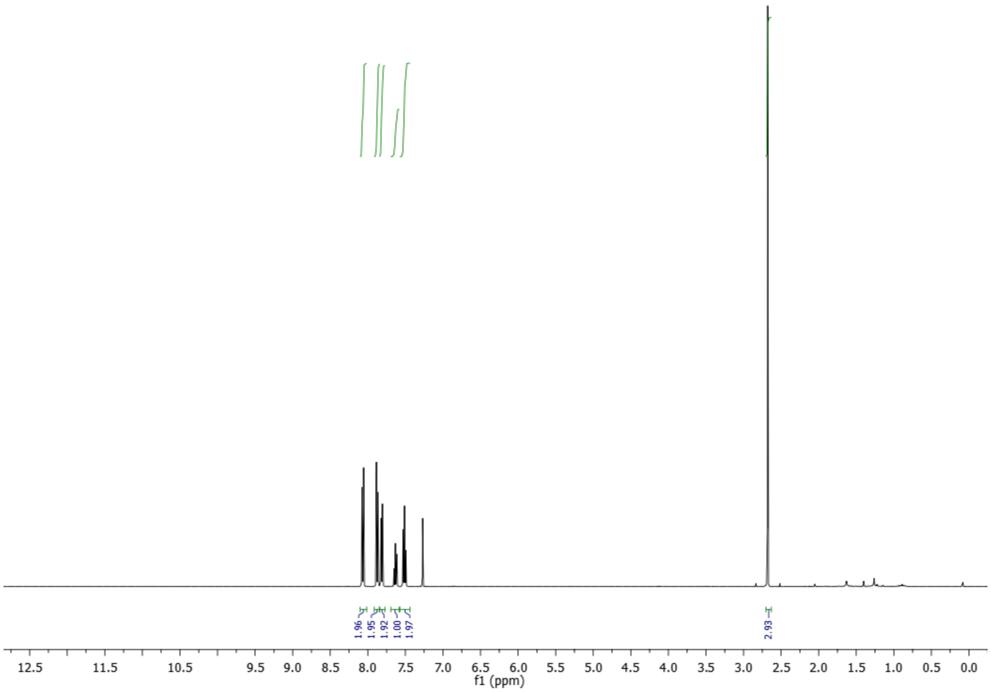
Methyl 4-benzoylbenzoate (**2.1.11Ag**). $CDCl_3$, 400 MHz:

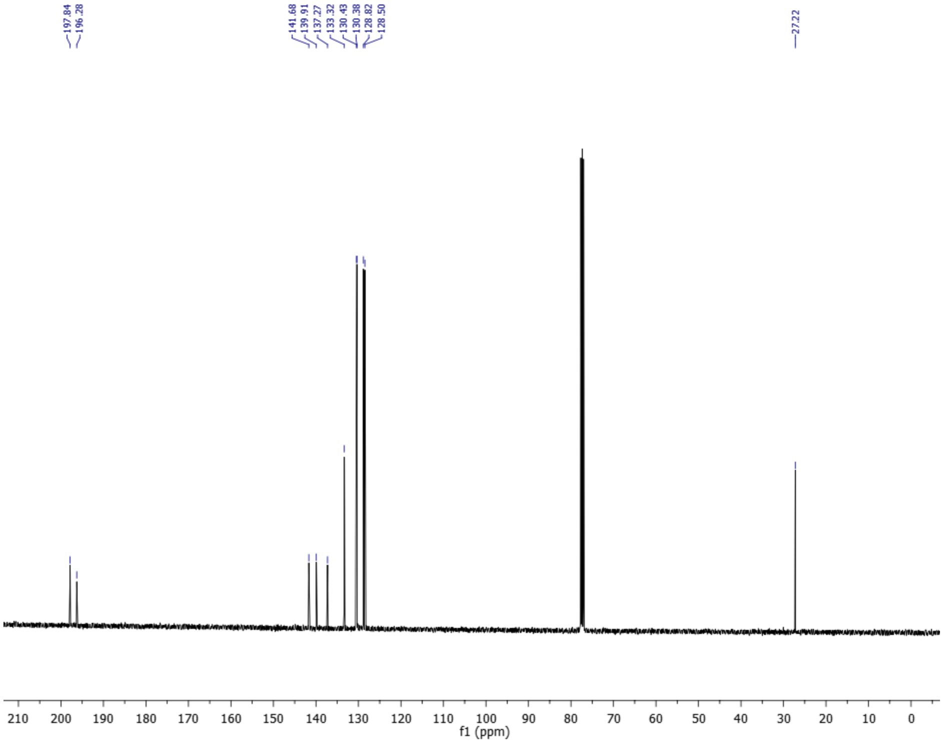




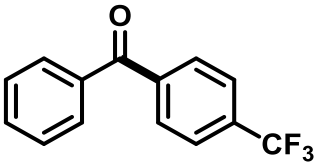


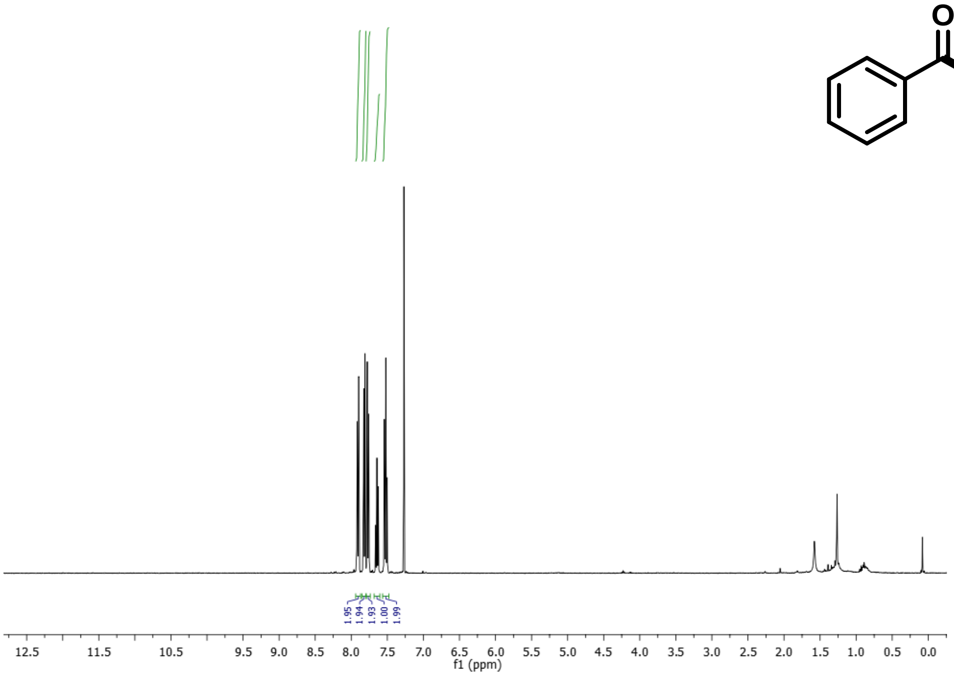
Ethyl 3-benzoylbenzoate (**2.1.11Ah**). $CDCl_3$, 400 MHz:

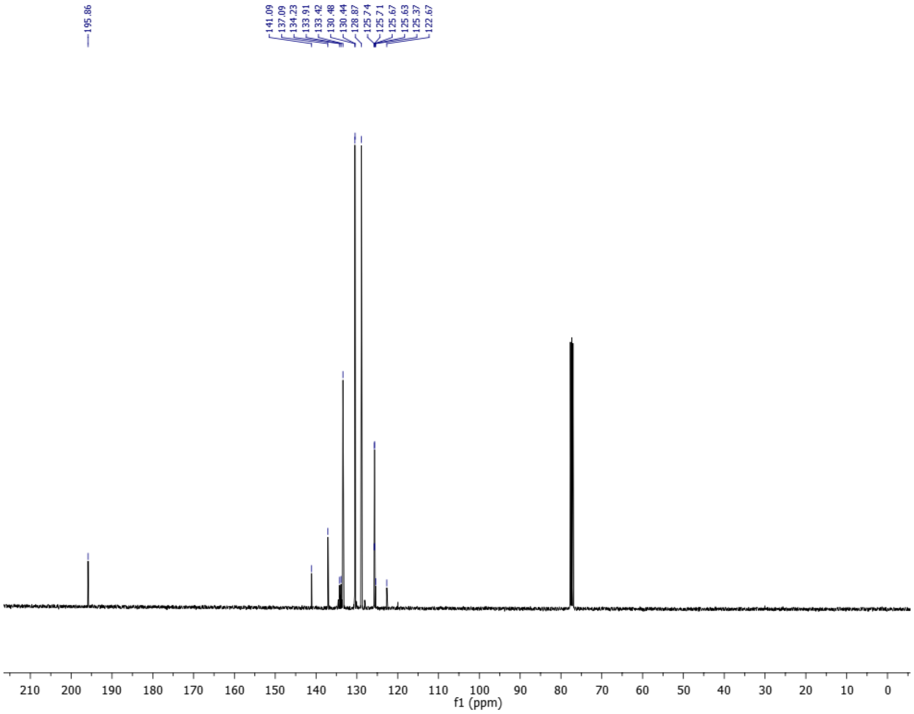




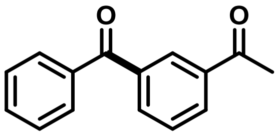
Phenyl (4-trifluoromethyl)phenyl methanone (**2.1.11Ai**). $CDCl_3$, 400 MHz:

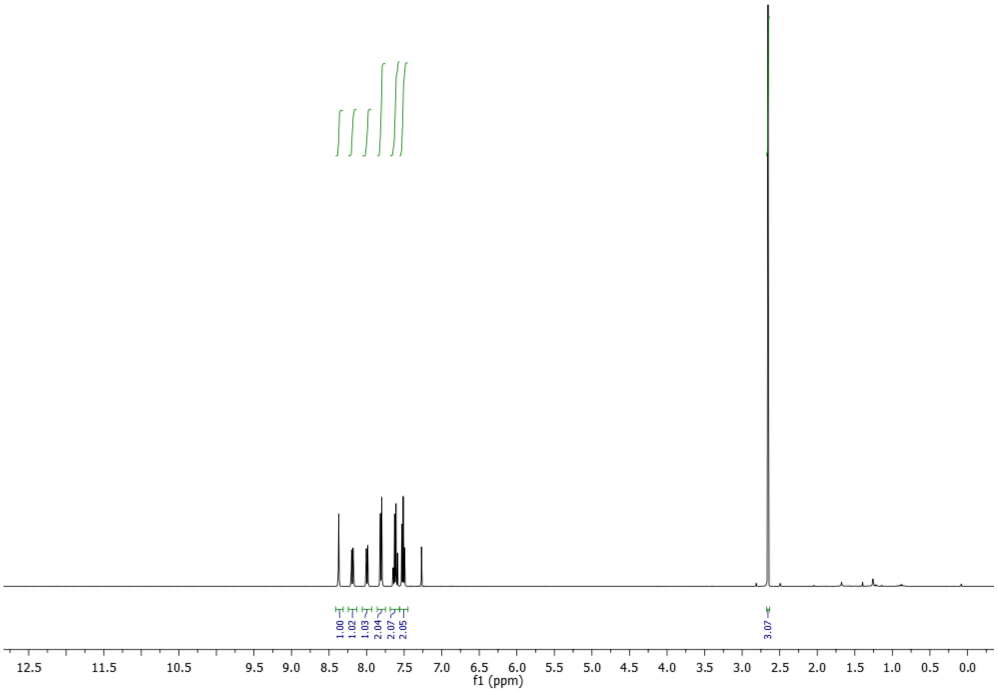


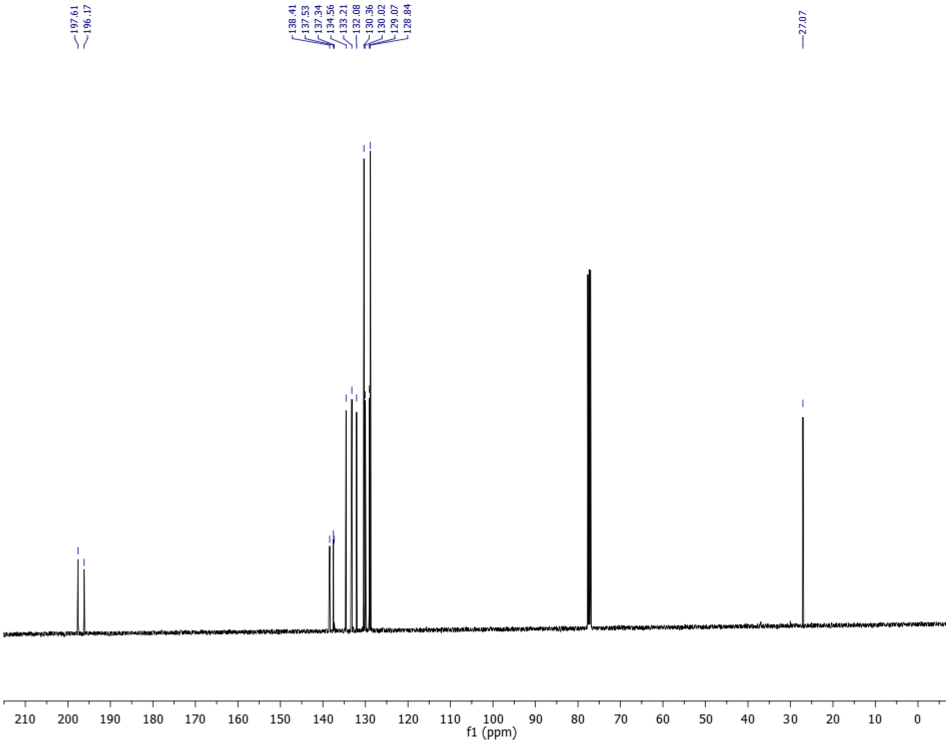




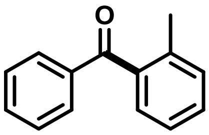
3-Acetylphenyl-(phenyl) methanone (**2.1.11Aj**).$CDCl_3$, 400 MHz:

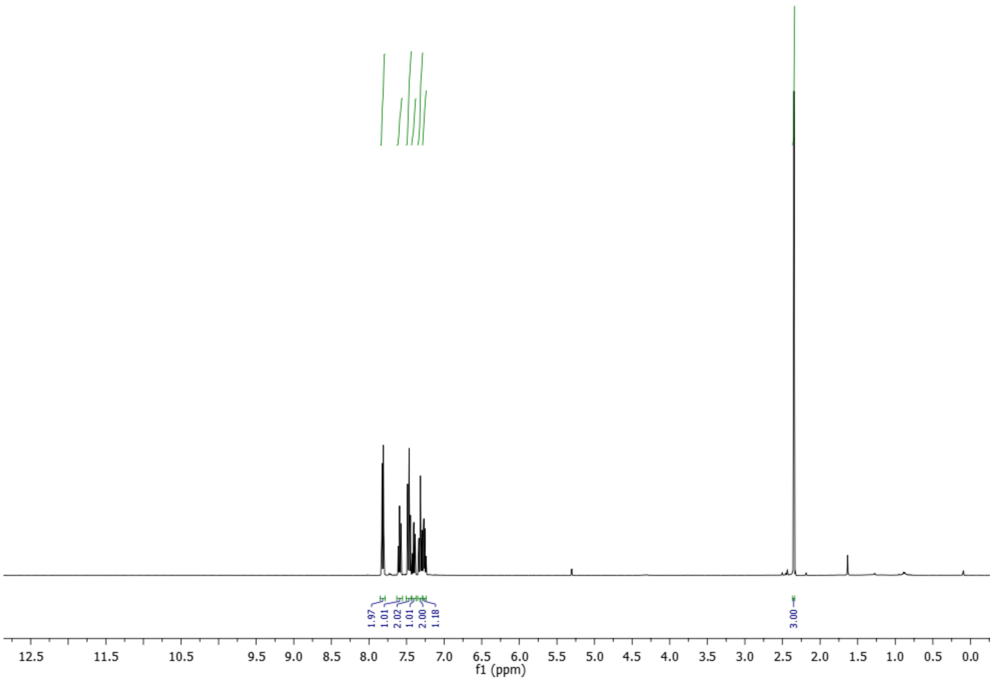


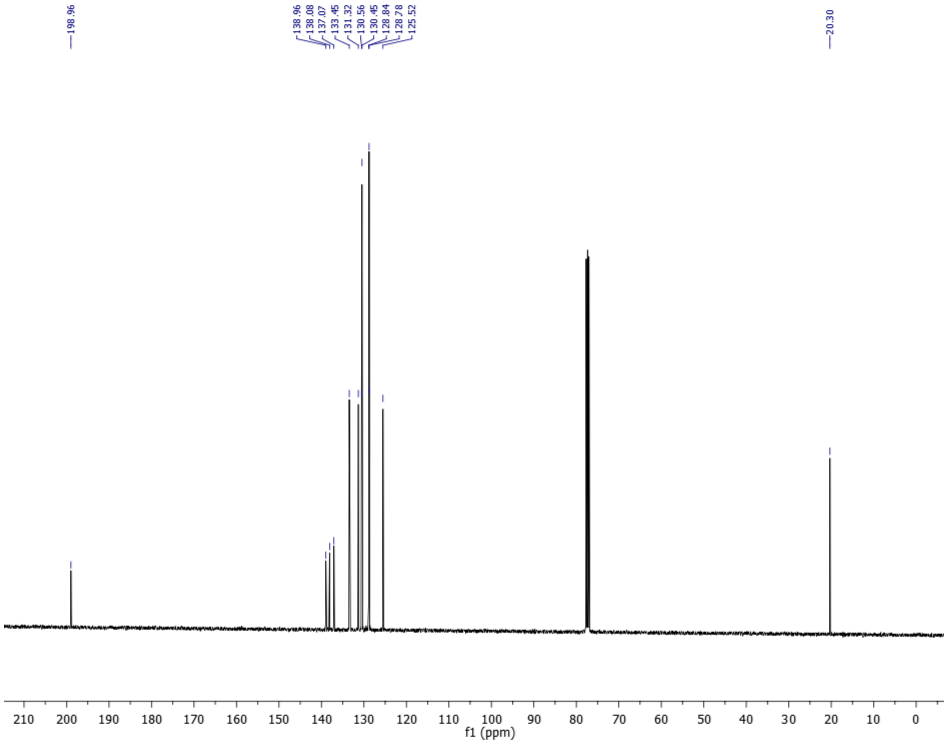




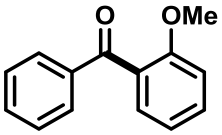
Phenyl(o-tolyl) methanone (**2.1.11Ak**). CDCl$_3$, 400 MHz:

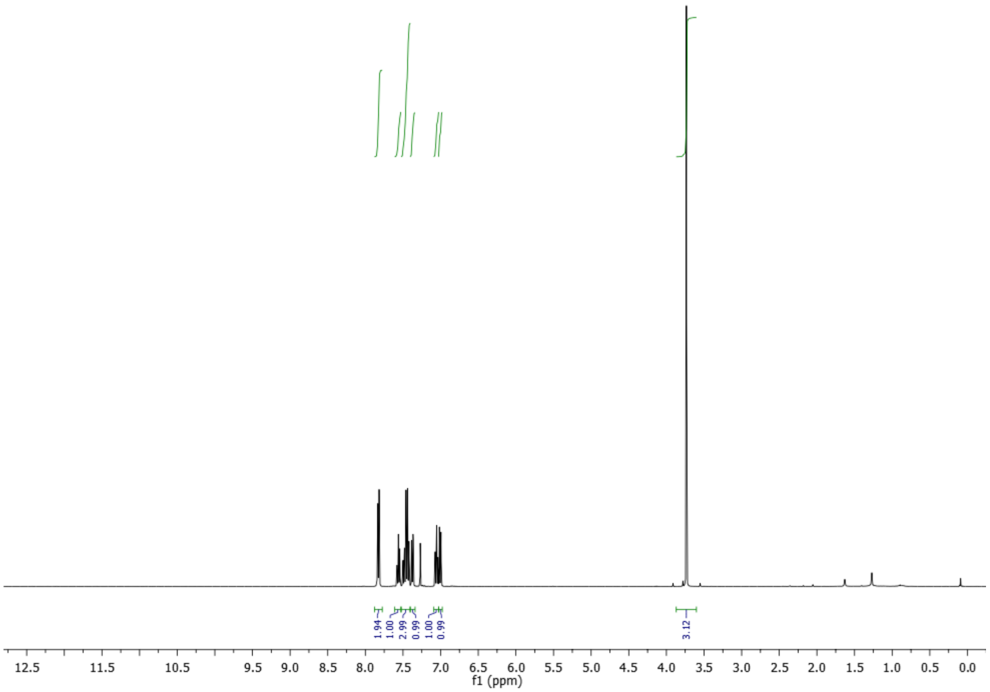


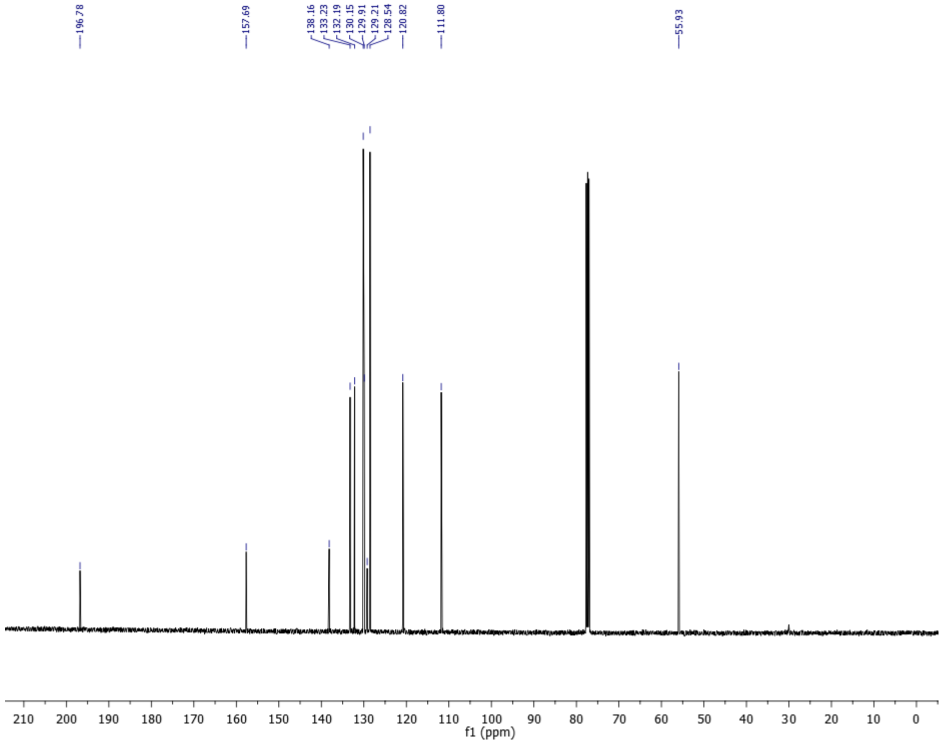




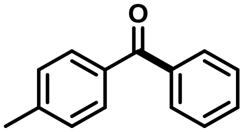
2-Methoxy(Phenyl)phenyl methanone (**2.1.11Al**). $CDCl_3$, 400 MHz:

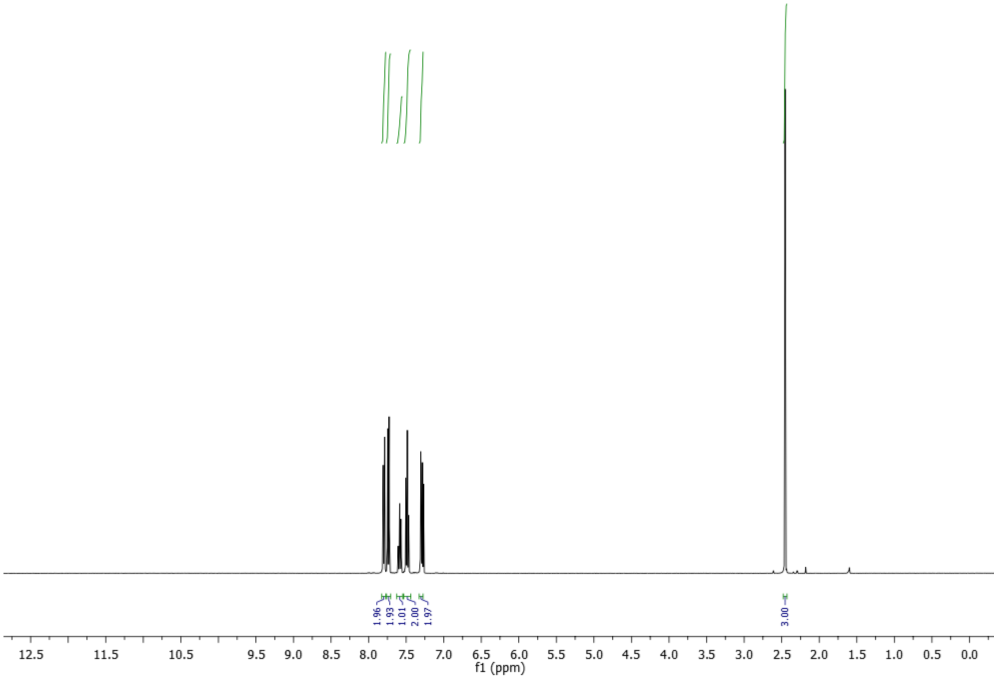


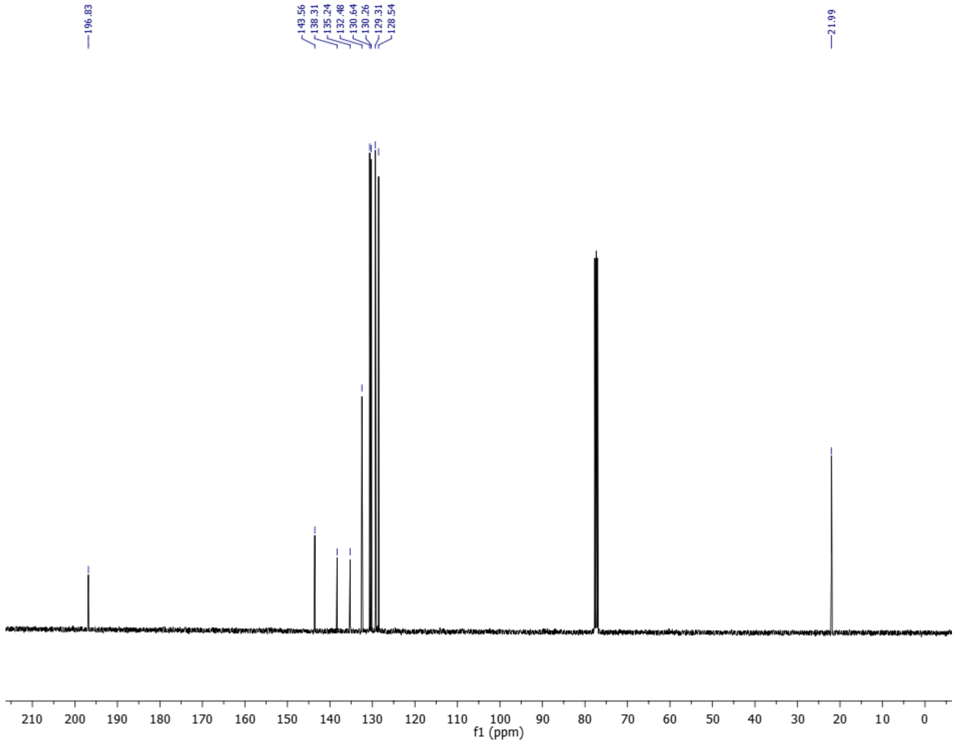




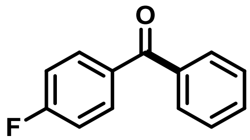
Phenyl (p-tolyl) methanone (**2.1.11Ca**). $CDCl_3$, 400 MHz:

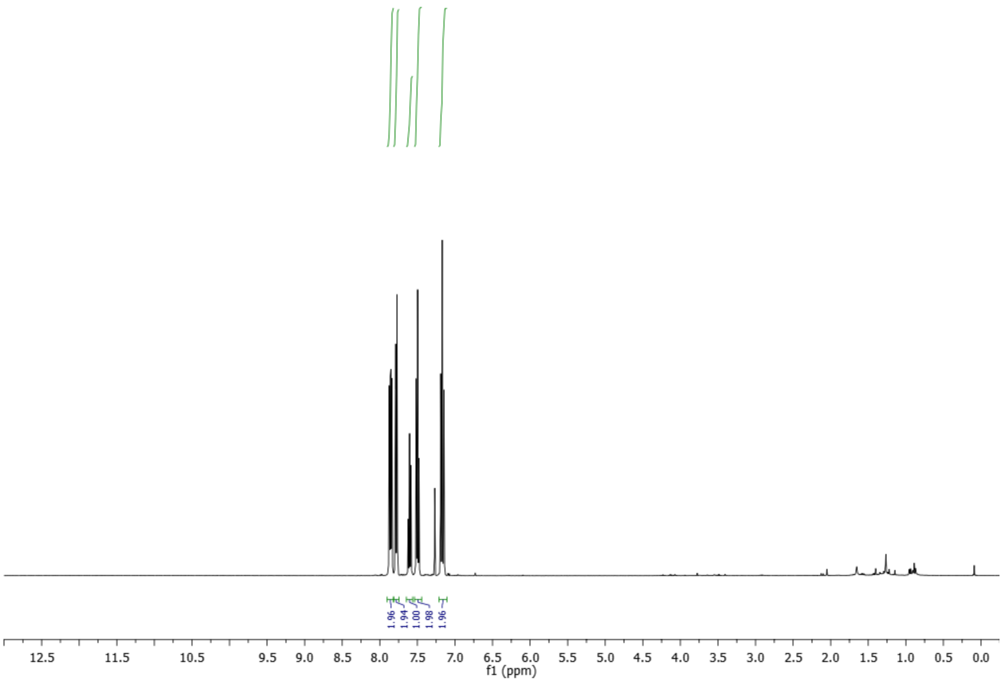


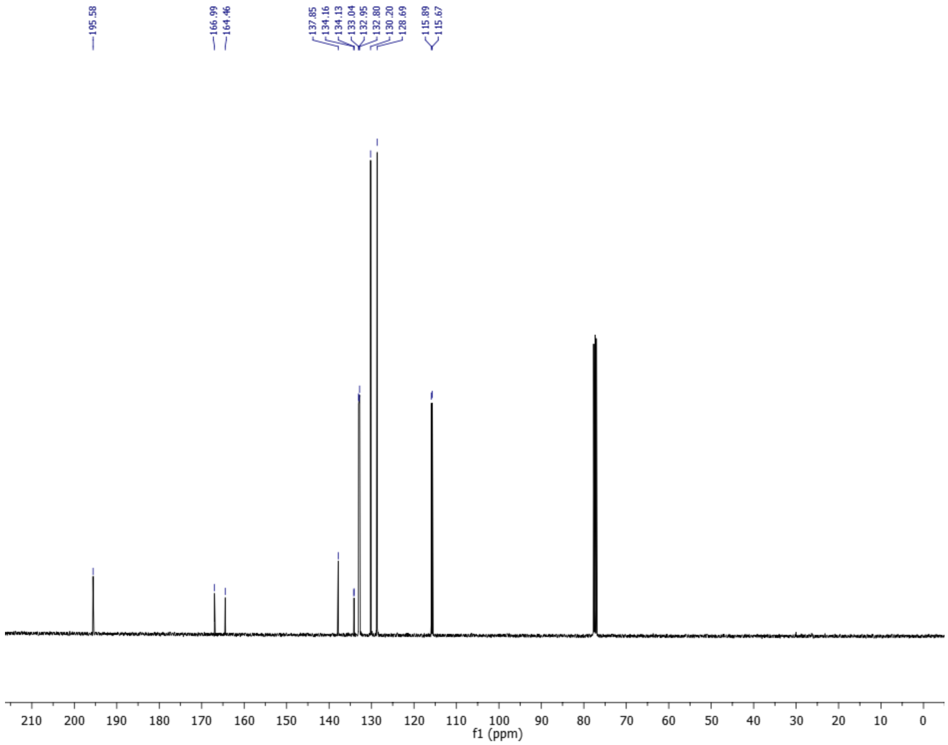


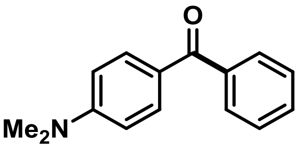


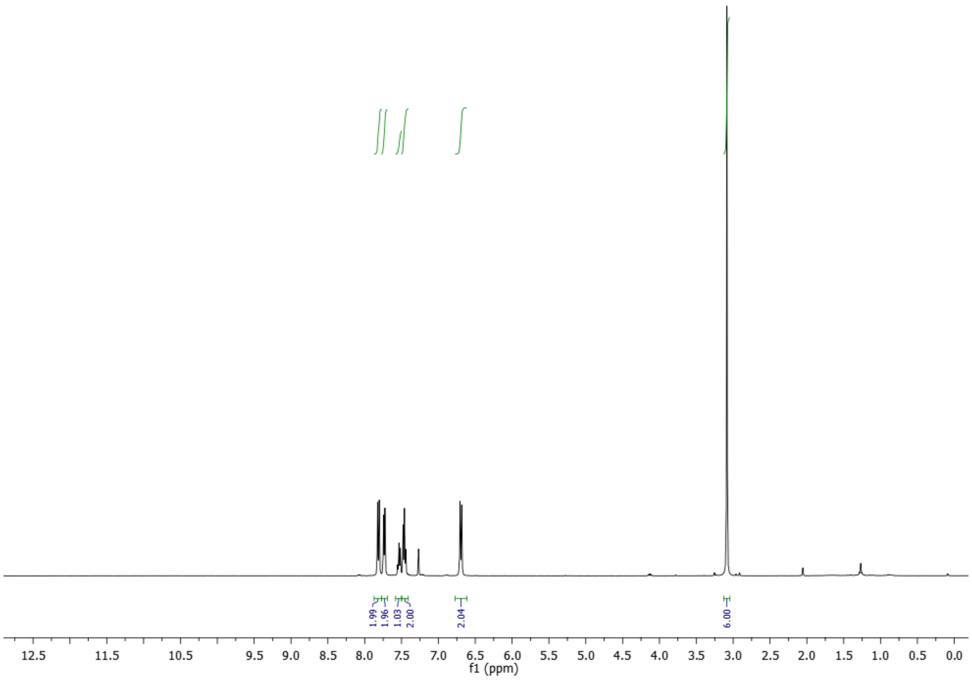
4-Fluorophenyl-(phenyl)methanone (**2.1.11Da**). CDCl$_3$, 400 MHz:

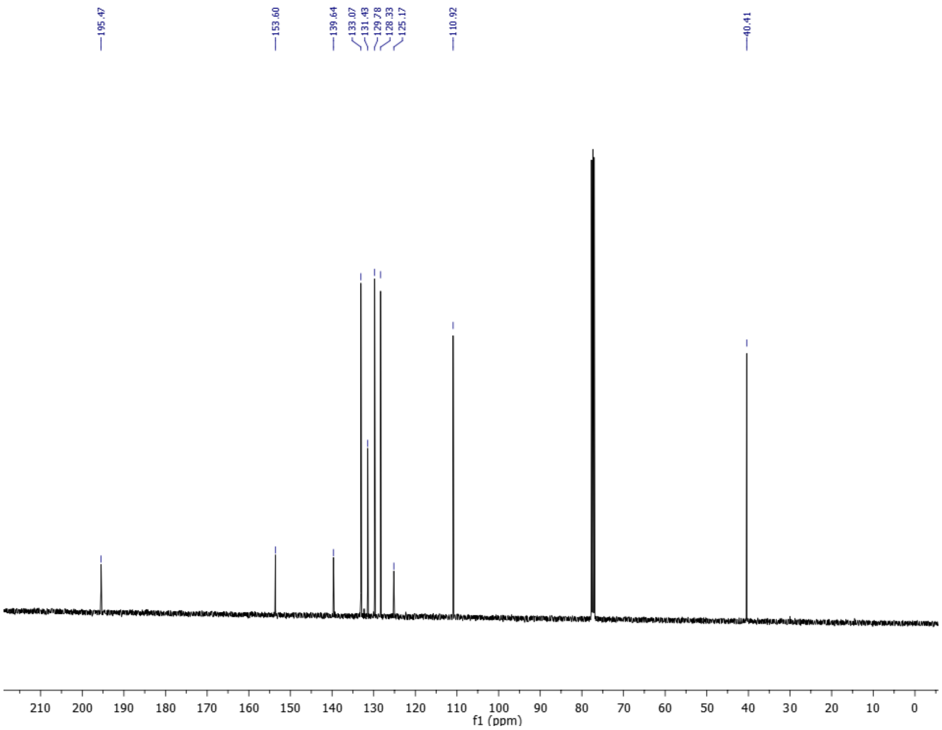


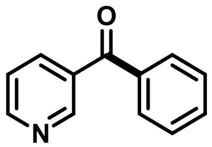




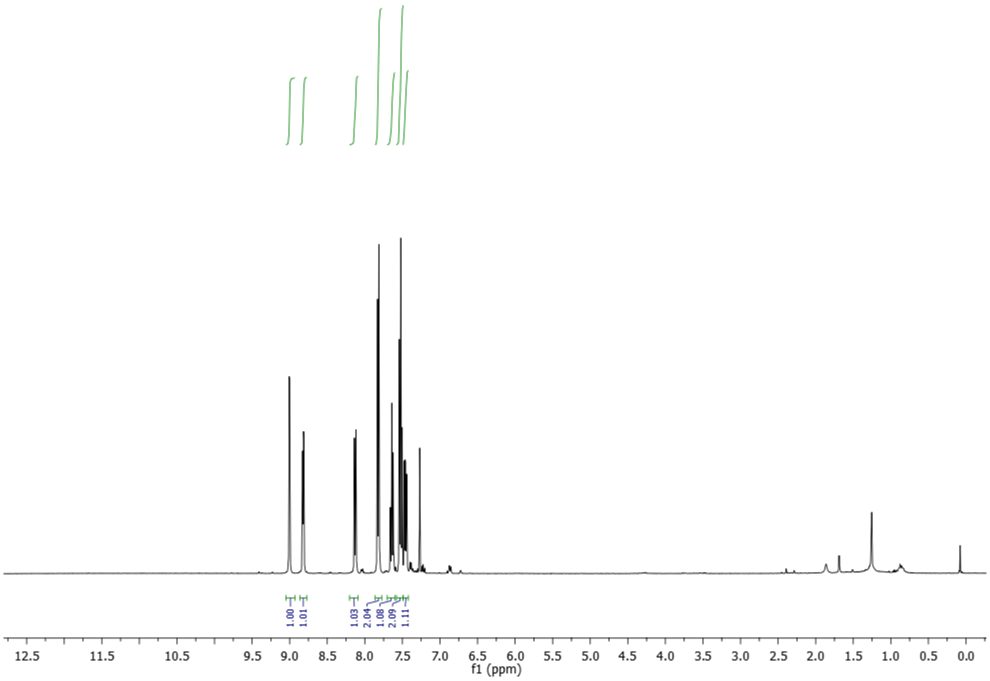
4-(N,N-Dimethylamino)benzophenone (**2.1.11Ha**).$CDCl_3$, 400 MHz: 

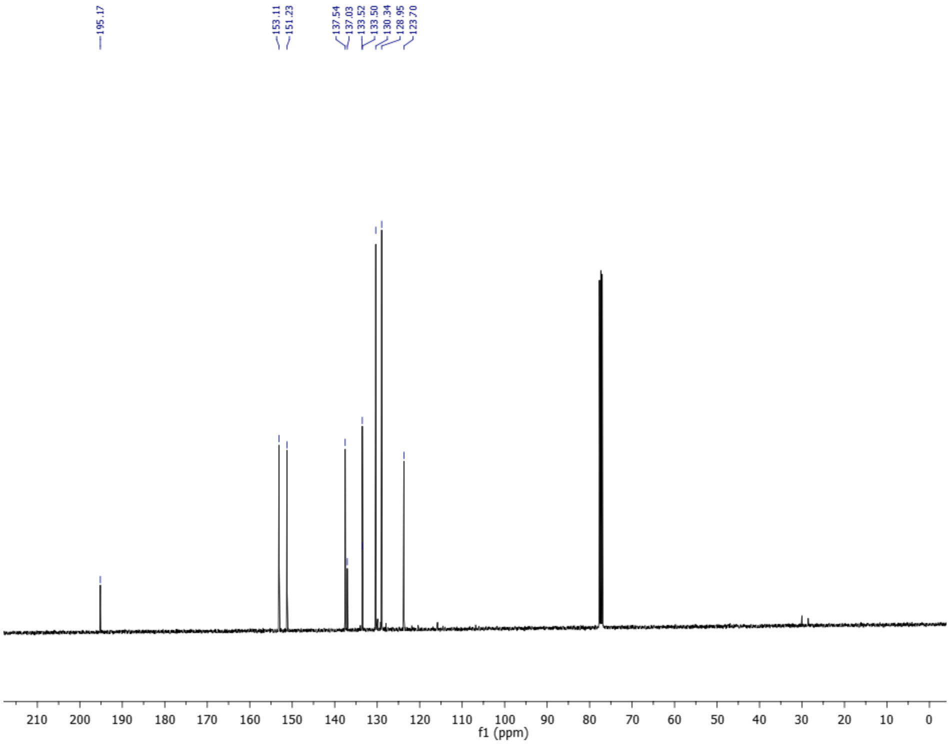


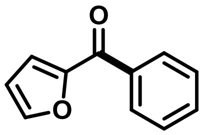




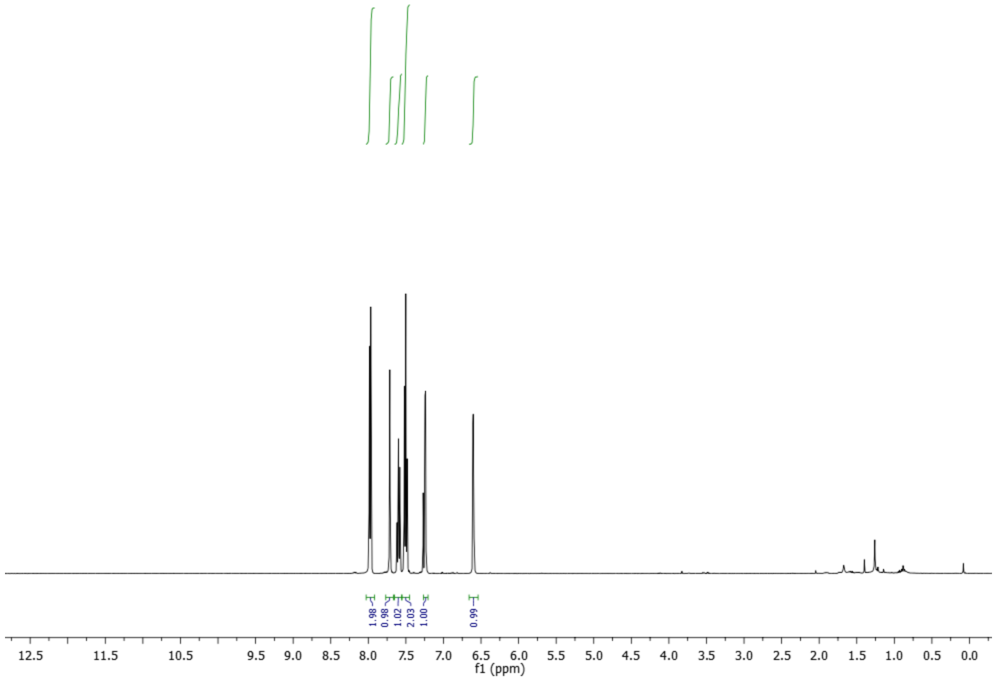
3-Benzoyle pyridine (**2.1.11Ia**). $CDCl_3$, 400 MHz:

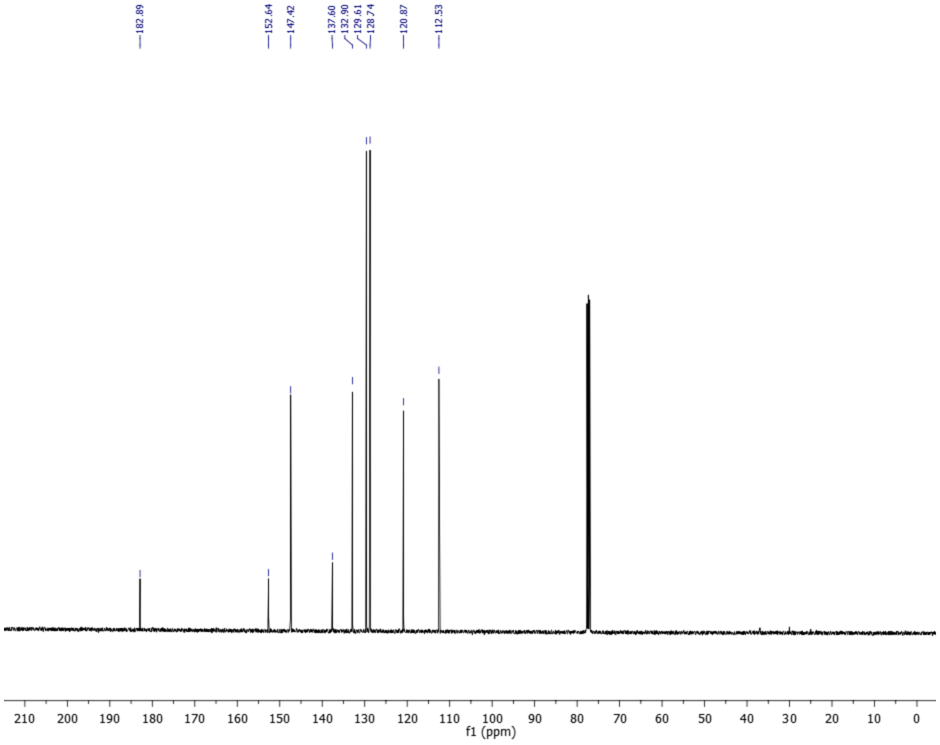




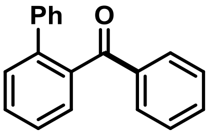


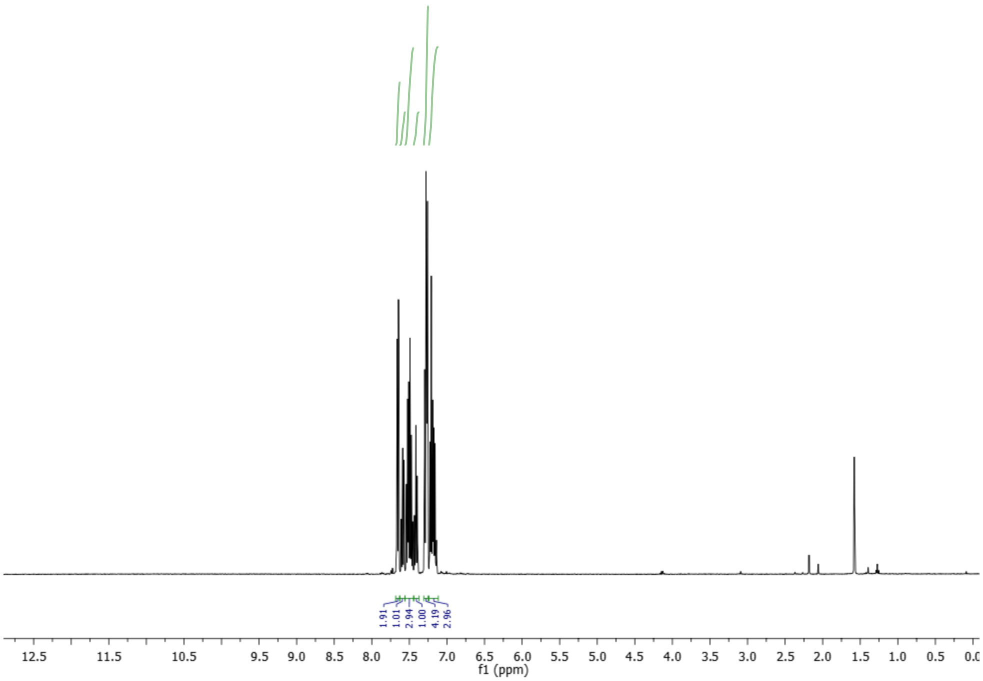
Furan-3-yl(phenyl) methanone (**2.1.11Ja**). $CDCl_3$, 400 MHz:

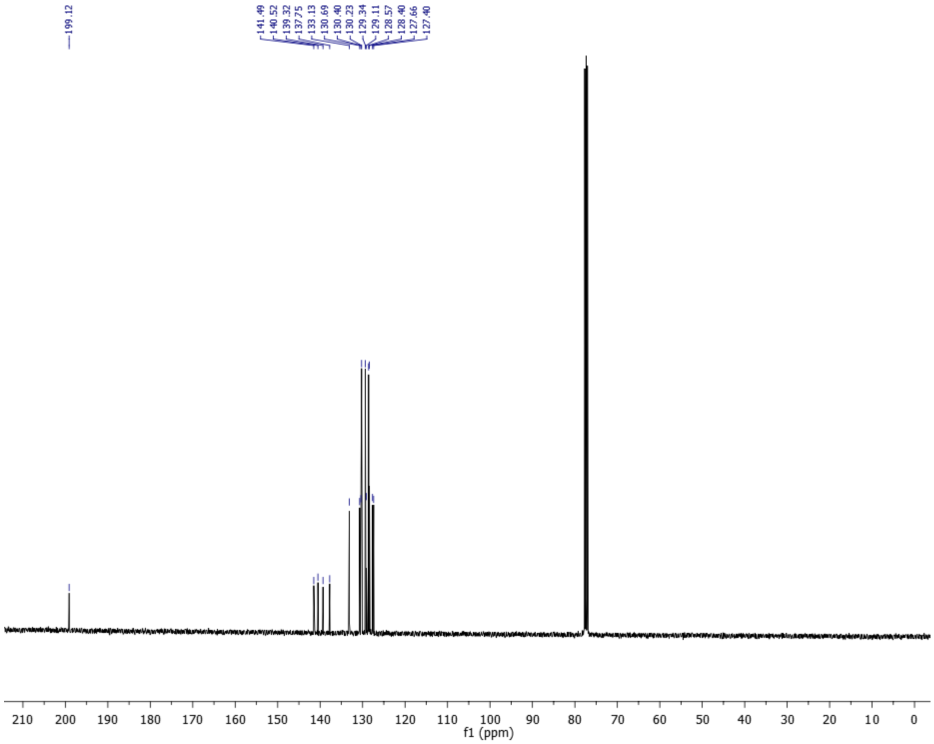




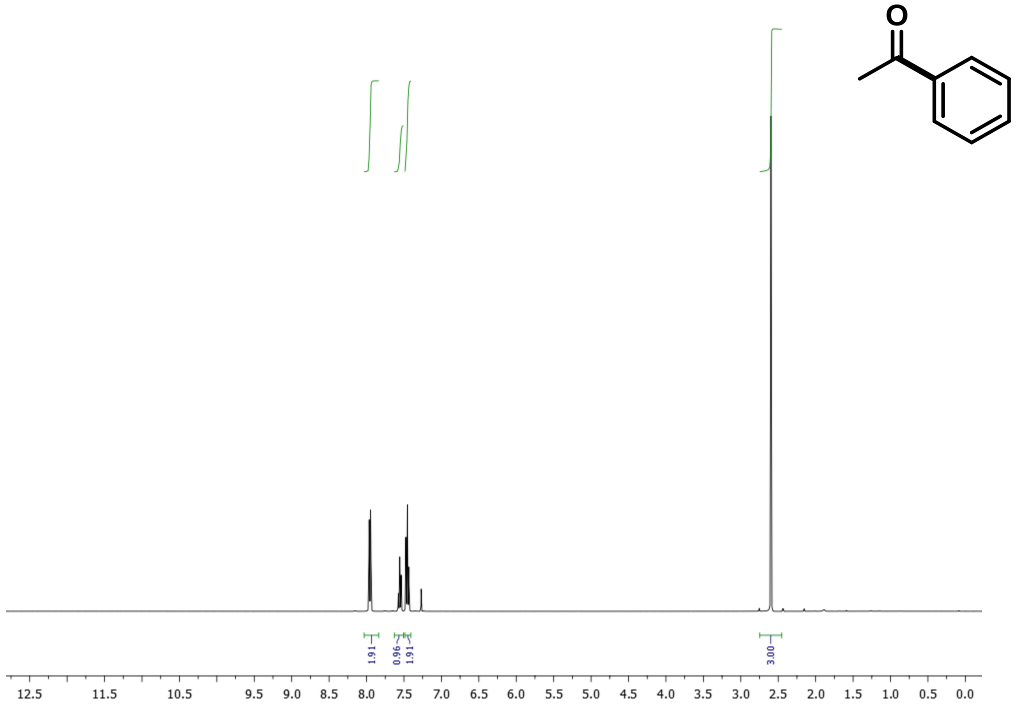
Biphenyl-2-yl phenyl methanone (**2.1.11La**). $CDCl_3$, 400 MHz:

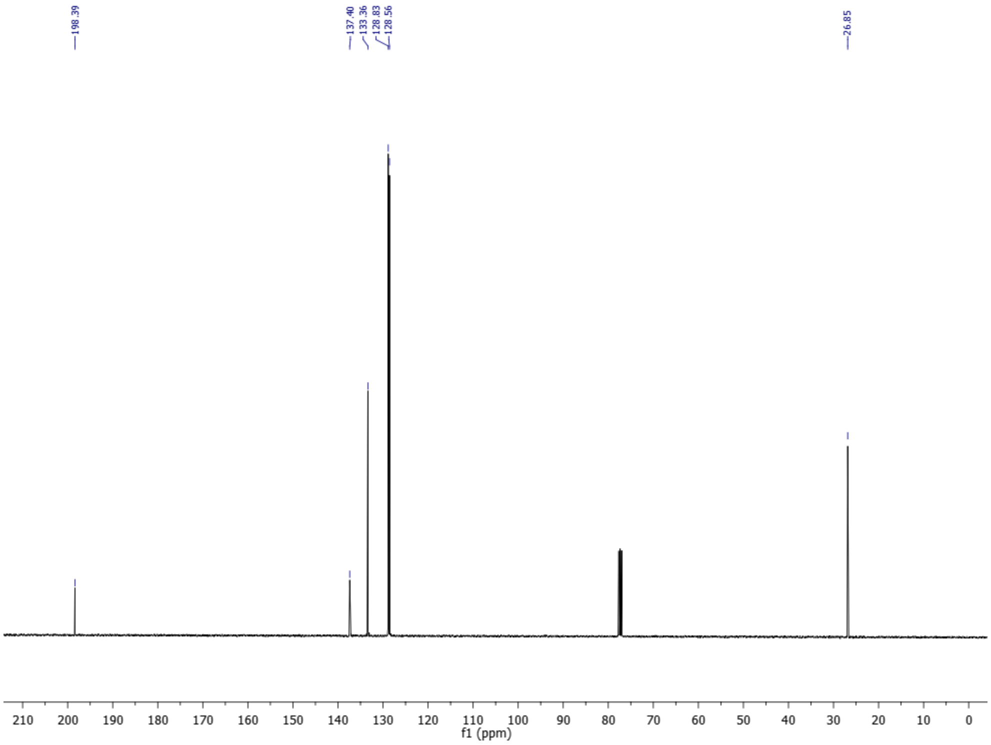


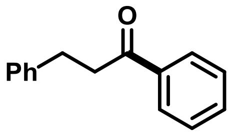




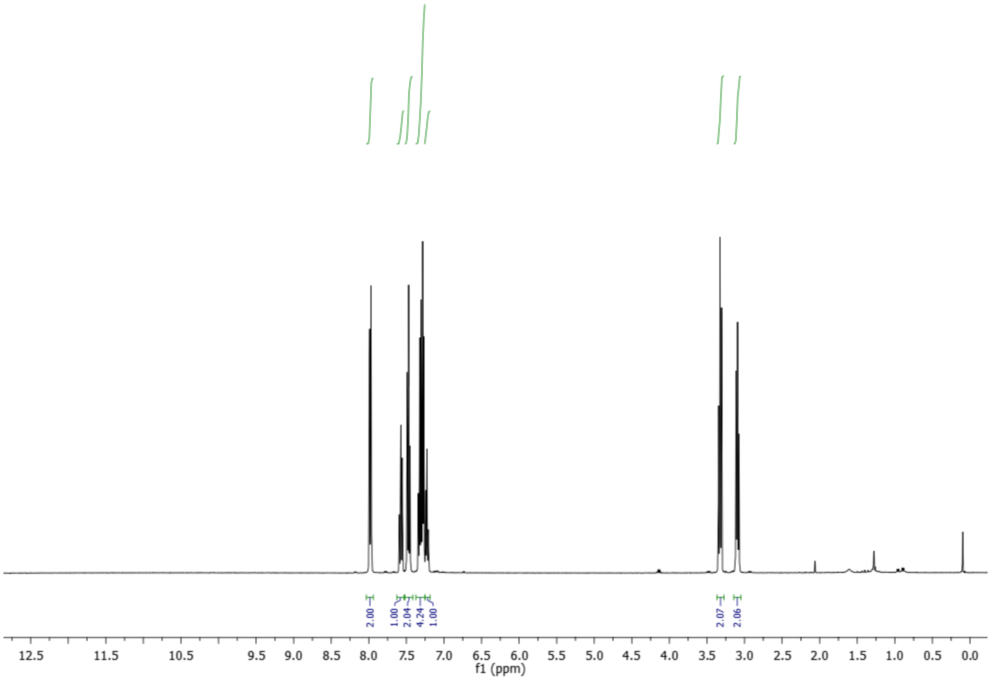
Acetophenone (**2.1.11Ma**). $CDCl_3$, 400MHz:

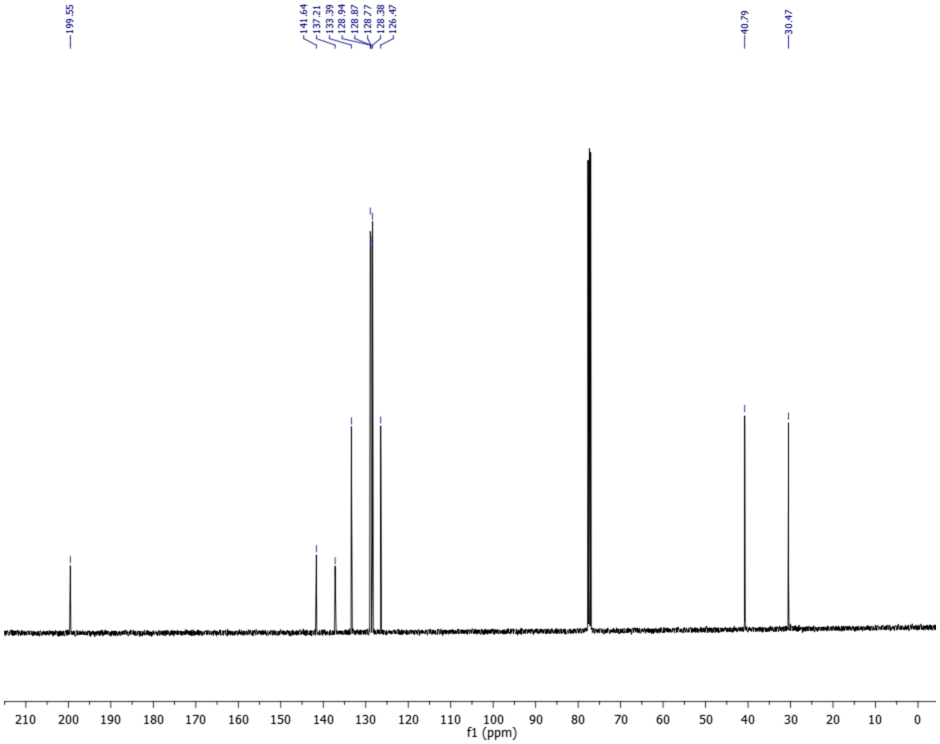


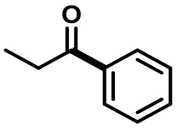




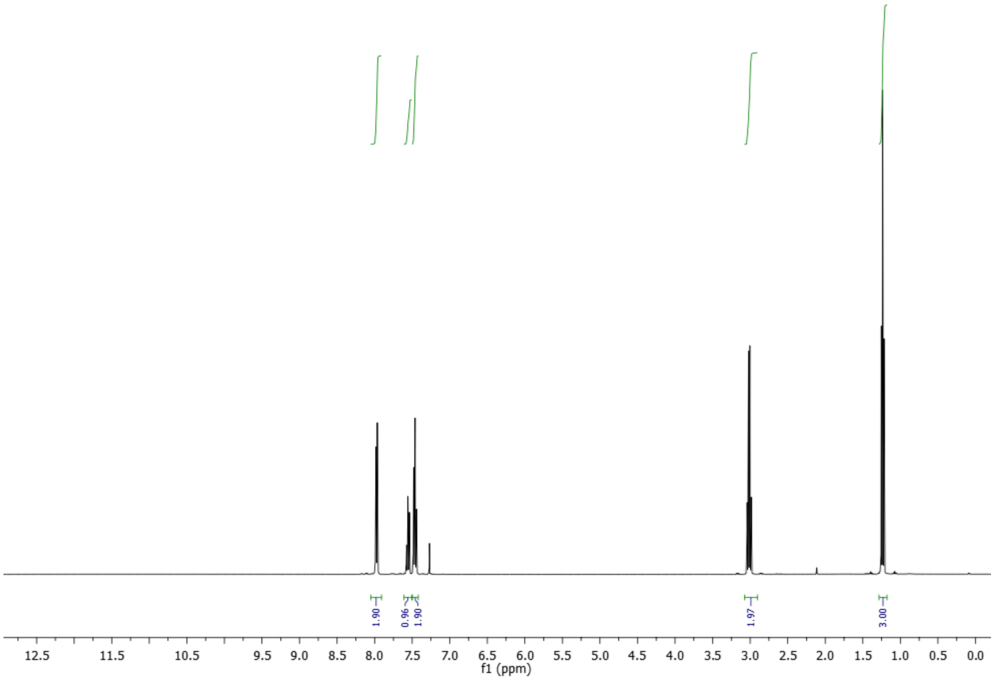
1,3-Diphenylpropan-1-one (**2.1.11Na**). $CDCl_3$, 400 MHz:

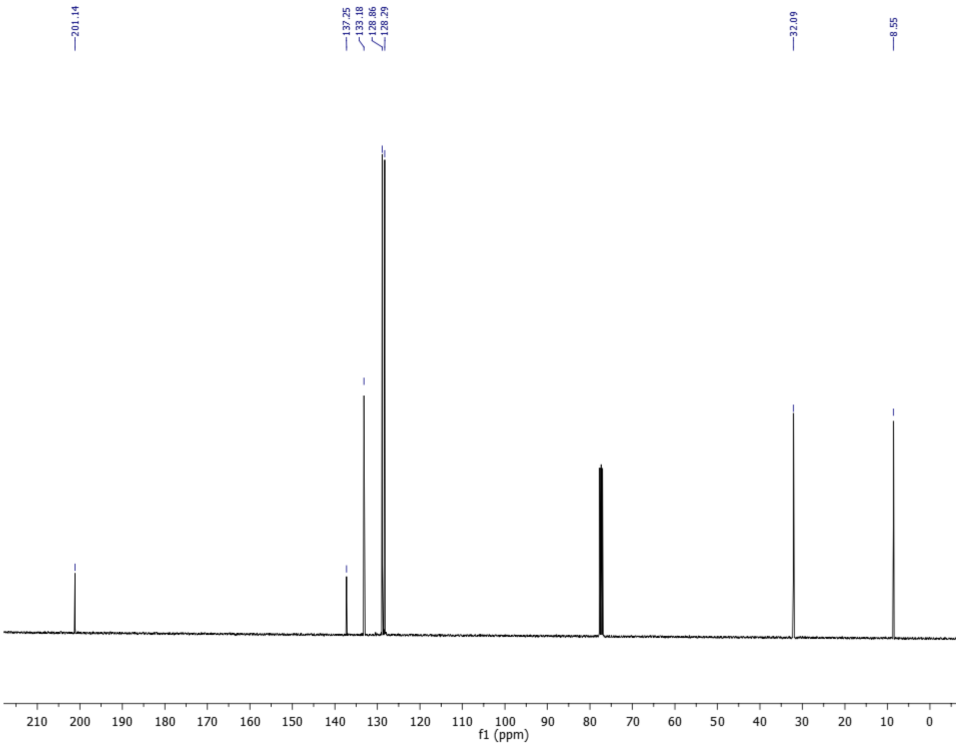


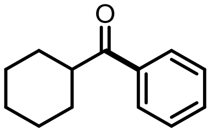




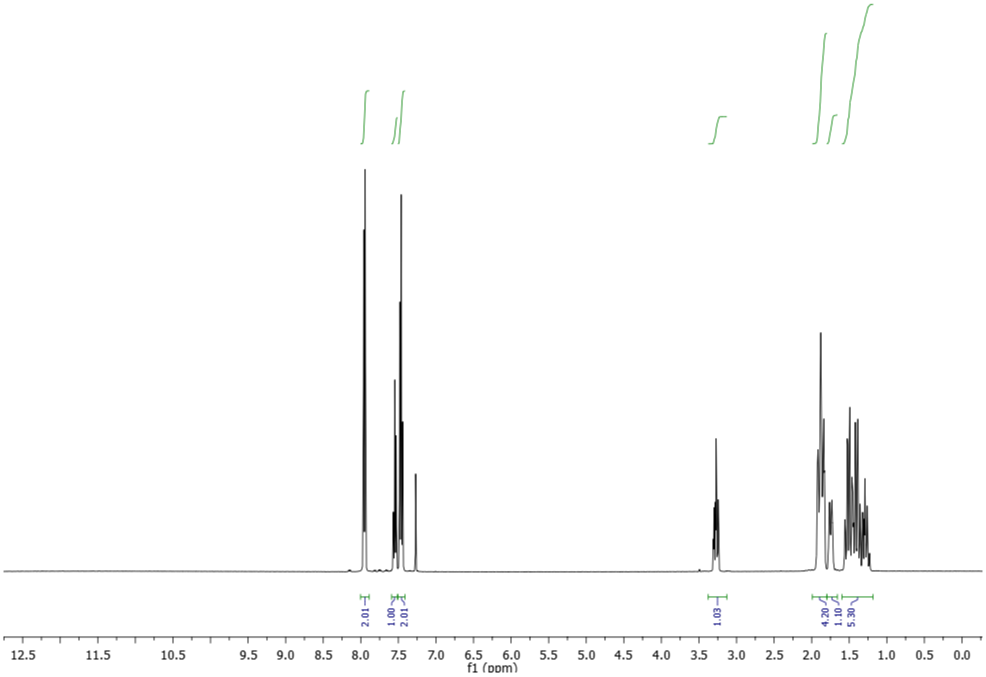
Propiophenone (**2.1.11Oa**). $CDCl_3$, 400 MHz:

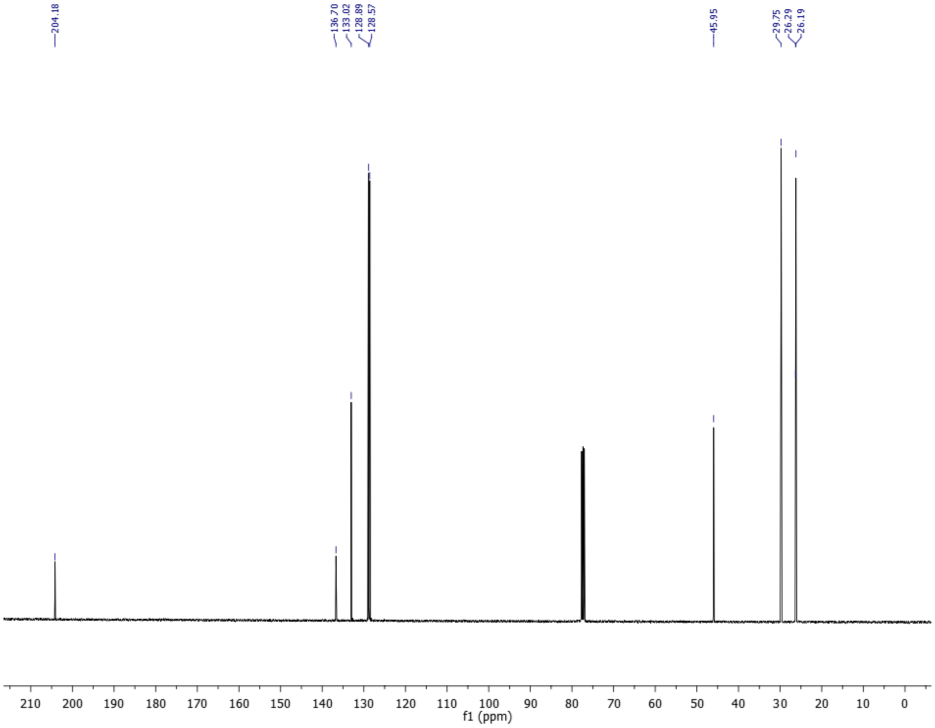


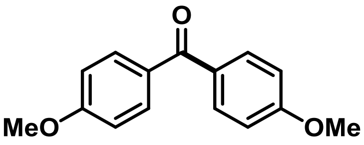


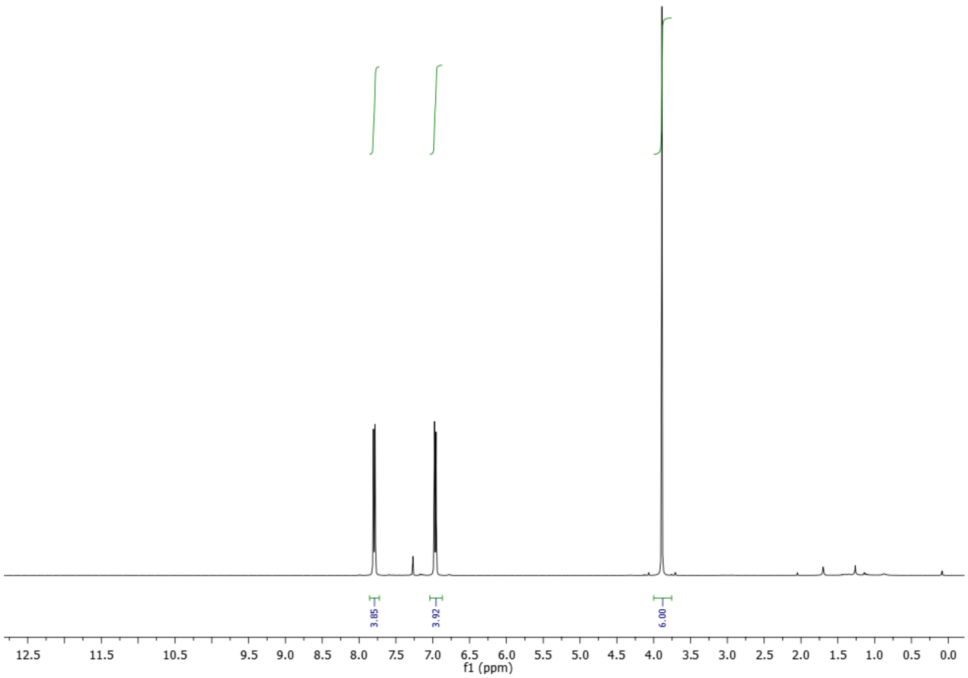


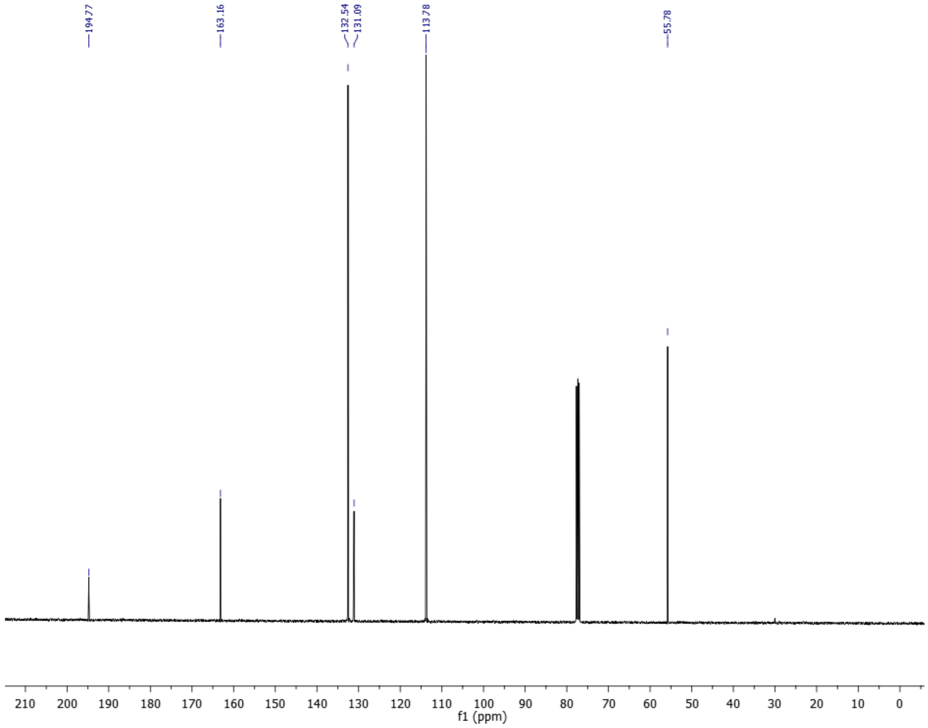
Cyclohexyl phenyl methanone (**2.1.11Pa**). $CDCl_3$, 400 MHz:



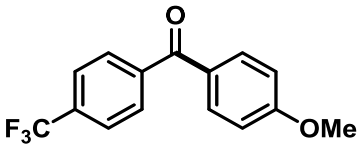


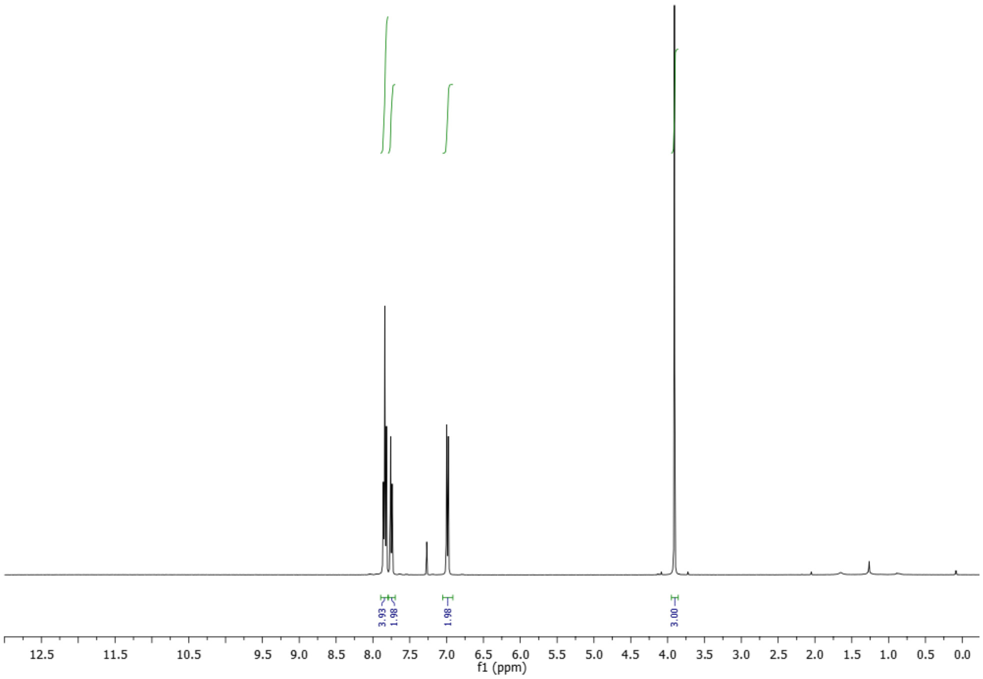
Bis(4-methoxyphenyl)methanone (**2.1.11Ec**). $CDCl_3$, 400MHz: 

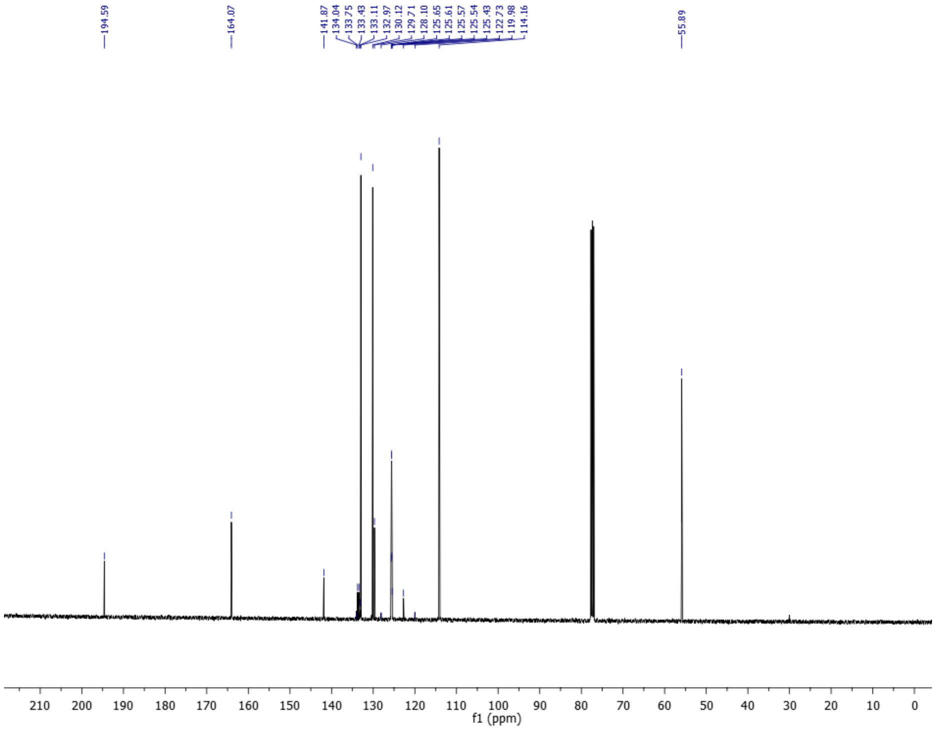




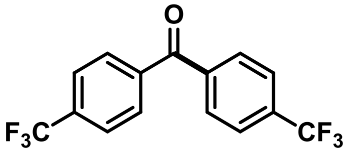
4-Methoxyphenyl-(4-(trifluoromethyl)phenyl)methanone (**2.1.11Fc**). $CDCl_3$, 400 MHz

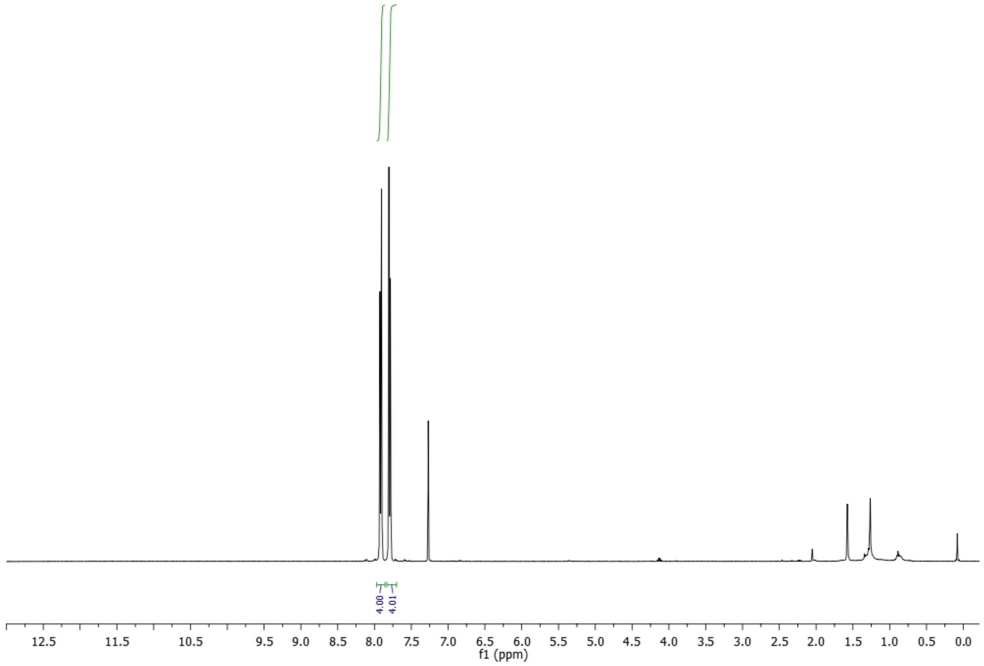


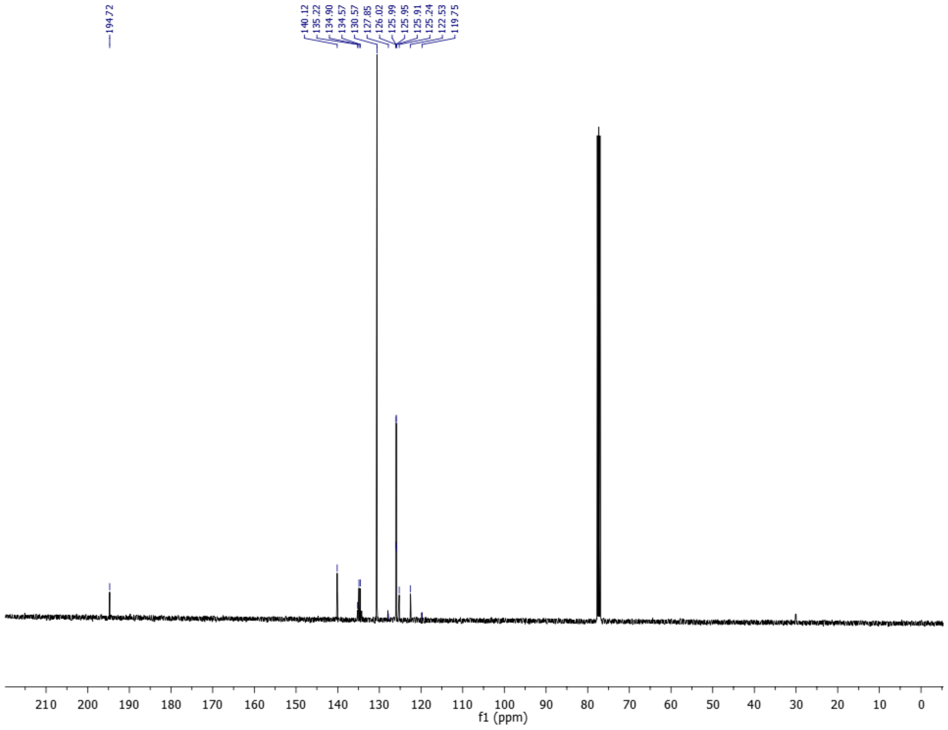


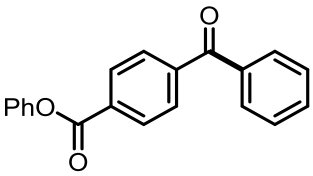


Bis(4-trifluoromethyl)(phenyl)methanone (**2.1.11Fi**). $CDCl_3$, 400MHz:

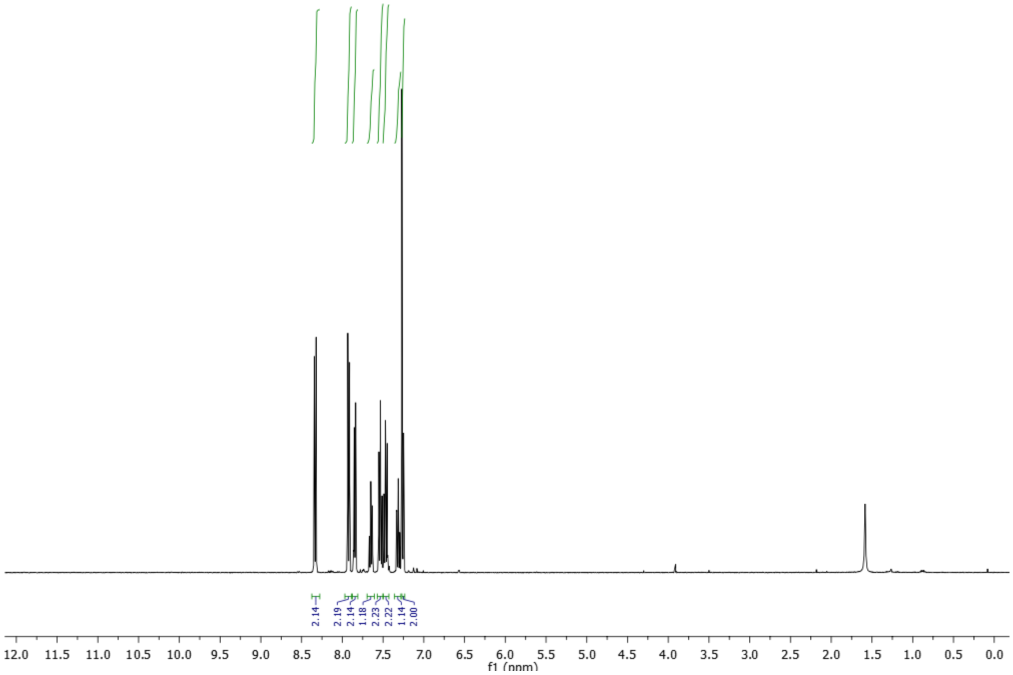


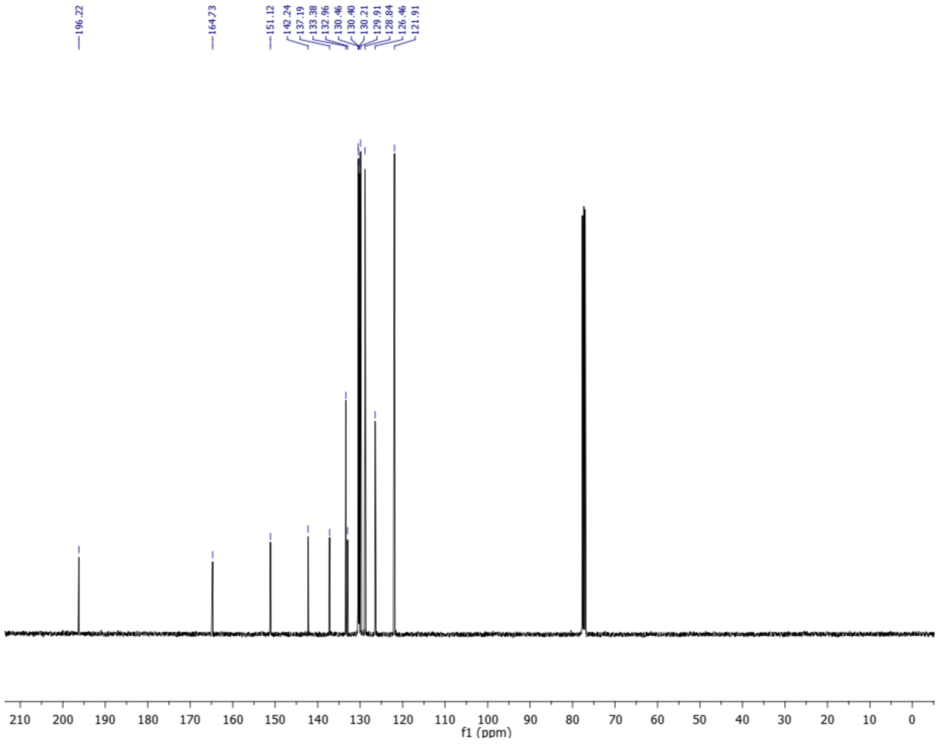




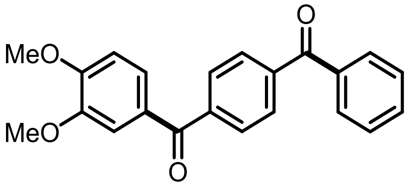


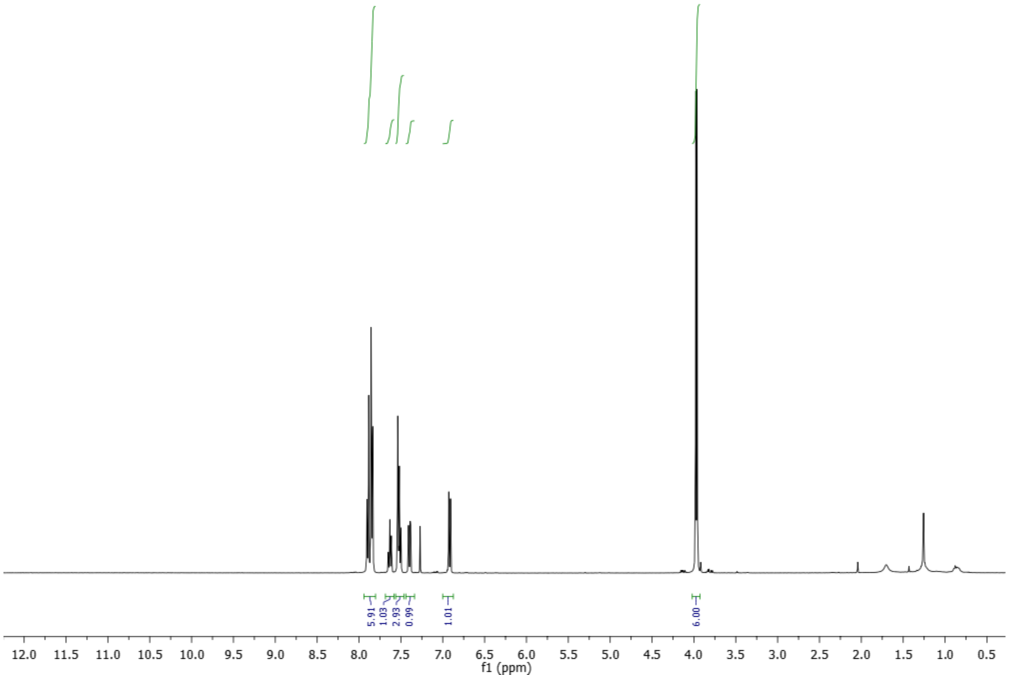
Phenyl 4-benzoylbenzoate (**2.1.21**). $CDCl_3$, 400 MHz:

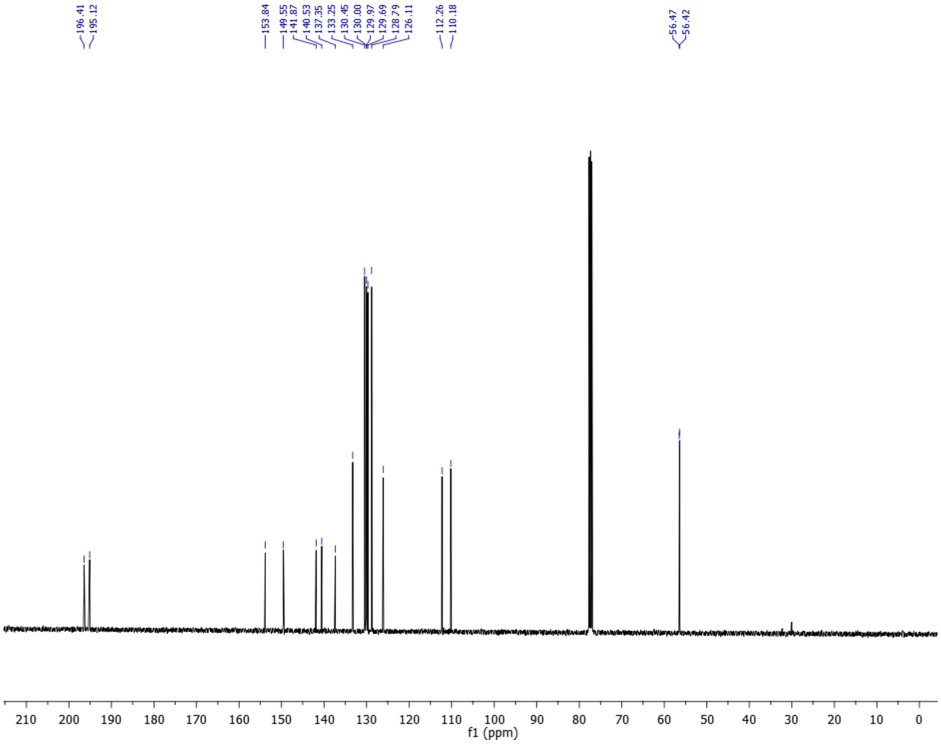


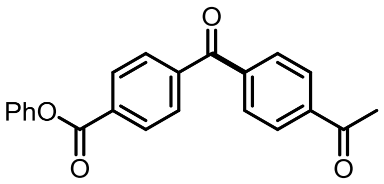


4-Benzoylphenyl(3,4-dimethoxyphenyl)methanone (**2.1.22**). $CDCl_3$, 400 MHz

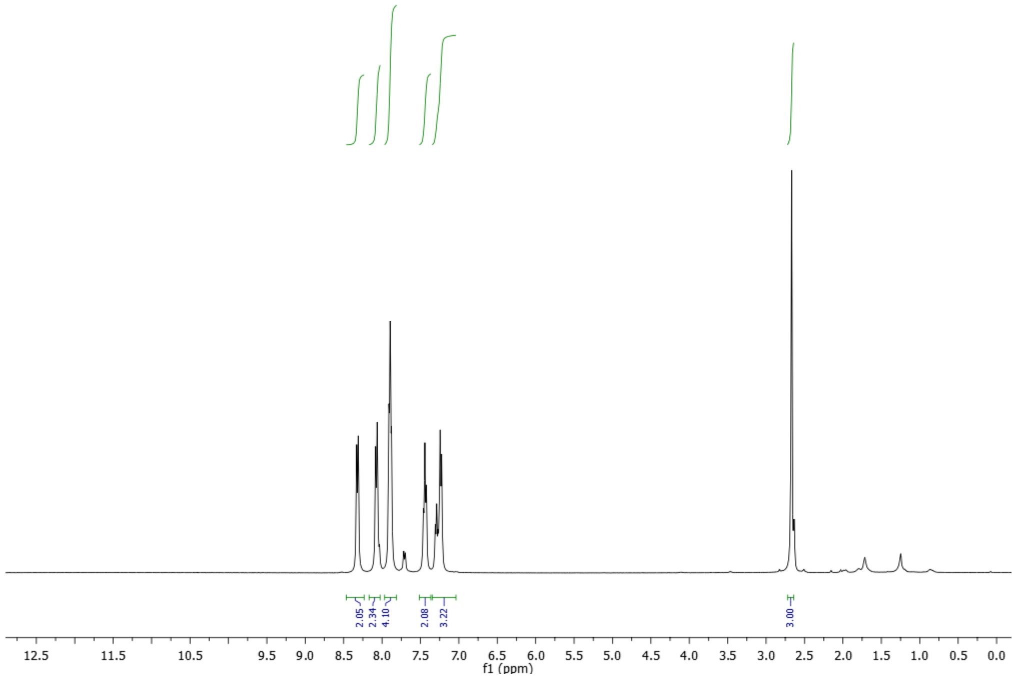


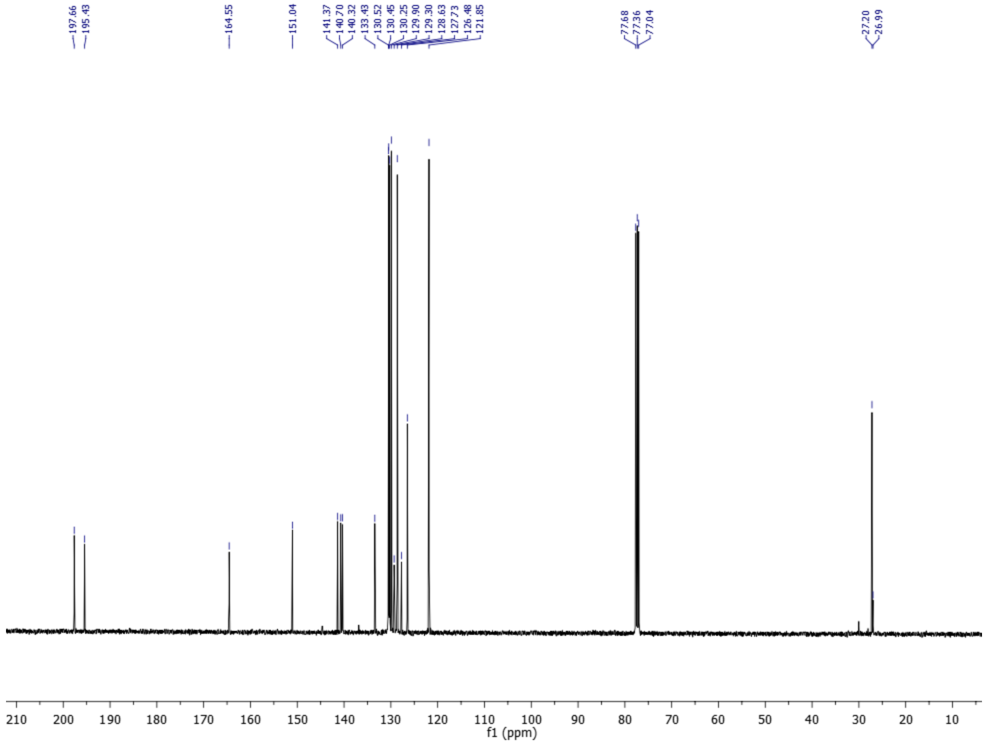




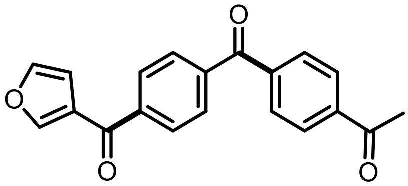


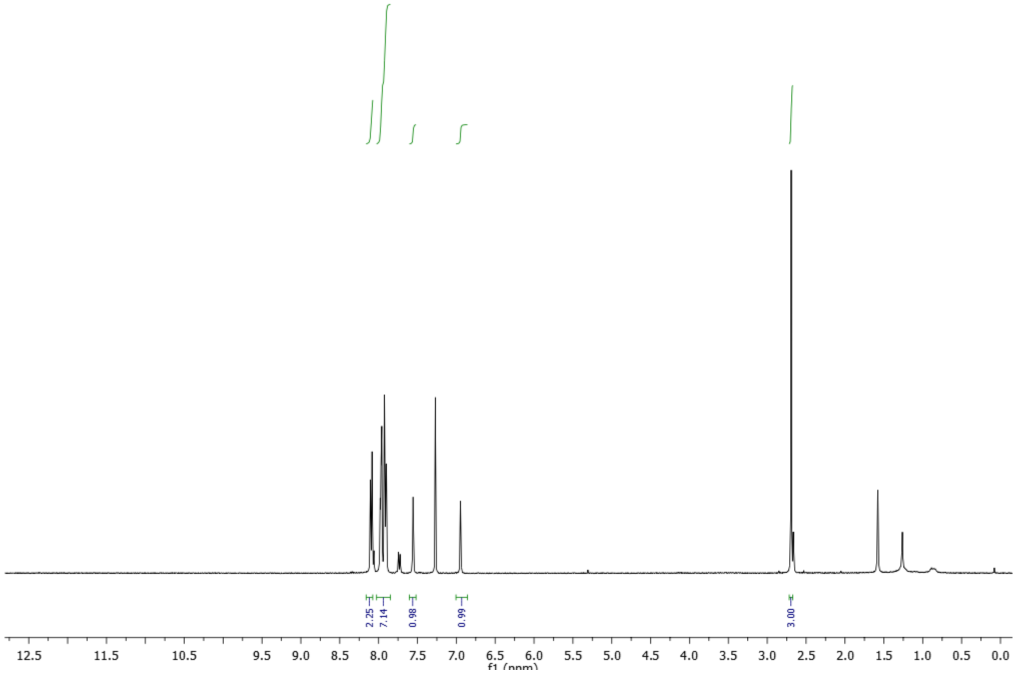
Phenyl 4-(4-acetylbenzoyl) benzoate (**2.1.24**). CDCl$_3$, 400MHz:

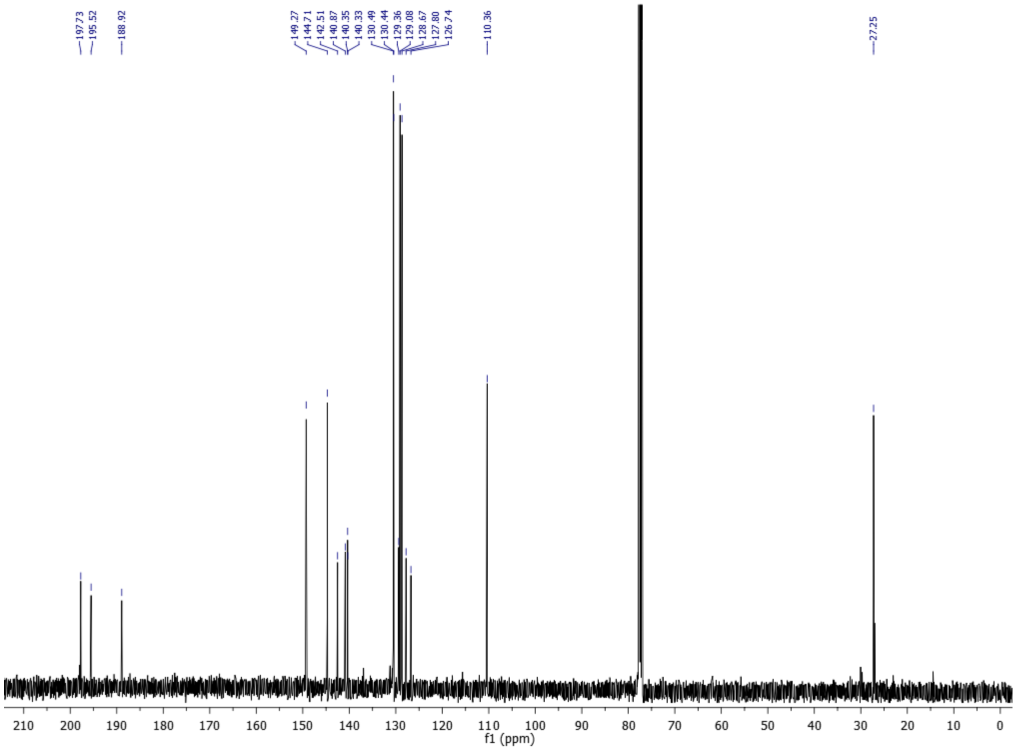




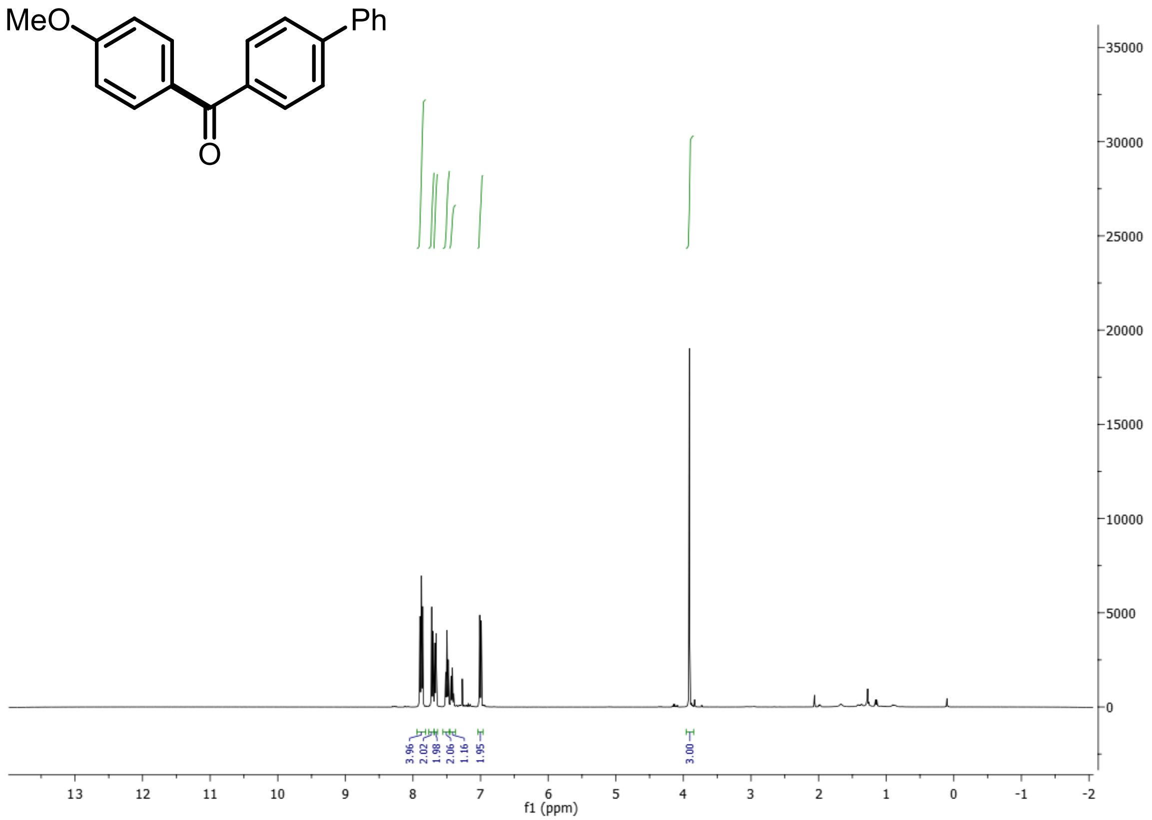
1-(4-(4-(Furan-3-carbonyl)benzoyl)phenyl)ethan-1-one (**2.1.25**), $CDCl_3$, 400 MHz:

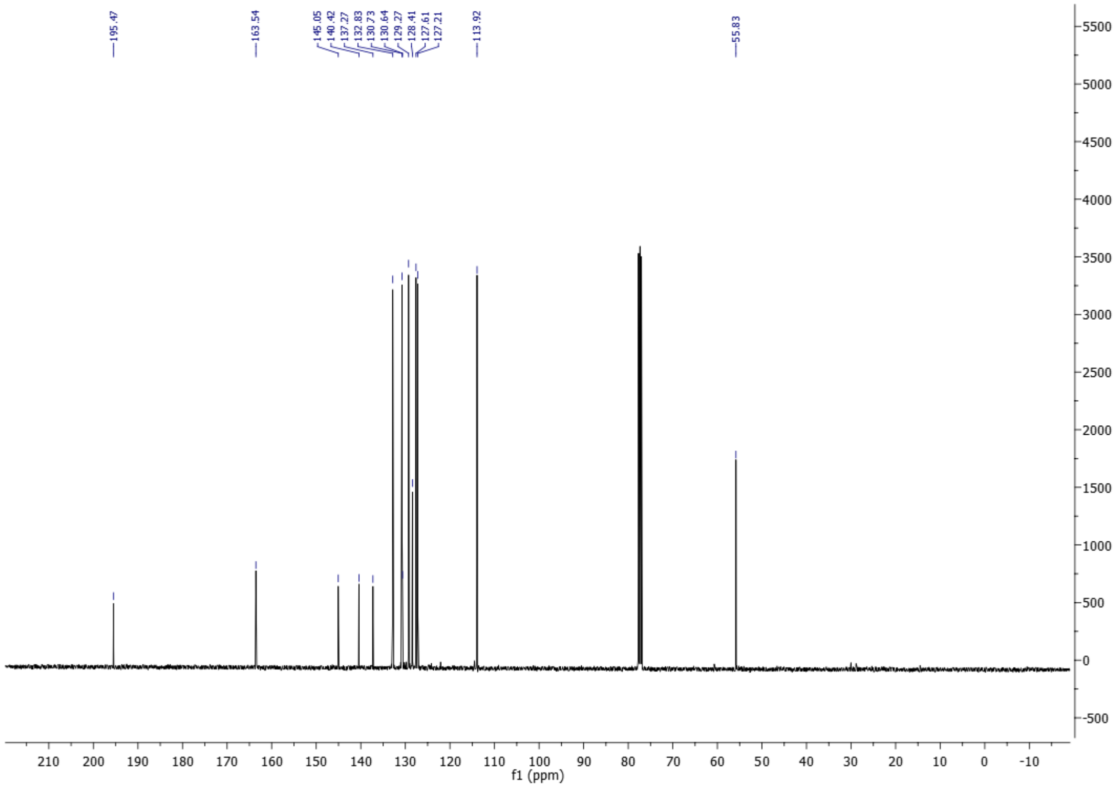




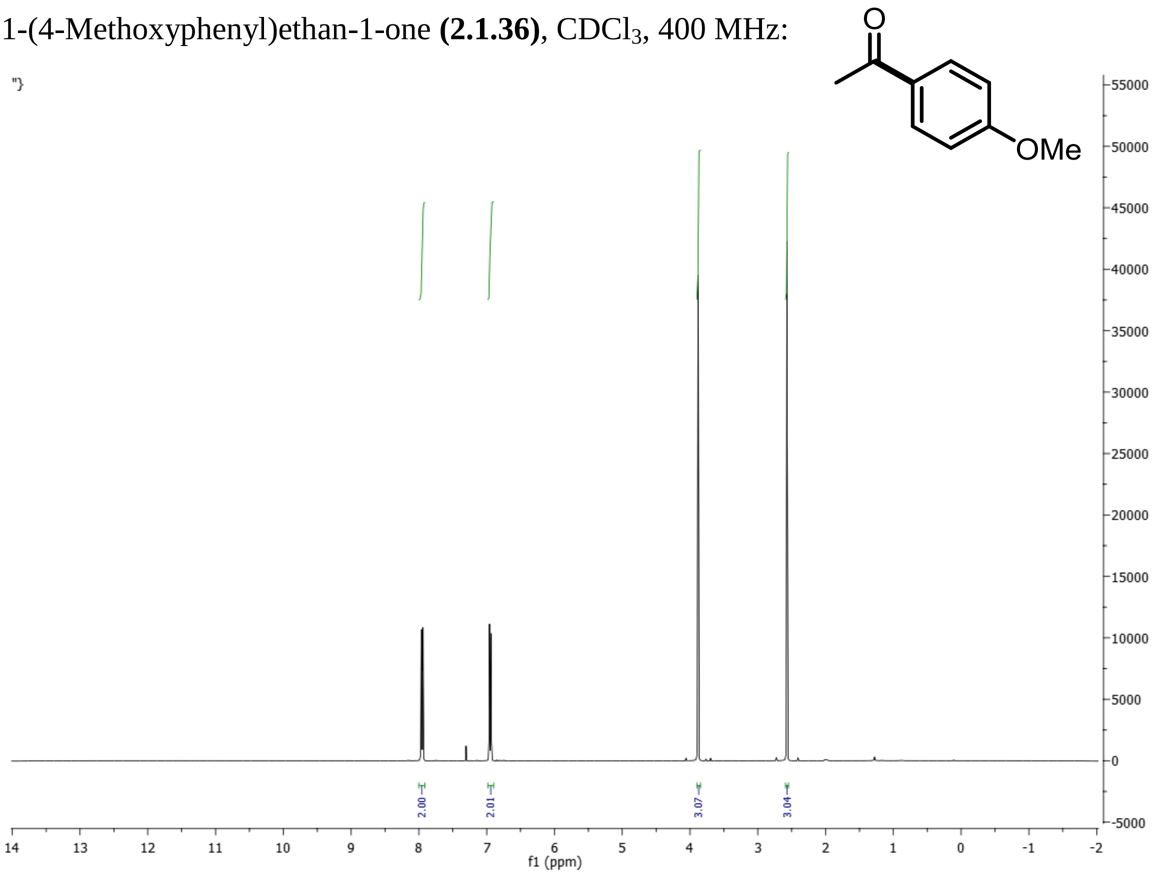


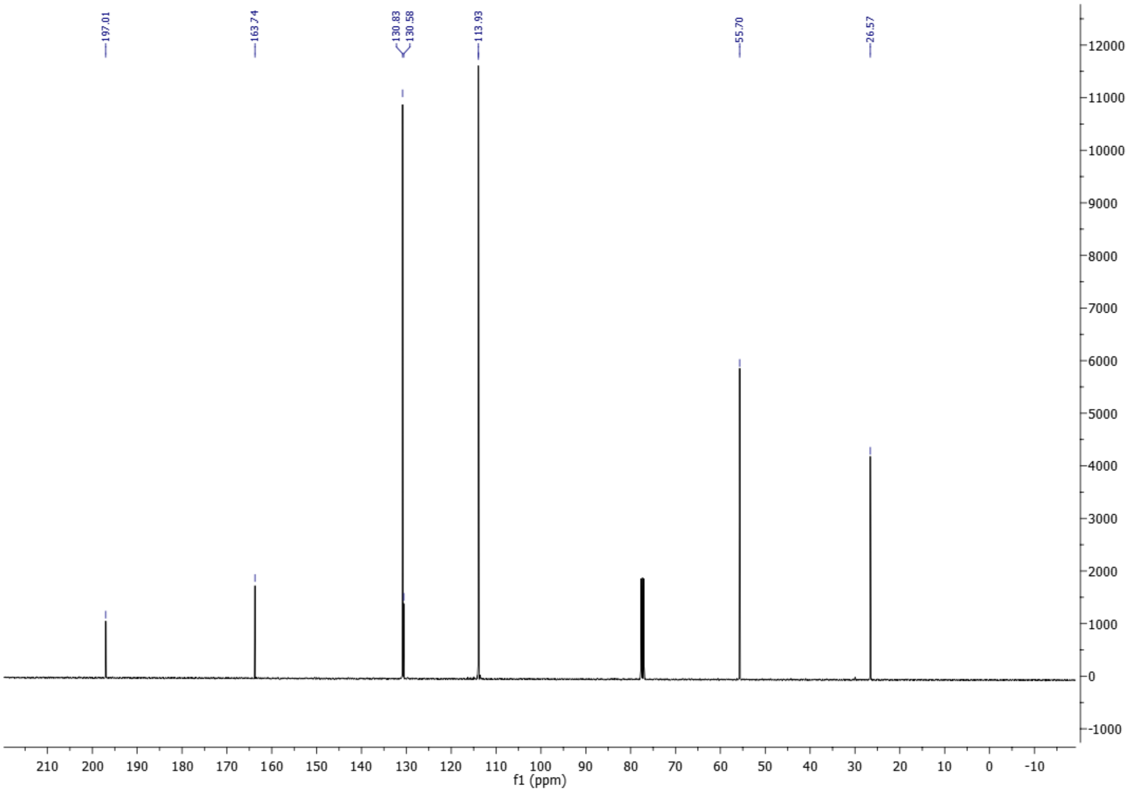
[1,1'-Biphenyl]-4-yl(4-methoxyphenyl)methanone **(2.1.31)**, $CDCl_3$, 400 MHz:





1-(4-Methoxyphenyl)ethan-1-one **(2.1.36)**, $CDCl_3$, 400 MHz:

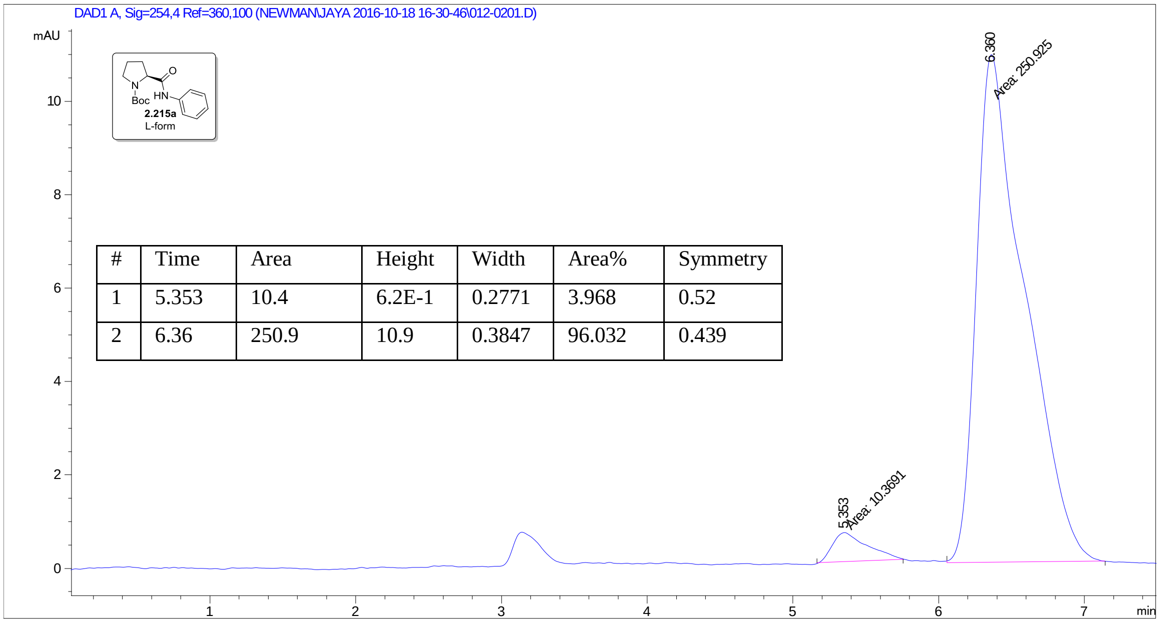




HPLC analysis of proline derivatives:

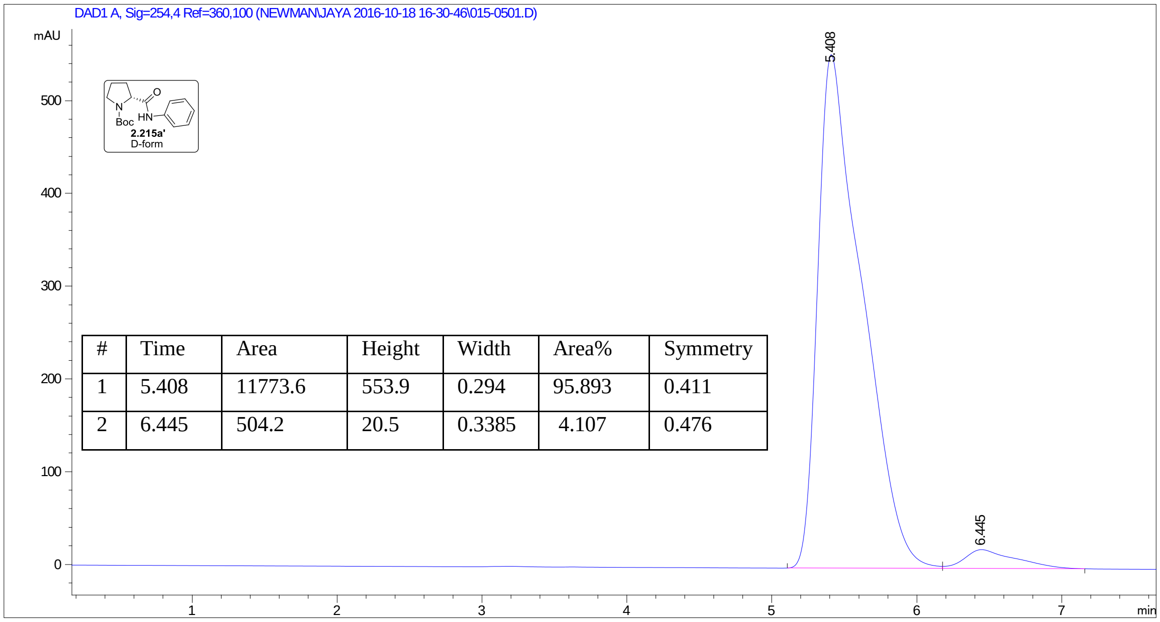
Enantiomeric excesses from equation 1 were determined by synthesizing both D and L isomers and comparing their HPLC traces.

Compound **2.2.15a**: 92% ee was determined by chiral HPLC (chiralcel OD-H, n-hexane/i-PrOH = 90/10, 1 mL/min, 254 nm): t_R (minor) = 5.3 min, t_R (major) = 6.3 min.



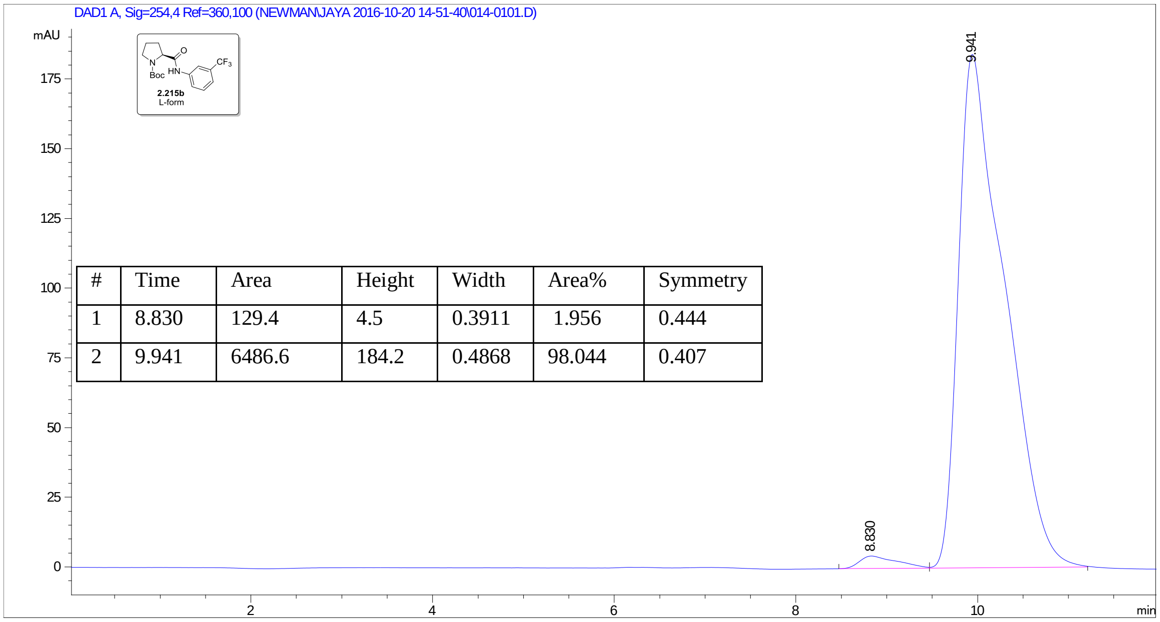
#	Time	Area	Height	Width	Area%	Symmetry
1	5.353	10.4	6.2E-1	0.2771	3.968	0.52
2	6.36	250.9	10.9	0.3847	96.032	0.439

Compound **2.2.15a'**: 92% ee was determined by chiral HPLC (chiralcel OD-H, n-hexane/i-PrOH = 90/10, 1 mL/min, 254 nm): t_R (minor) = 6.4 min, t_R (major) = 5.4 min.



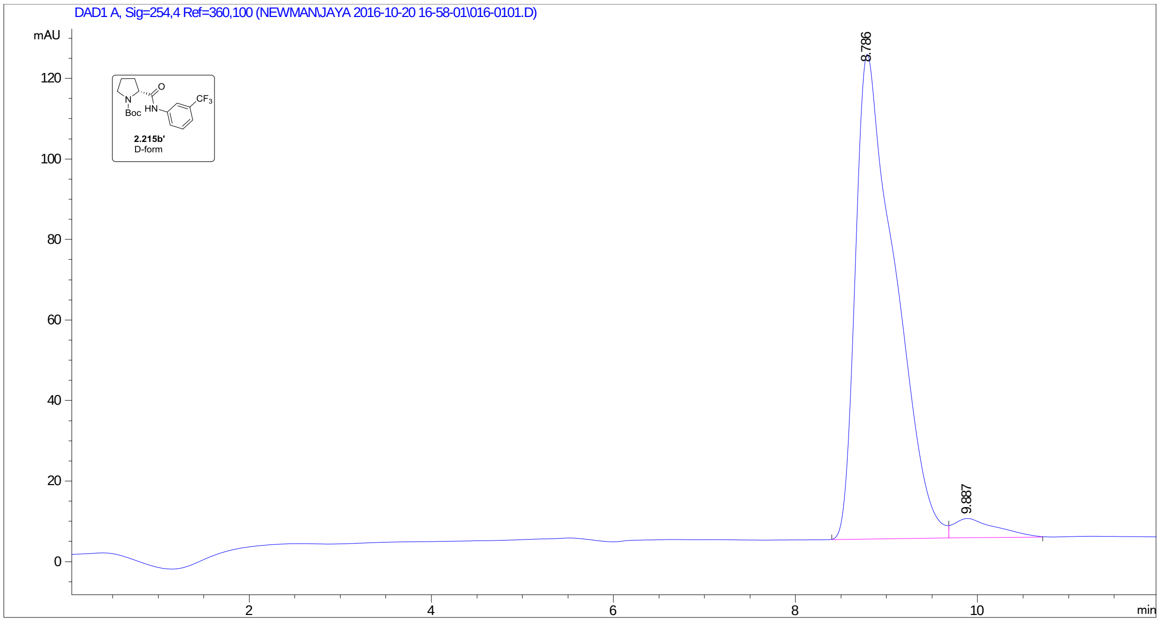
#	Time	Area	Height	Width	Area%	Symmetry
1	5.408	11773.6	553.9	0.294	95.893	0.411
2	6.445	504.2	20.5	0.3385	4.107	0.476

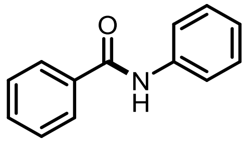
Compound **2.2.15b**: 96% ee was determined by chiral HPLC (chiralcel OD-H, n-hexane/i-PrOH = 90/10, 0.5 mL/min, 254 nm): t_R (minor) = 8.8 min, t_R (major) = 9.9 min.



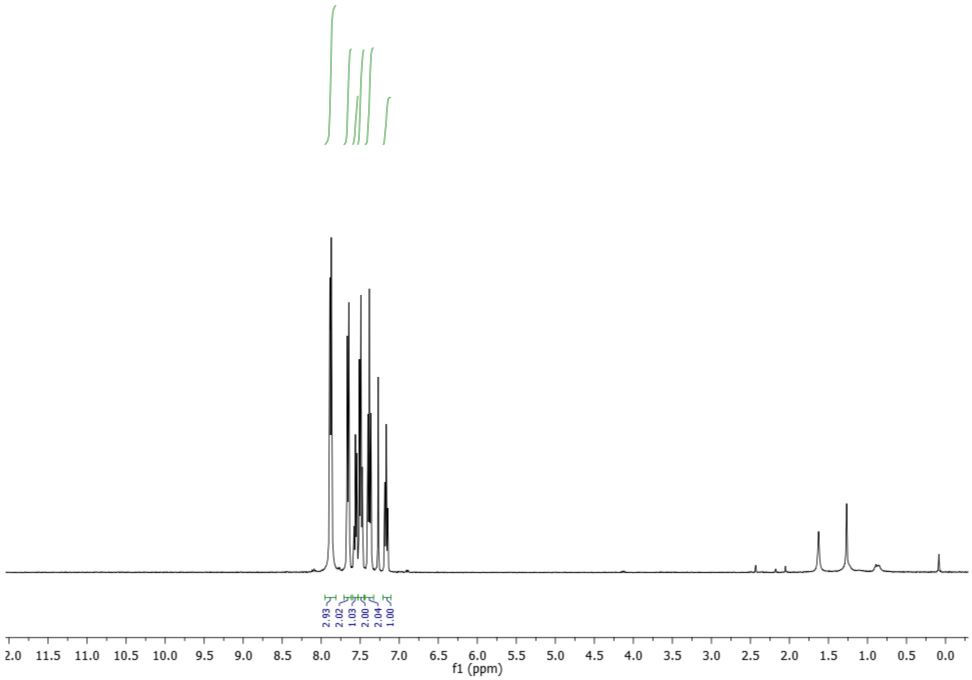
#	Time	Area	Height	Width	Area%	Symmetry
1	8.830	129.4	4.5	0.3911	1.956	0.444
2	9.941	6486.6	184.2	0.4868	98.044	0.407

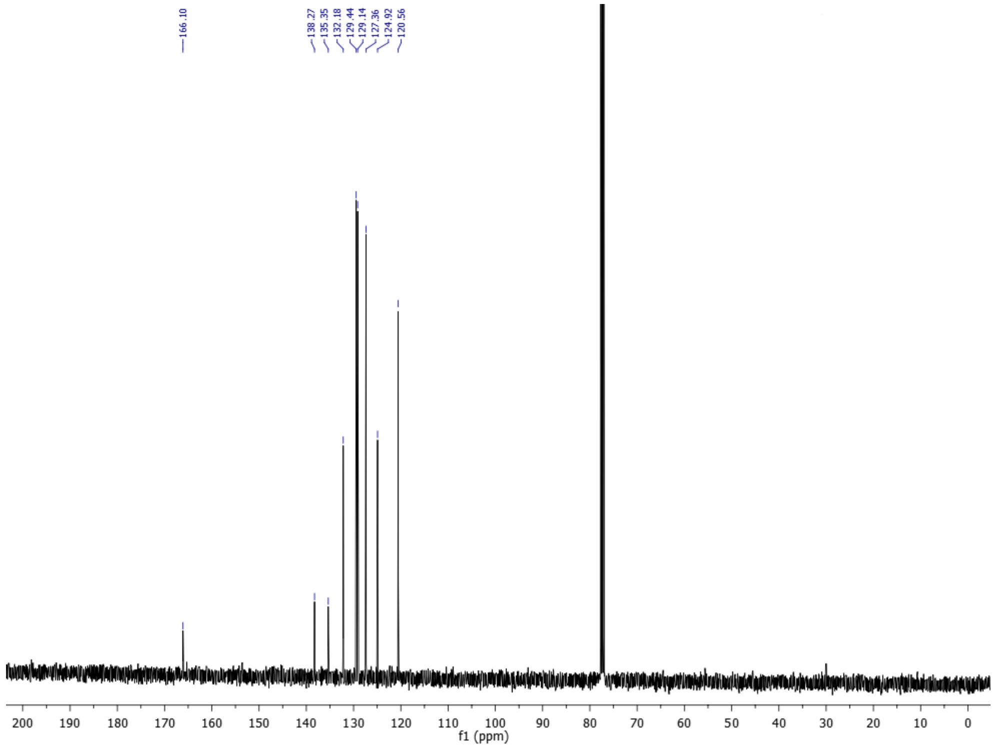
Compound **2.2.15b`**: Due to the poor baseline resolution, e.r. was not calculated for the D-form, and was only used to confirm the identity of the major and minor enantiomers in the HPLC of the L- form.



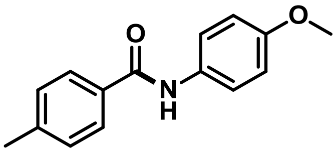


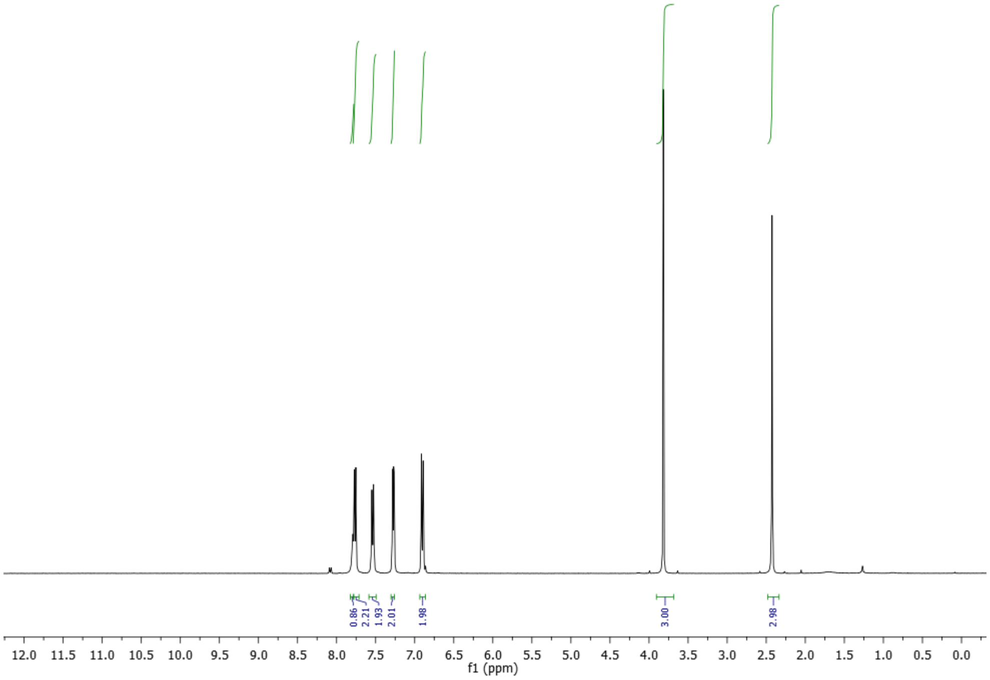
Benzanilide (**2.2.13a**) $CDCl_3$, 400 MHz:

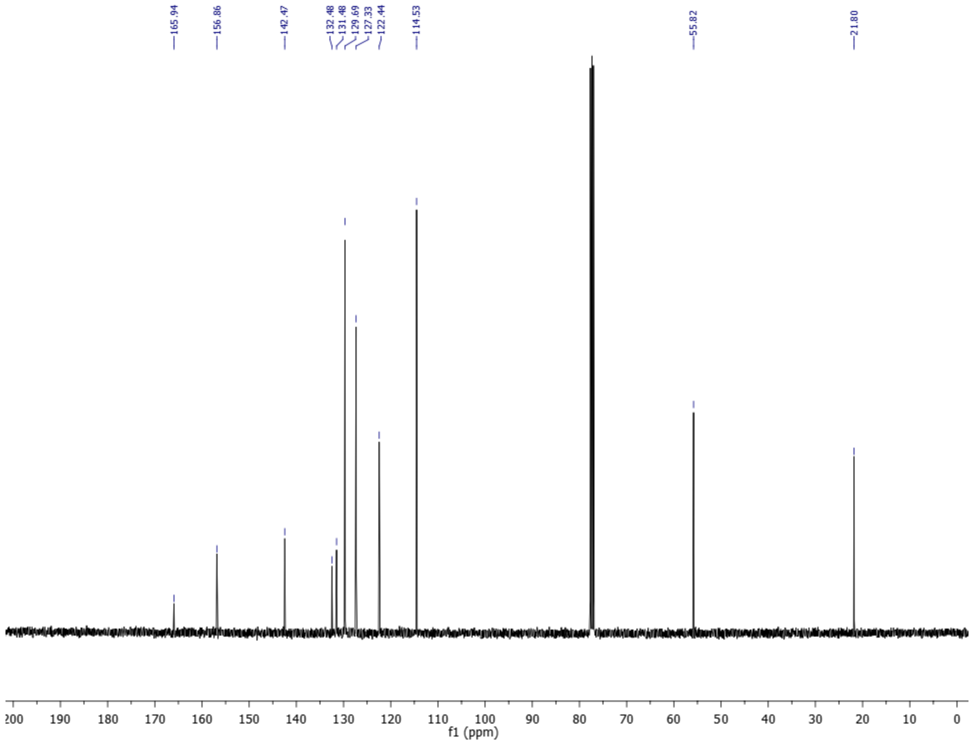




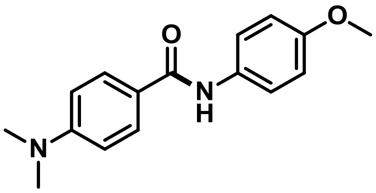
N-(4-Methoxyphenyl)-4-methylbenzamide (**2.2.13b**) $CDCl_3$, 400 MHz:

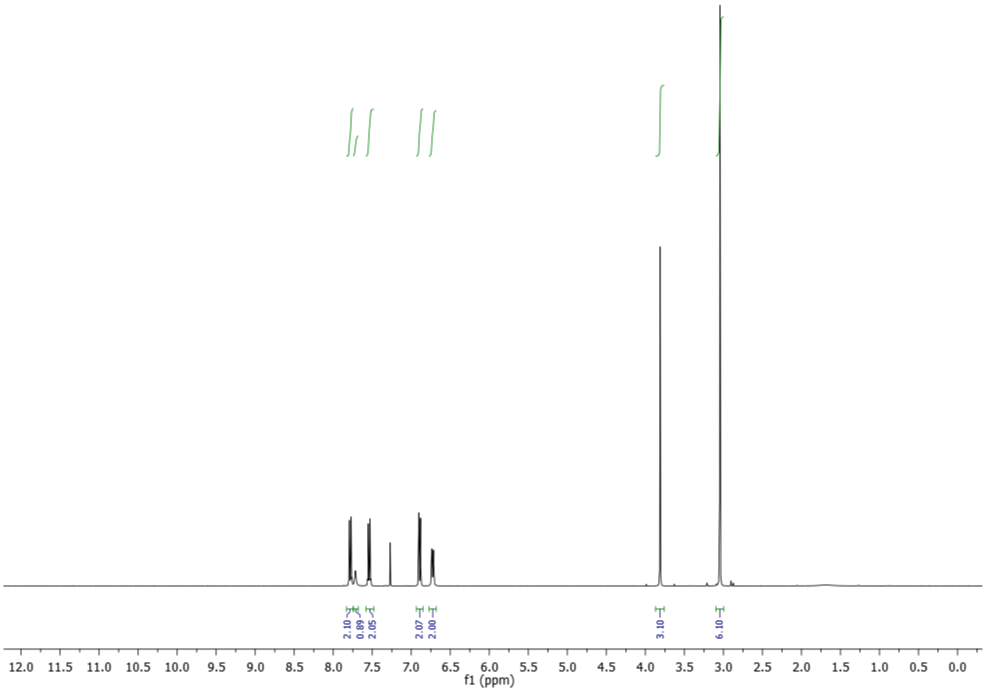


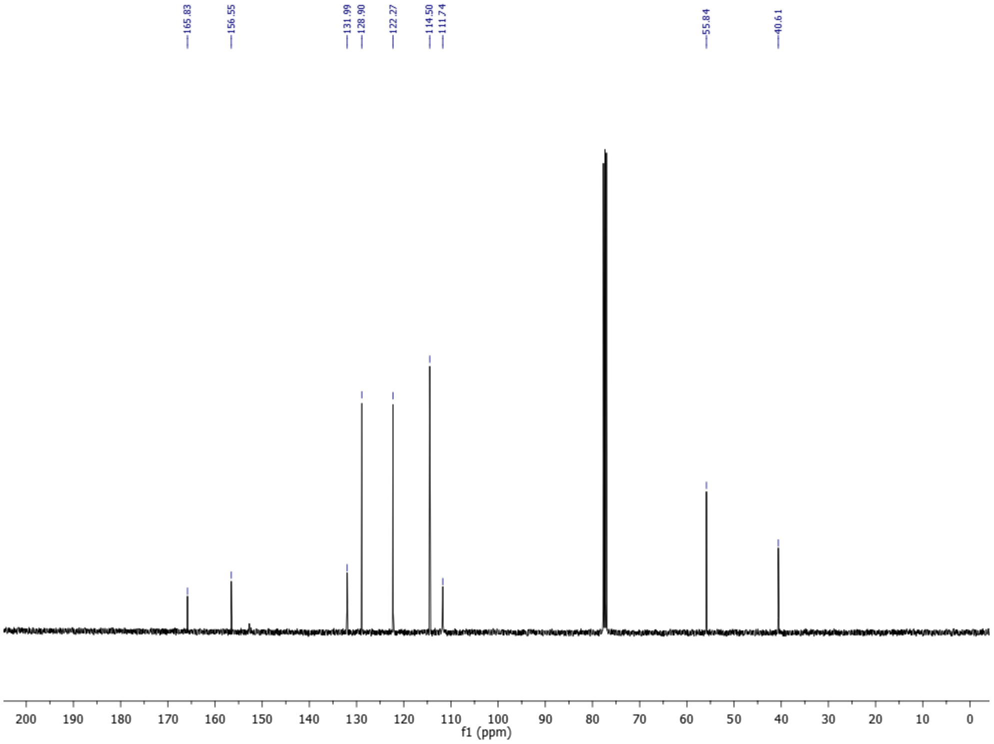




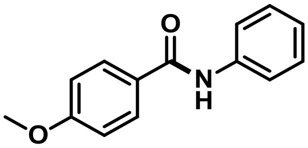
4-(Dimethylamino)-N-(4-methoxyphenyl)benzamide (**2.2.13c**) $CDCl_3$,400MHz

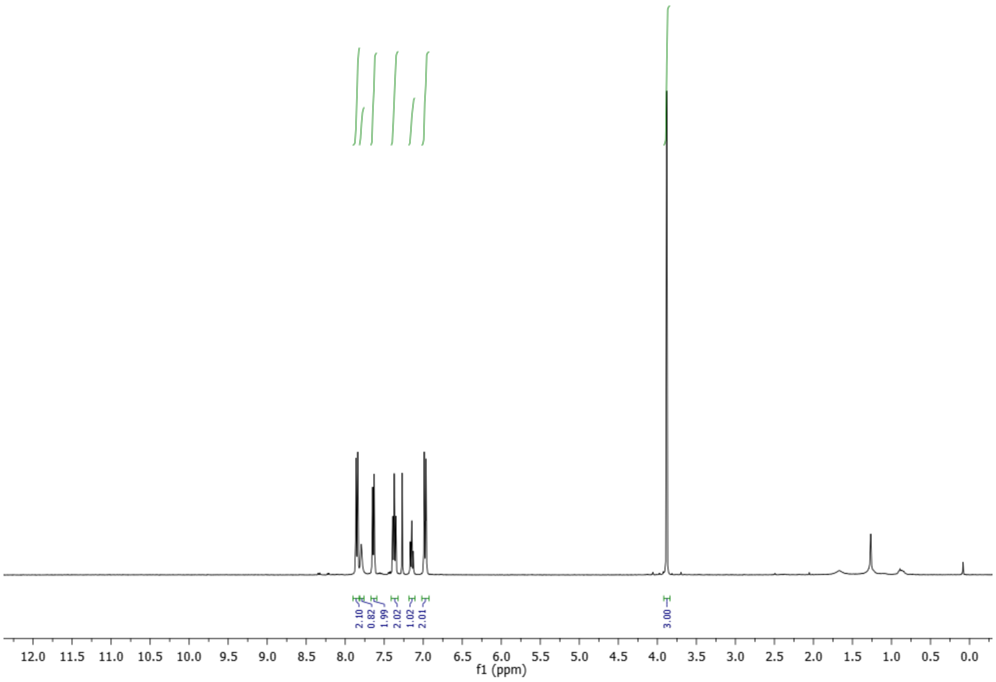


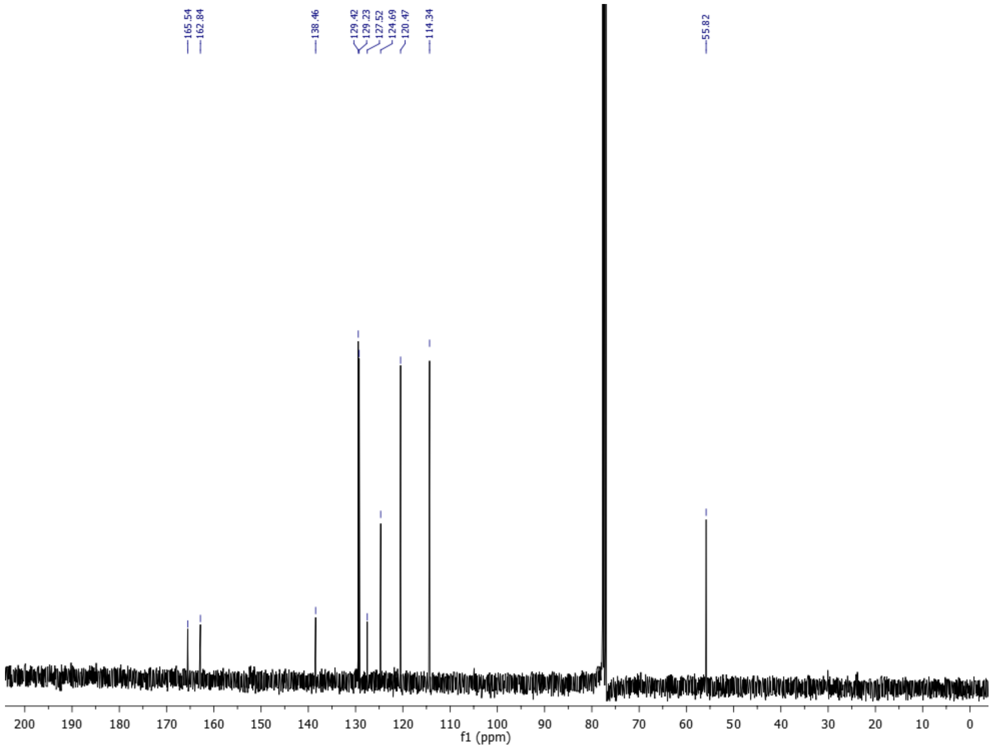


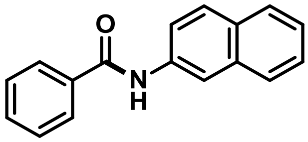


4-Methoxy-N-phenylbenzamide (**2.2.13d**) CDCl$_3$, 400MHz:

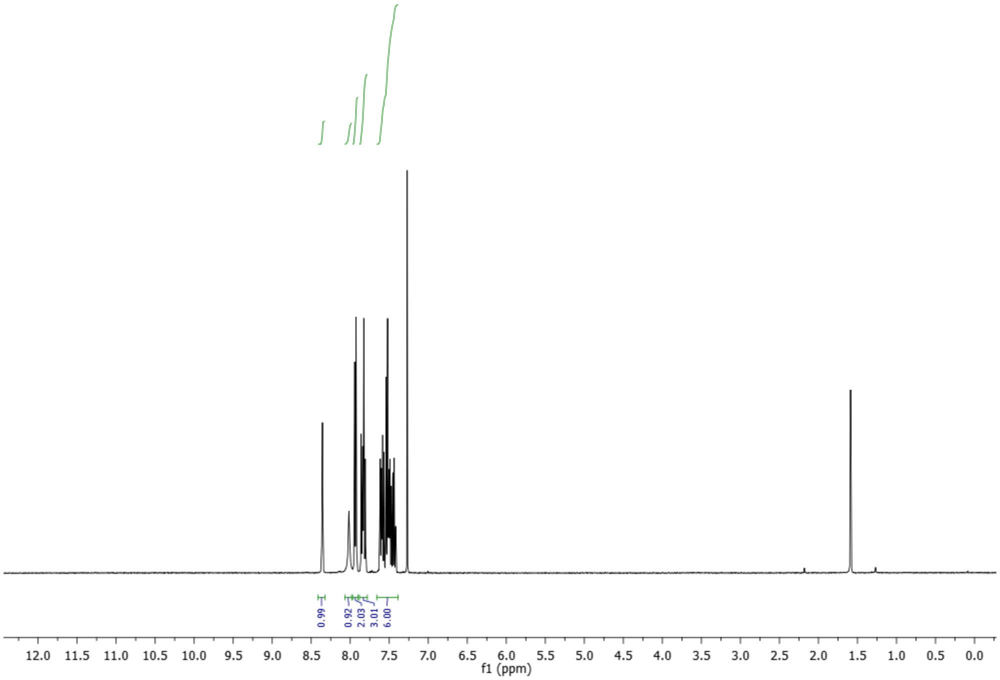


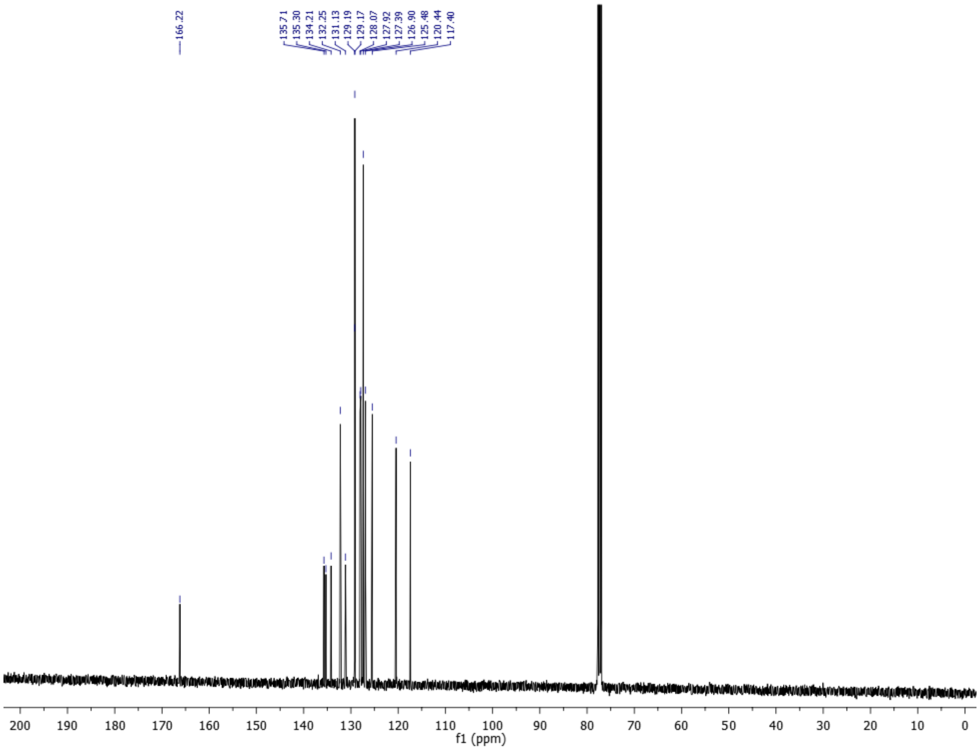


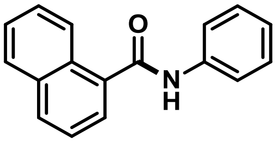




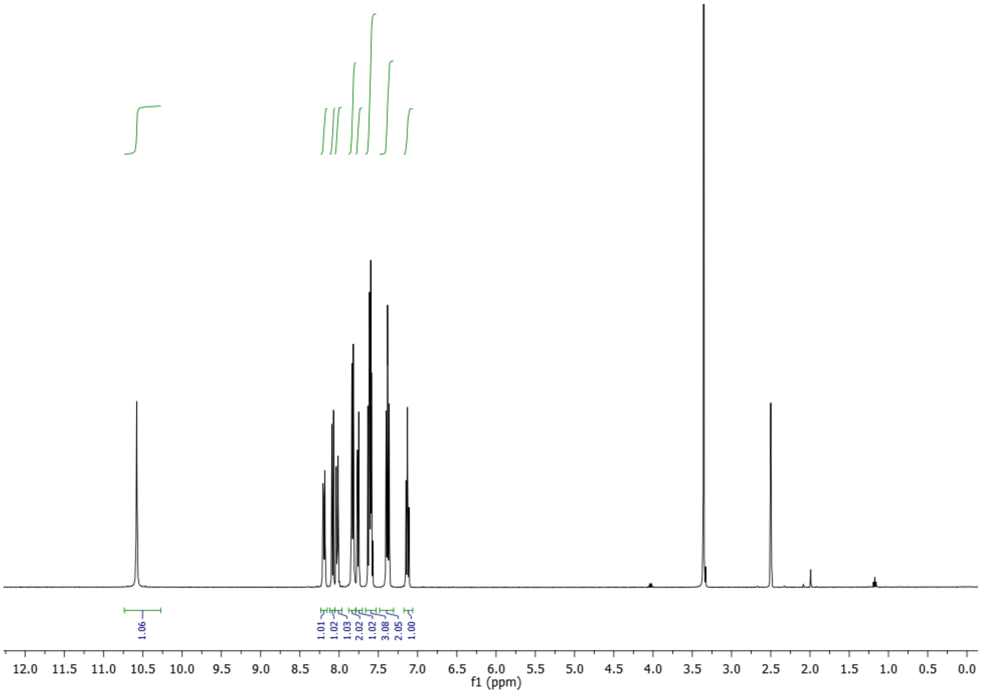
N-(Naphthalen-2-yl) benzamide (**2.2.13e**) $CDCl_3$, 400MHz:

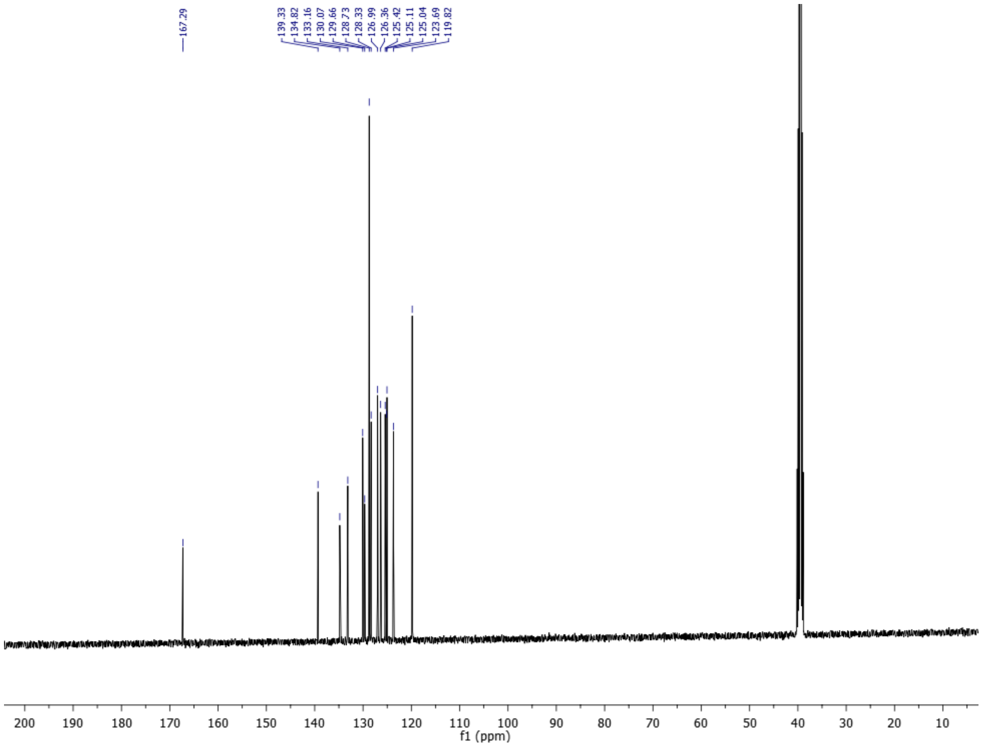




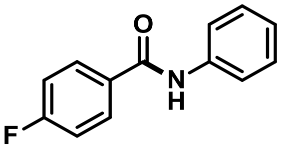


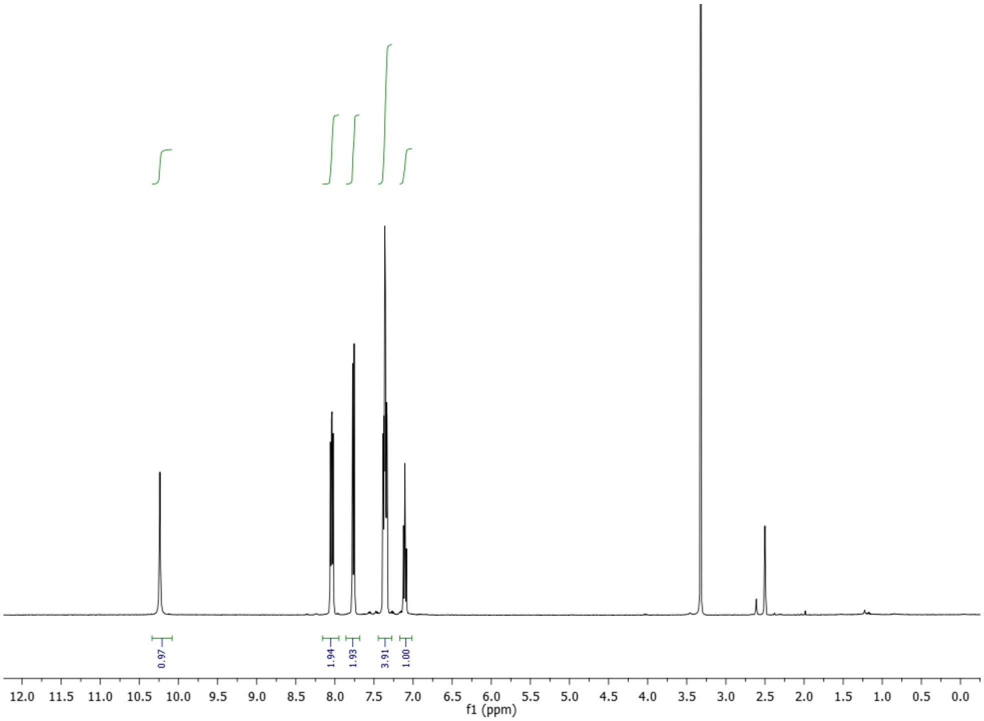
N-Phenyl-1-naphthamide (**2.2.13f**) DMSO, 400MHz:

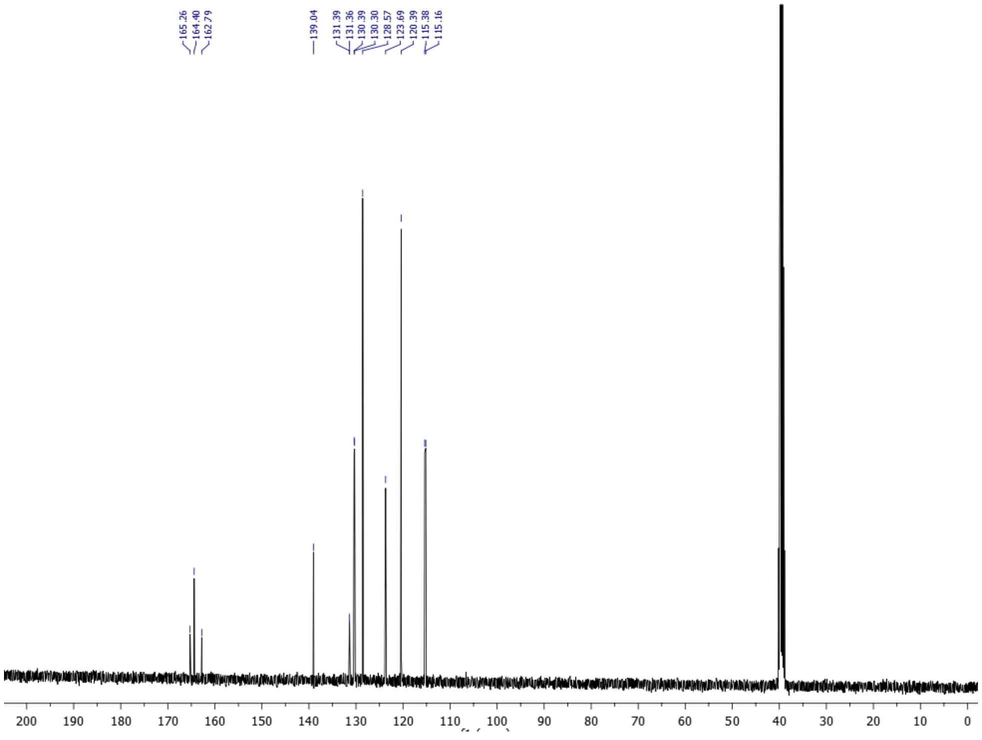


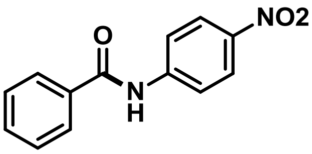


4-Fluoro-N-phenylbenzamide (**2.2.13g**) DMSO, 400MHz:

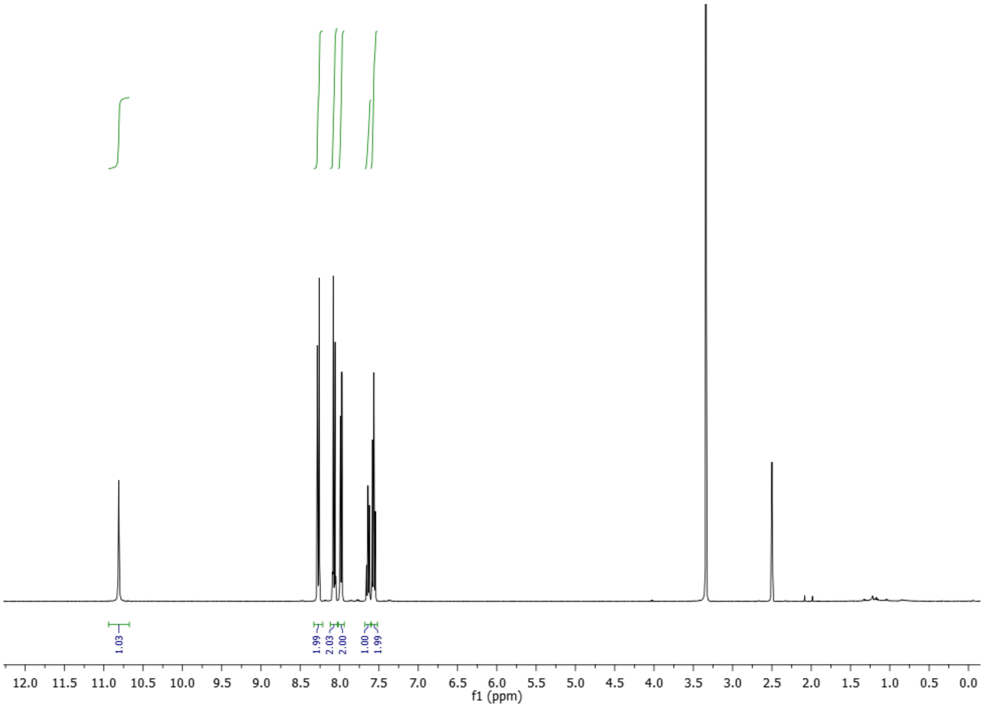


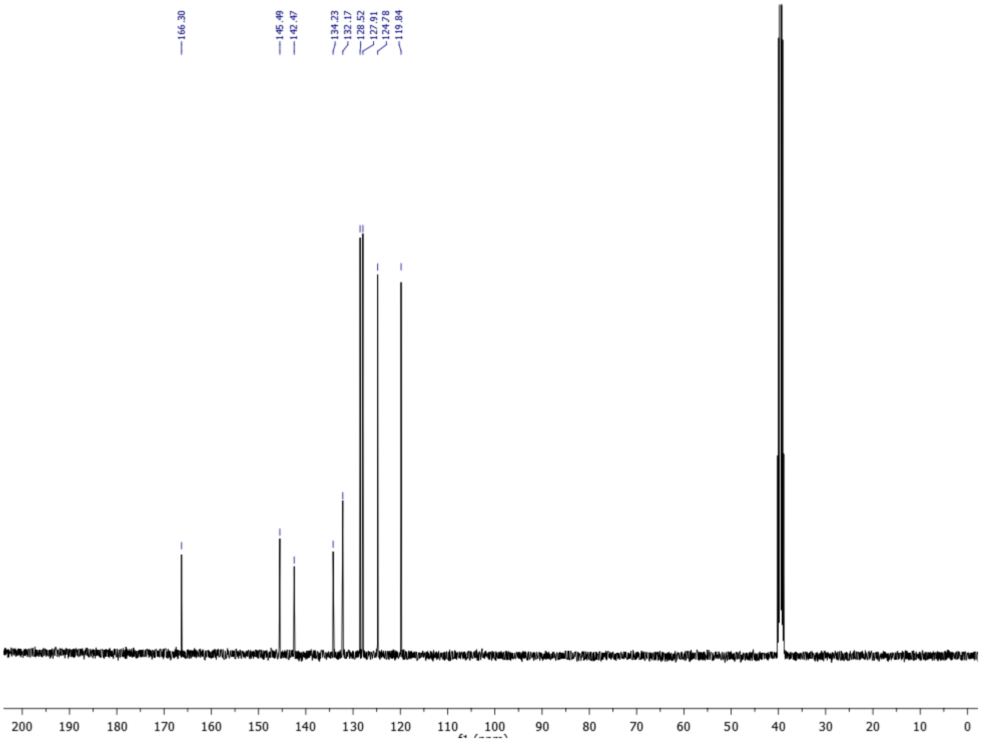




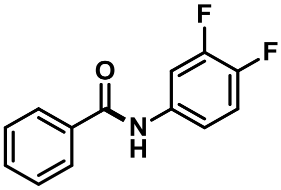


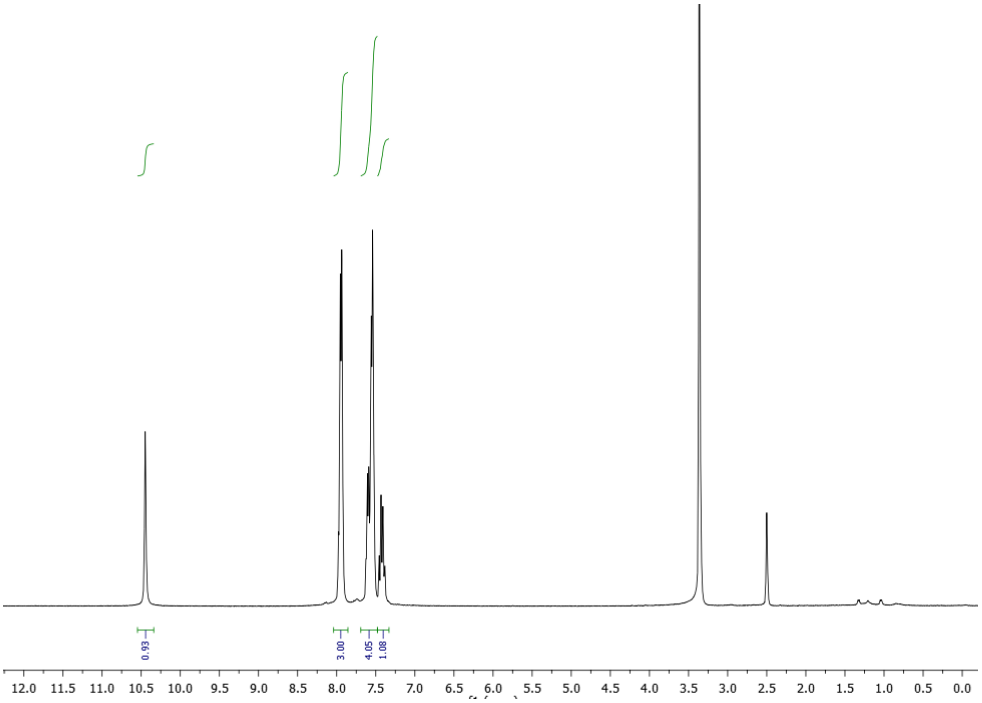
N-(4-Nitrophenyl)benzamide (**2.2.13h**) DMSO, 400 MHz:

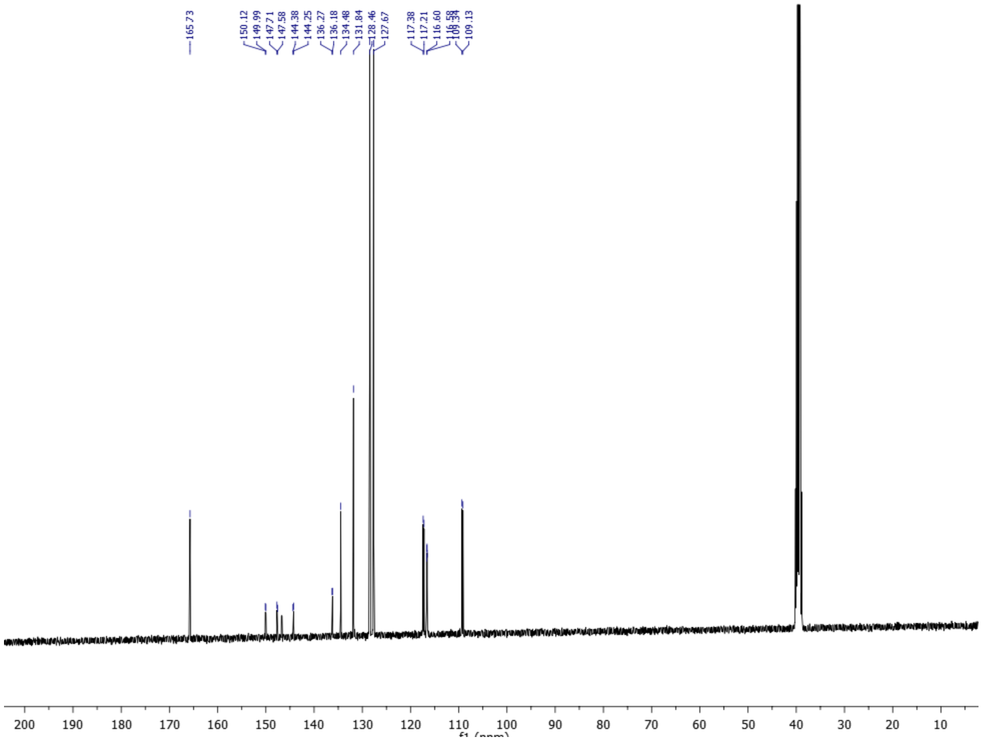




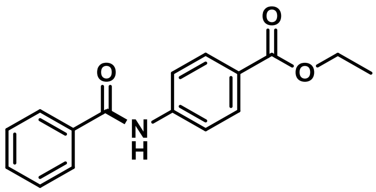
N-(3,4-Difluorophenyl)benzamide (**2.2.13i**) DMSO, 400 MHz:

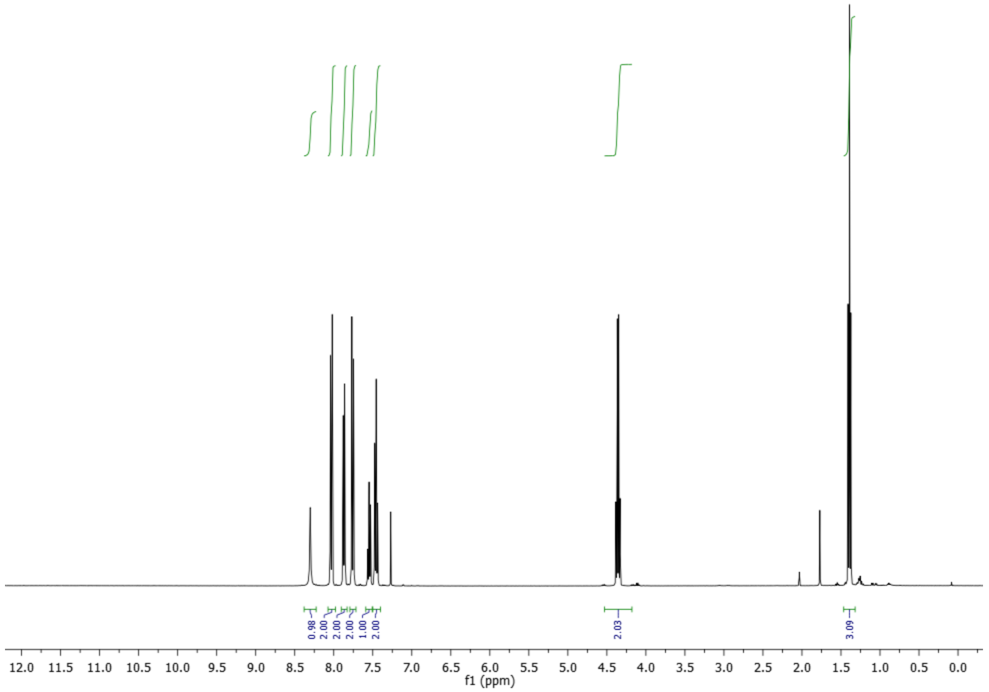


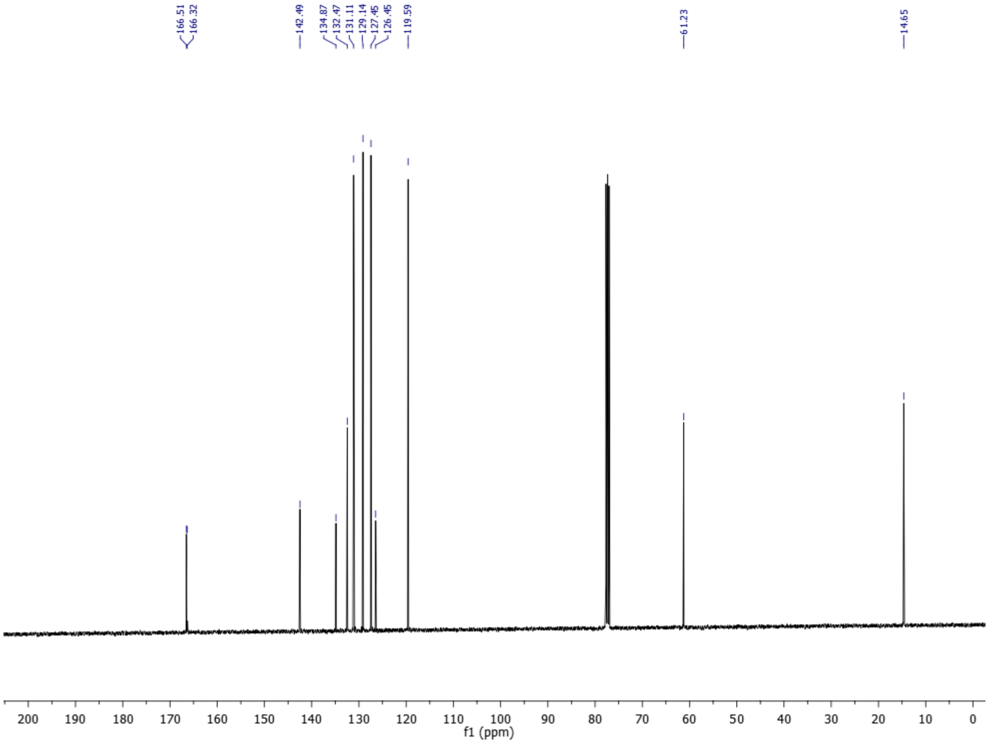




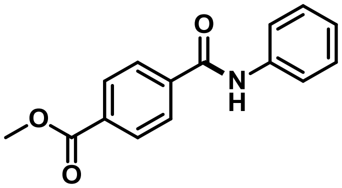
Ethyl 4-benzamidobenzoate (**2.2.13j**) CDCl$_3$, 400 MHz:

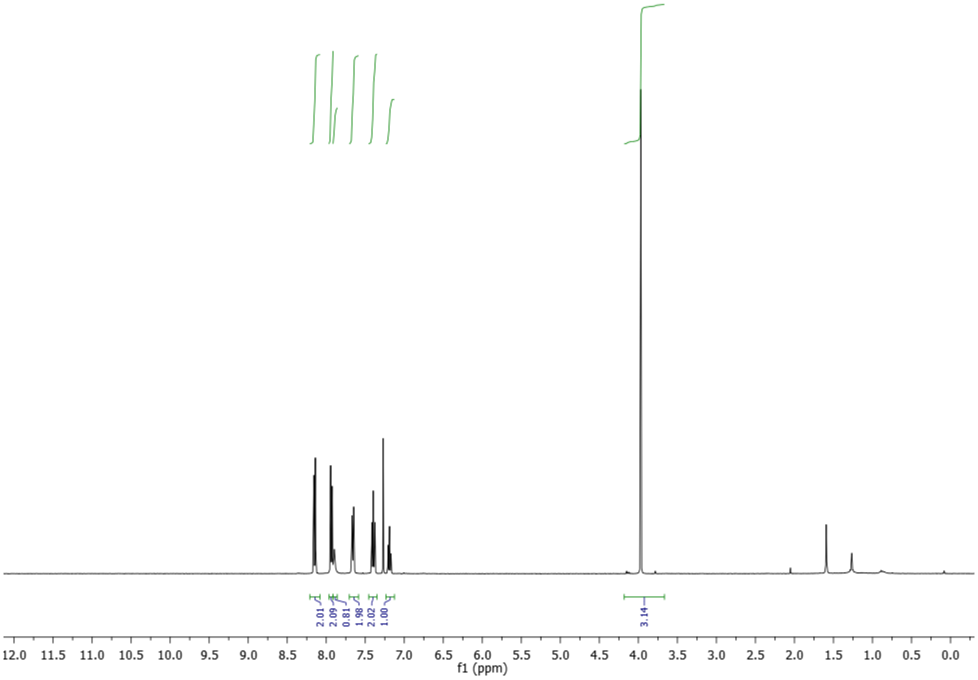


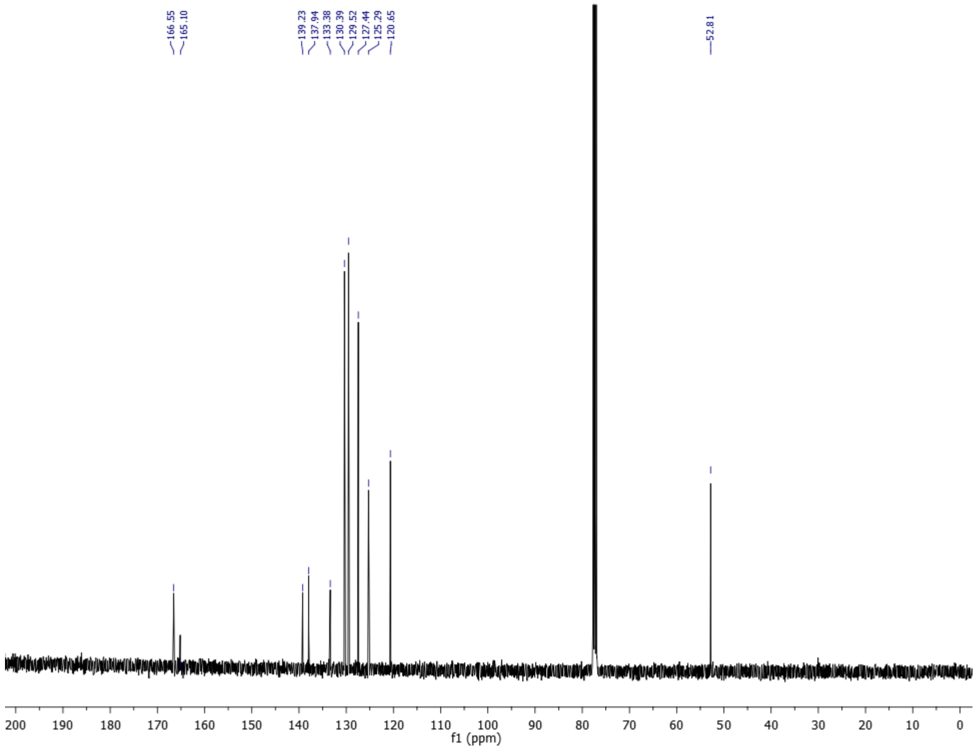




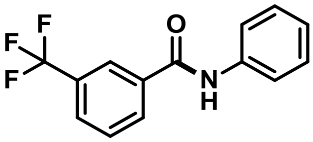
Methyl 4-(phenylcarbamoyl)benzoate (**2.2.13k**) $CDCl_3$, 400 MHz:

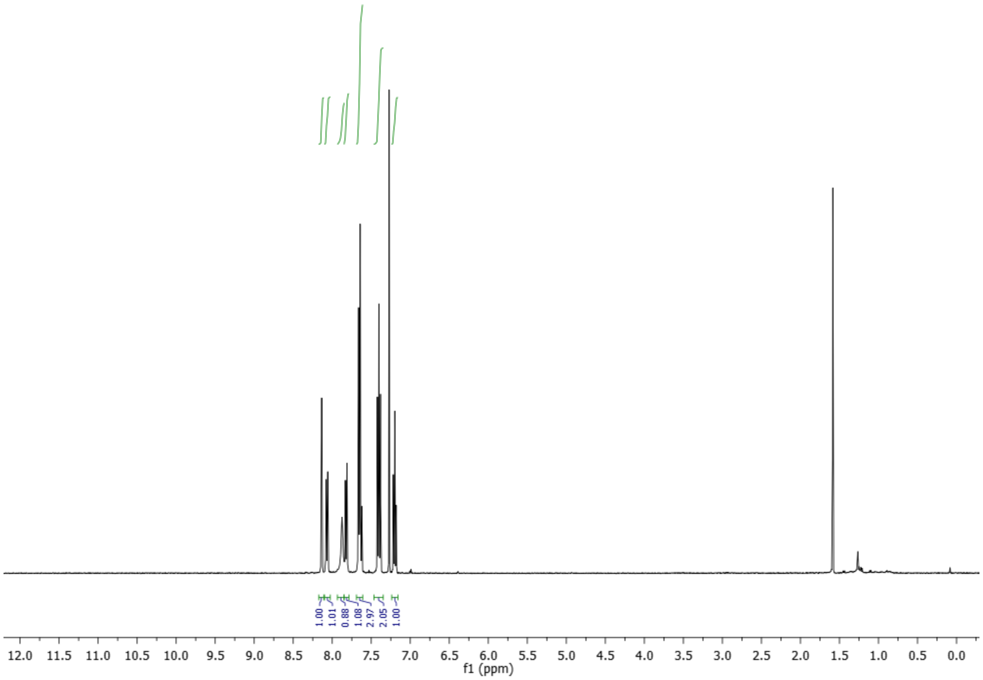


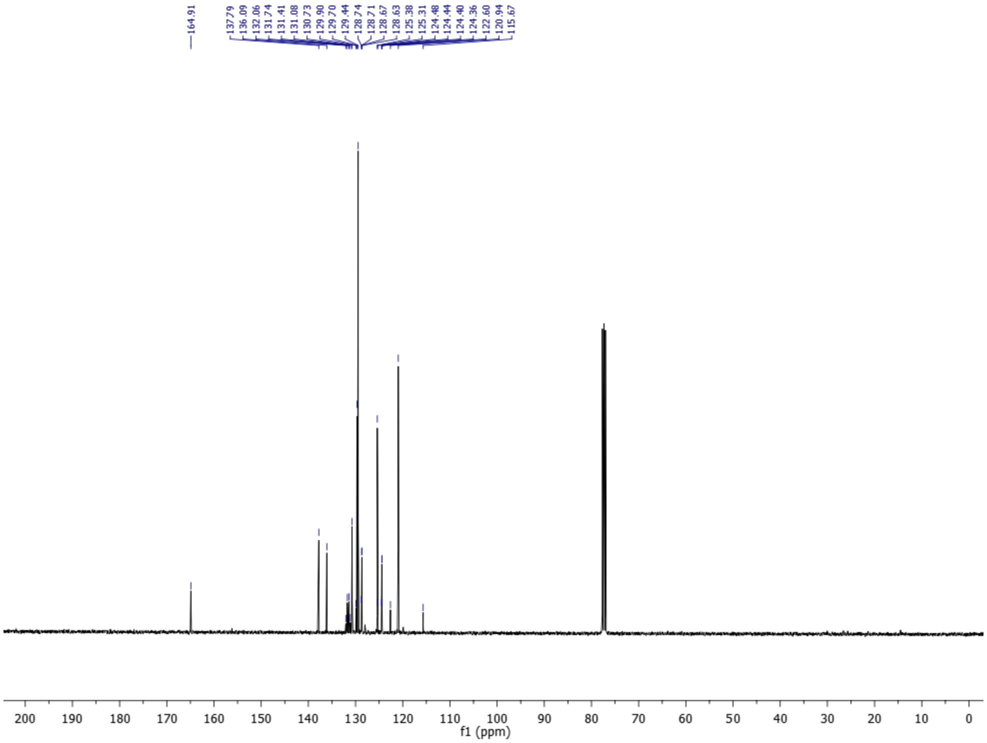




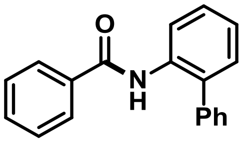
N-Phenyl-3-(trifluoromethyl)benzamide (**2.2.13l**) CDCl$_3$, 400 MHz:

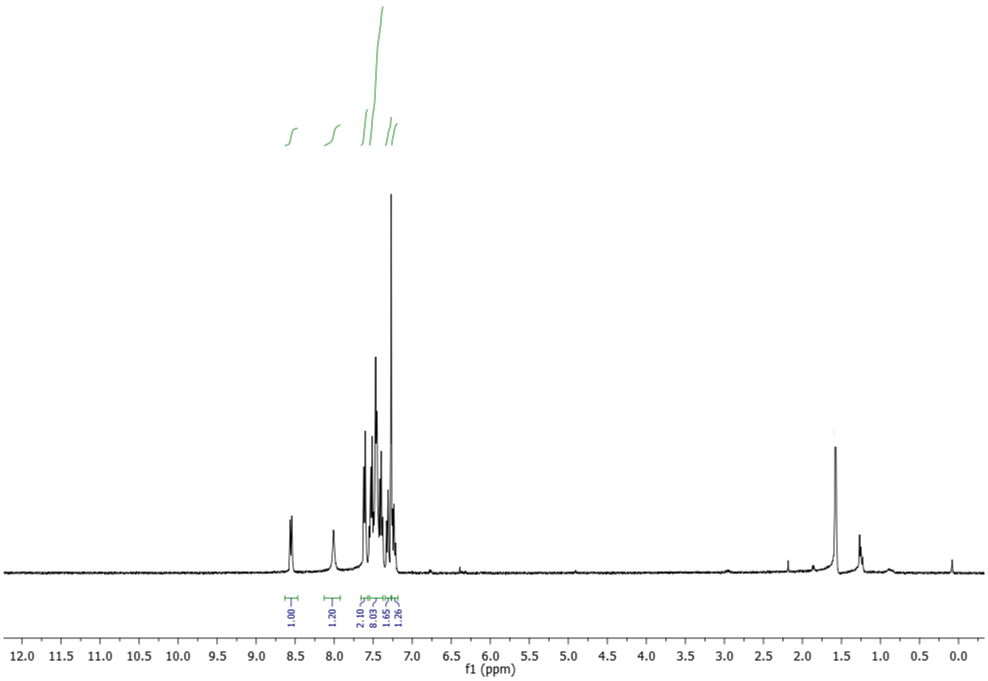


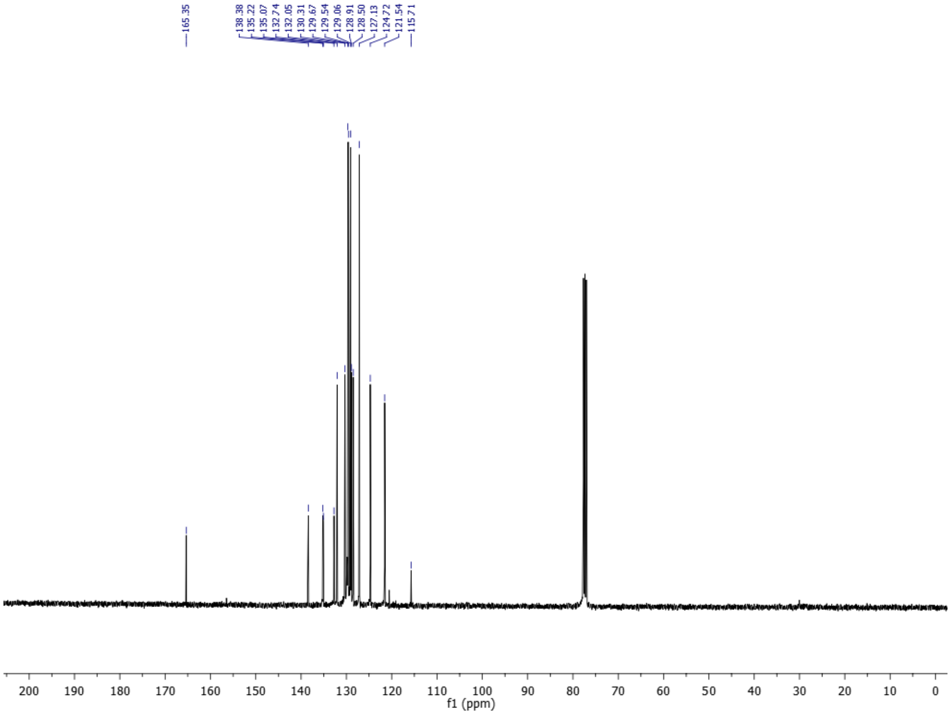




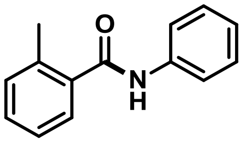
N-([1,1'-Biphenyl]-2-yl)benzamide (**2.2.13m**) $CDCl_3$, 400 MHz:

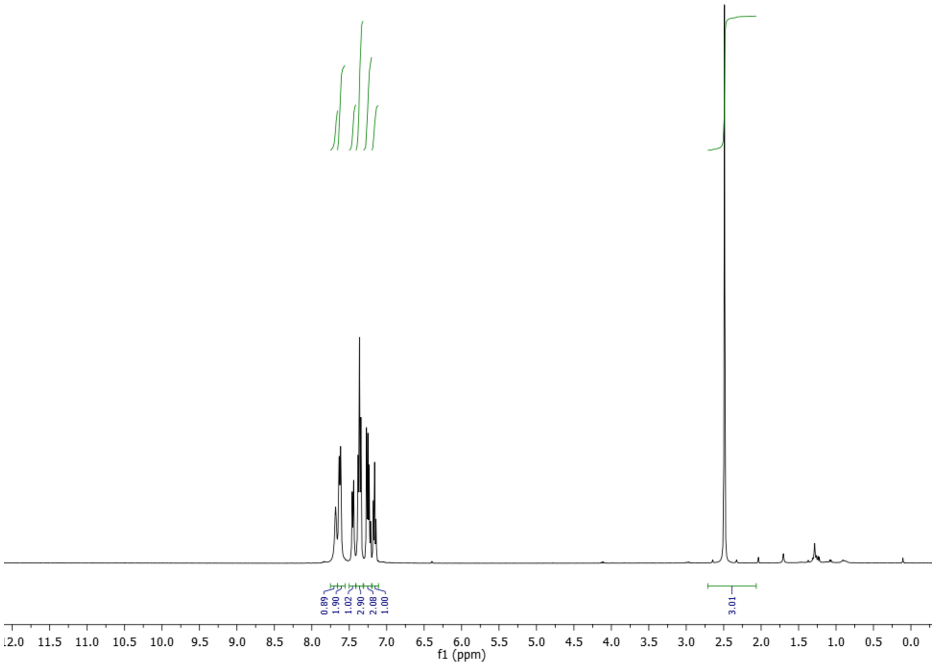


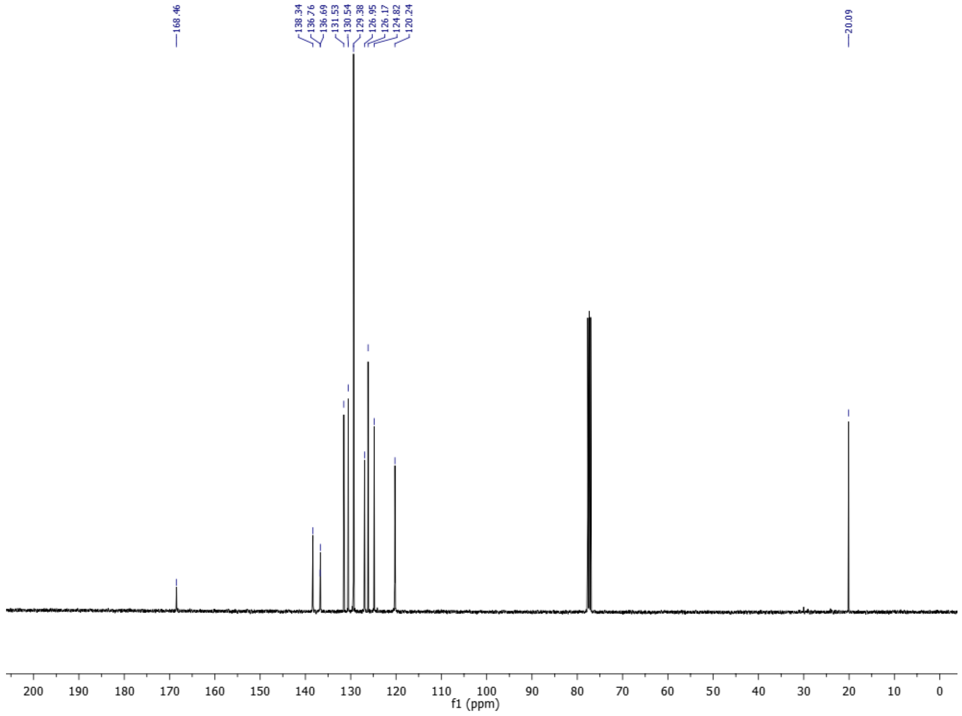




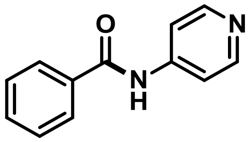
2-Methyl-N-phenylbenzamide (**2.2.13n**) $CDCl_3$, 400 MHz:

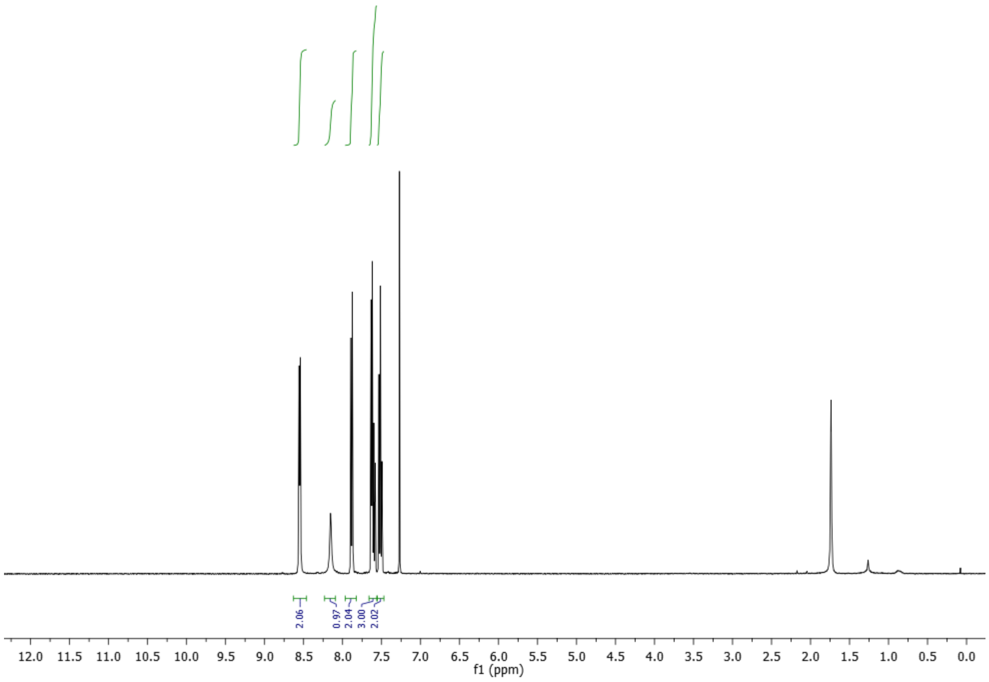


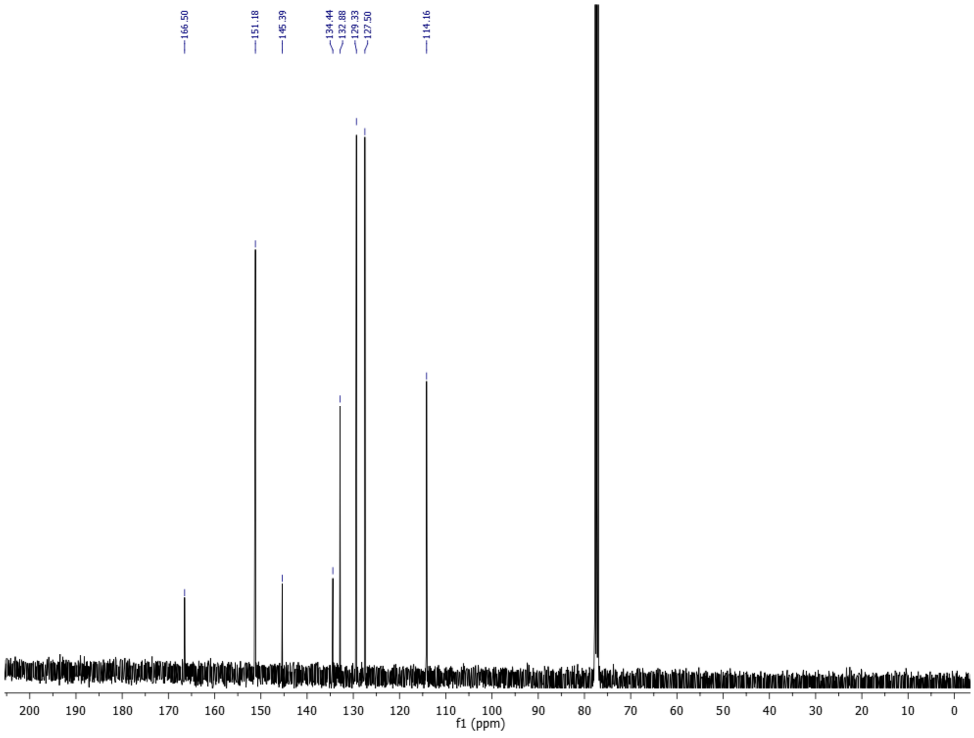


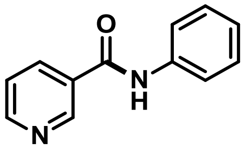


N-(Pyridin-4-yl)benzamide (**2.2.13o**) CDCl$_3$, 400 MHz:

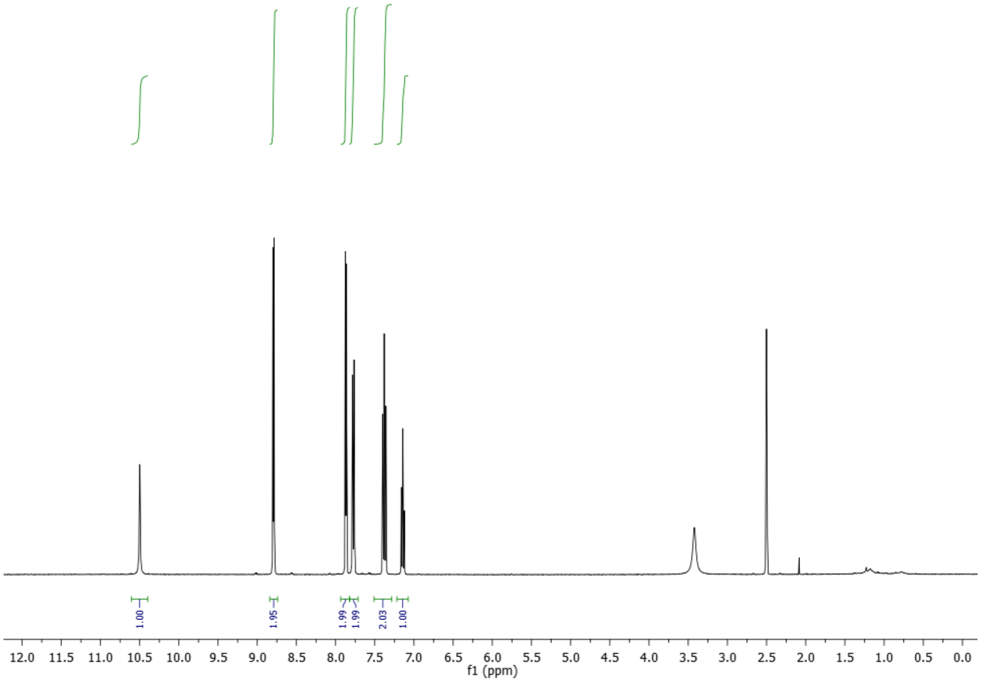


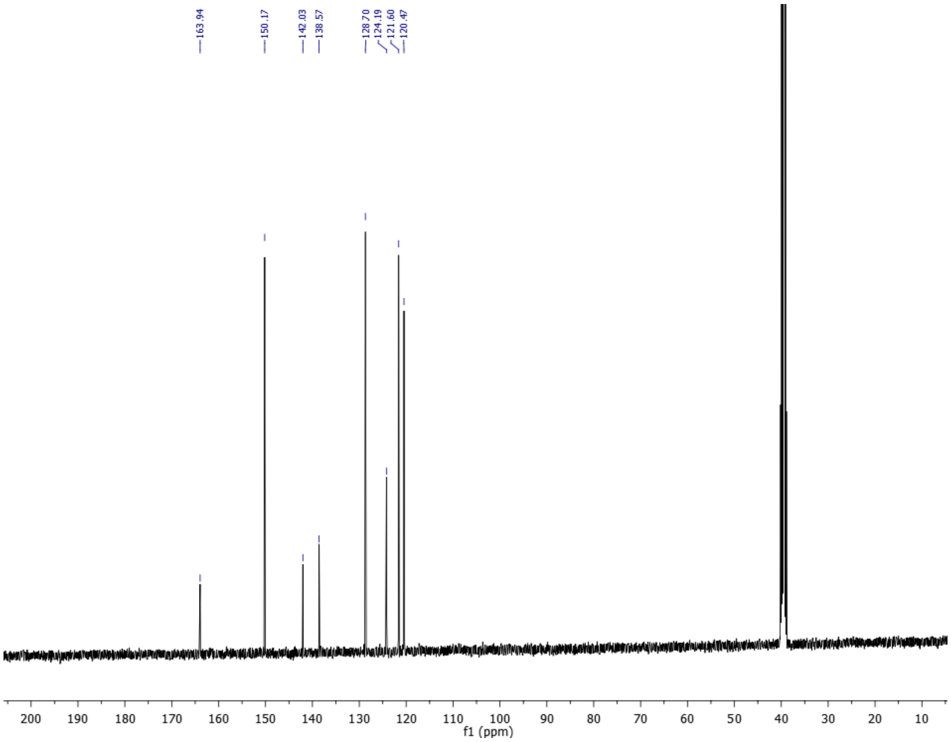




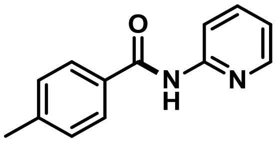


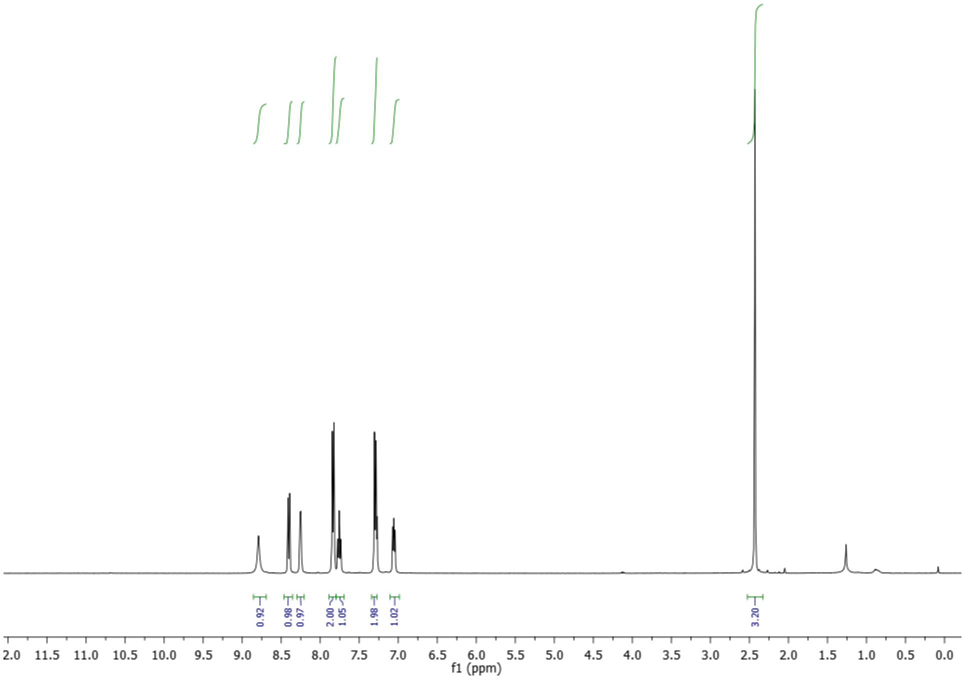
N-Phenylnicotinamide (**2.2.13p**) DMSO, 400 MHz:

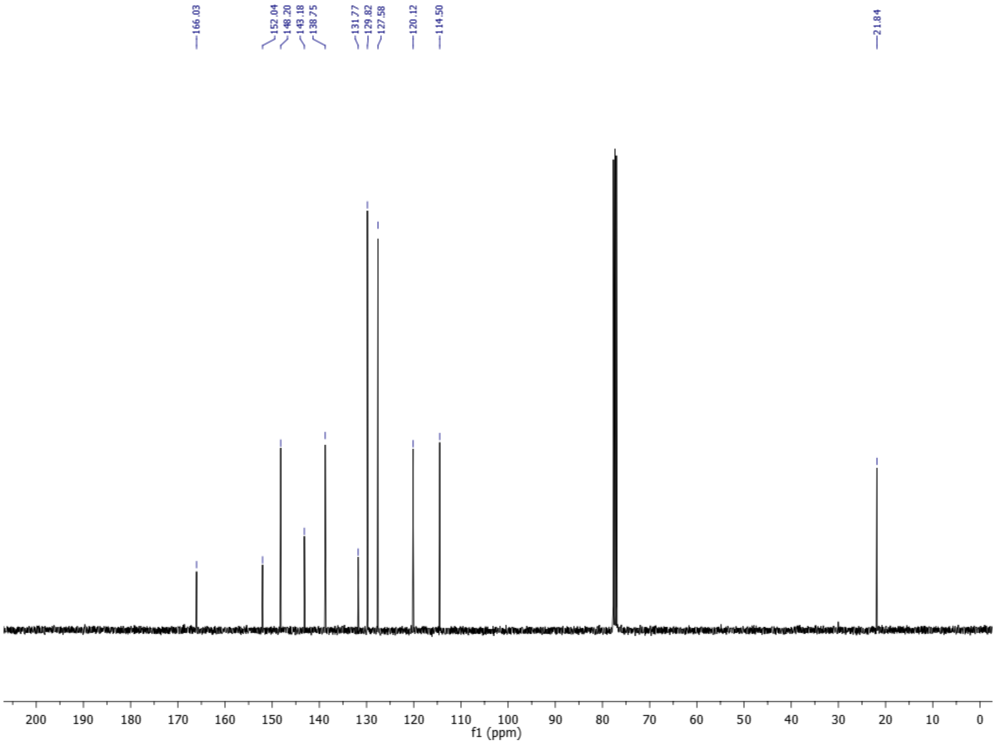


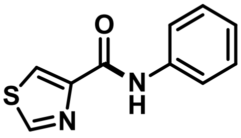


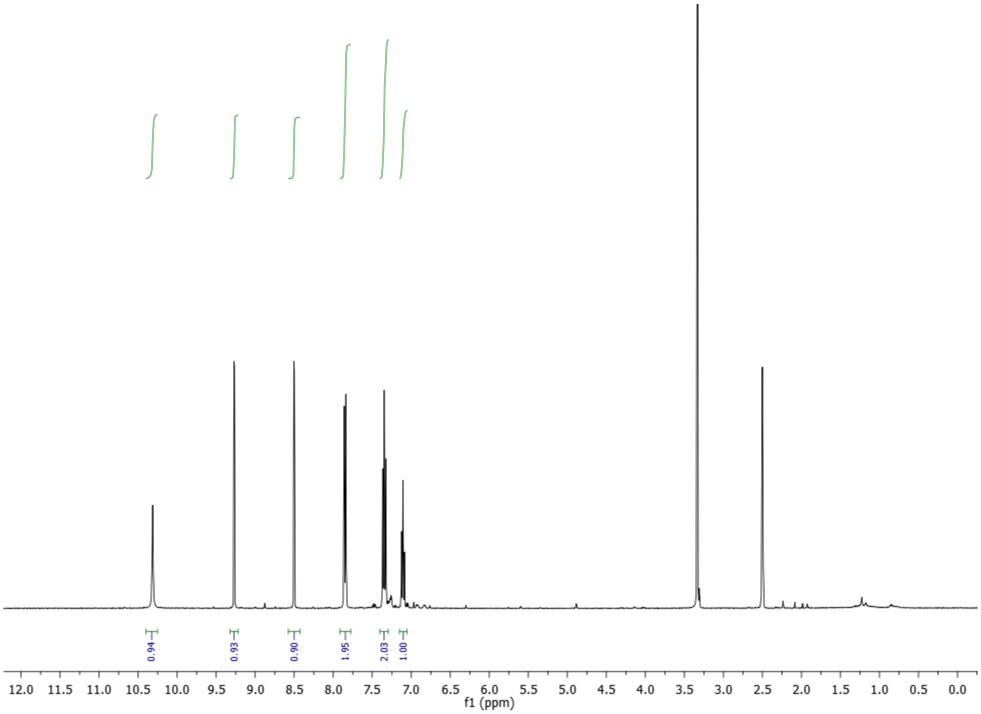
4-Methyl-N-(pyridin-2-yl)benzamide (**2.2.13q**) CDCl$_3$, 400 MHz:

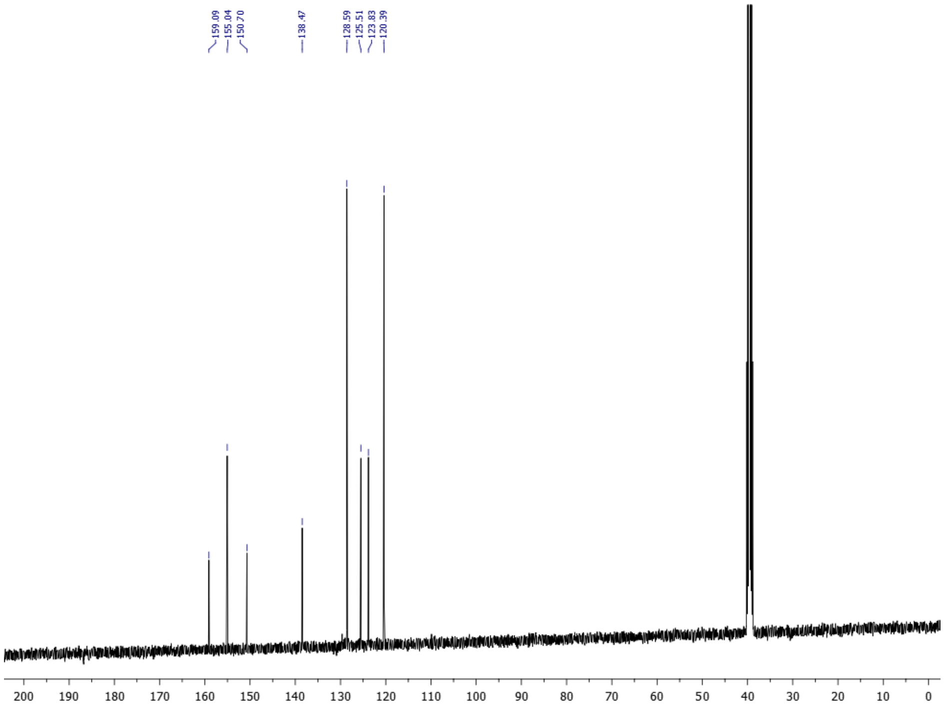




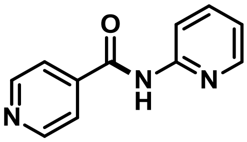


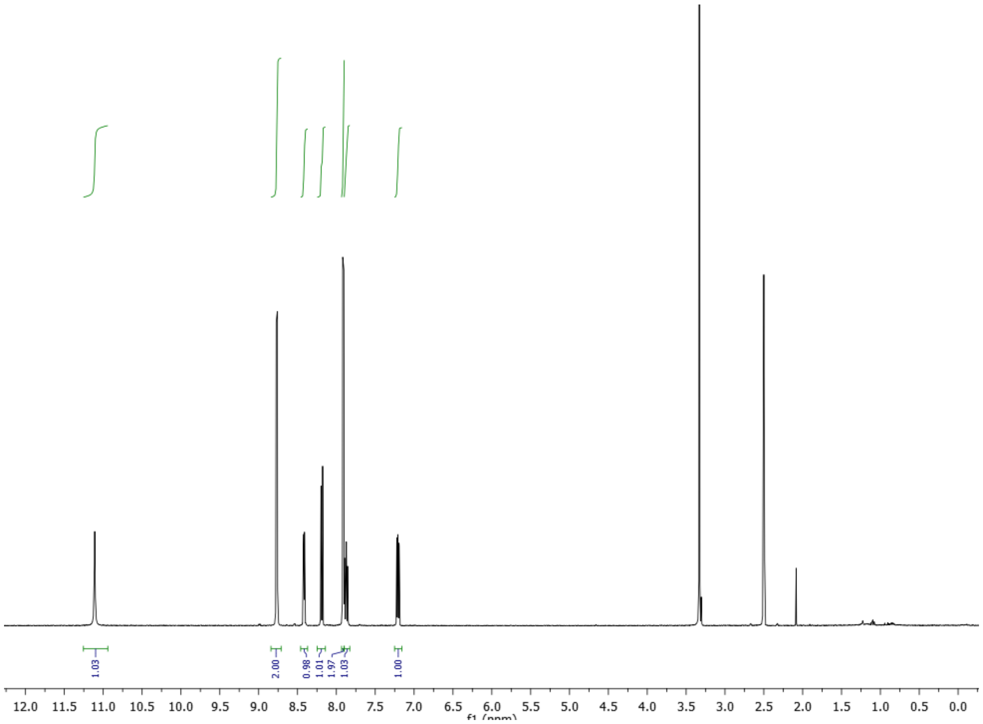
N-Phenylthiazole-4-carboxamide (**2.2.13r**) DMSO, 400 MHz: 

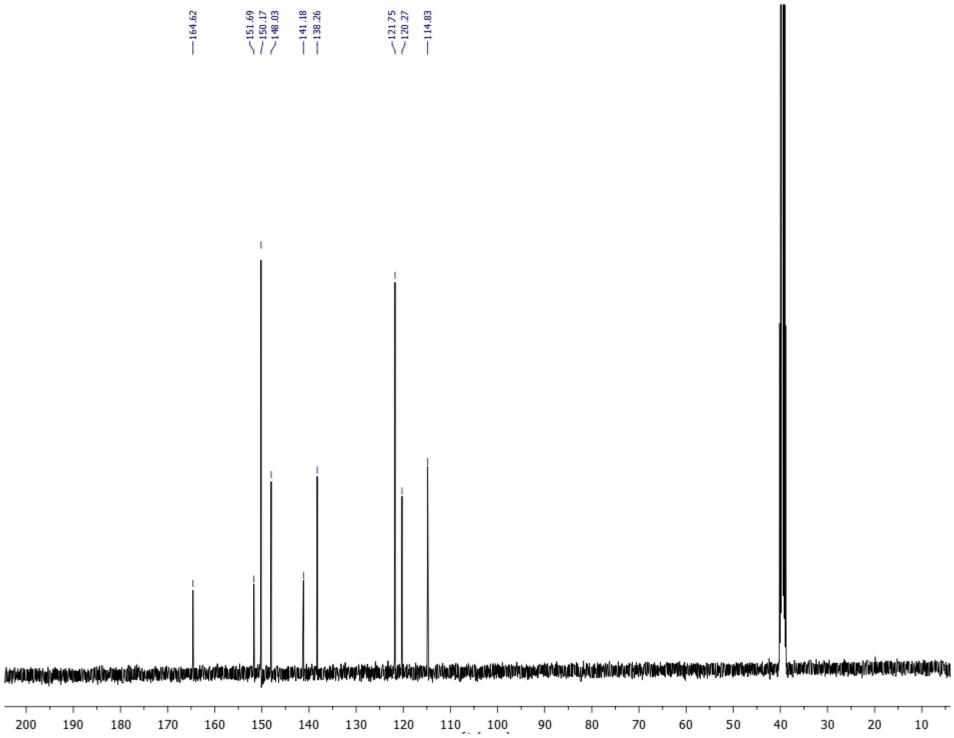




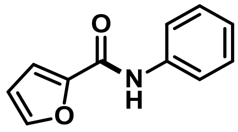
N-(Pyridin-2-yl)isonicotinamide (**2.2.13s**) DMSO, 400 MHz:

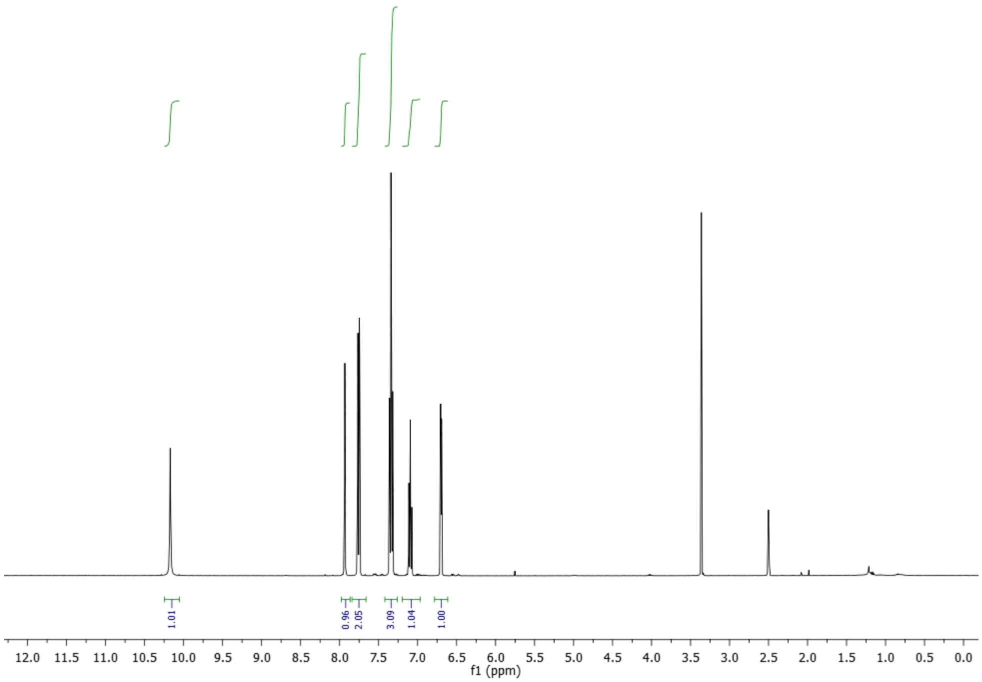


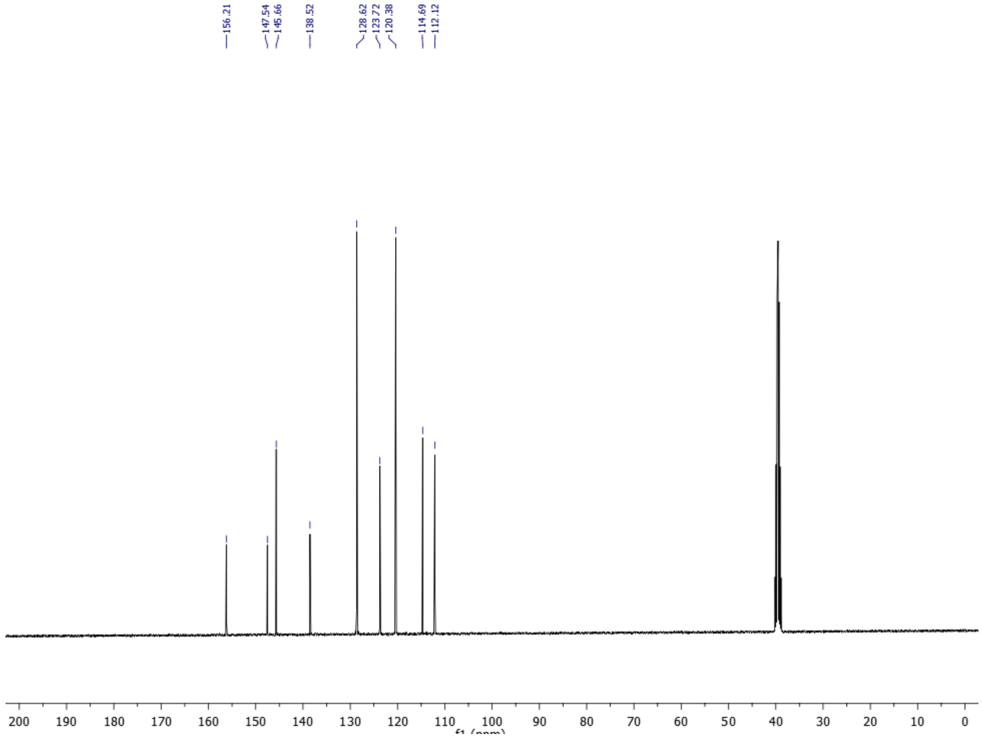




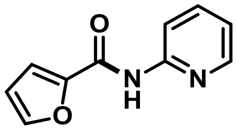
N-Phenylfuran-2-carboxamide (**2.2.13t**) DMSO, 400 MHz:

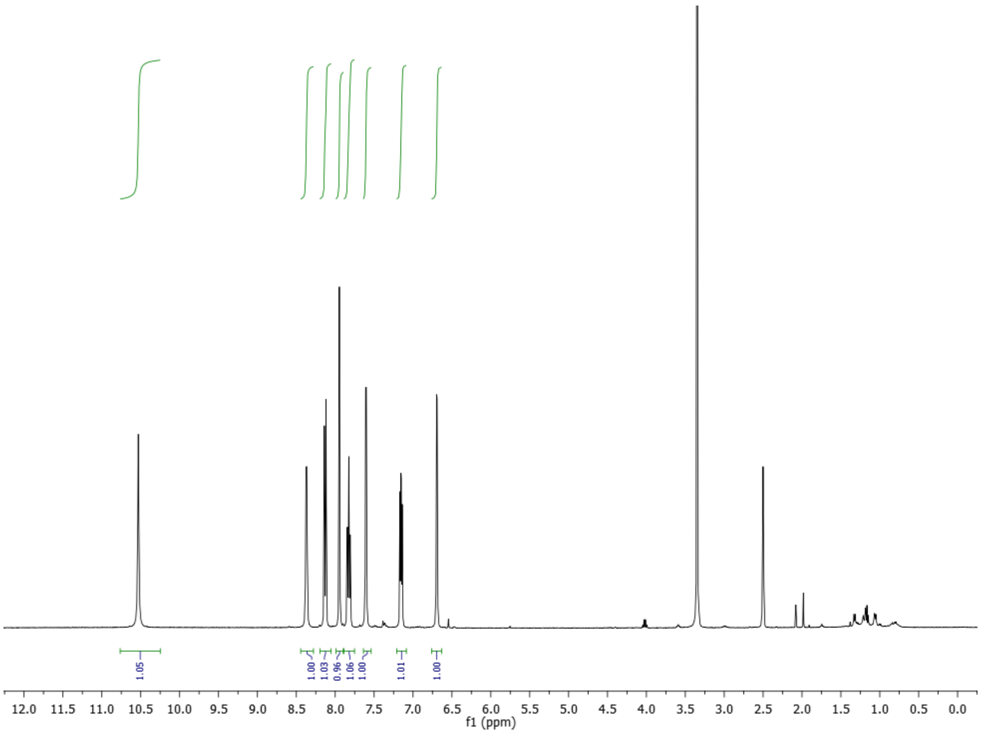


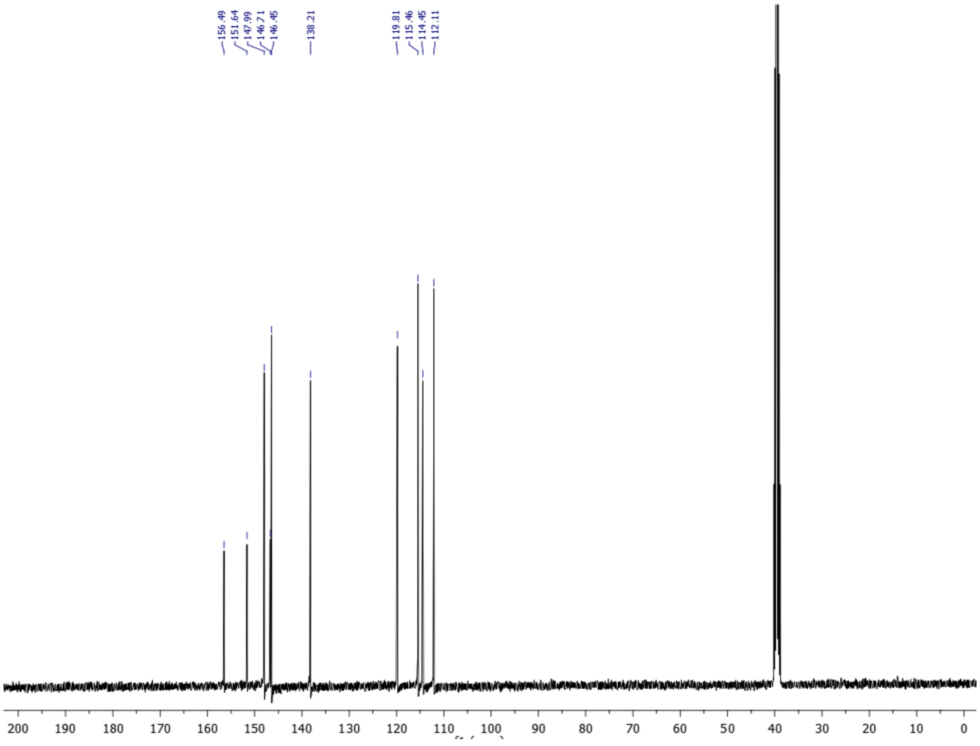




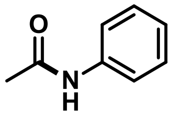
N-(Pyridin-2-yl) furan-2-carboxamide (**2.2.13u**) DMSO, 400 MHz:

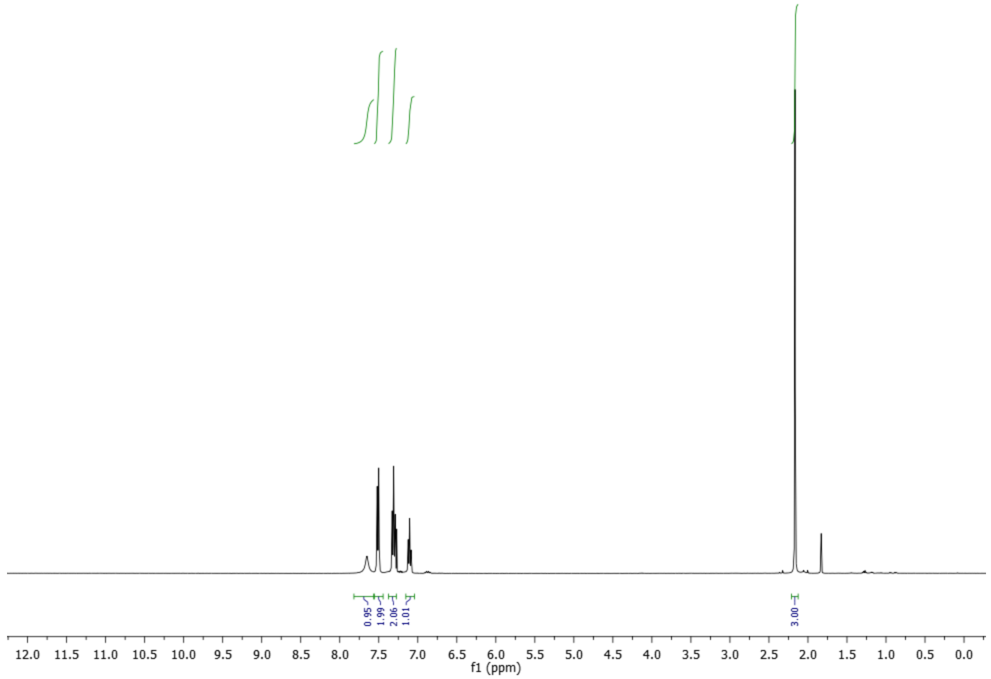


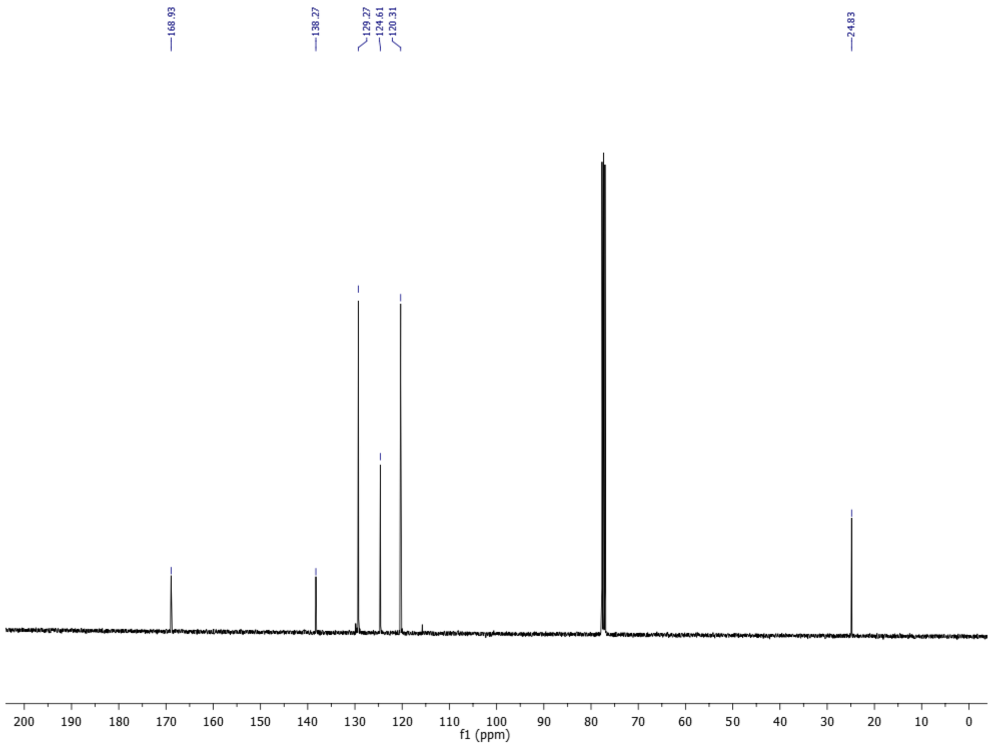




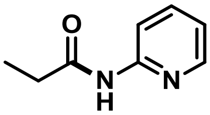
N-Phenylacetamide (**2.2.13v**) $CDCl_3$, 400 MHz:

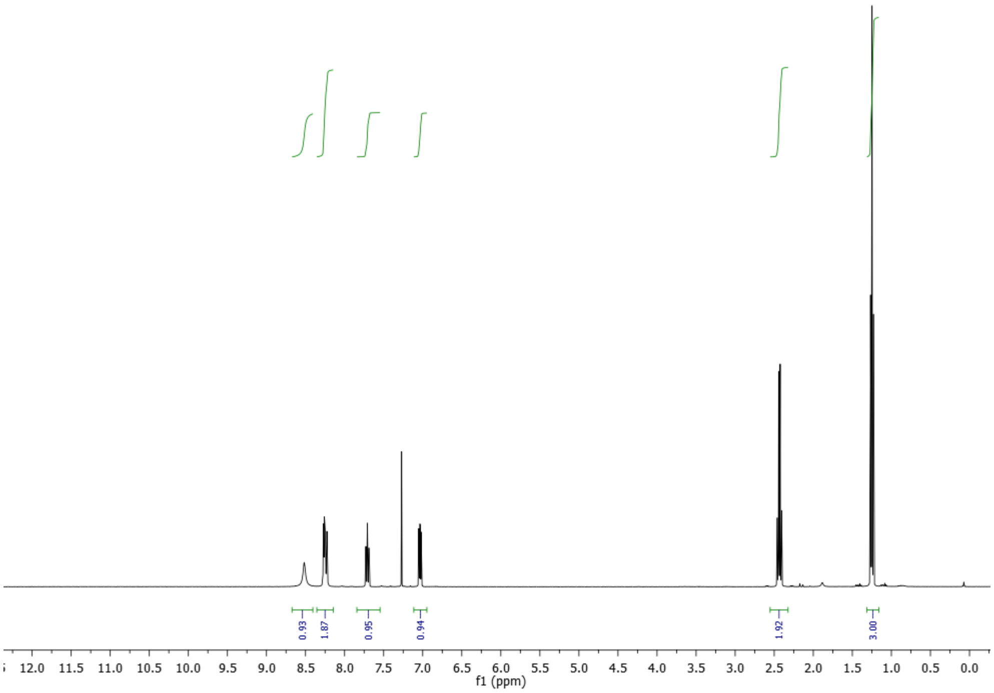


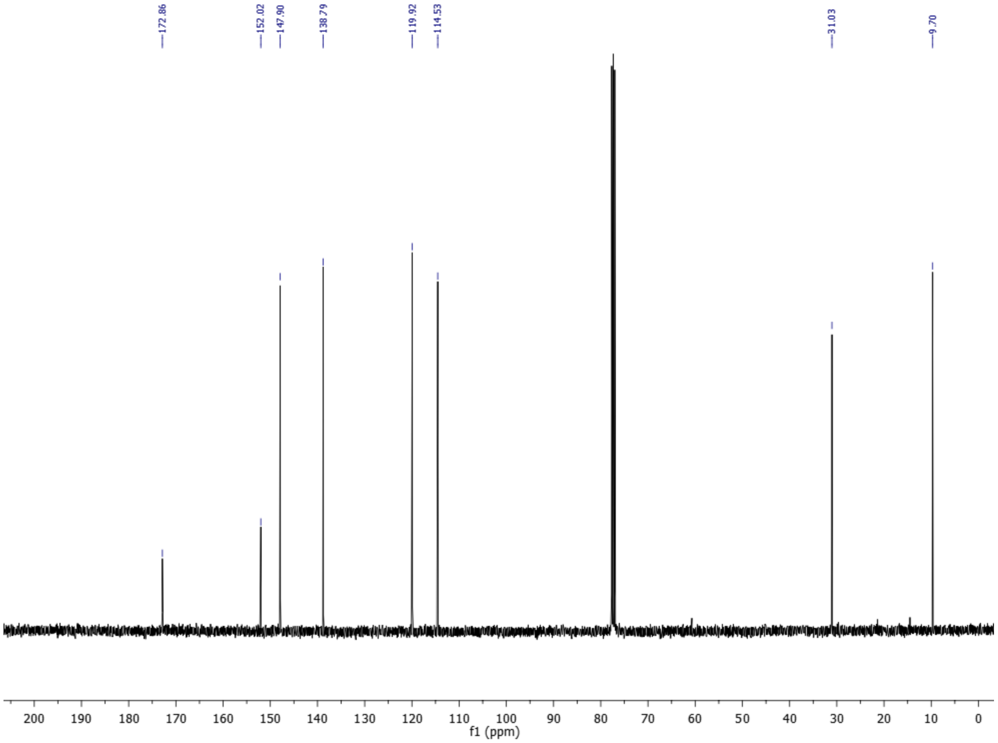




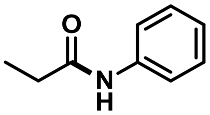
N-(Pyridin-2-yl)propionamide (**2.2.13w**) $CDCl_3$, 400 MHz:

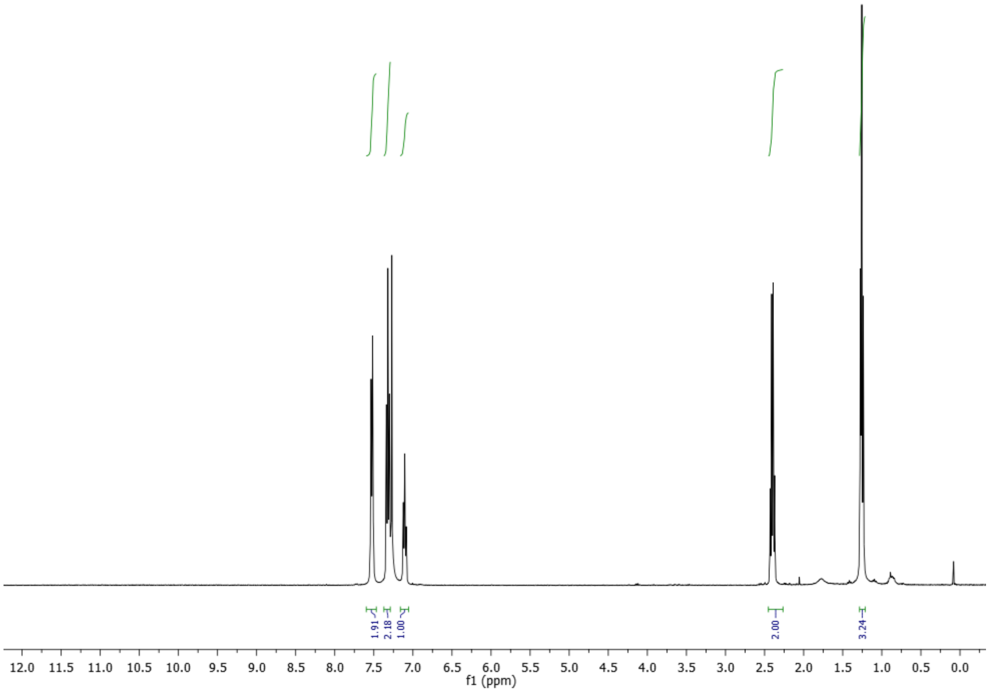


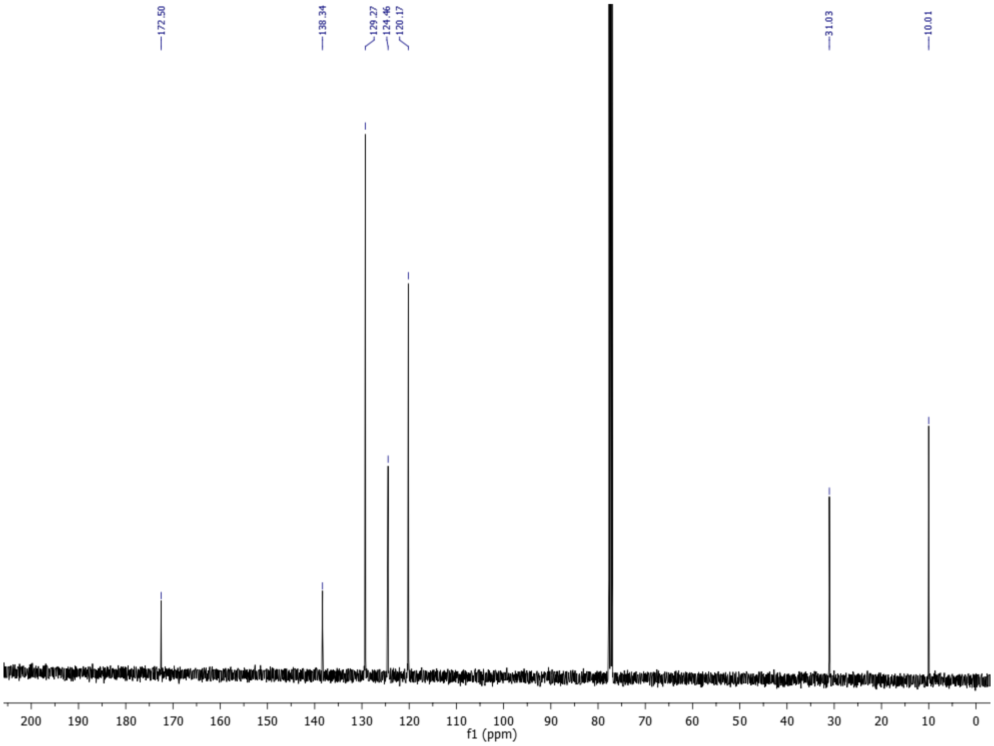




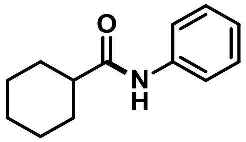
N-Phenylpropionamide (**2.2.13x**) $CDCl_3$, 400 MHz:

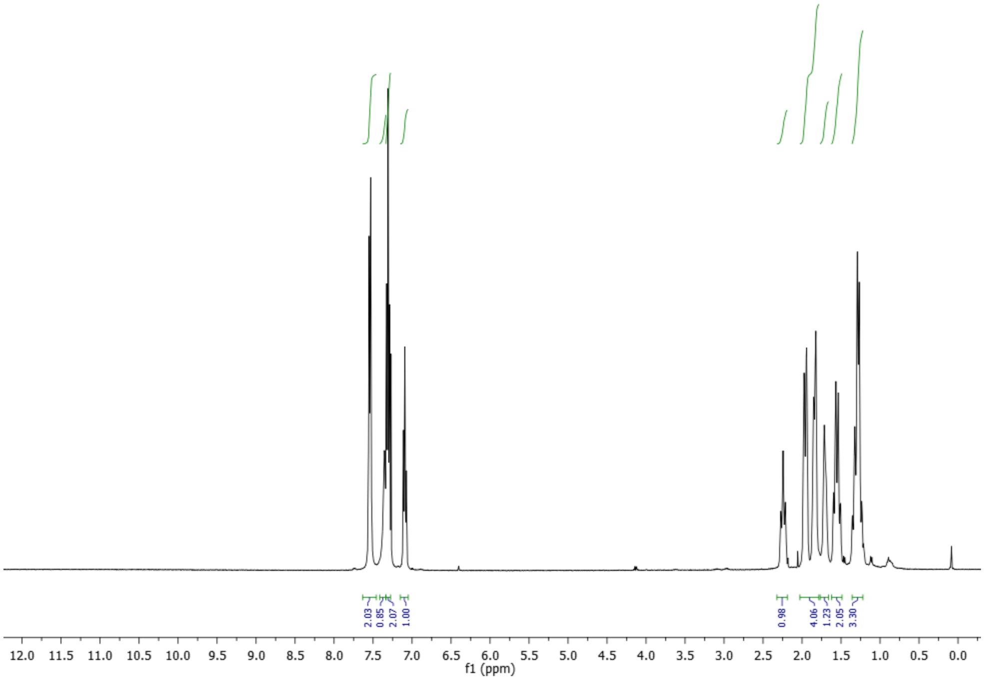


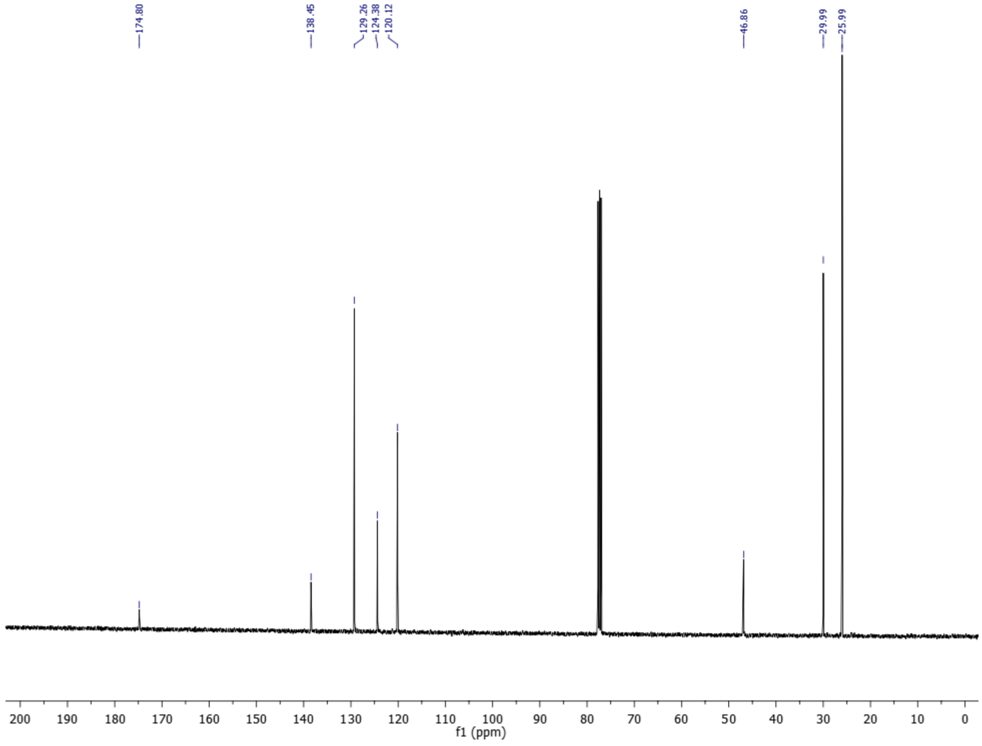




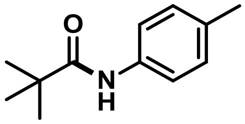
N-Phenylcyclohexanecarboxamide (**2.2.13y**) CDCl$_3$, 400 MHz:

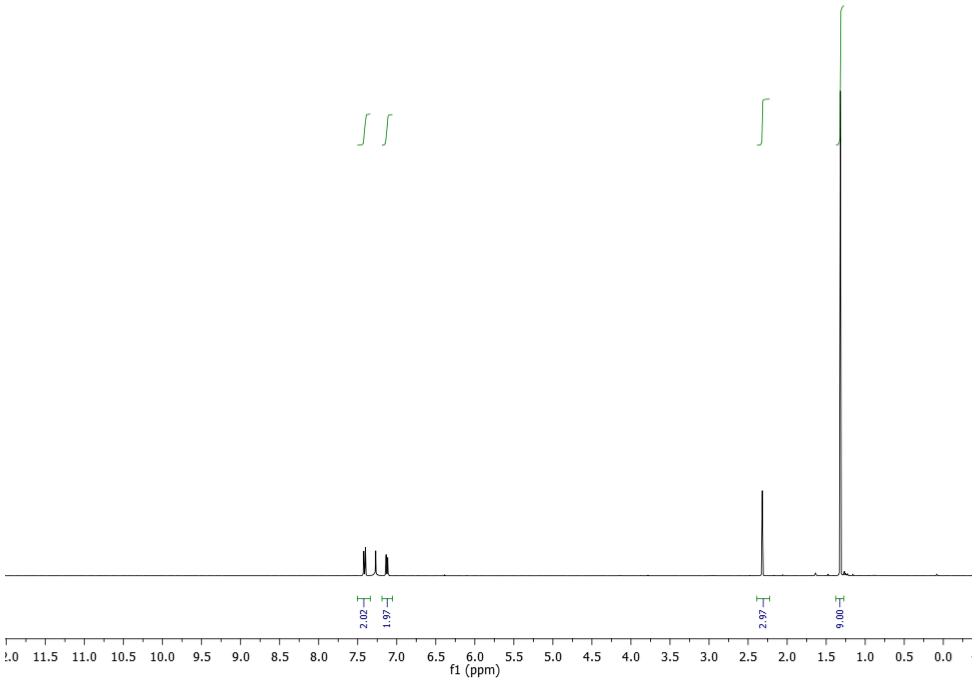


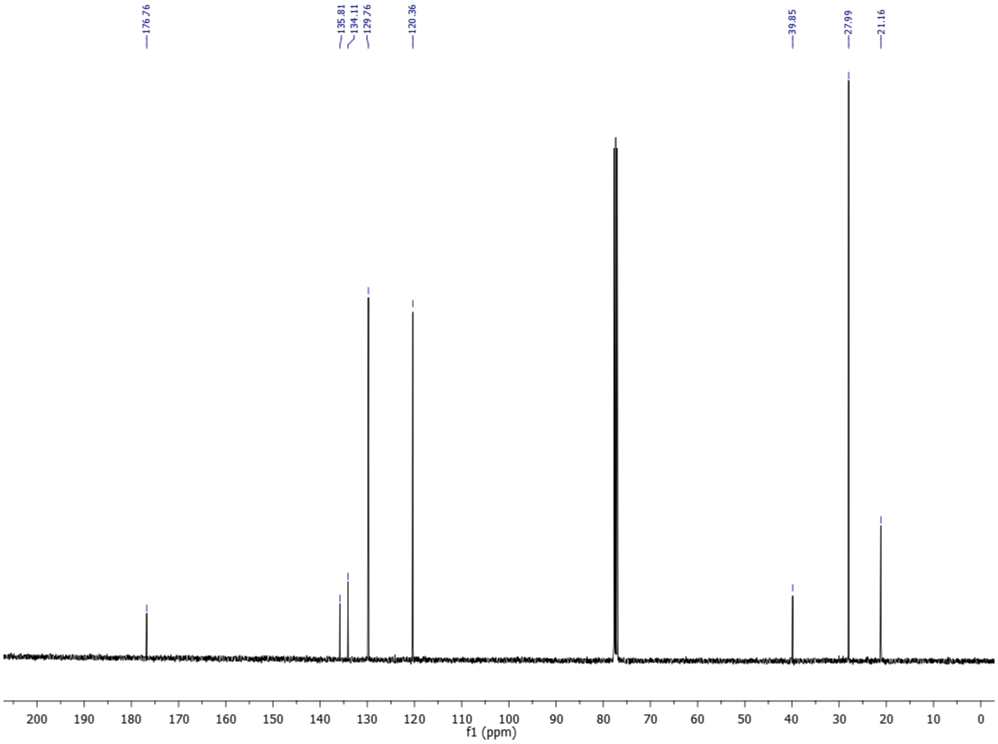




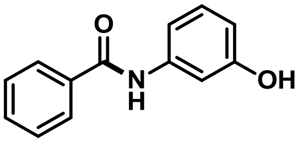
N-(*p*-Tolyl) pivalamide (**2.2.13z**) $CDCl_3$, 400 MHz:

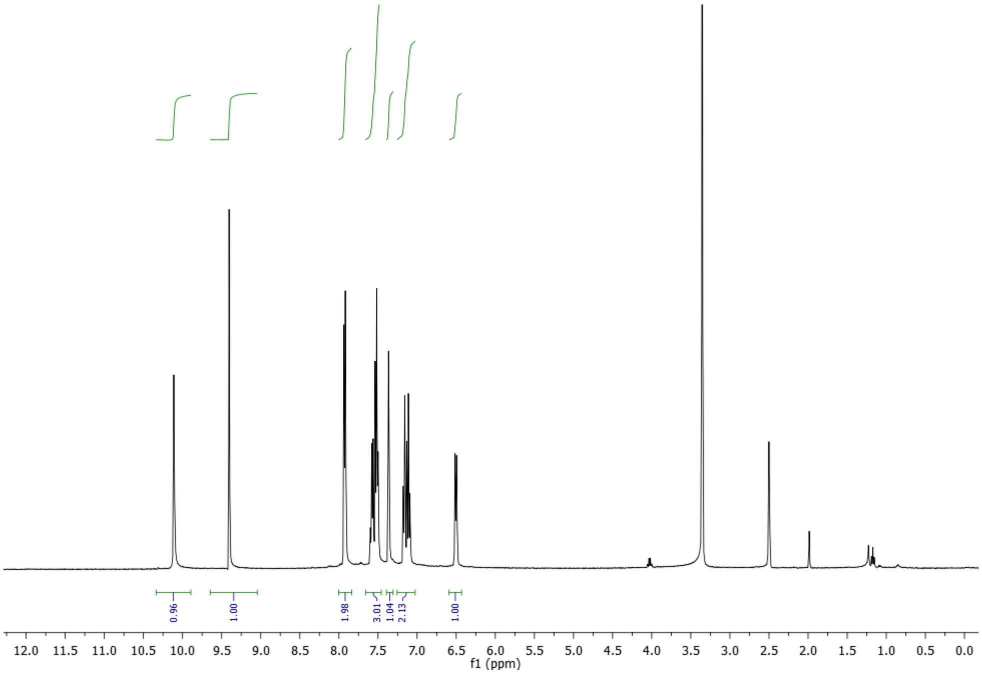


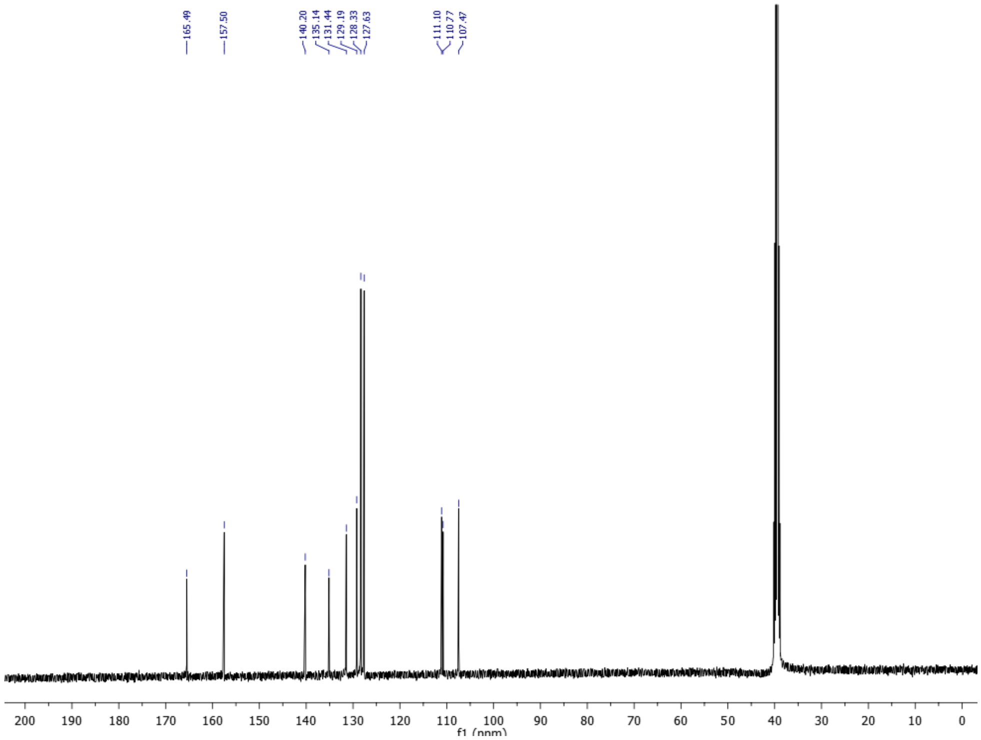




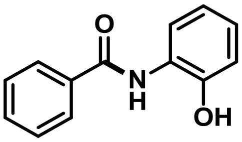
N-(3-Hydroxyphenyl)benzamide (**2.2.13aa**) DMSO, 400 MHz:

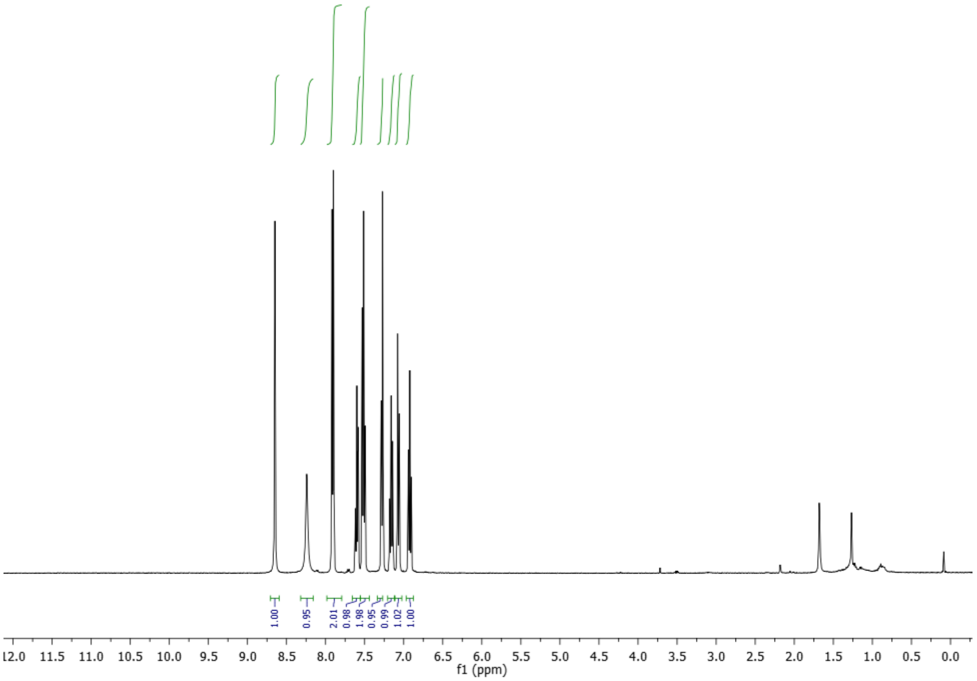


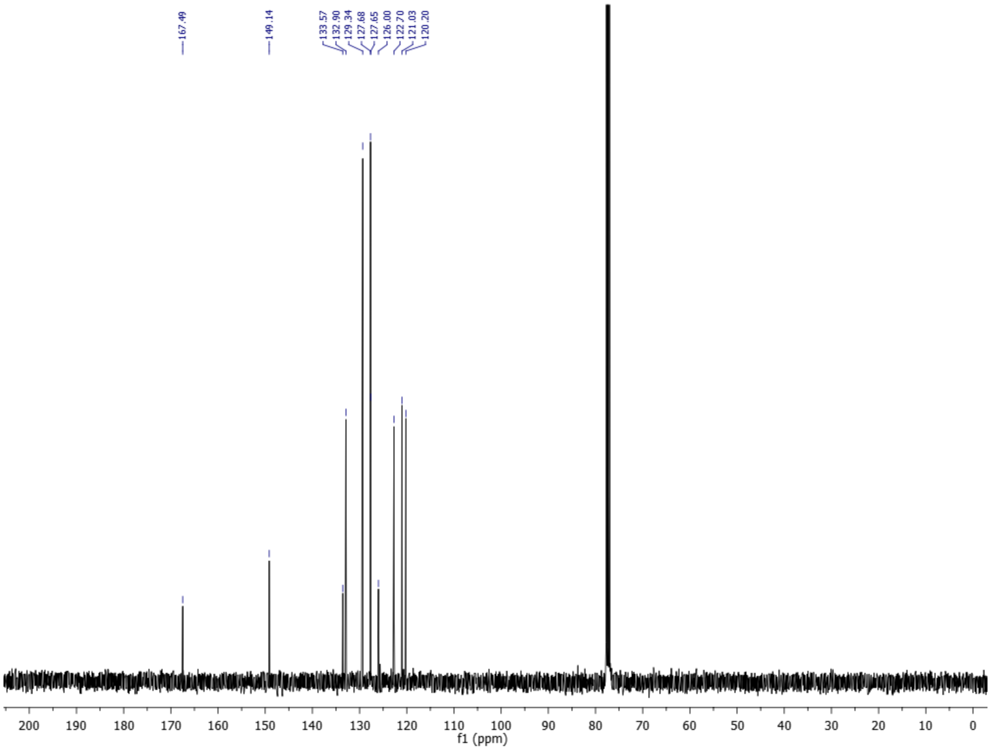




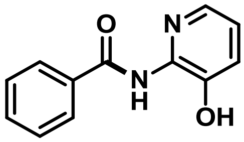
N-(2-Hydroxyphenyl)benzamide (**2.2.13ab**) CDCl$_3$, 400 MHz:

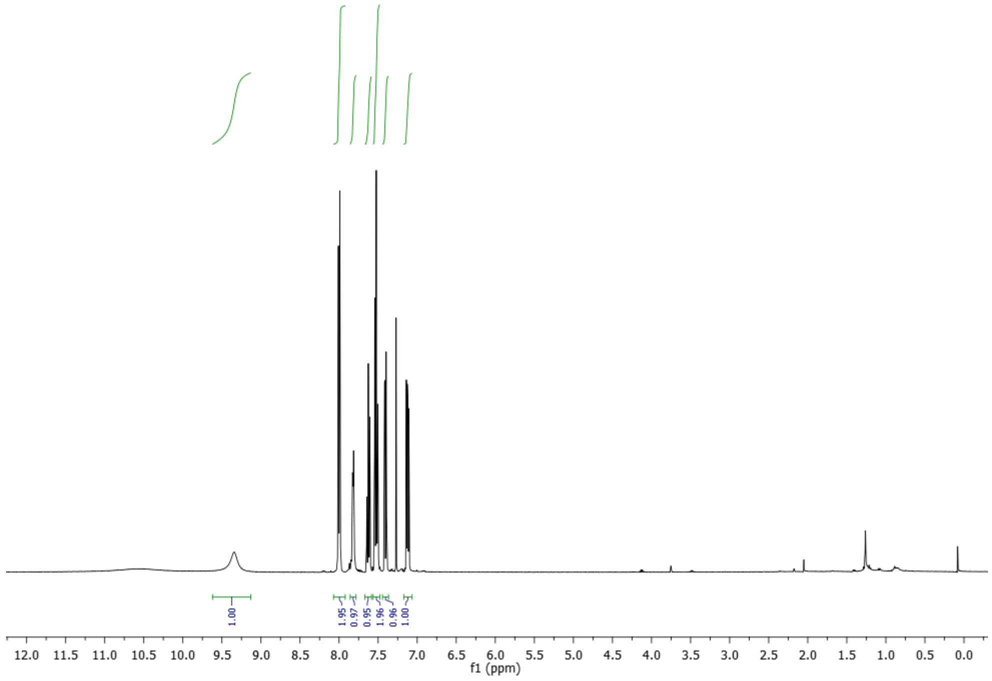


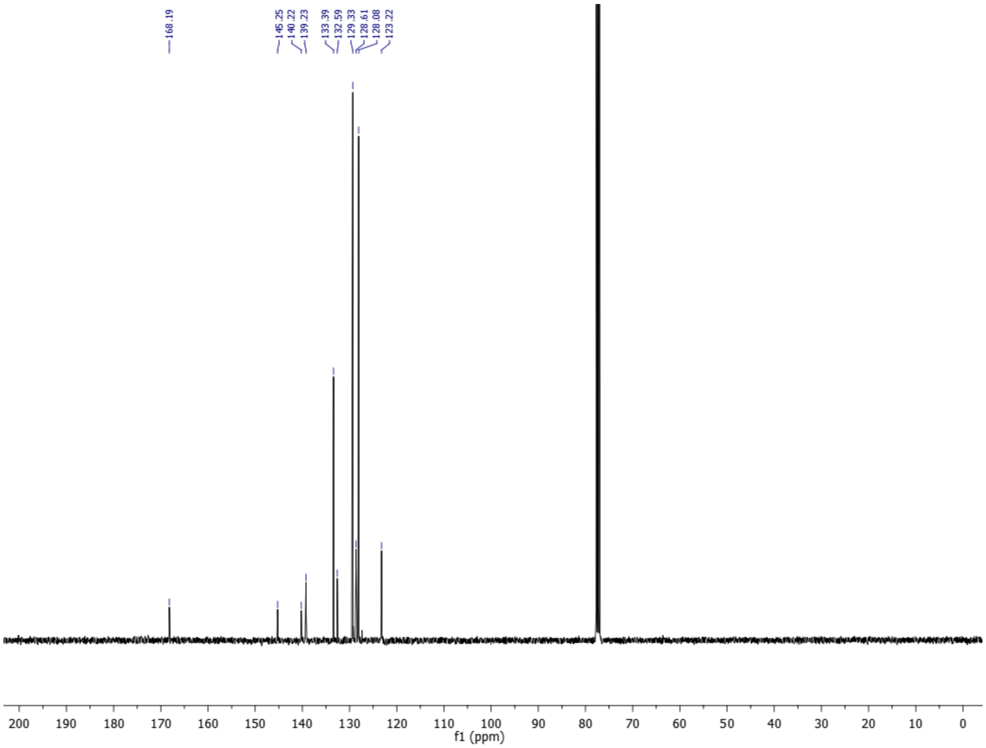




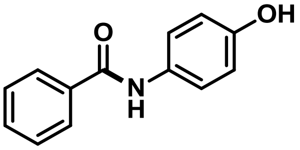
N-(3-Hydroxypyridin-2-yl)benzamide (**2.2.13ac**) CDCl$_3$, 400 MHz:

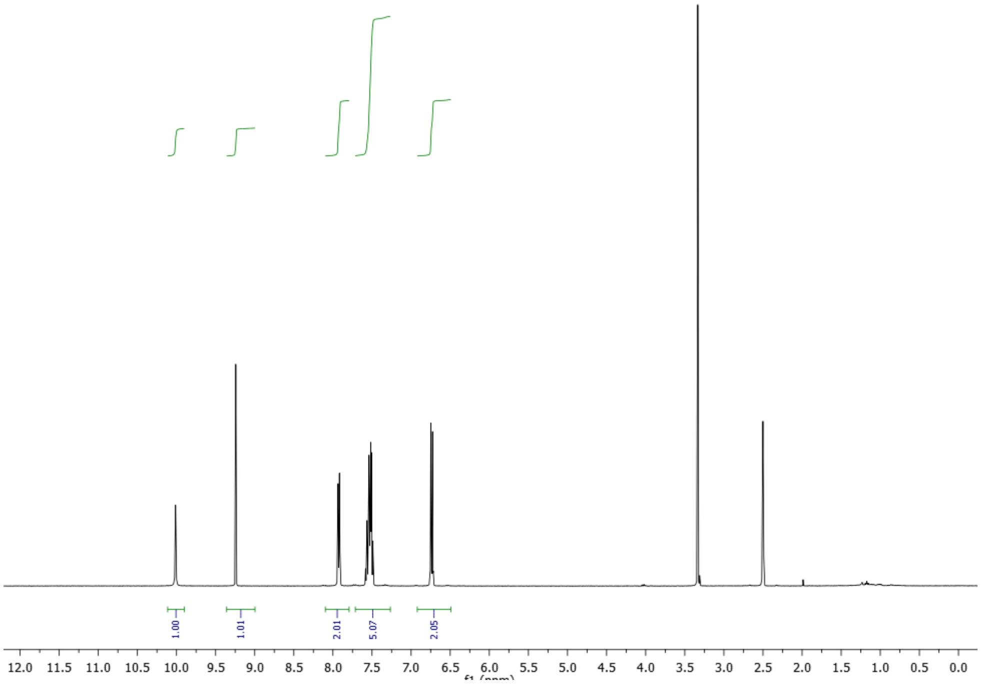


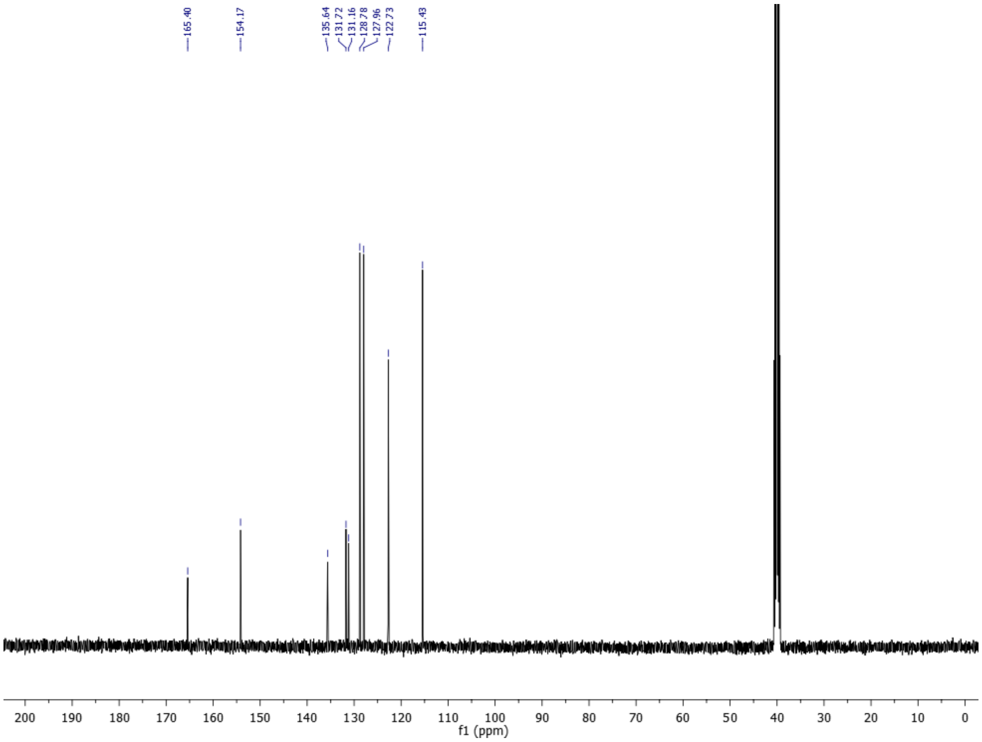




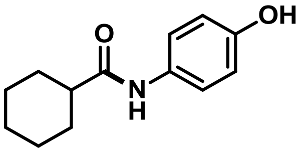
N-(4-Hydroxyphenyl)benzamide (**2.2.13ad**) DMSO, 400 MHz:

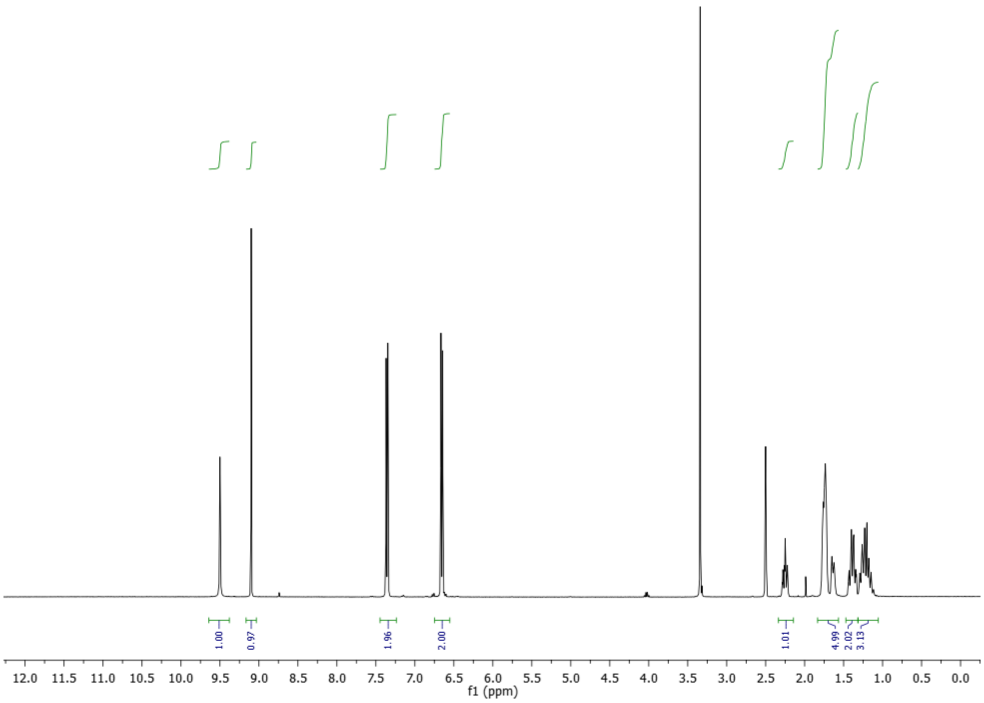


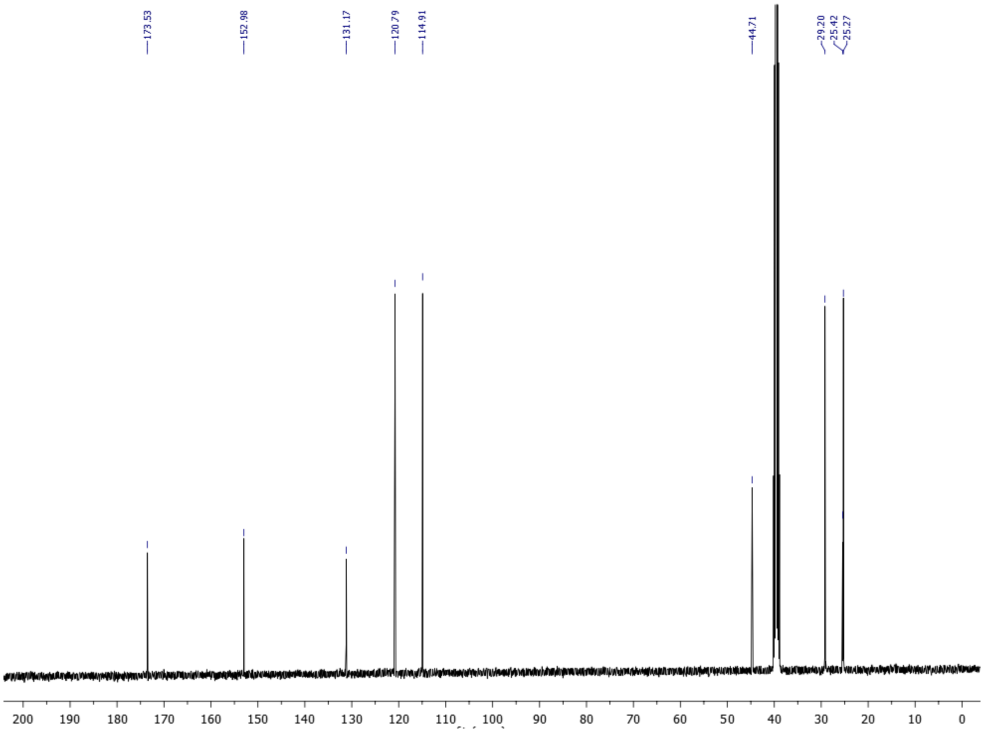




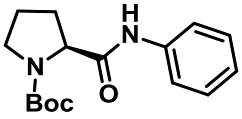
N-(4-Hydroxyphenyl)cyclohexanecarboxamide (**2.2.13ae**) DMSO, 400 MHz:

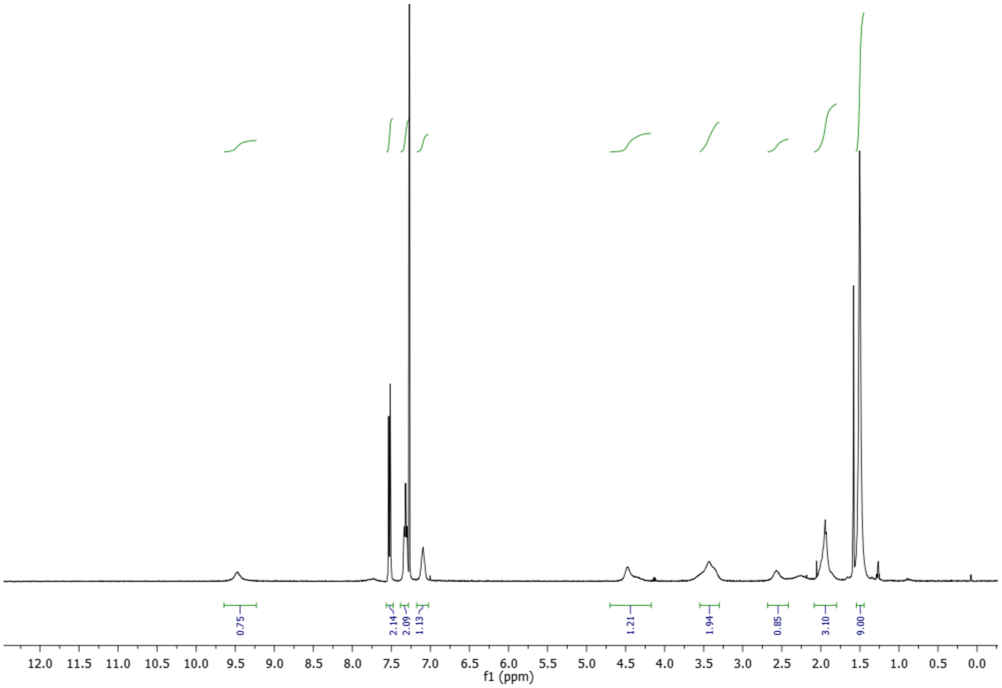


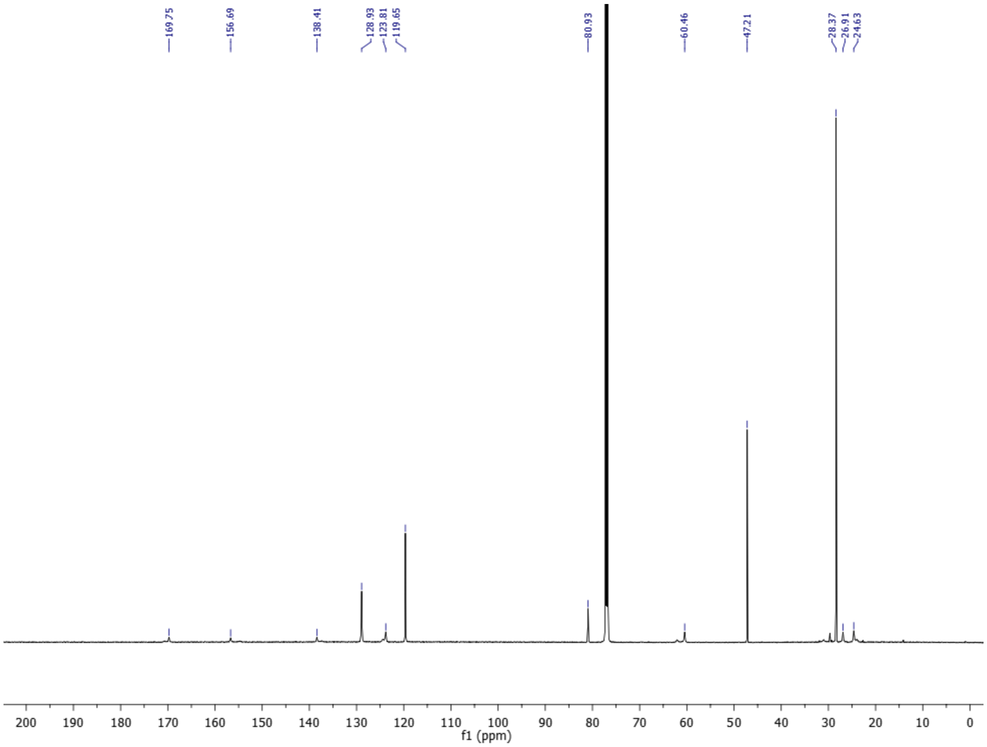




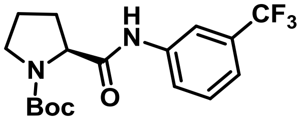
N-(4-Hydroxyphenyl)cyclohexanecarboxamide (**2.2.15a**) CDCl$_3$,(^{1}HNMR, ^{13}CNMR)=(400, 150 MHz) :

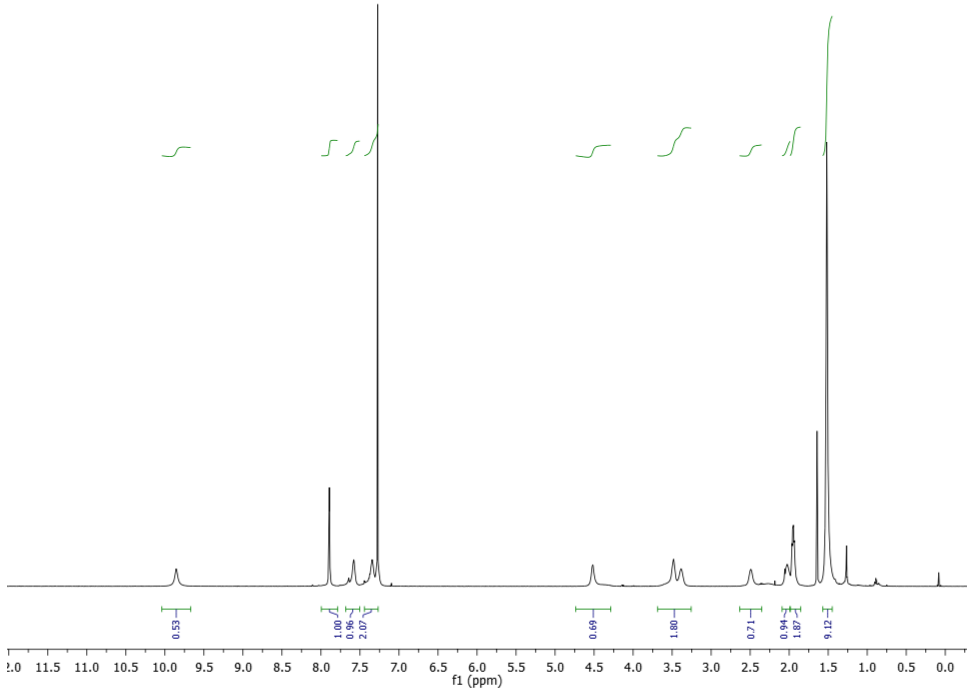


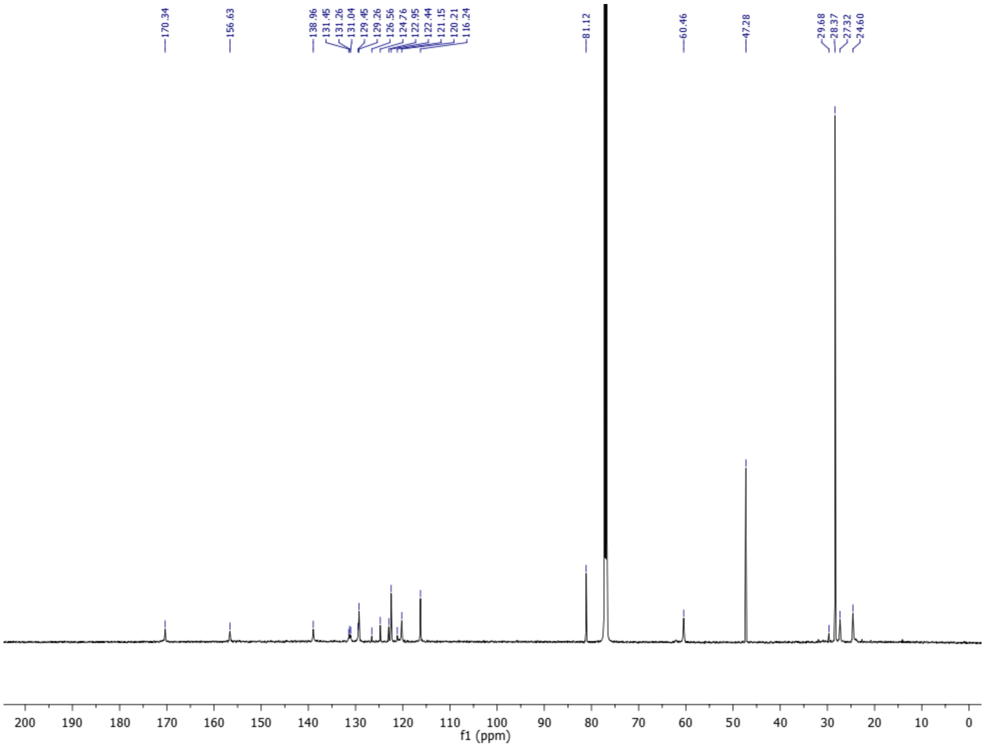




N-(4-Hydroxyphenyl)cyclohexanecarboxamide (**2.2.15b**) $CDCl_3$, 600 MHz :



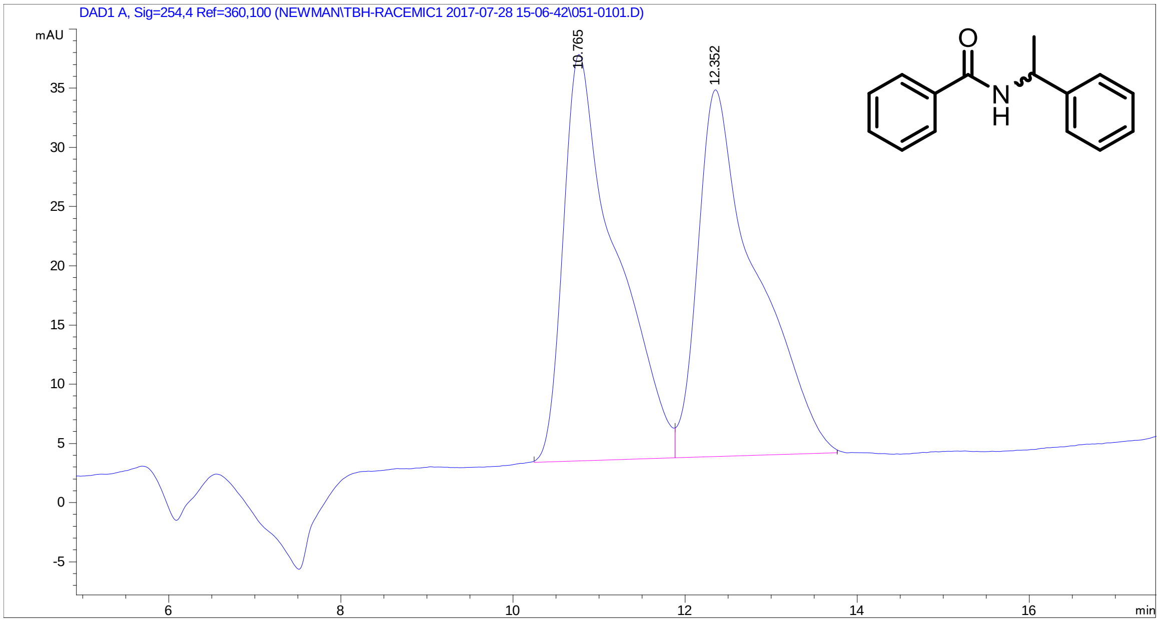




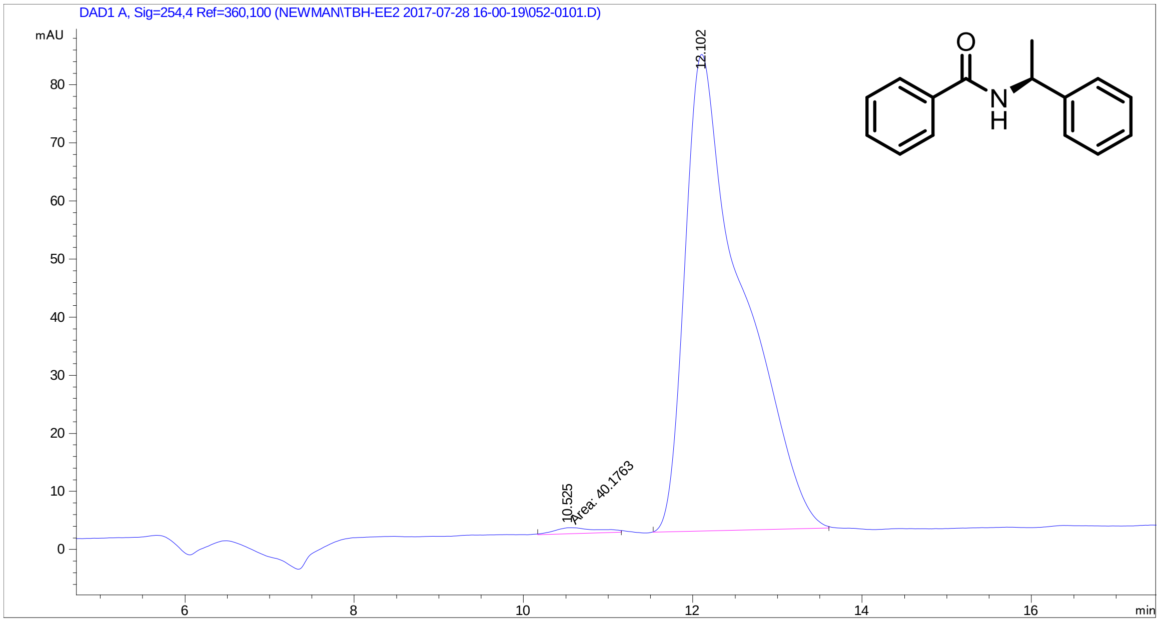
8.2 Appendix2 : ^{1}H, ^{13}C NMR spectra and HPLC traces from Chapter 3

Compound: (S)-N-(1-Phenylethyl)benzamide

Method: Chiralcel OD-H, 10% IPA in hexanes, 1.0 mL/min, 254 nm.



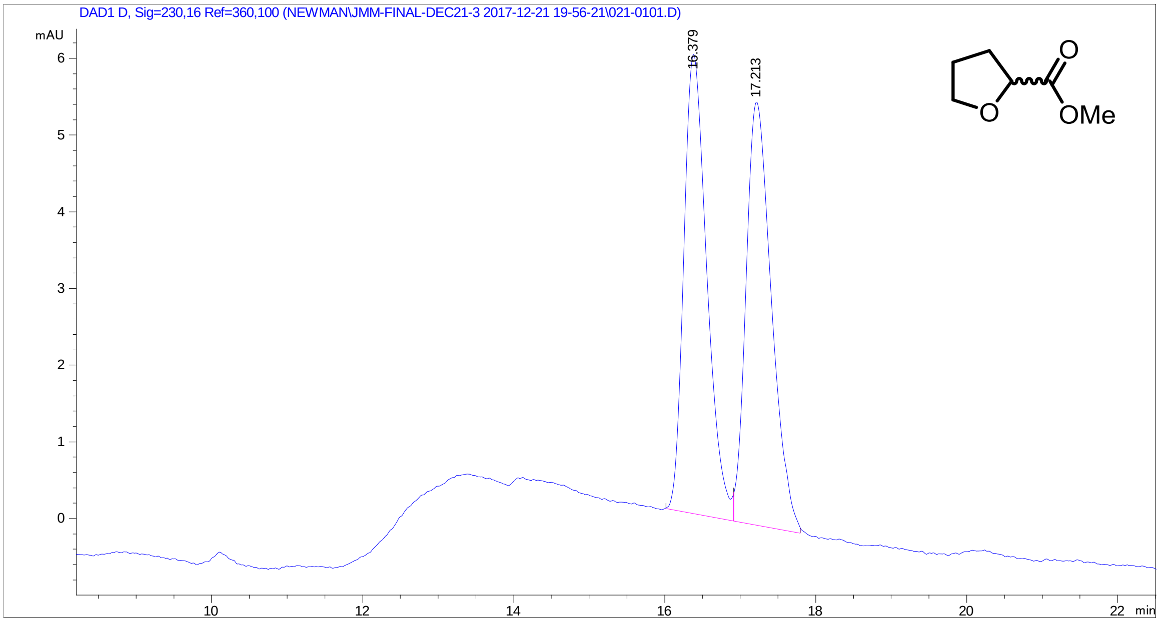
#	Time	Area	Height	Width	Area%	Symmetry
1	10.765	1464.8	34.4	0.5914	49.966	0.393
2	12.352	1466.8	31	0.66	50.034	0.402



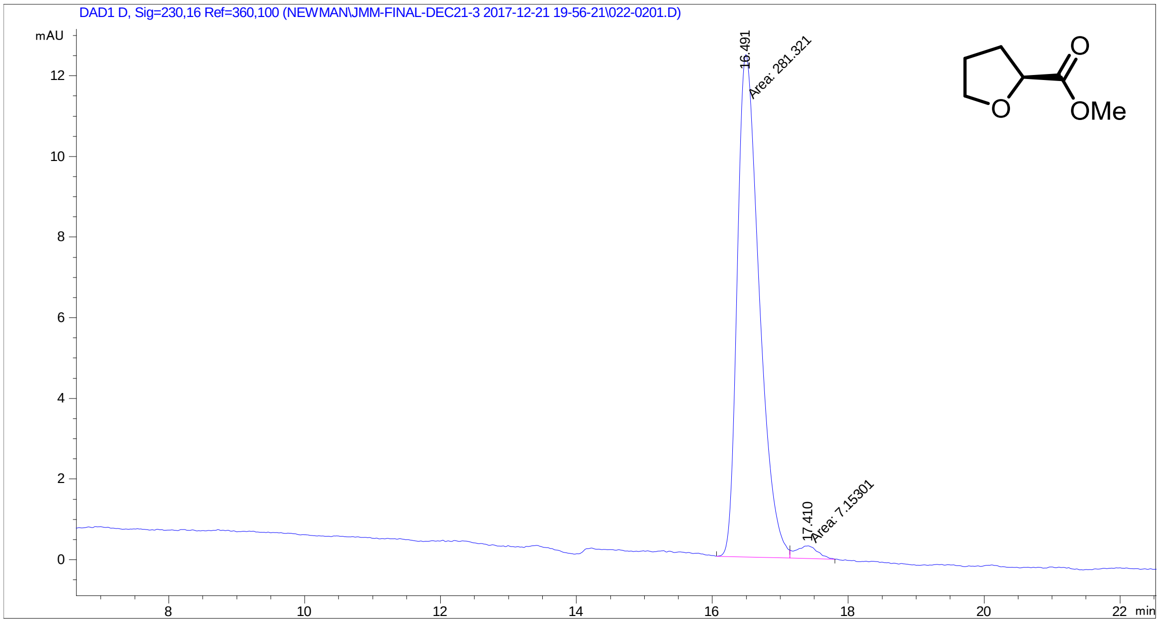
#	Time	Area	Height	Width	Area%	Symmetry
1	10.525	40.2	1.1	0.611	1.027	0.495
2	12.102	3872.7	82.1	0.6503	98.973	0.382

Compound: (S)-Methyl tetrahydrofuran-2-carboxylate

Method: Chiralcel AD-H, 1.5% IPA in hexanes, 0.80 mL/min, 230 nm.



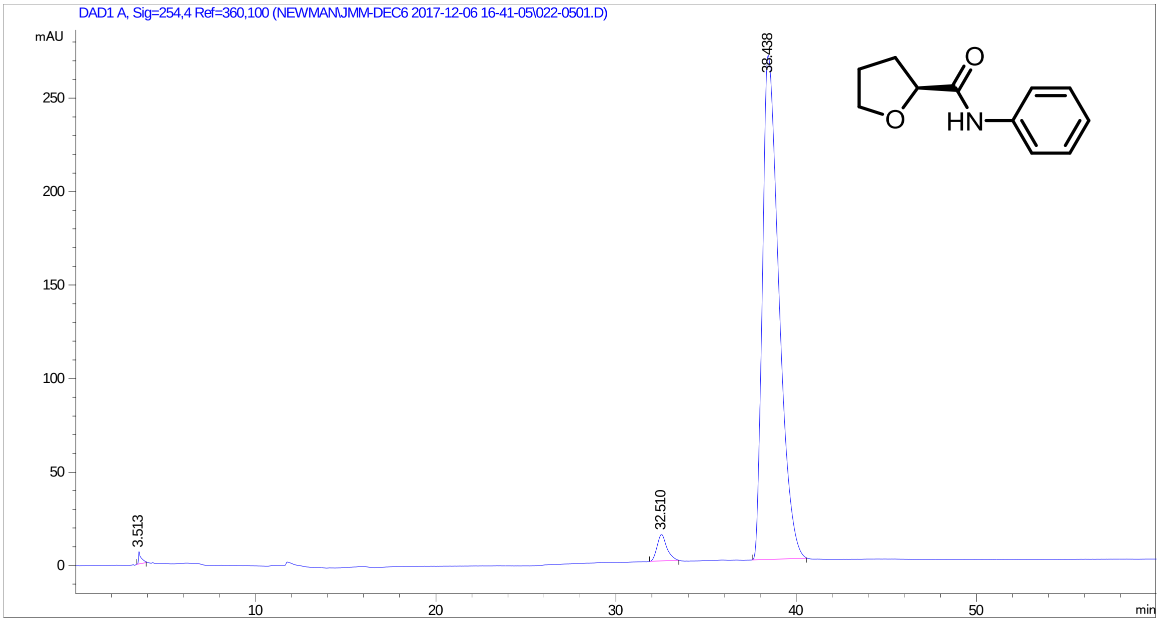
#	Time	Area	Height	Width	Area%	Symmetry
1	16.379	127.4	6	0.3242	49.595	0.683
2	17.213	129.5	5.5	0.3597	50.405	0.663



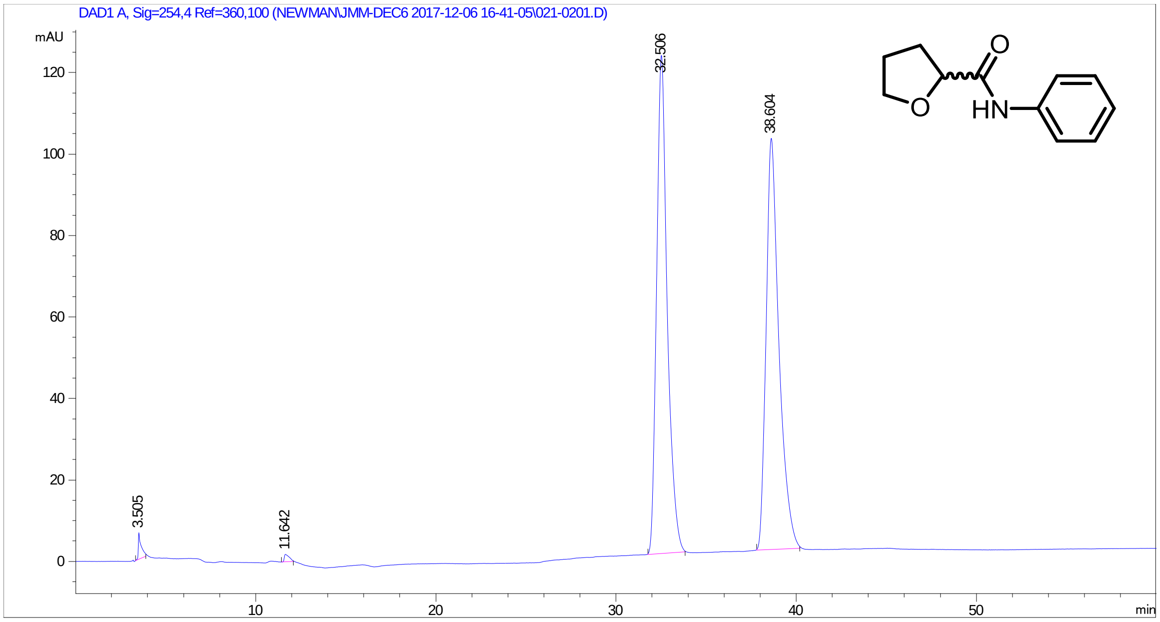
#	Time	Area	Height	Width	Area%	Symmetry
1	16.491	281.3	12.5	0.376	97.520	0.622
2	17.41	7.2	3.2E-1	0.3438	2.480	0.222

Compound: (S)-N-Phenyloxolane-2-carboxamide

Method: Chiracel AD-H, 2% → 5% IPA in hexanes, 1.0 mL/min, 254 nm.



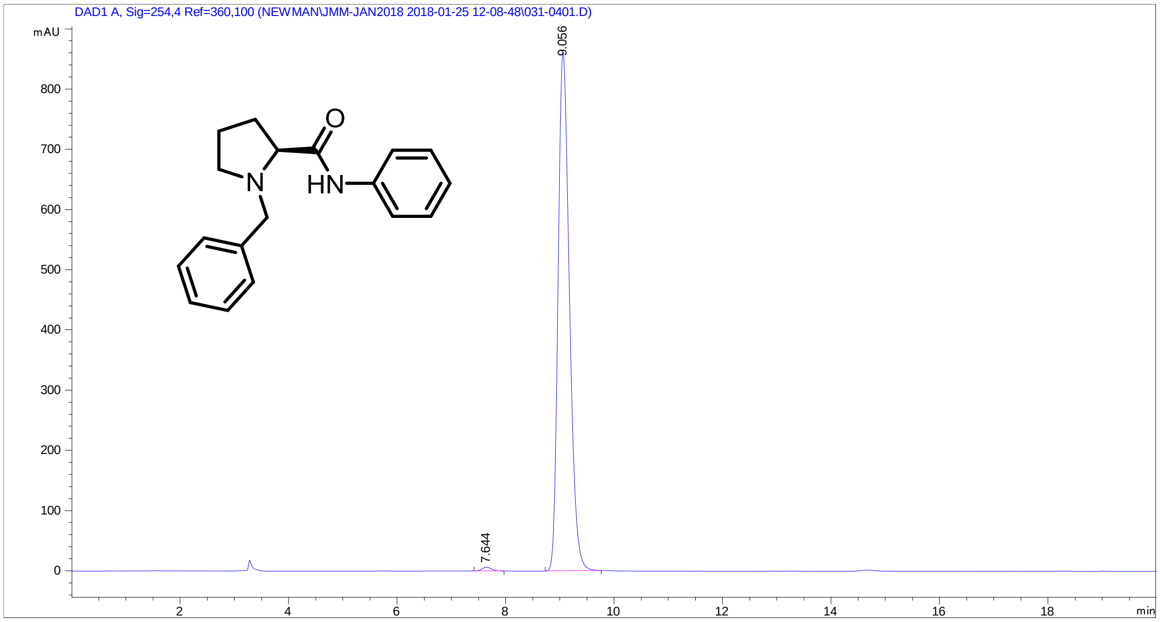
#	Time	Area	Height	Width	Area%	Symmetry
1	32.51	551.7	14.3	0.5585	3.109	0.753
2	38.438	17191.9	269.7	0.9536	96.891	0.51



#	Time	Area	Height	Width	Area%	Symmetry
1	32.506	5017.5	122.3	0.6025	50.015	0.752
2	38.604	5014.5	101	0.7134	49.985	0.622

Compound: (S)-1-Benzyl-N-phenylpyrrolidine-2-carboxamide

Method: Chiracel AD-H, 7% IPA in hexanes, 1.0 mL/min flow rate, 254 nm.



#	Time	Area	Height	Width	Area%	Symmetry
1	7.644	78.8	6.3	0.1899	0.625	0.826
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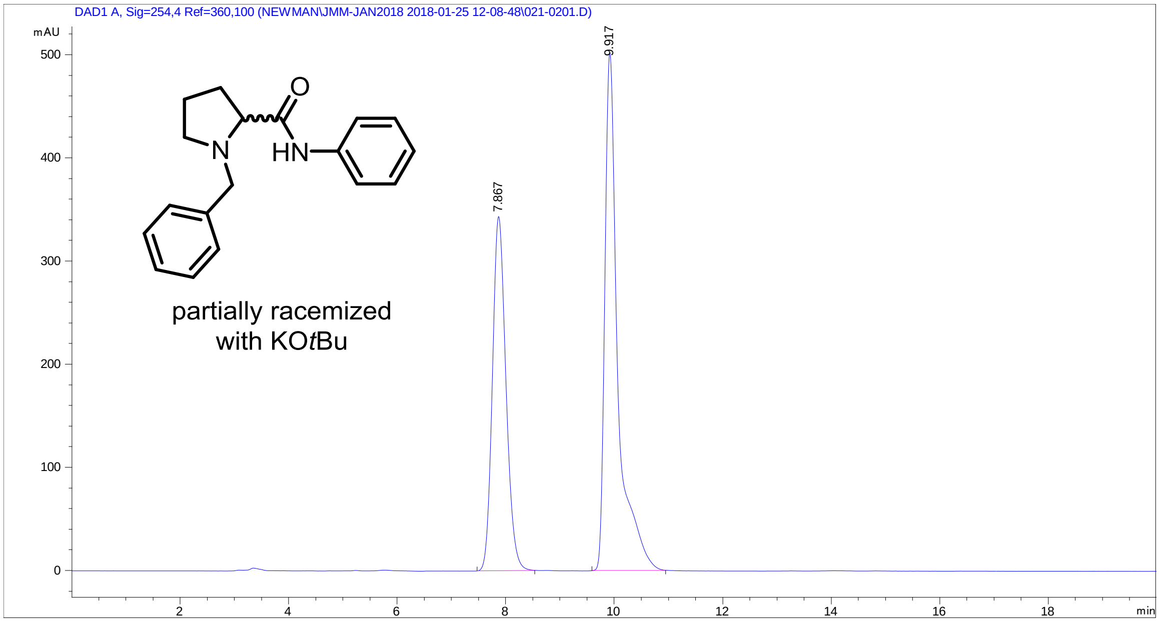
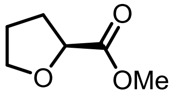


#	Time	Area	Height	Width	Area%	Symmetry
1	7.867	5960.4	343.6	0.2664	41.599	0.801
2	9.917	8367.8	502.6	0.2462	58.401	0.544

(S)-Methyl tetrahydrofuran-2-carboxylate (**3.84**). $CDCl_3$, 400 MHz:



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Current Data Parameters
NAME     JMM-06-30-1A-DRY-13C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_          20180408
Time               0.54
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               51200
SOLVENT          CDCl3
NS                 512
DS                   0
SWH          24038.461 Hz
FIDRES        0.469501 Hz
AQ           1.0649600 sec
RG                  64
DW              20.800 usec
DE                6.00 usec
TE               300.0 K
D1          1.00000000 sec
d11         0.03000000 sec
DELTA       0.89999998 sec
TD0                  1

======== CHANNEL f1 ========
NUC1               13C
P1                7.40 usec
PL1              -3.00 dB
SFO1       100.6706101 MHz

======== CHANNEL f2 ========
CPDPRG[2           waltz16
NUC2                    1H
PCPD2             90.00 usec
PL2               -4.00 dB
PL12              13.72 dB
PL13              18.01 dB
SFO2       400.3216013 MHz

F2 - Processing parameters
SI               65536
SF         100.6605356 MHz
WDW                 EM
SSB      0
LB                1.00 Hz
GB       0
PC                1.40
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Current Data Parameters
NAME     JMM-06-30-1A-DRY-1H
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
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Time               0.33
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               49152
SOLVENT          CDCl3
NS                  16
DS                   0
SWH           6421.233 Hz
FIDRES        0.130640 Hz
AQ           3.8273025 sec
RG                80.6
DW              77.867 usec
DE                6.00 usec
TE               297.9 K
D1          1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                1H
P1               11.70 usec
PL1              -4.00 dB
SFO1       400.3223900 MHz

F2 - Processing parameters
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WDW                 EM
SSB      0
LB                0.10 Hz
GB       0
PC                1.00
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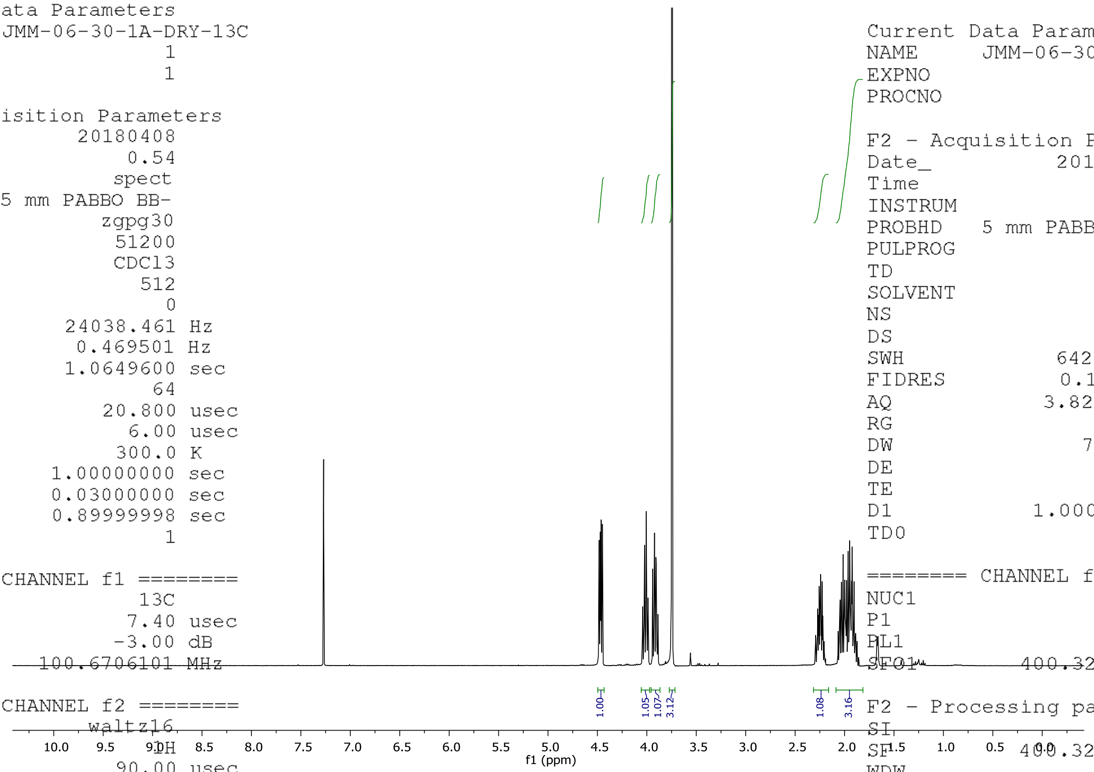
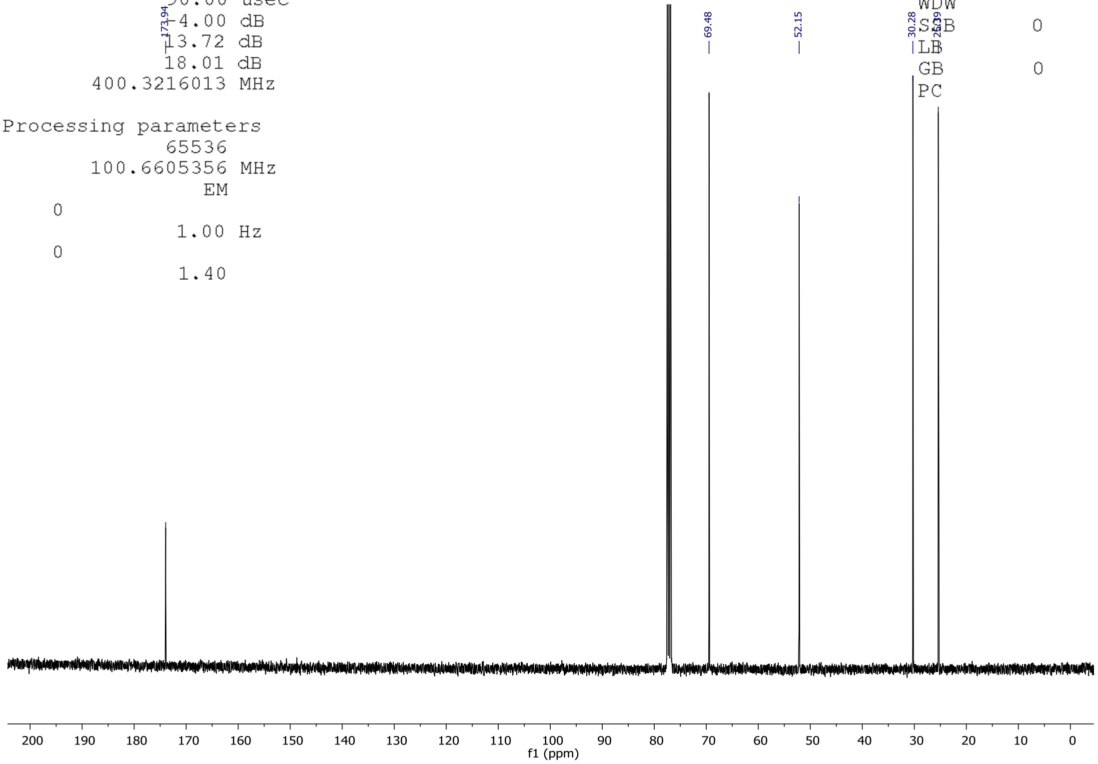
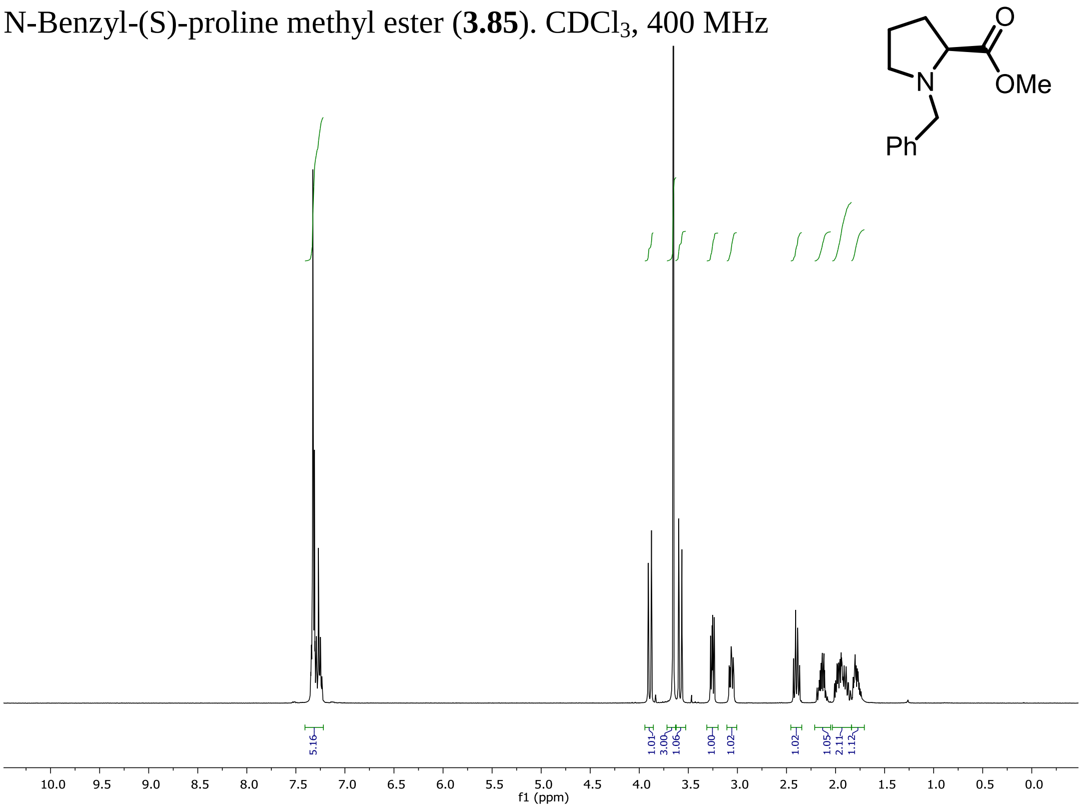
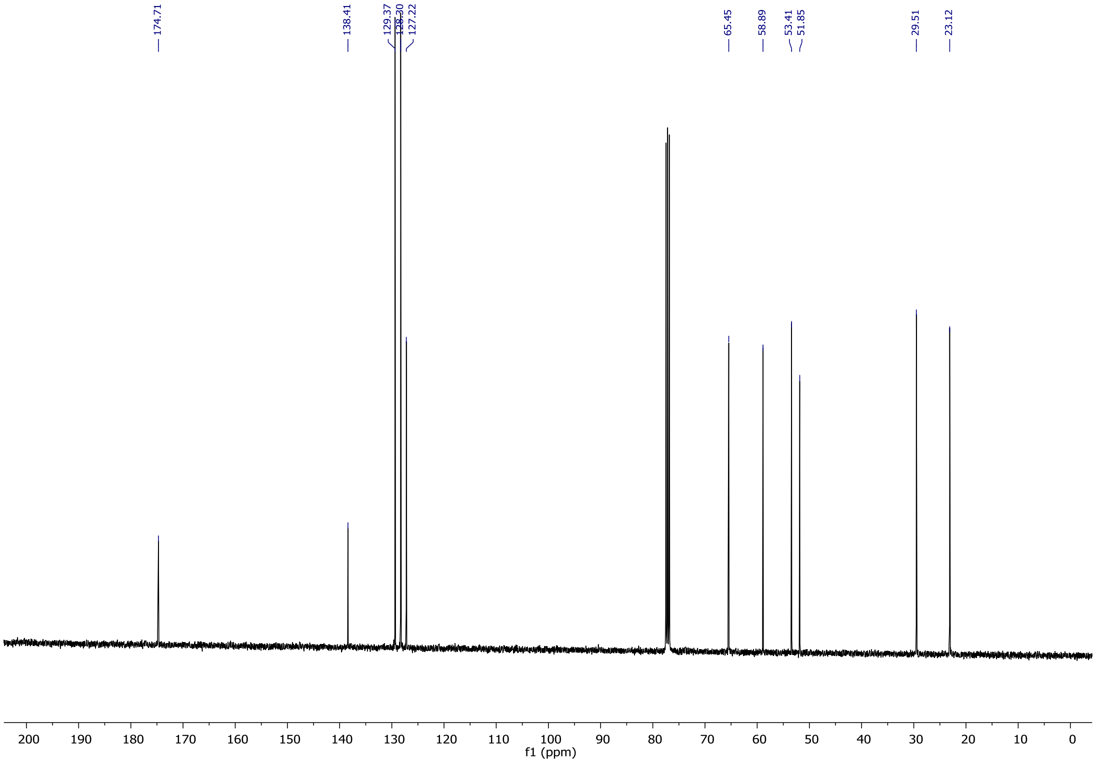


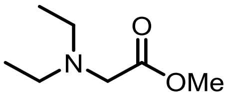


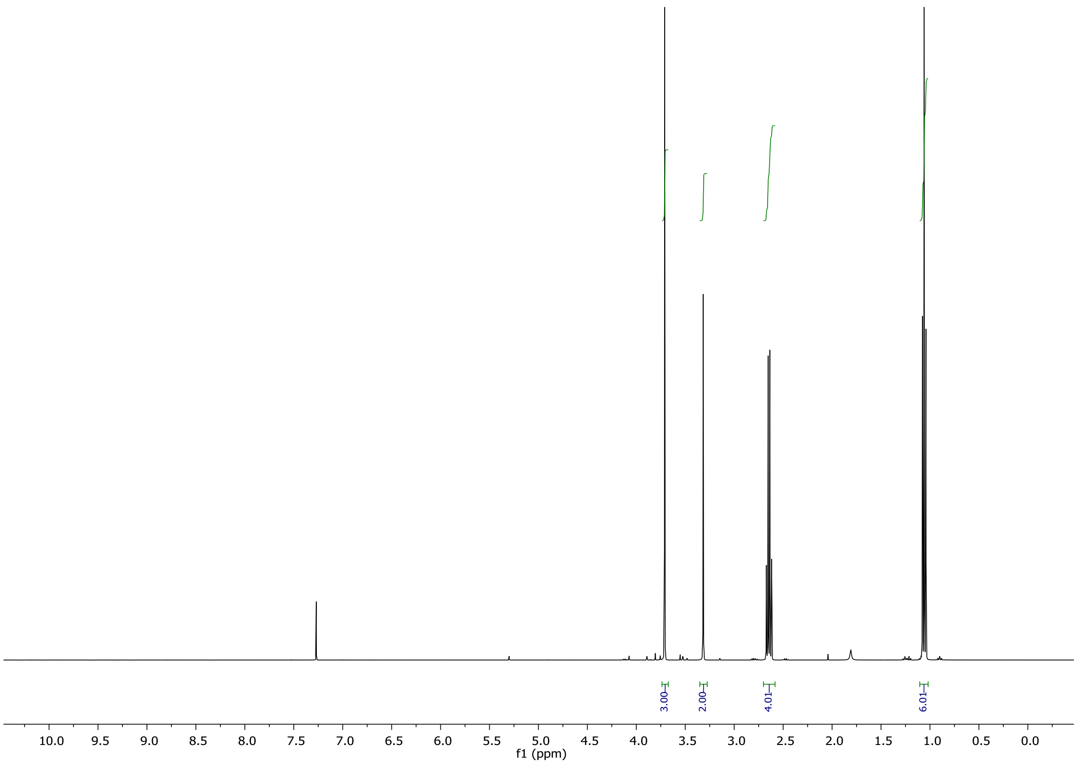
N-Benzyl-(S)-proline methyl ester (**3.85**). CDCl$_3$, 400 MHz

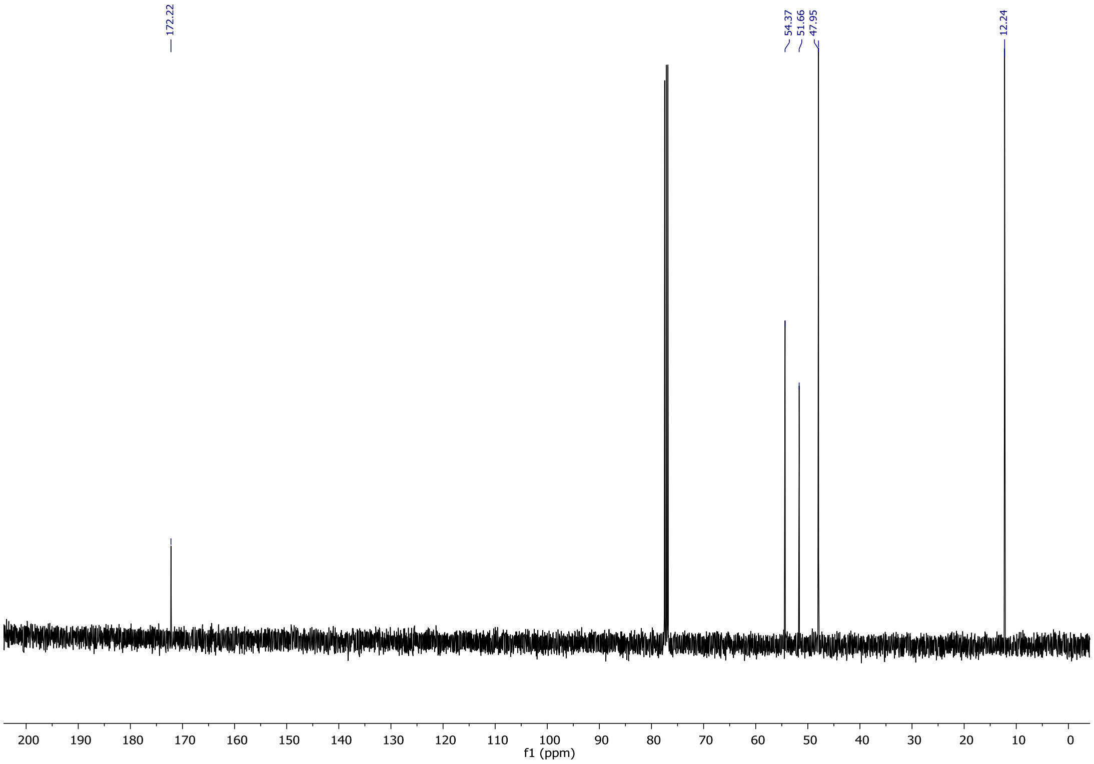




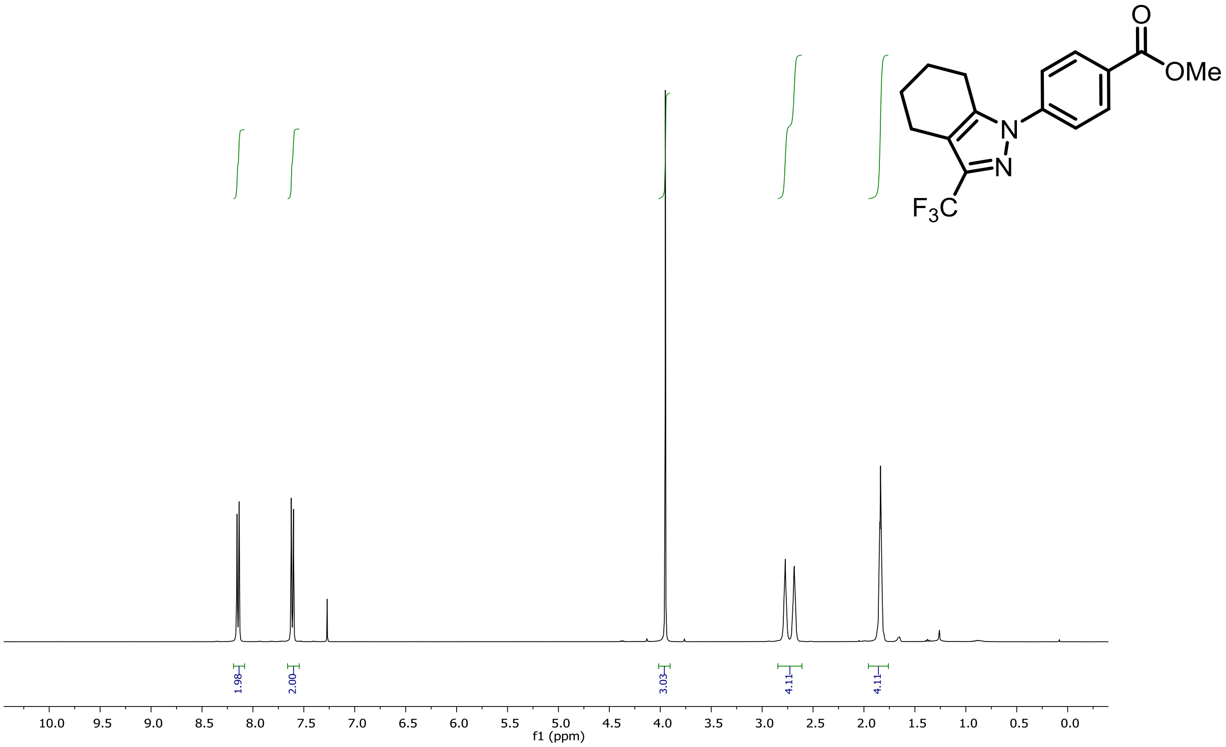
N, N-Diethylglycine methyl ester (**3.74**). CDCl$_3$, 400MHz\

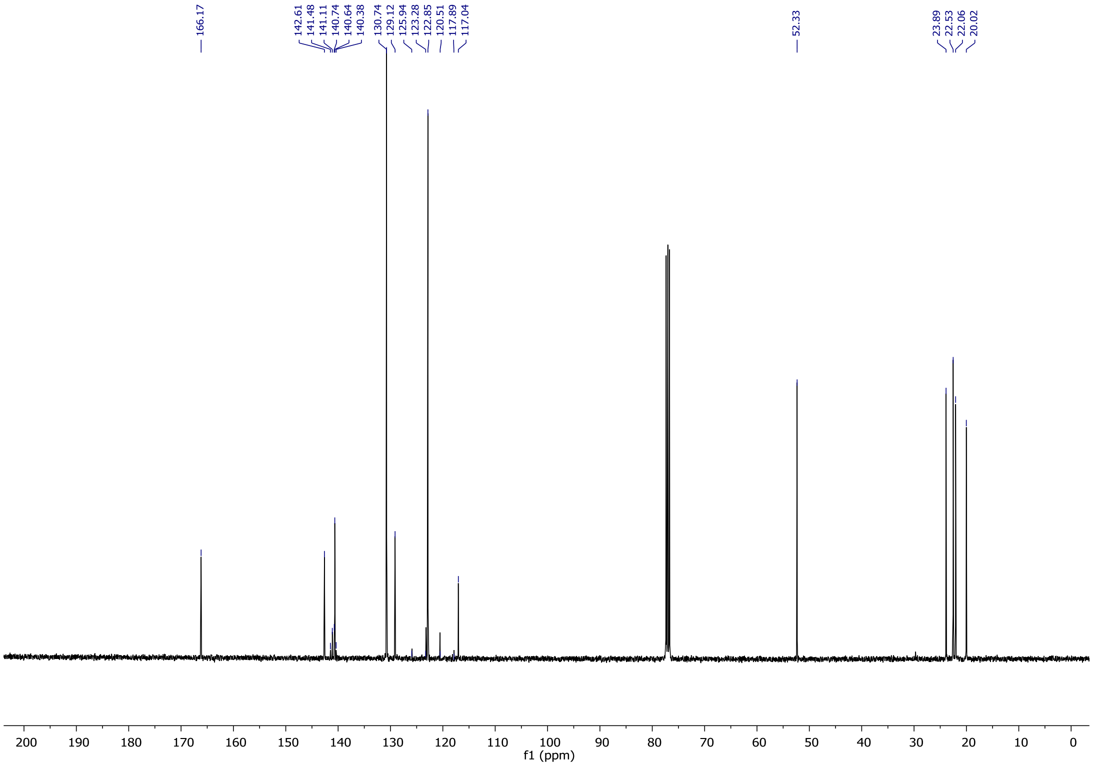




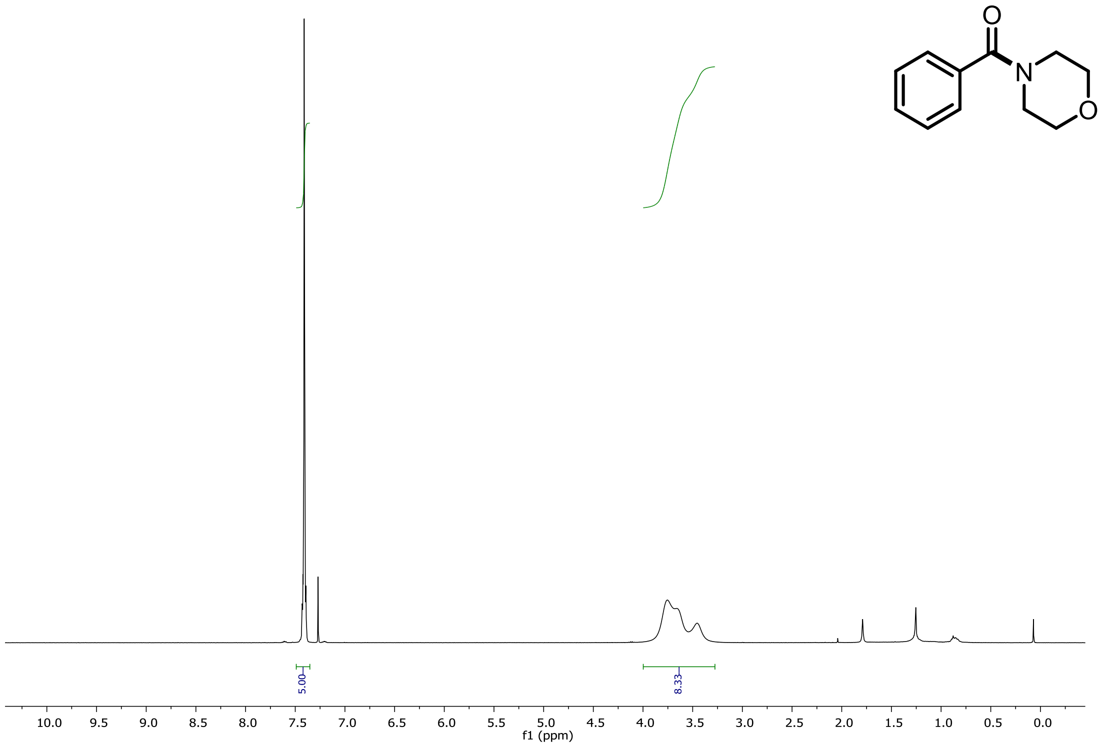


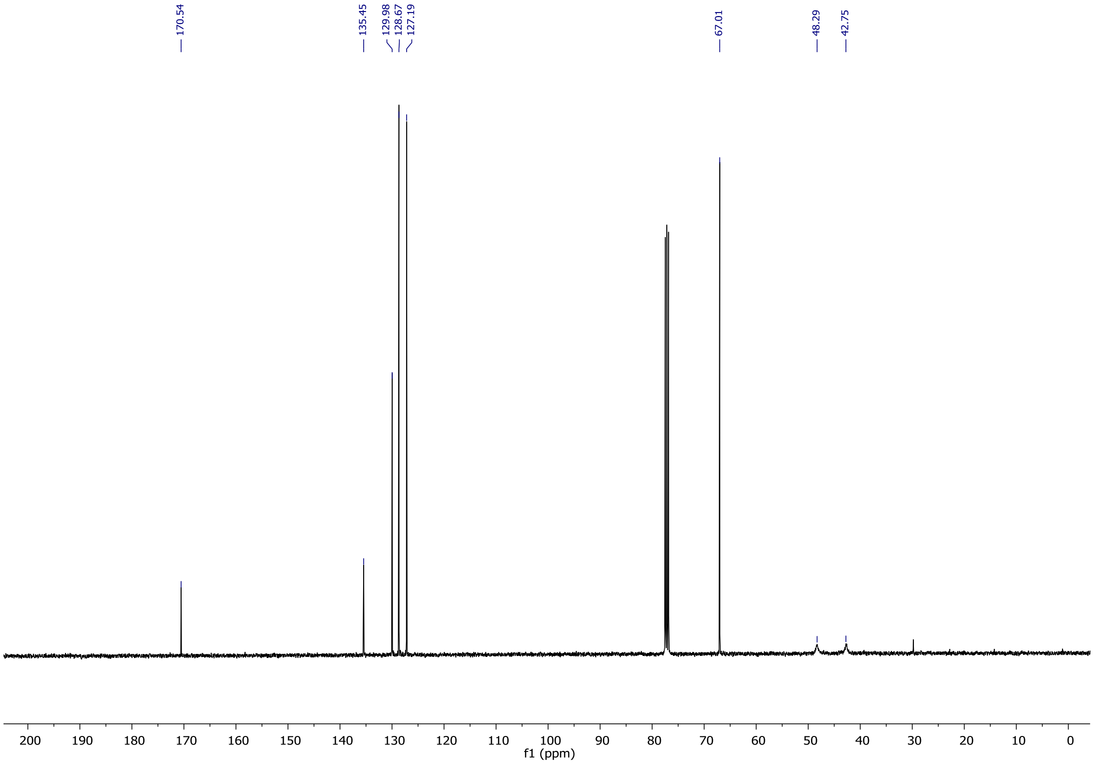
Methyl 4-[3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzoate (**3.9**). $CDCl_3$, 400 MHz:



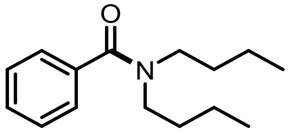


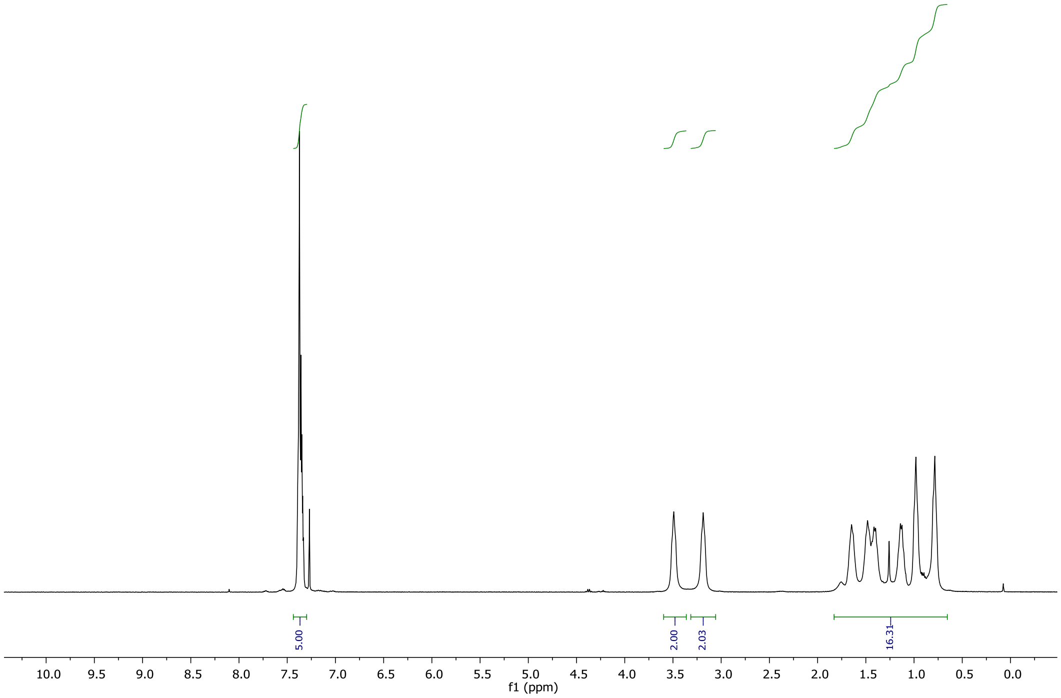
Benzoylmorpholine (**3.16**). CDCl$_3$, 400 MHz:

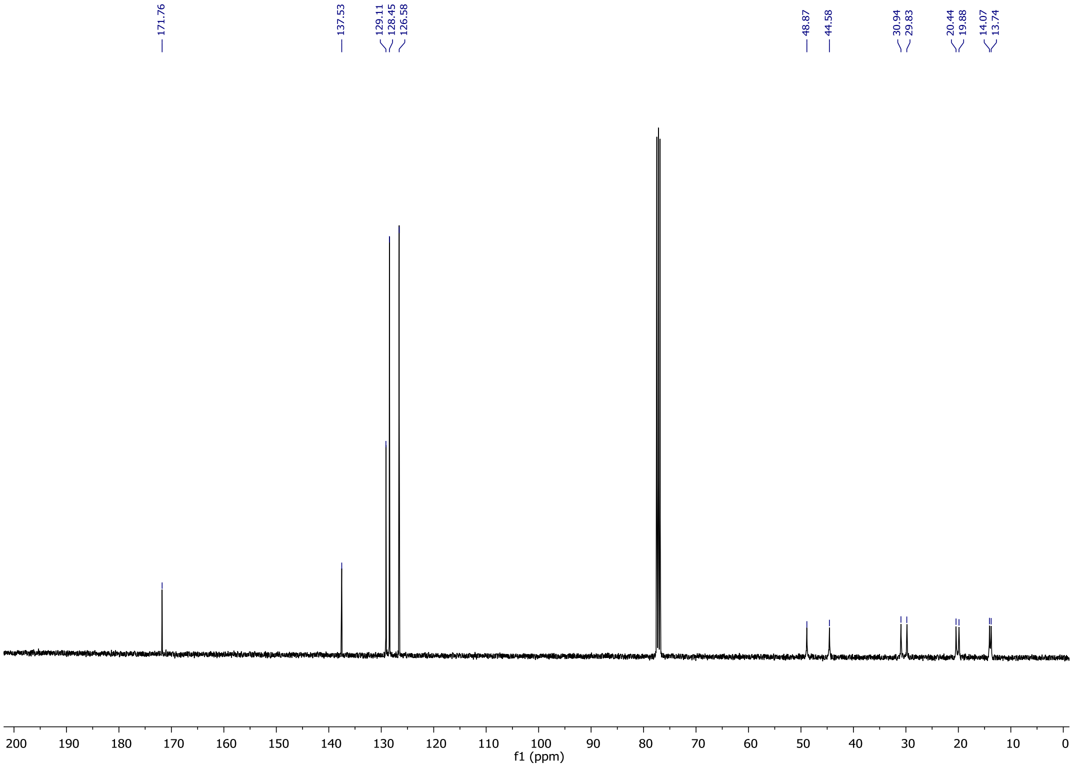




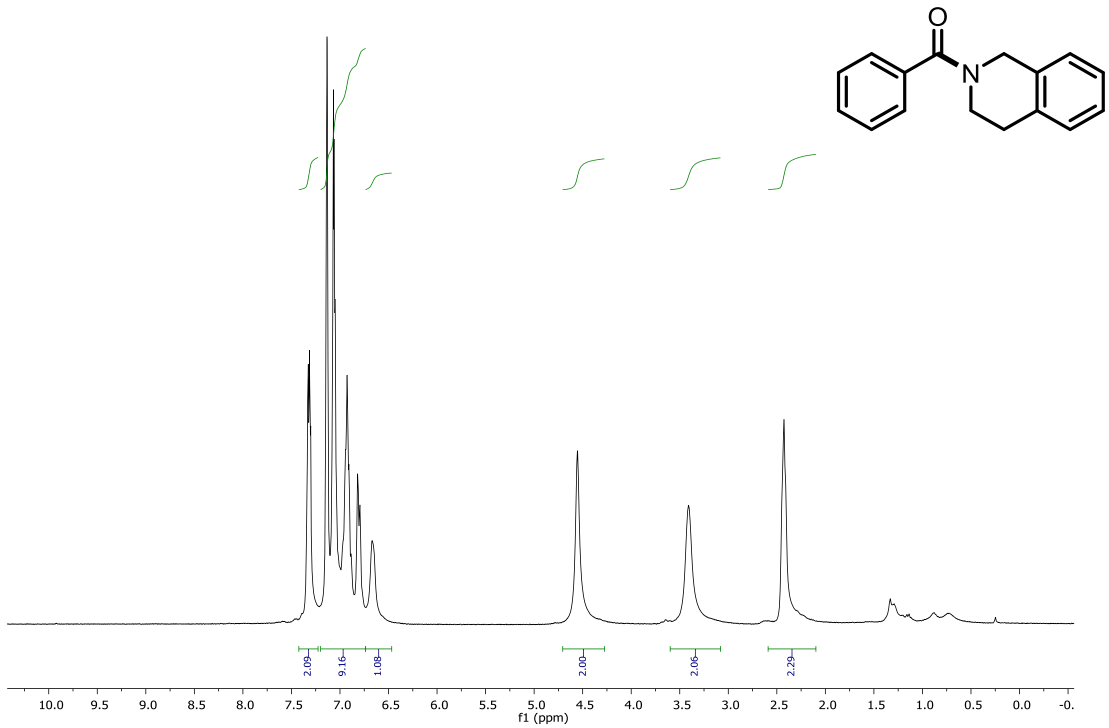
N,N-Dibutylbenzamide (**3.27**). $CDCl_3$, 400 MHz:

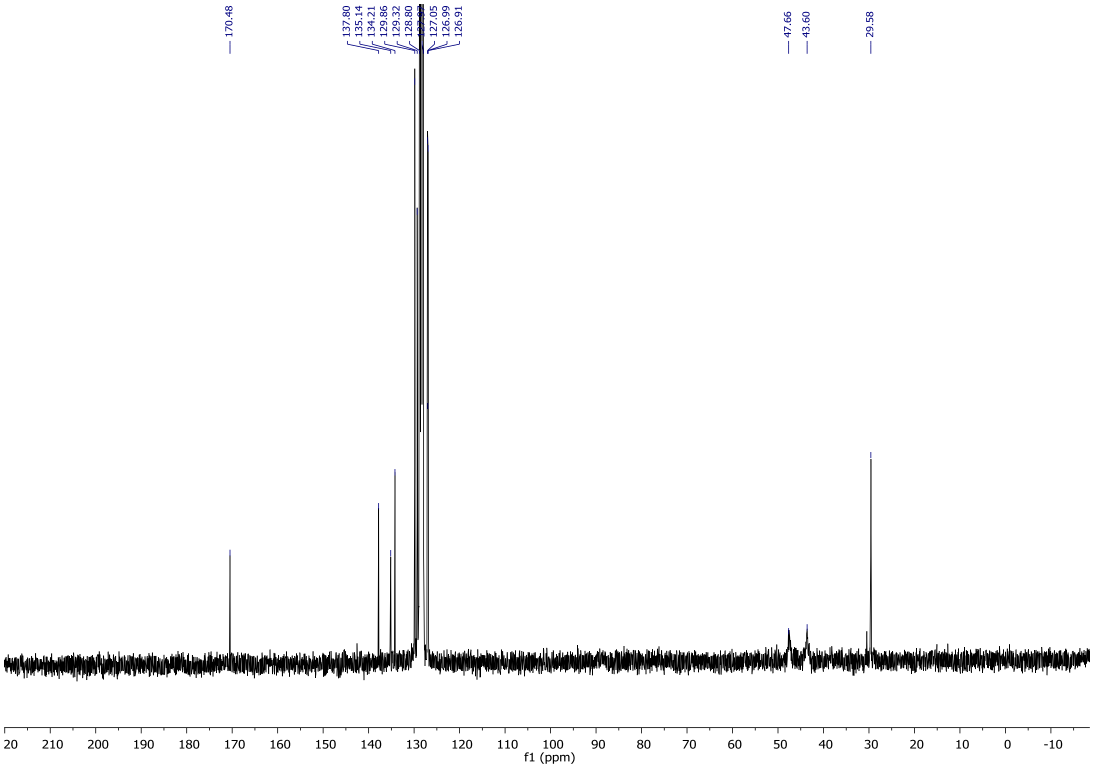




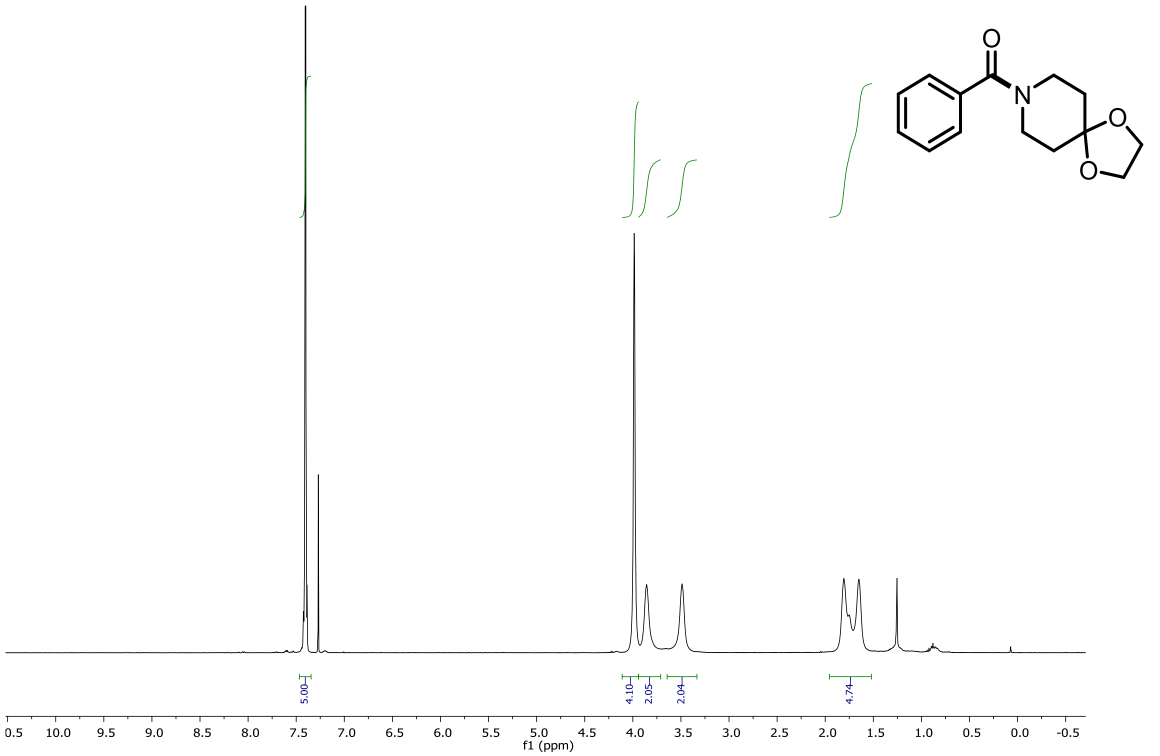


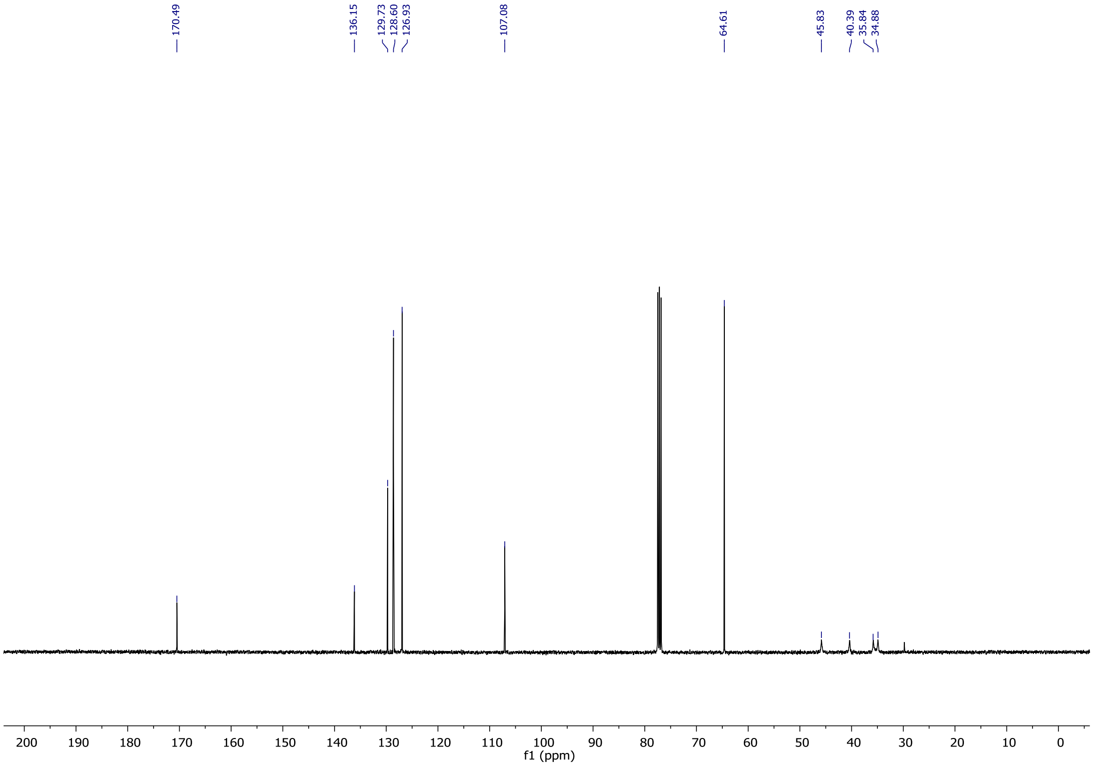
N-Benzoyl-1,2,3,4-tetrahydroisoquinoline (**3.23**). C_6D_6, 62°C, 300 MHz:



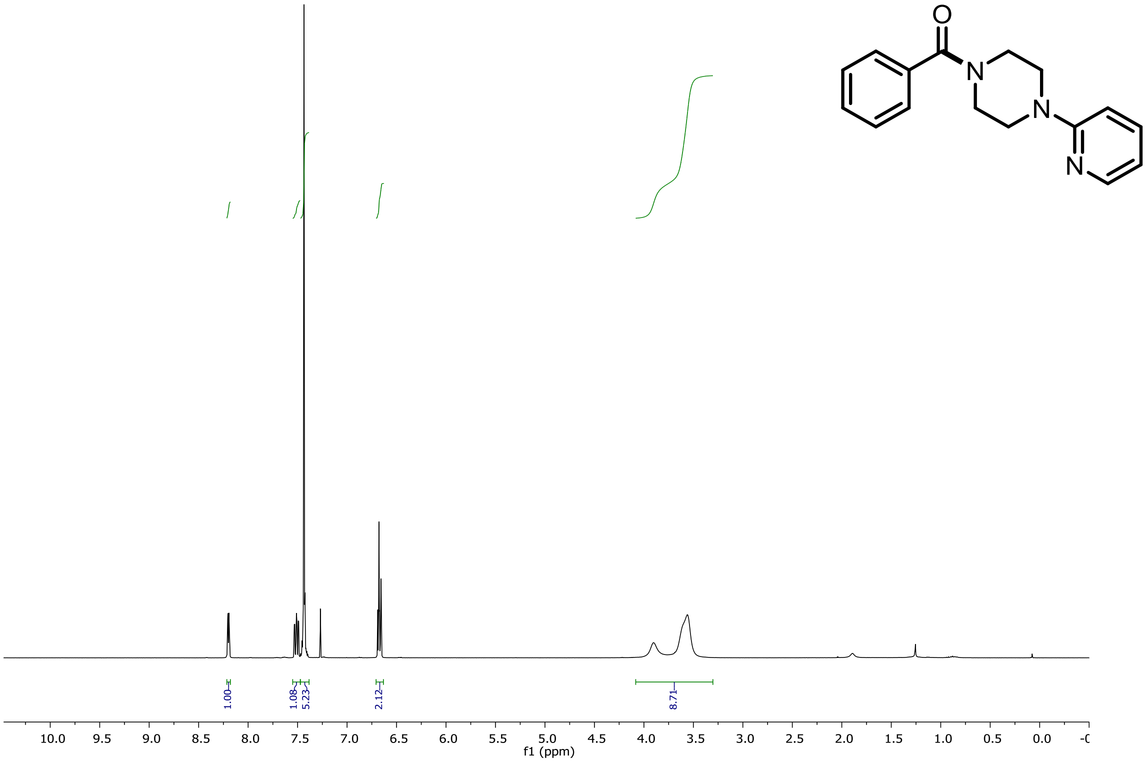


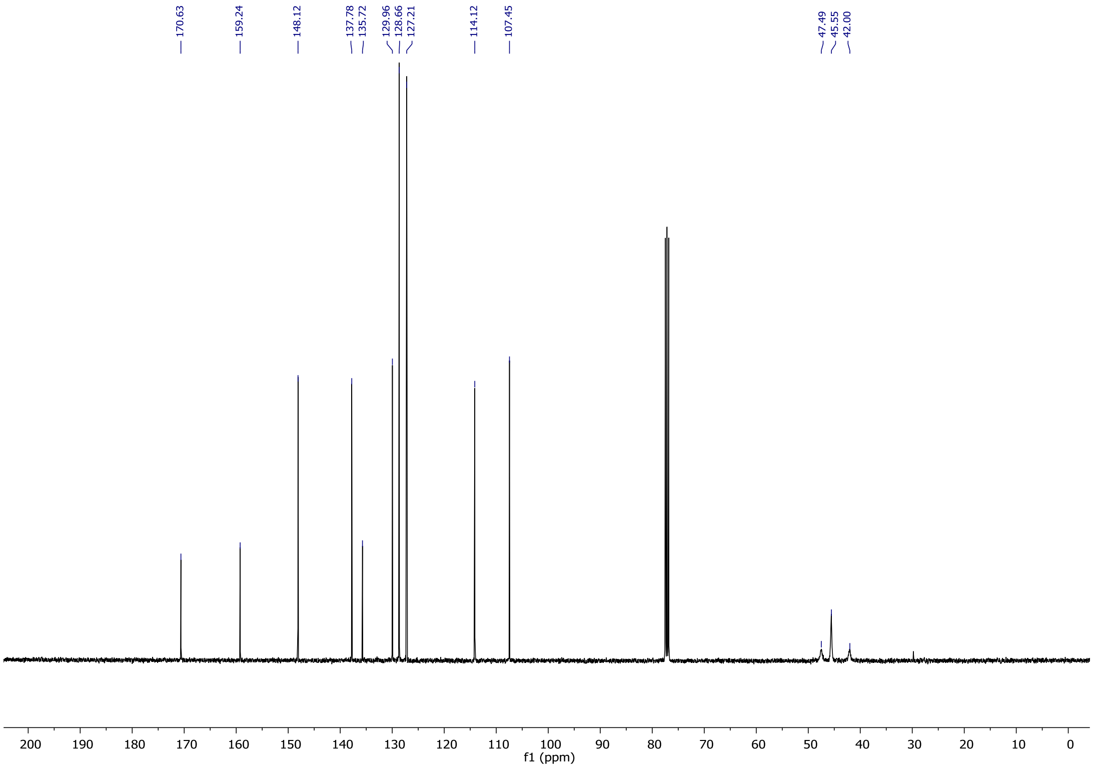
(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)phenylmethanone (**3.30**). CDCl3, 400 MHz:



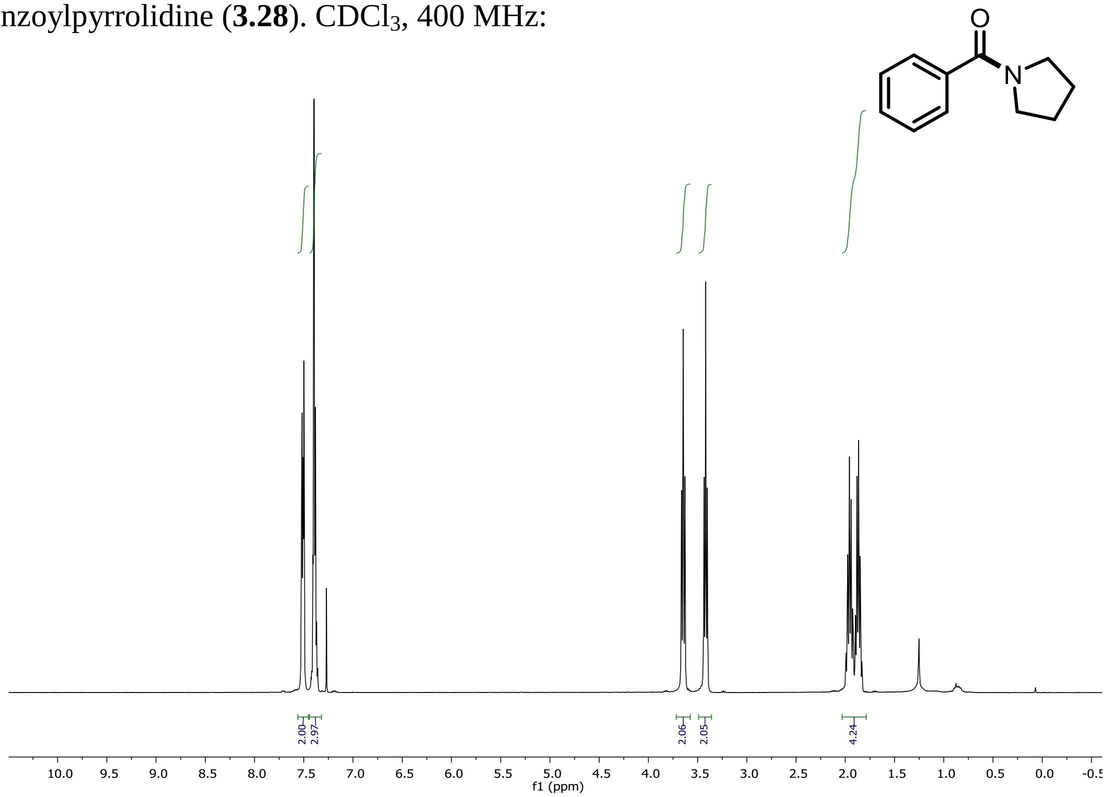


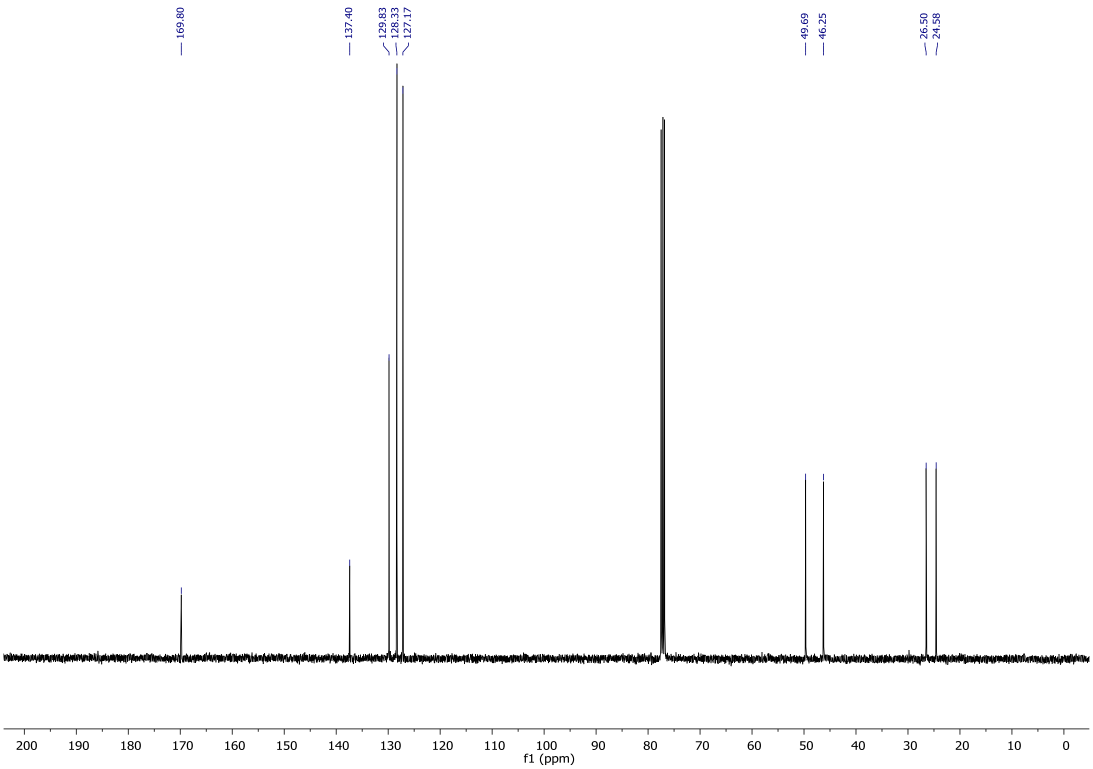
Phenyl(4-(pyridin-2-yl)piperazin-1-yl)methanone (**3.29**). $CDCl_3$, 400 MHz:



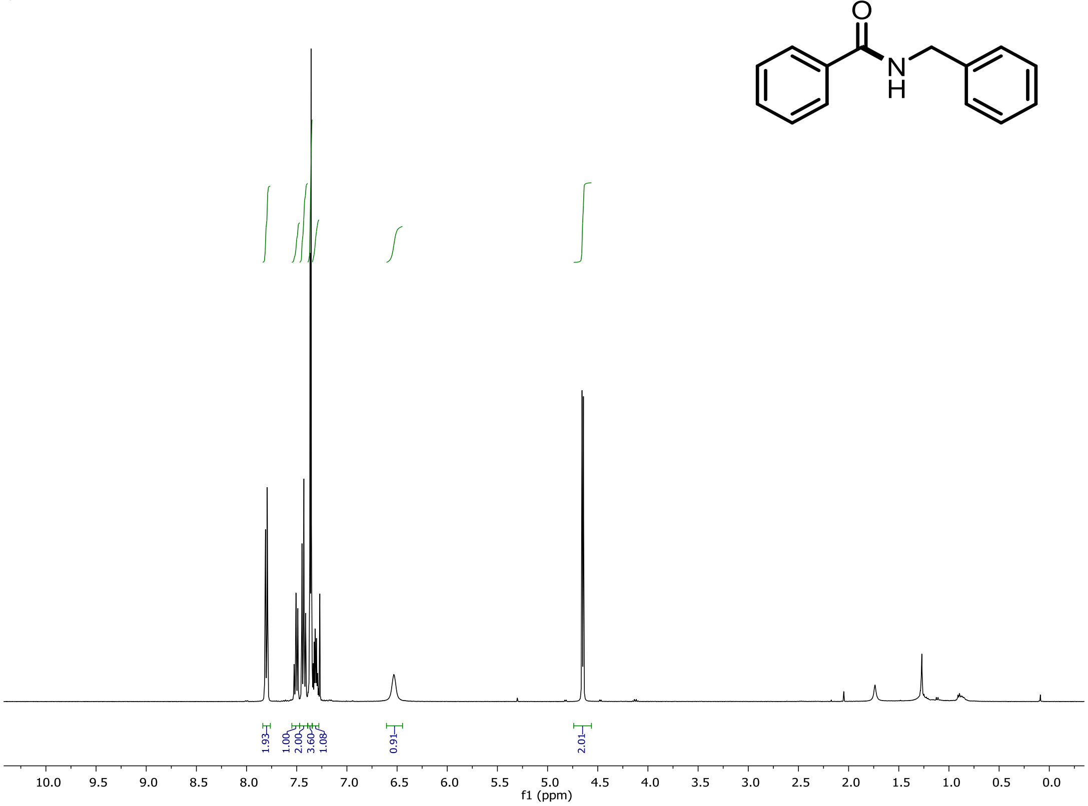


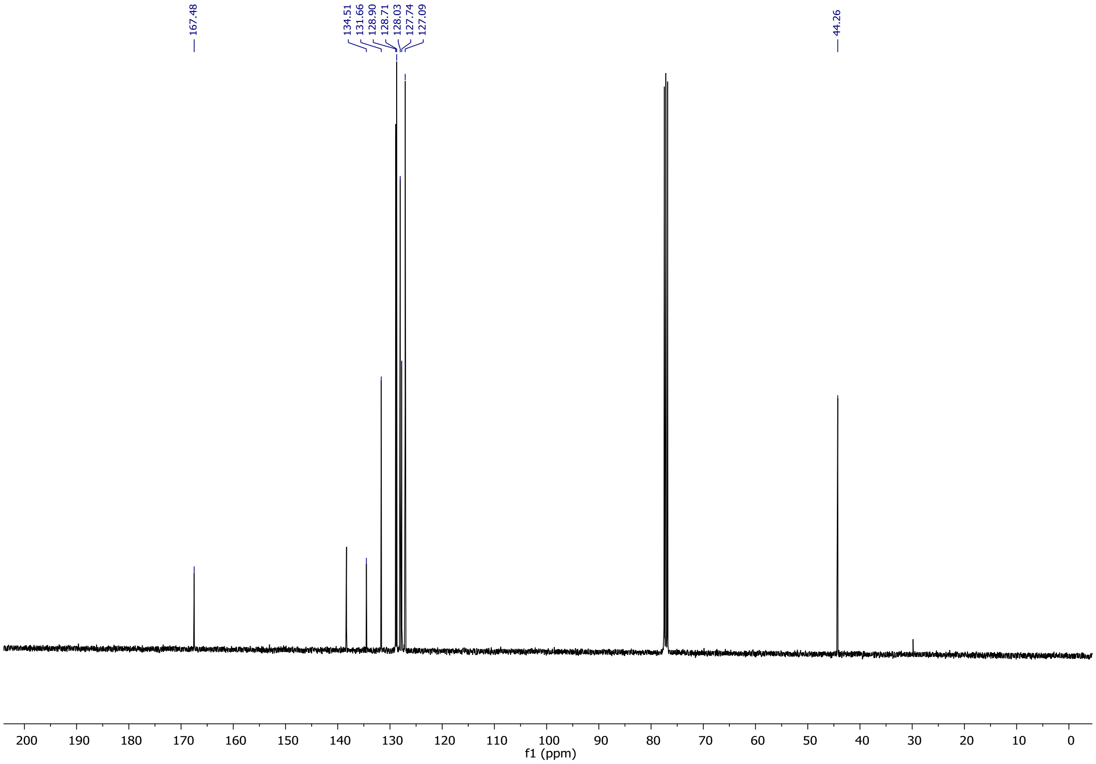
N-Benzoylpyrrolidine (**3.28**). $CDCl_3$, 400 MHz:



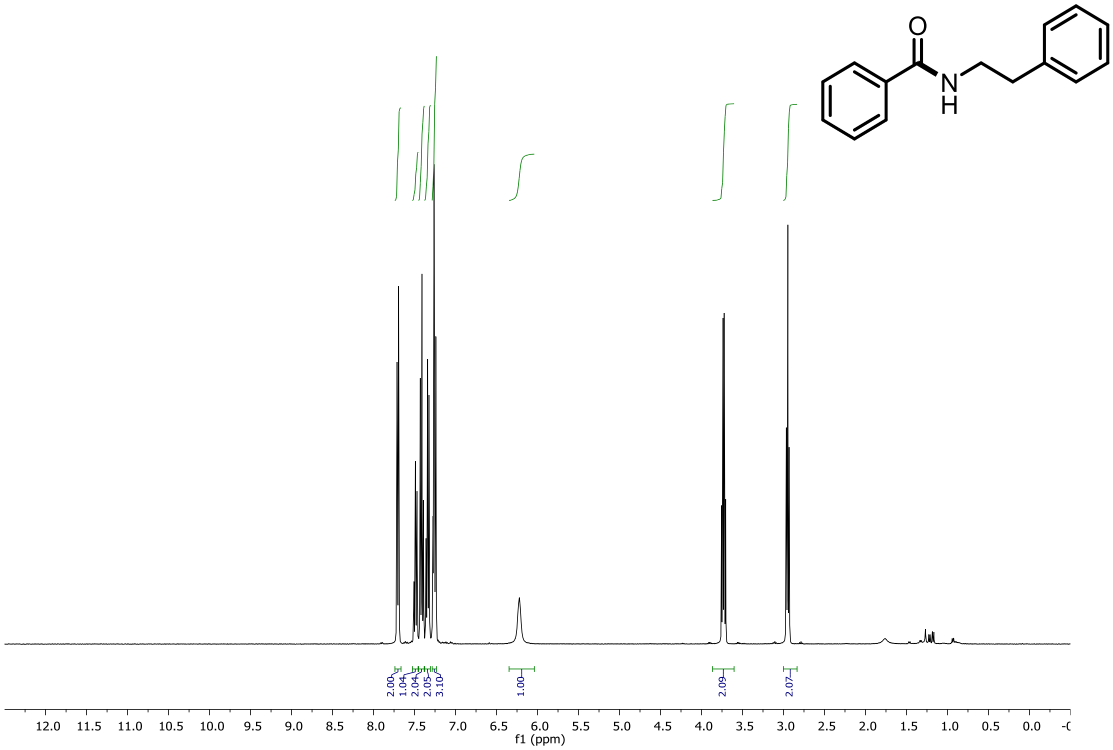


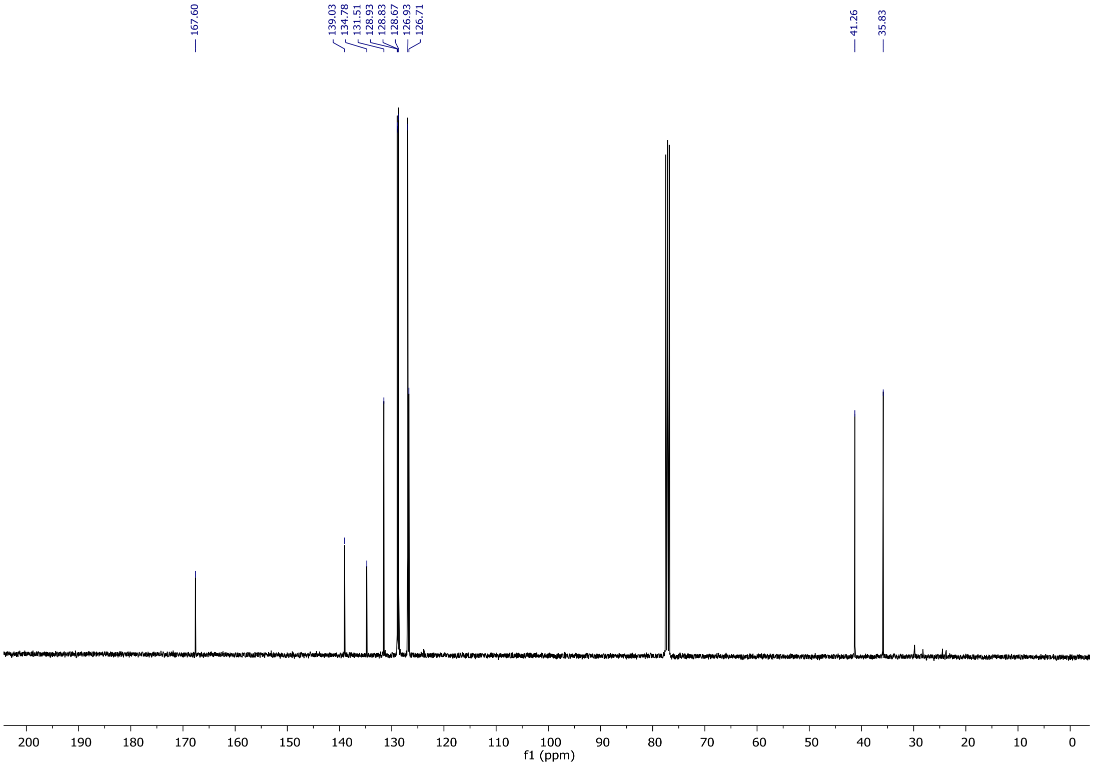
N-Benzylbenzamide (**3.31**). $CDCl_3$, 400 MHz:



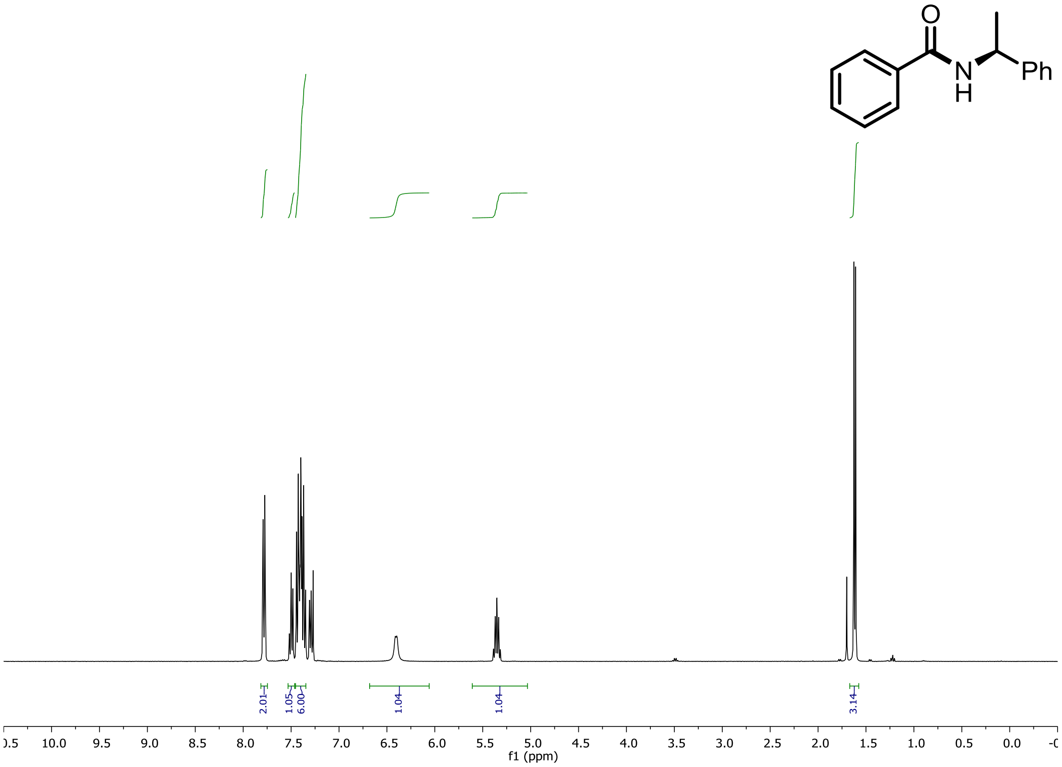


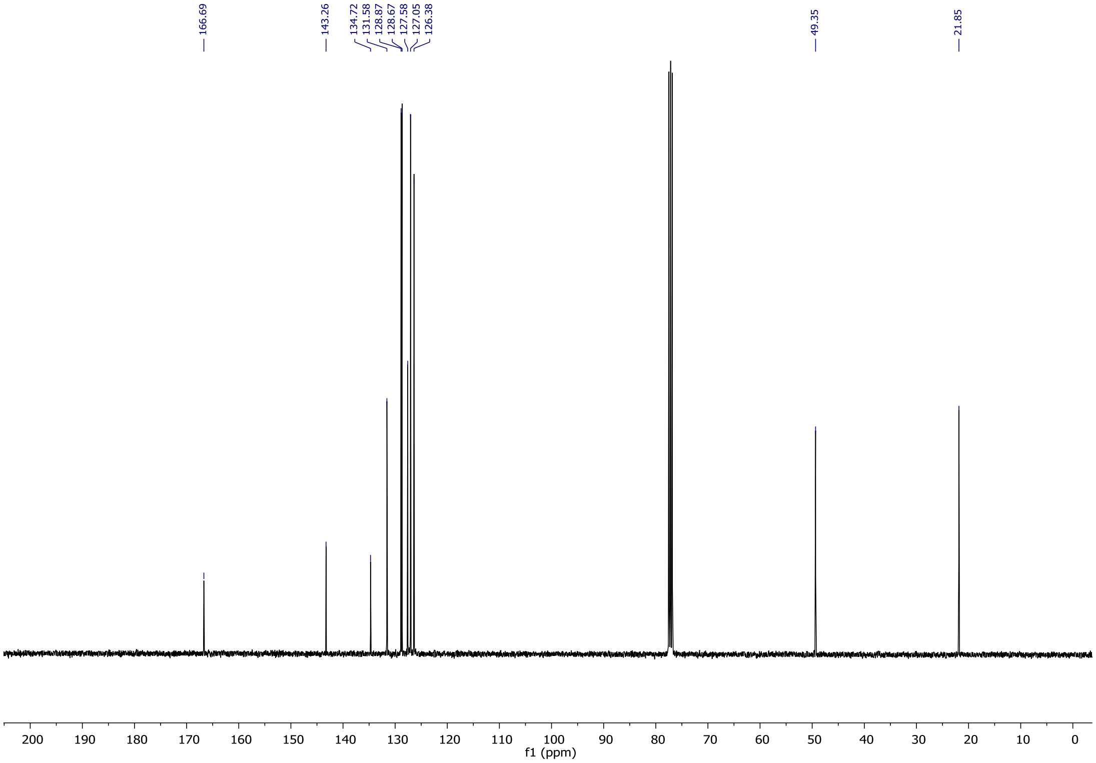
N-Phenethylbenzamide (**3.32**) $CDCl_3$, 400 MHz:



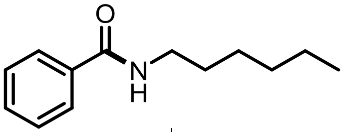


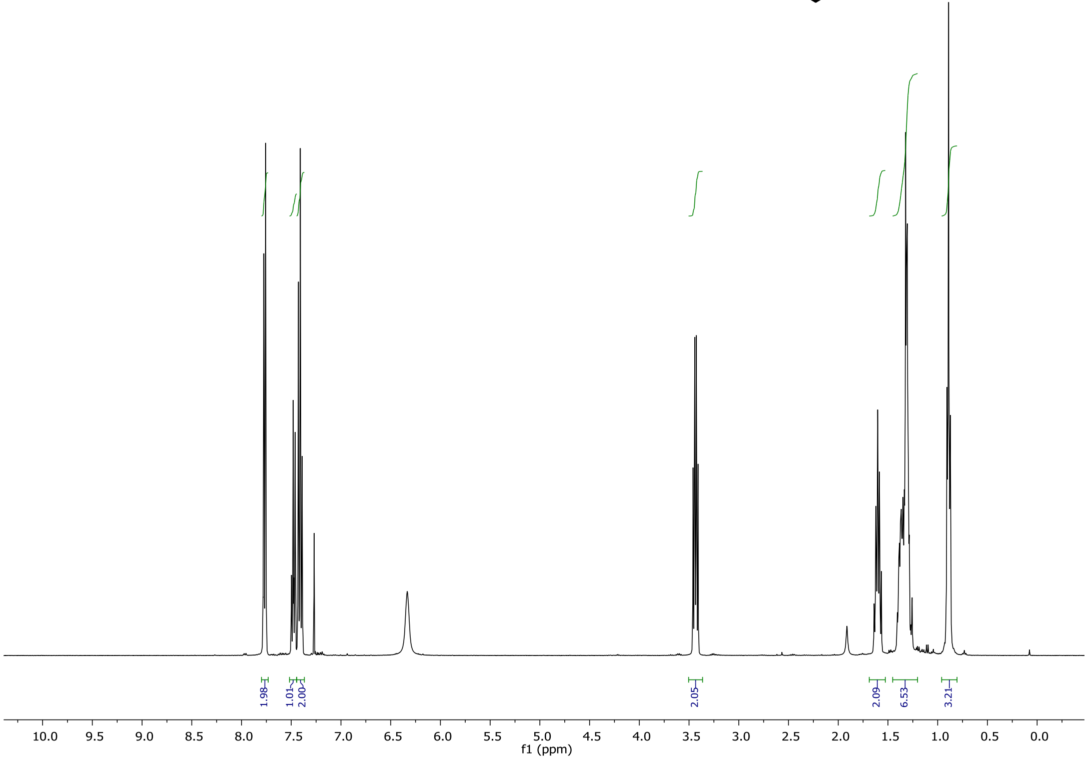
(S)-N-(1-Phenylethyl)benzamide (**3.22**) $CDCl_3$, 400 MHz:

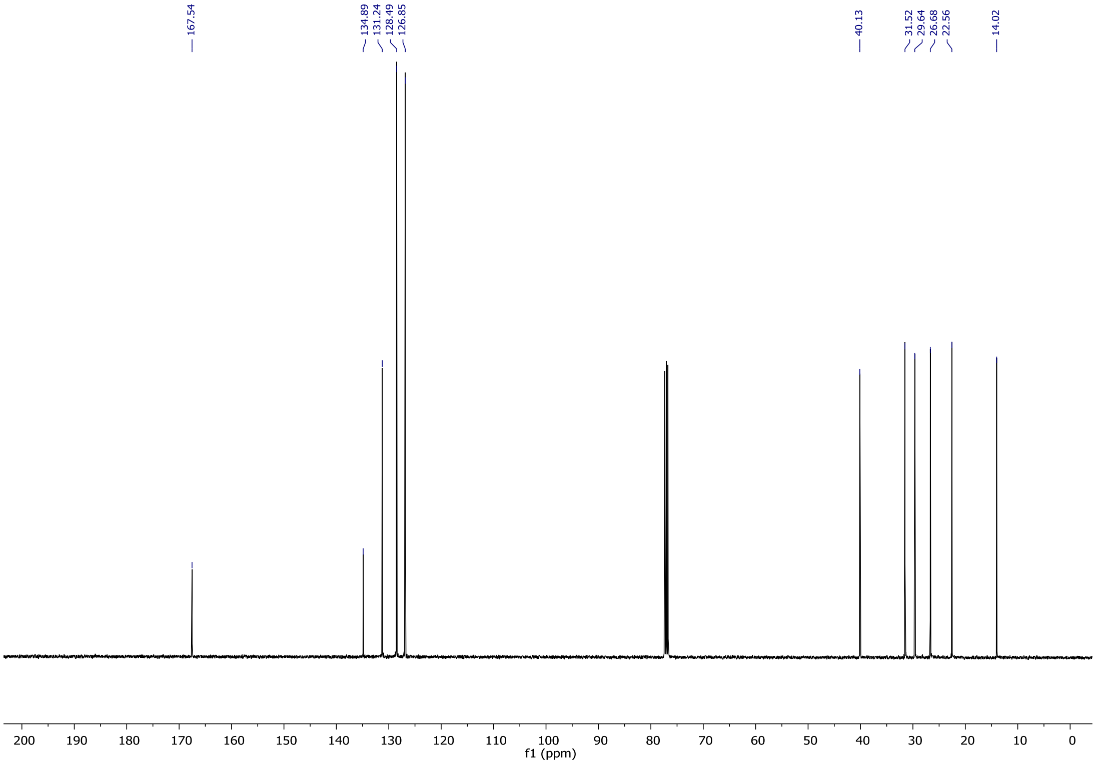




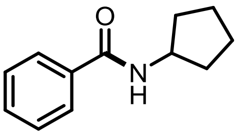
N-Hexylbenzamide (**3.20**) $CDCl_3$, 400 MHz:

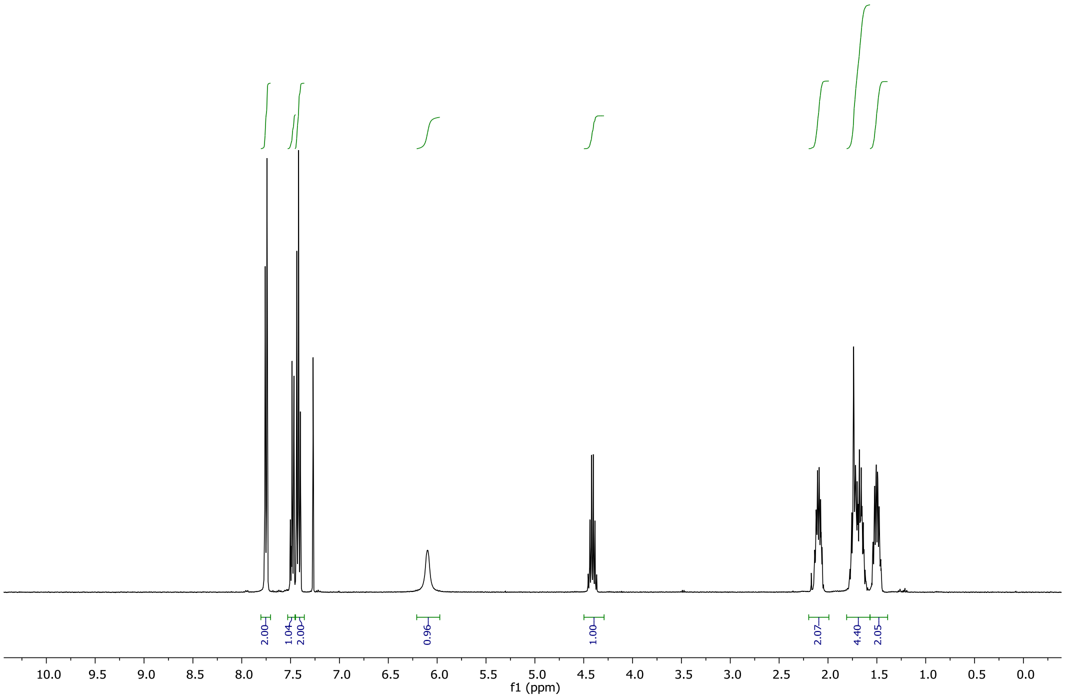


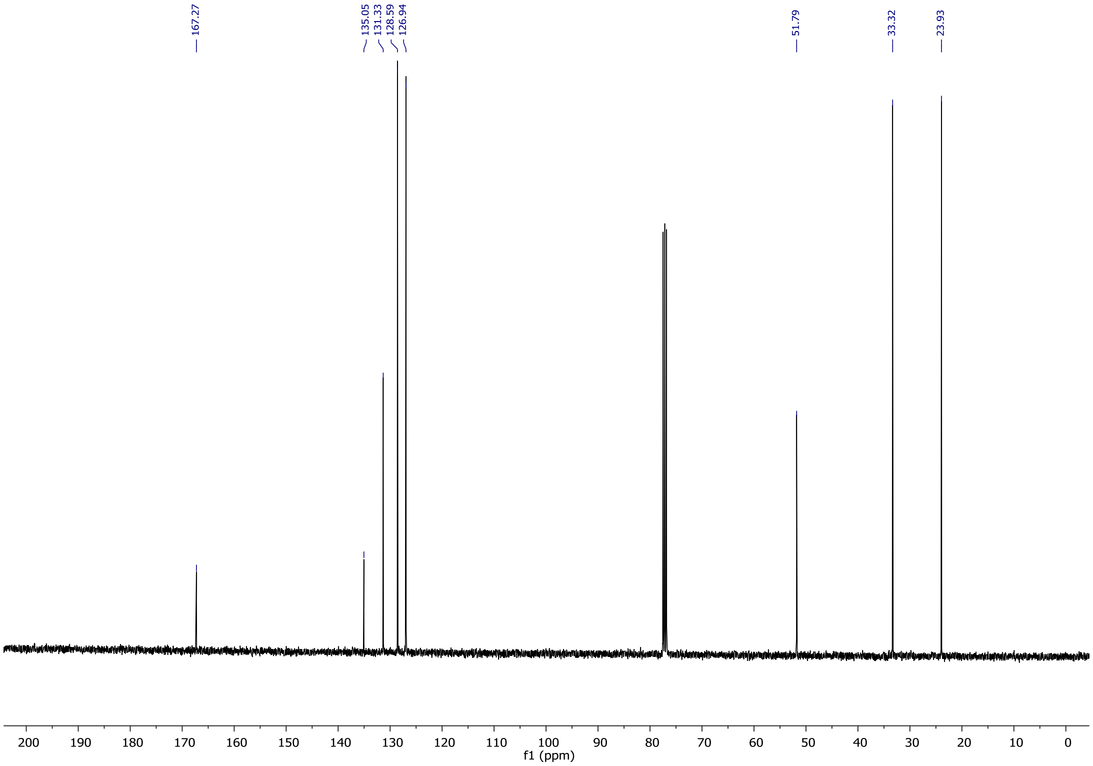




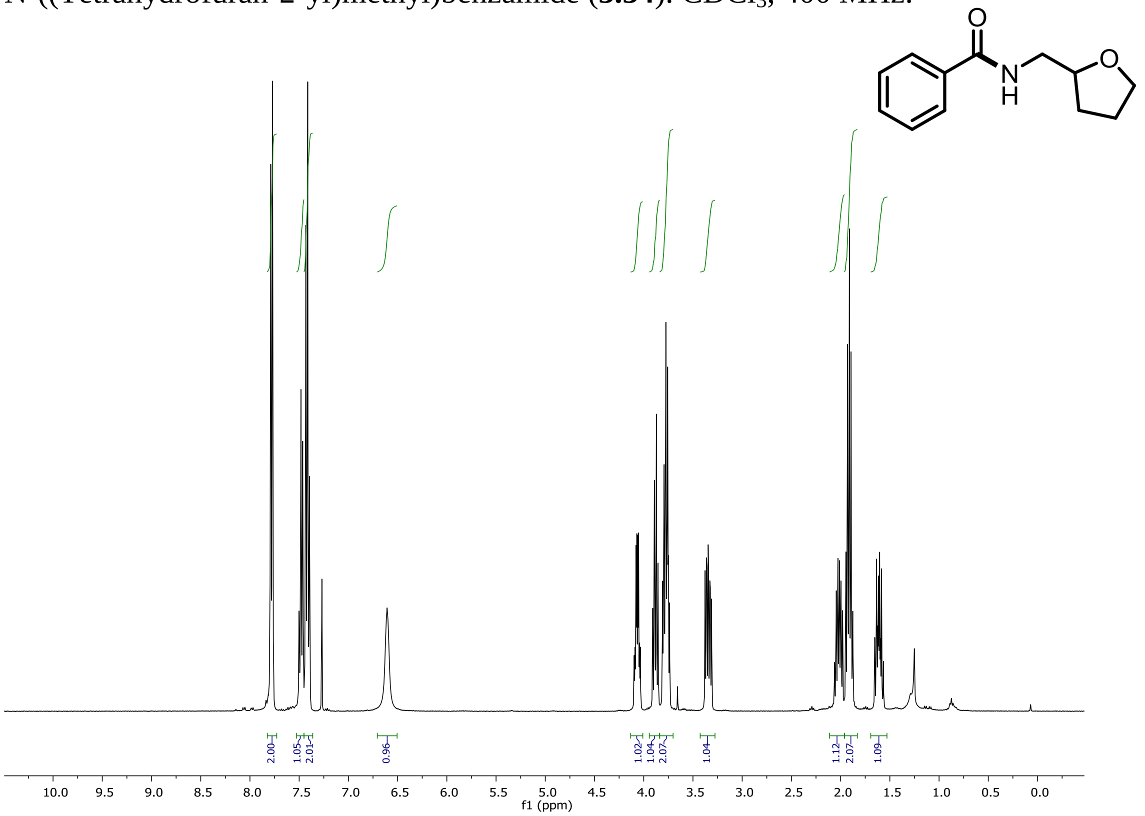
N-Cyclopentylbenzamide (**3.33**). $CDCl_3$, 400 MHz:

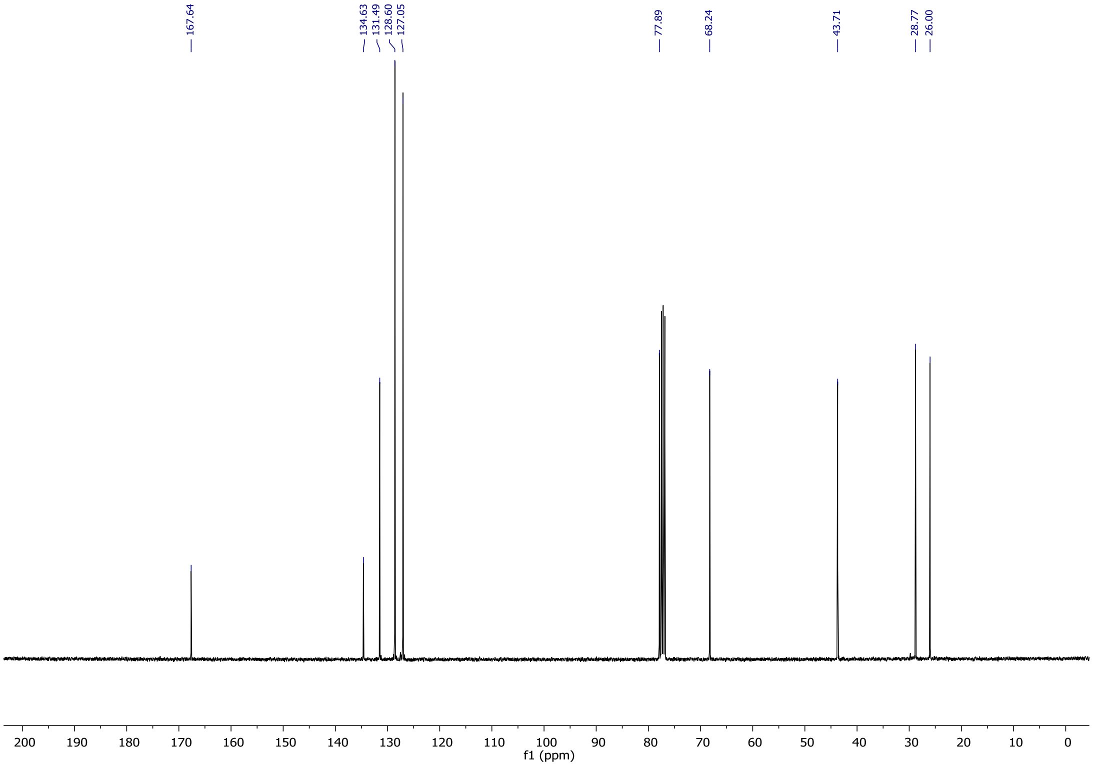




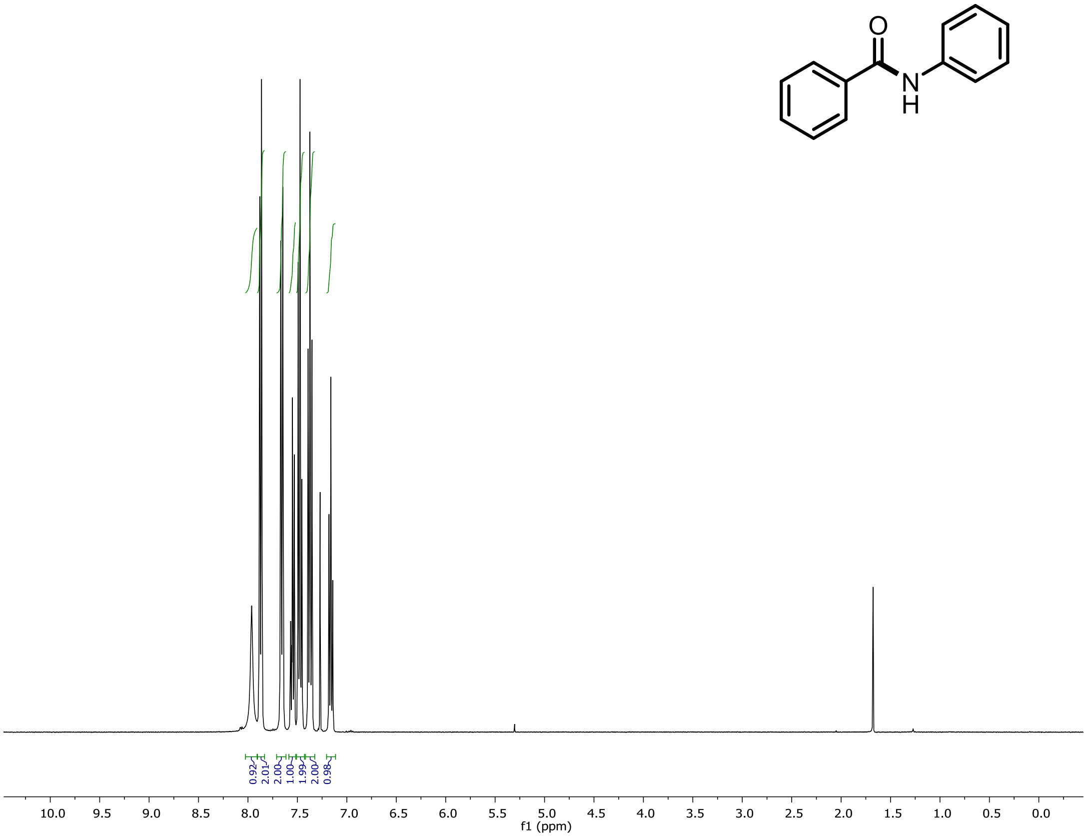


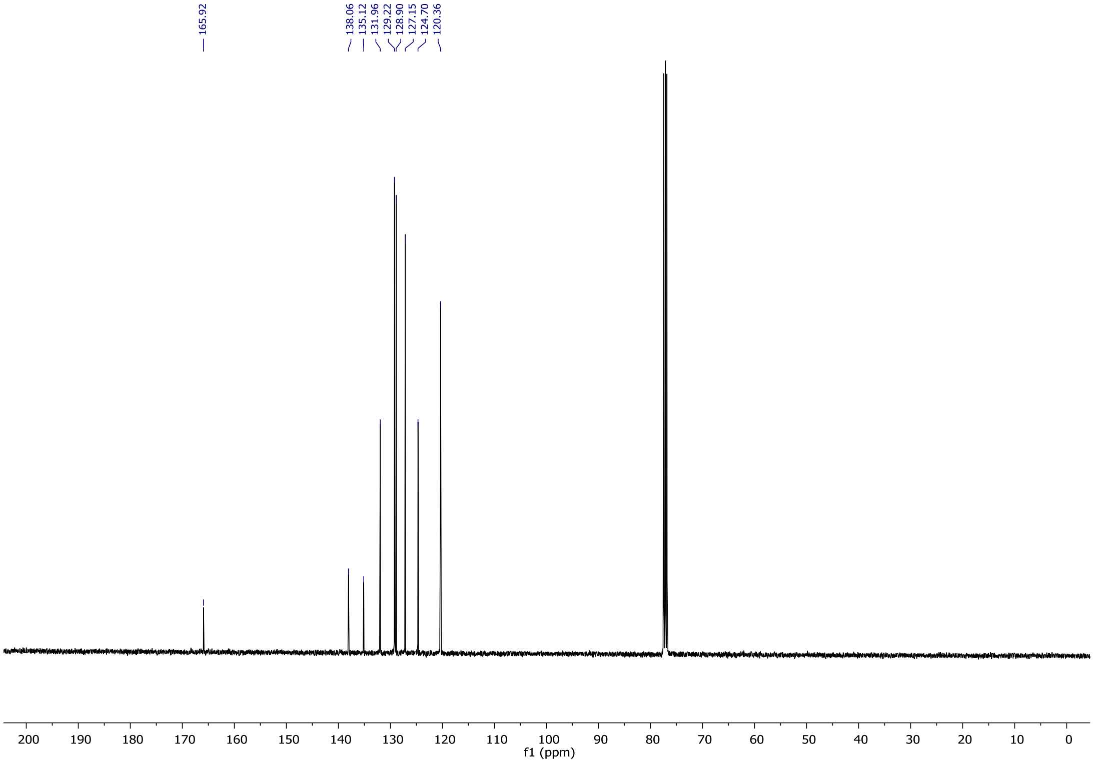
N-((Tetrahydrofuran-2-yl)methyl)benzamide (**3.34**). $CDCl_3$, 400 MHz:



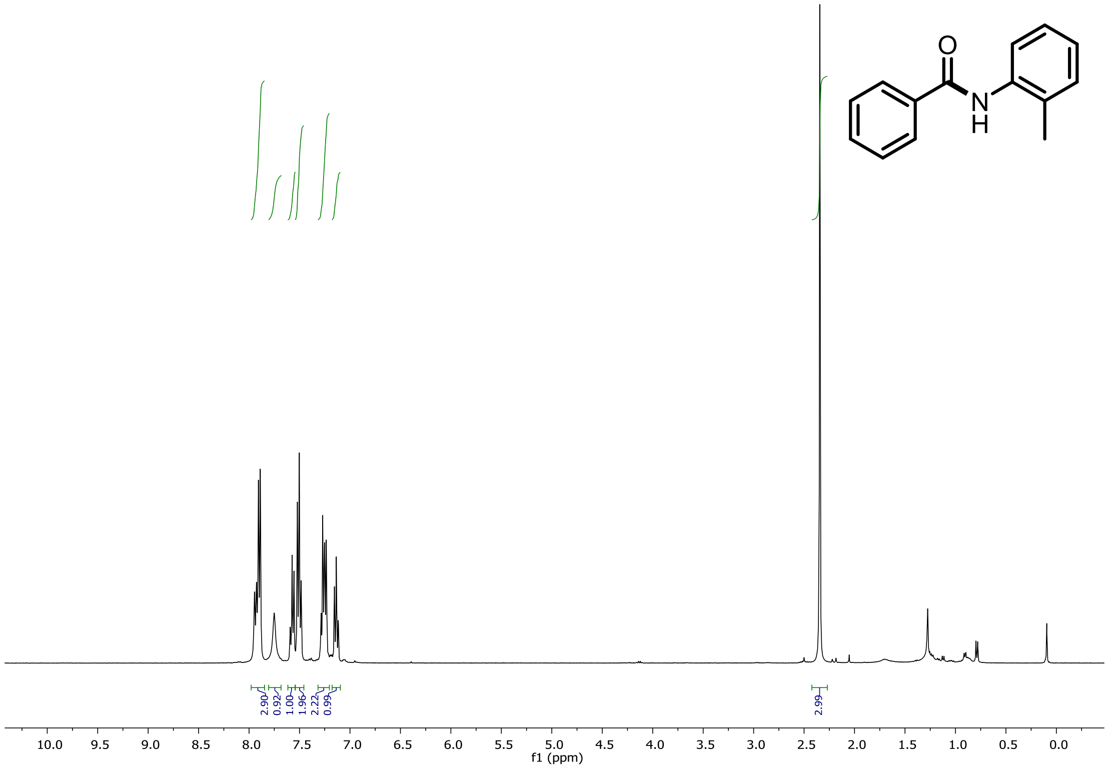


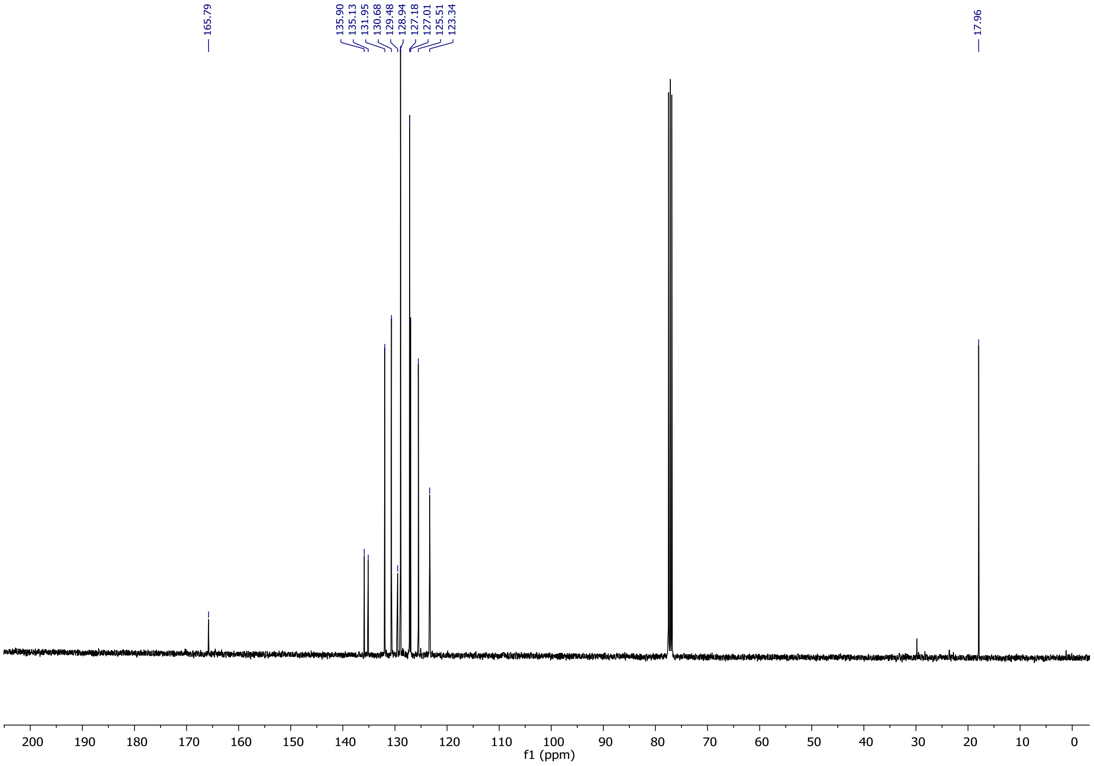
N-Phenylbenzamide (**3.14**). $CDCl_3$, 400 MHz:



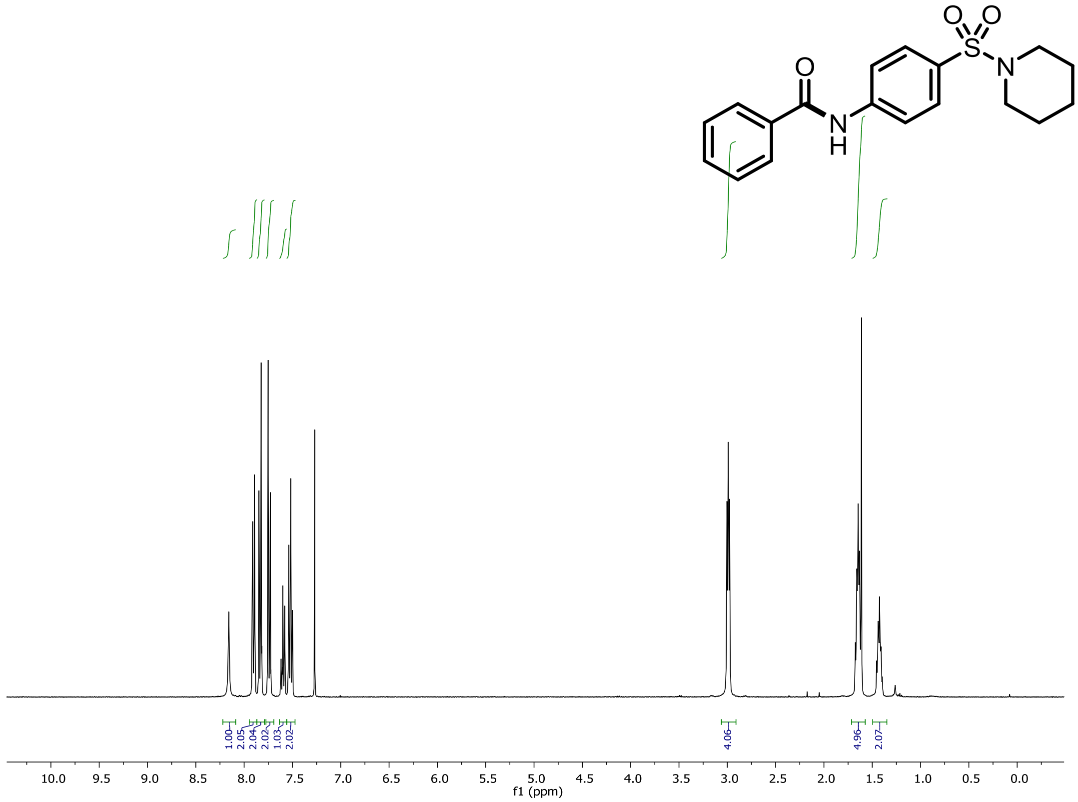


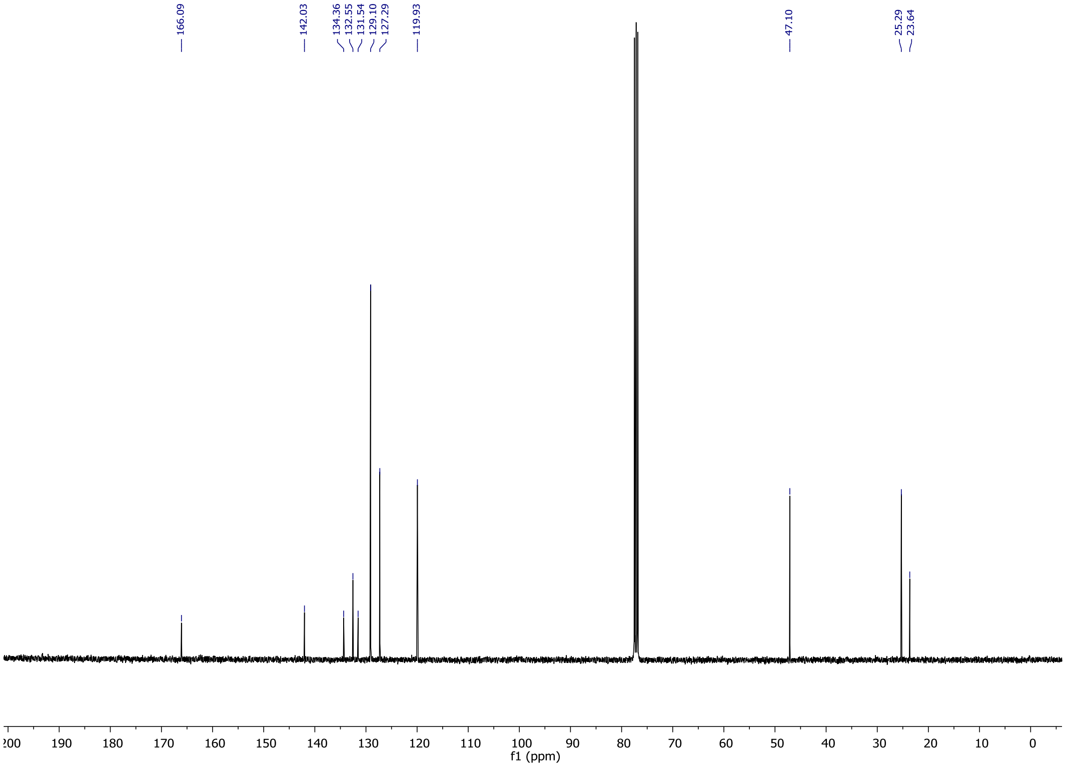
N-Benzoyl-2-methylaniline (**3.35**) $CDCl_3$, 400 MHz:



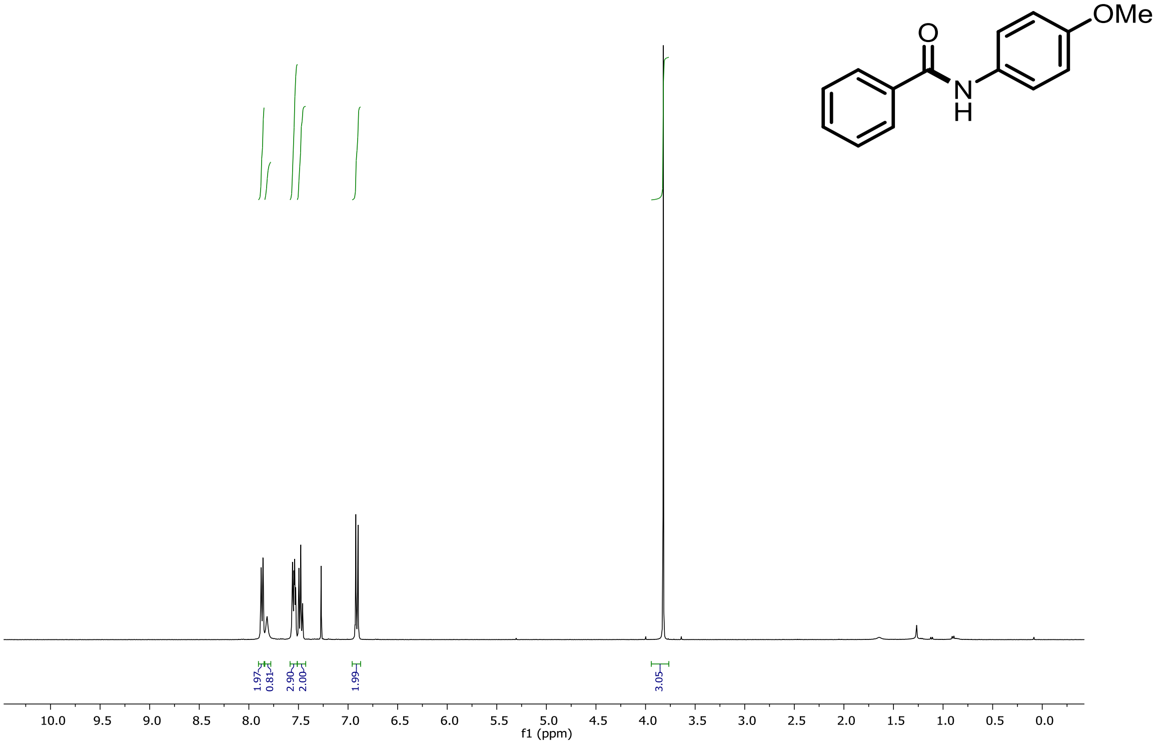


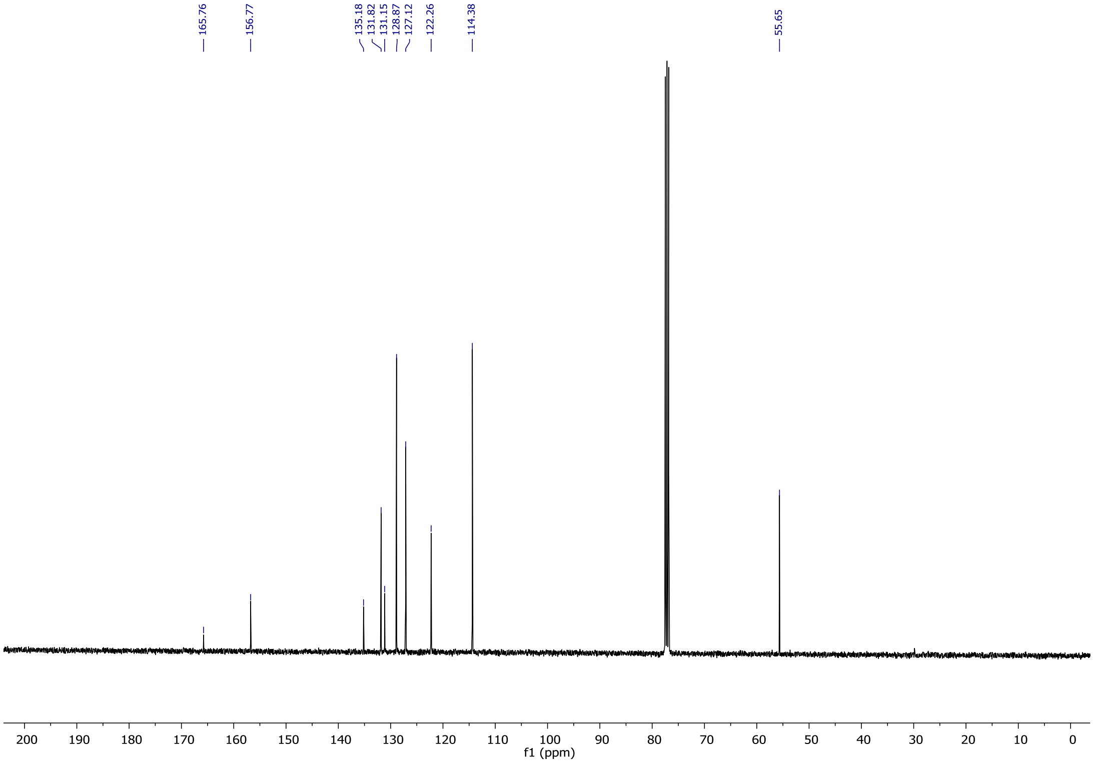
1-(N-Benzoyl-sulfanilyl)-piperidine (**3.36**). $CDCl_3$, 400 MHz:



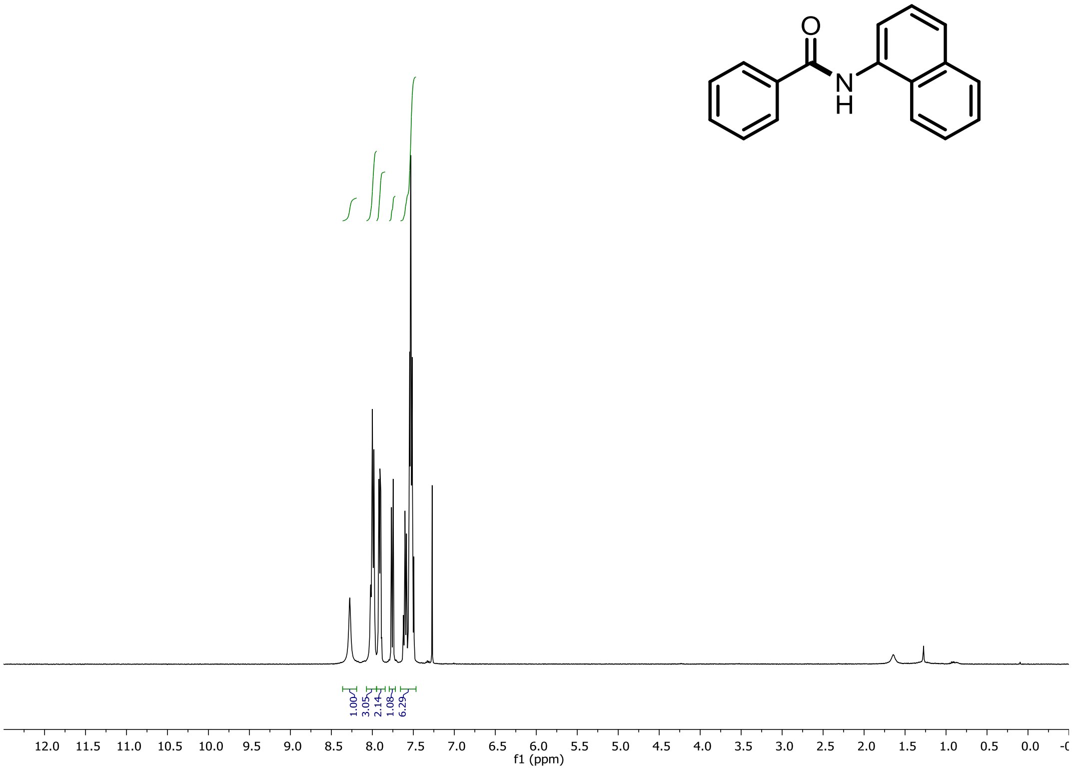


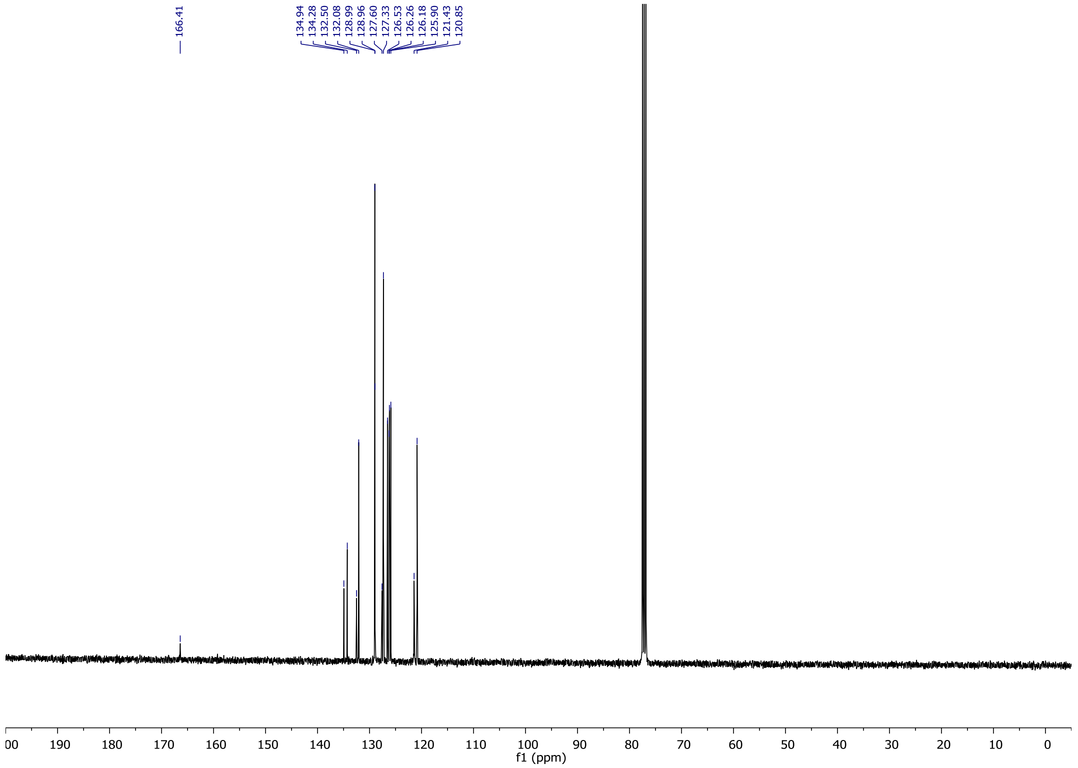
N-(*p*-Methoxyphenyl)benzamide (**3.38**). $CDCl_3$, 400 MHz:



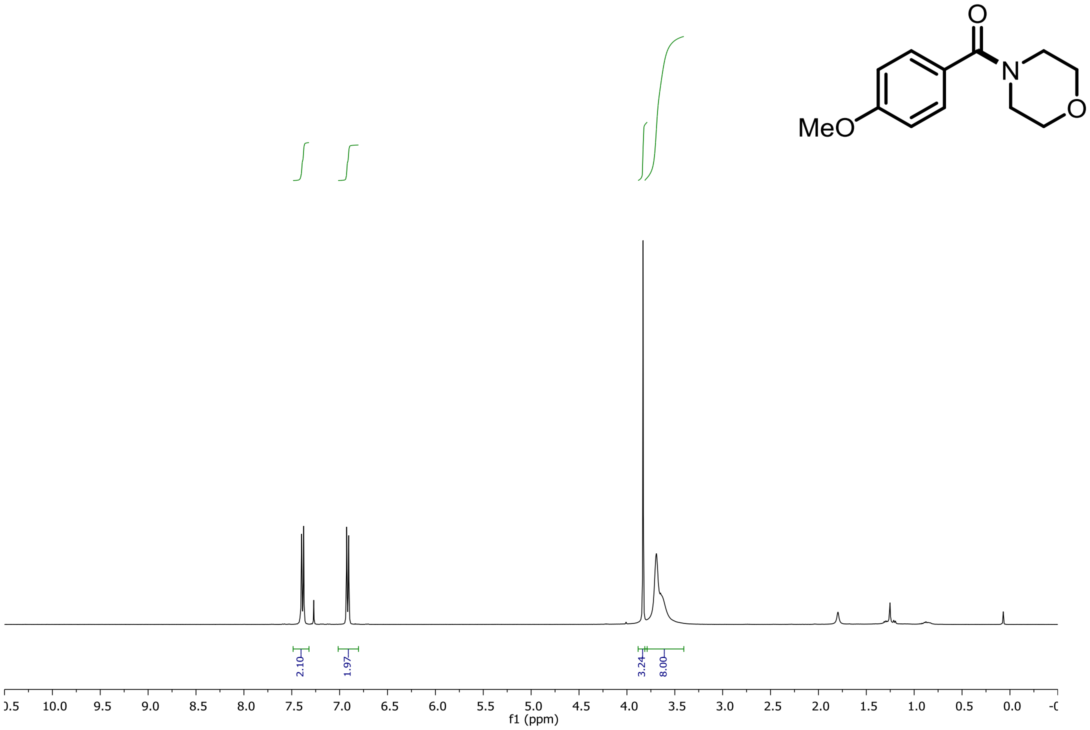


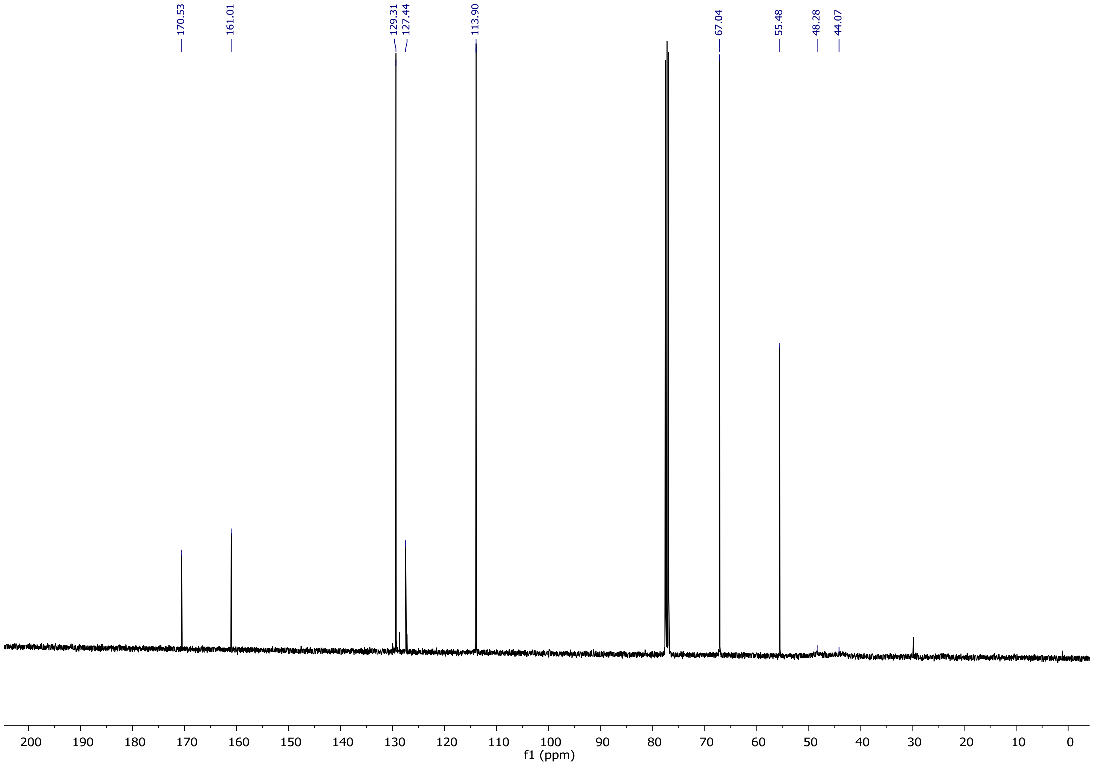
N-1-Naphthalenyl-benzamide (**3.39**). $CDCl_3$, 400 MHz:



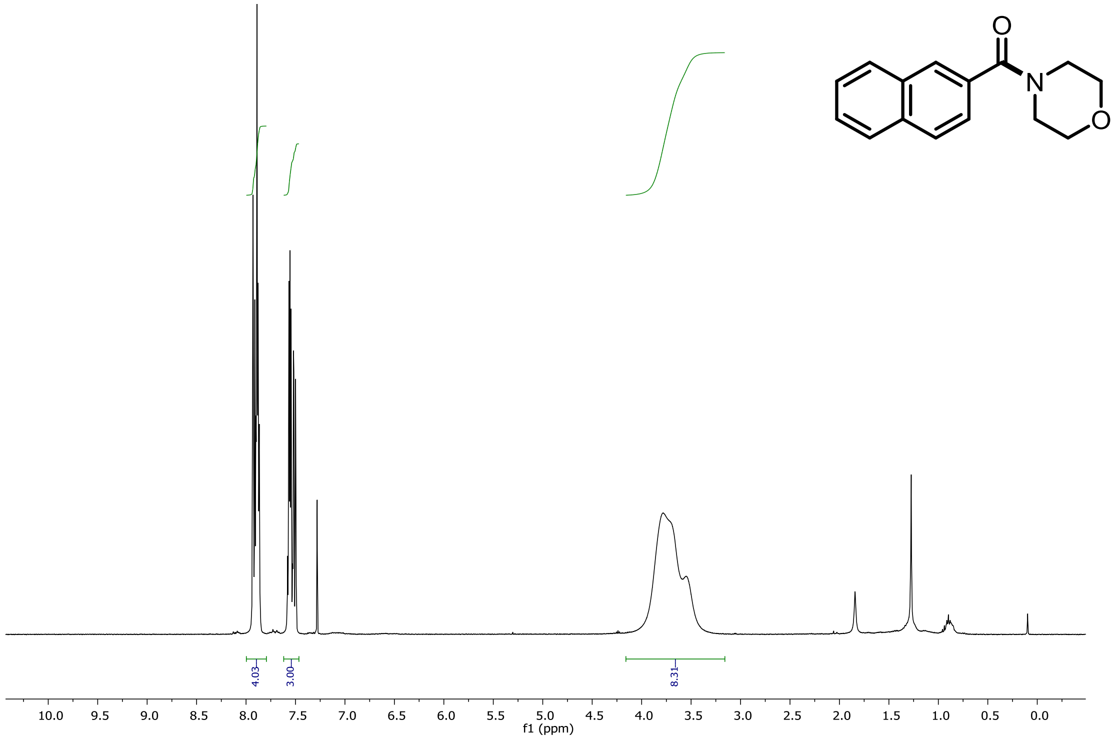


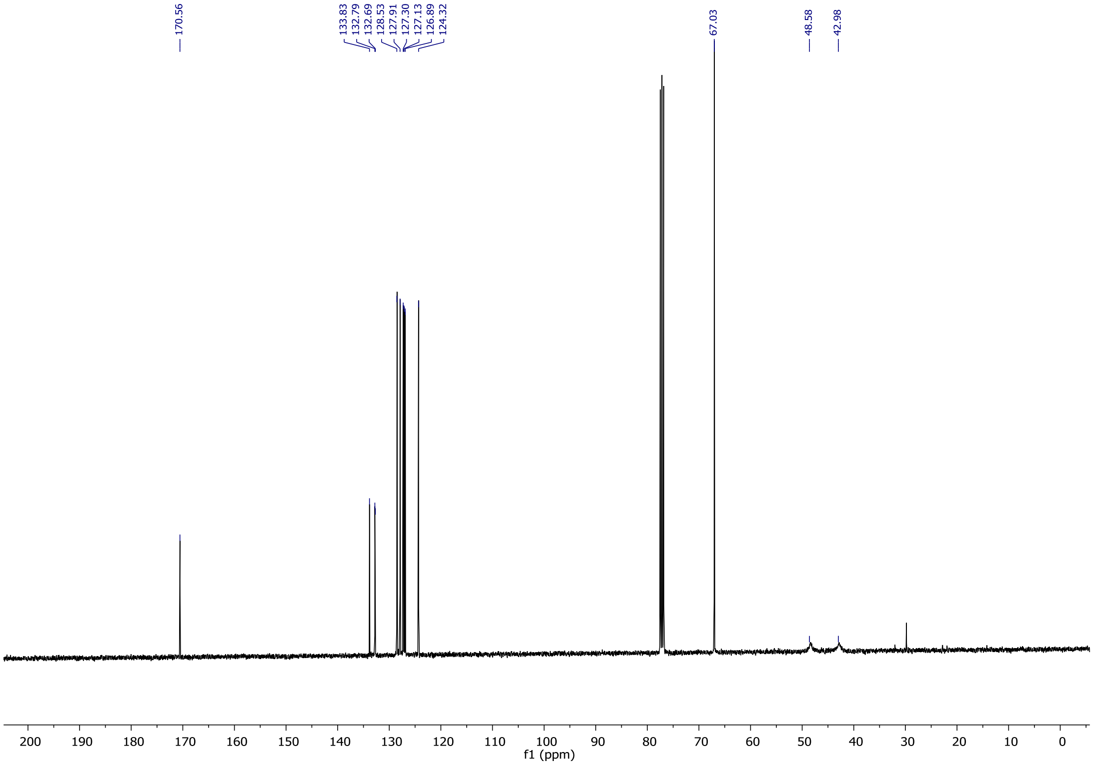
N-(4-Methoxybenzoyl)morpholine (**3.40**) $CDCl_3$, 400 MHz:



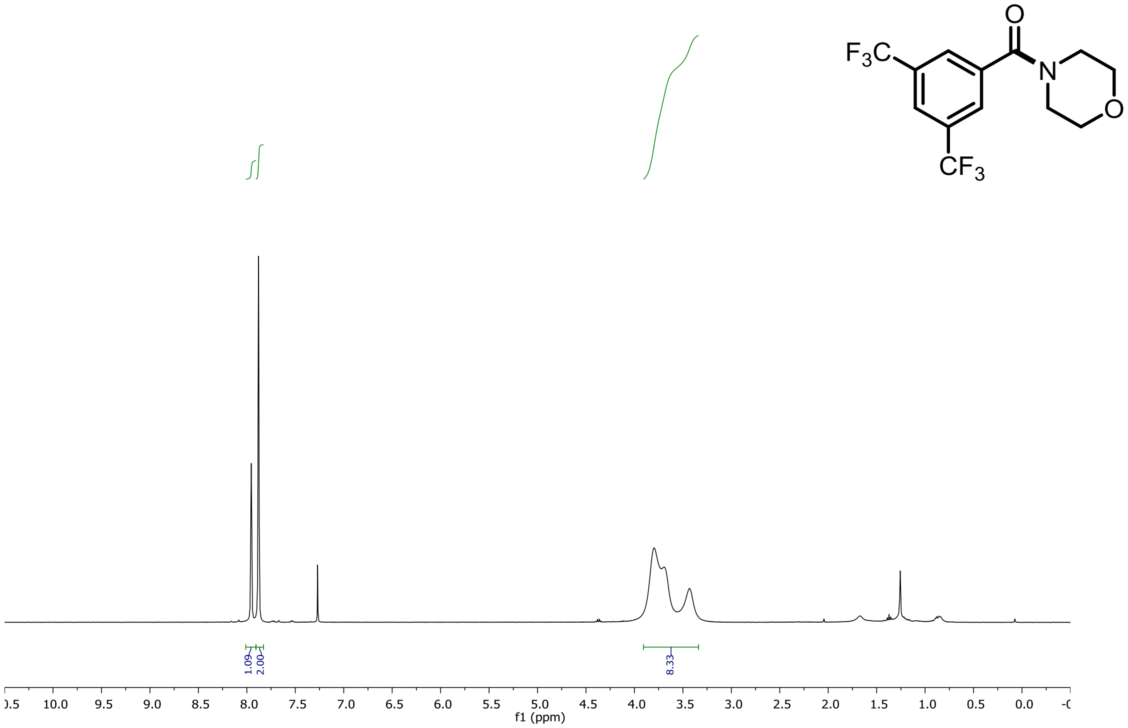


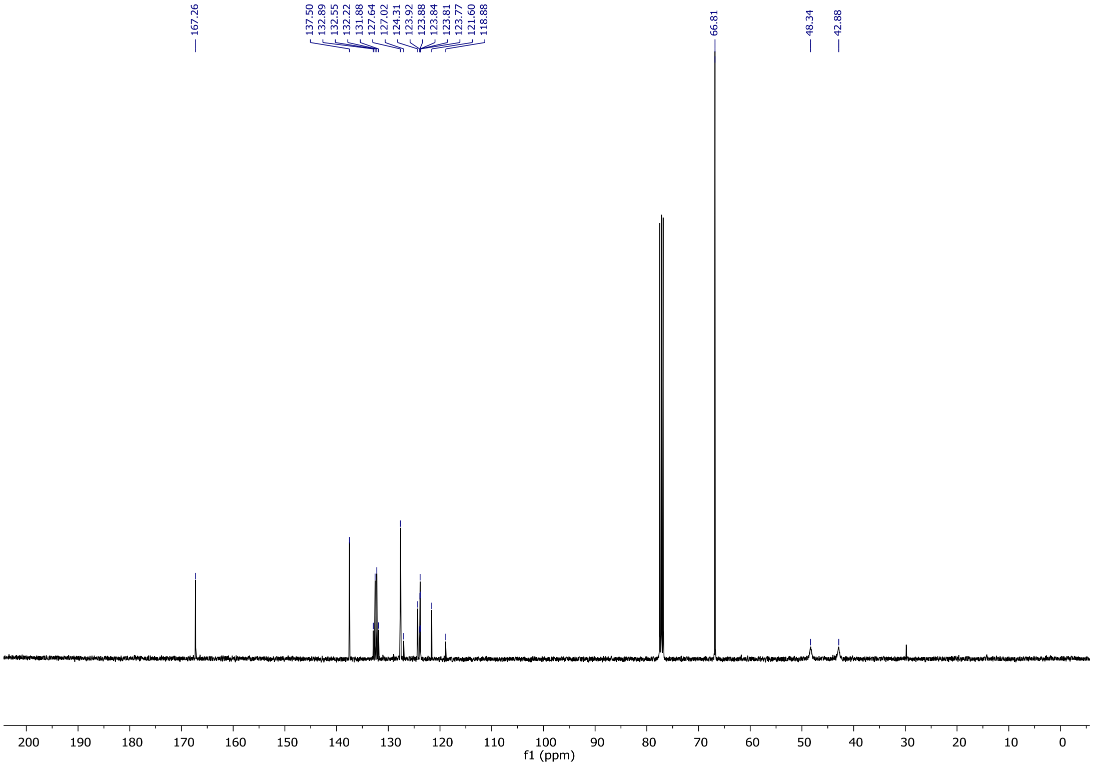
Morpholino(naphthalen-2-yl)methanone (**3.41**). $CDCl_3$, 400 MHz:



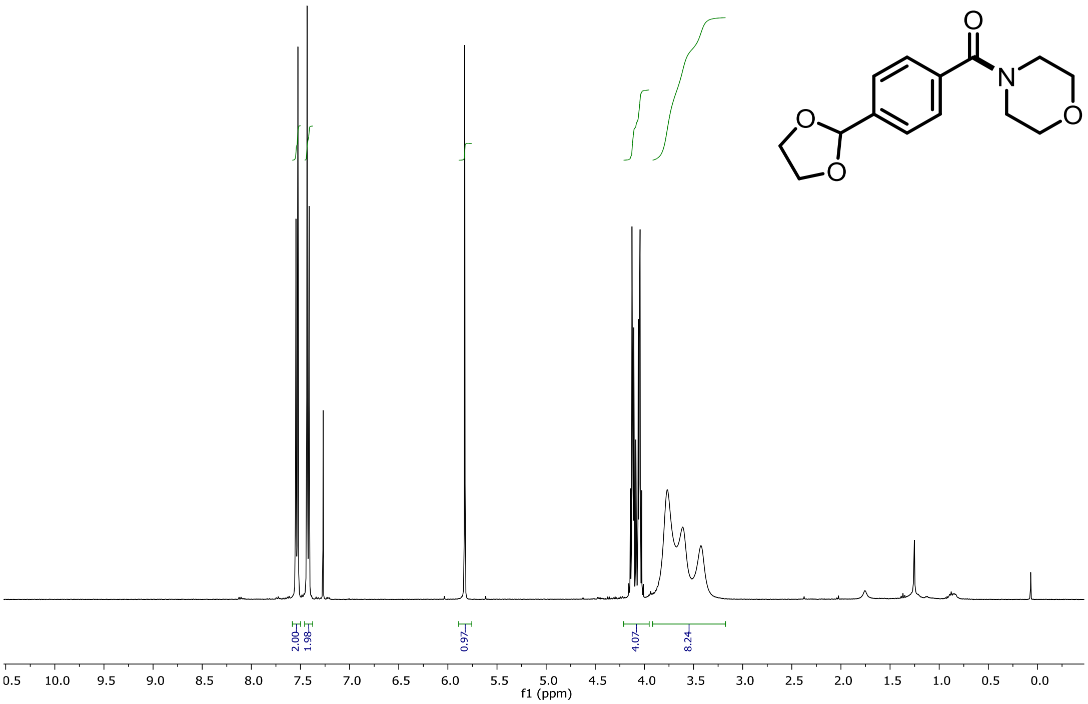


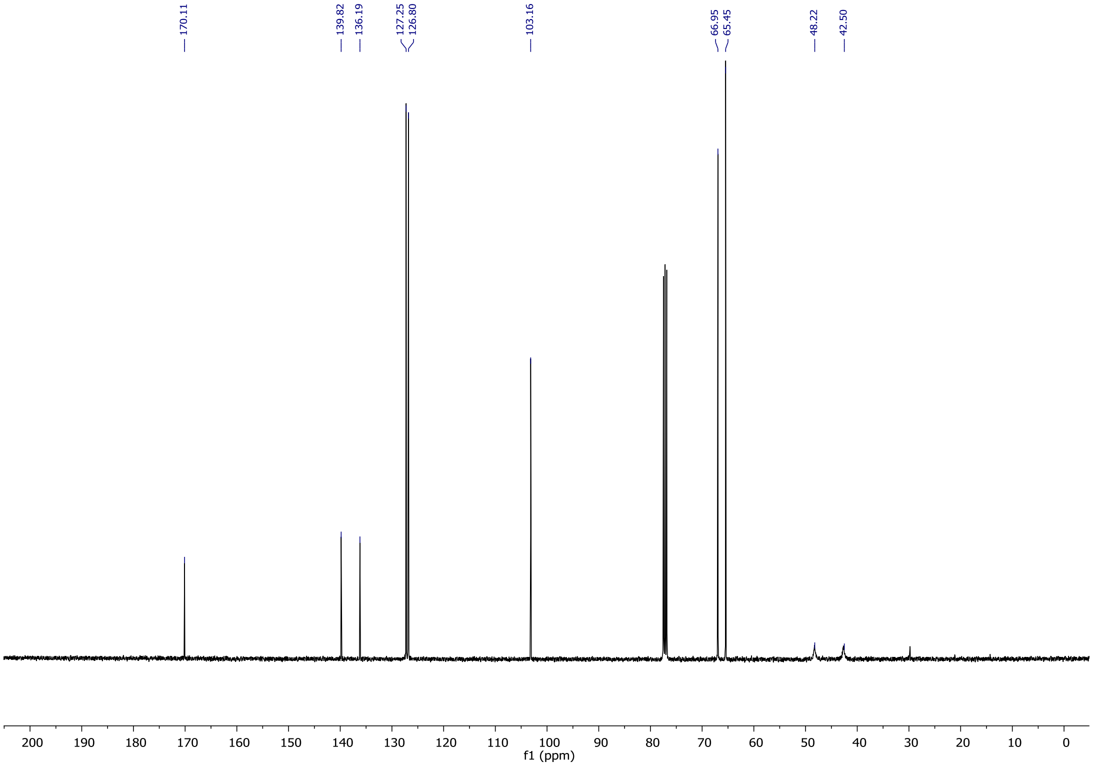
N-(3,5-Bis-trifluoromethylbenzoyl)morpholine (**3.42**). $CDCl_3$, 400 MHz:



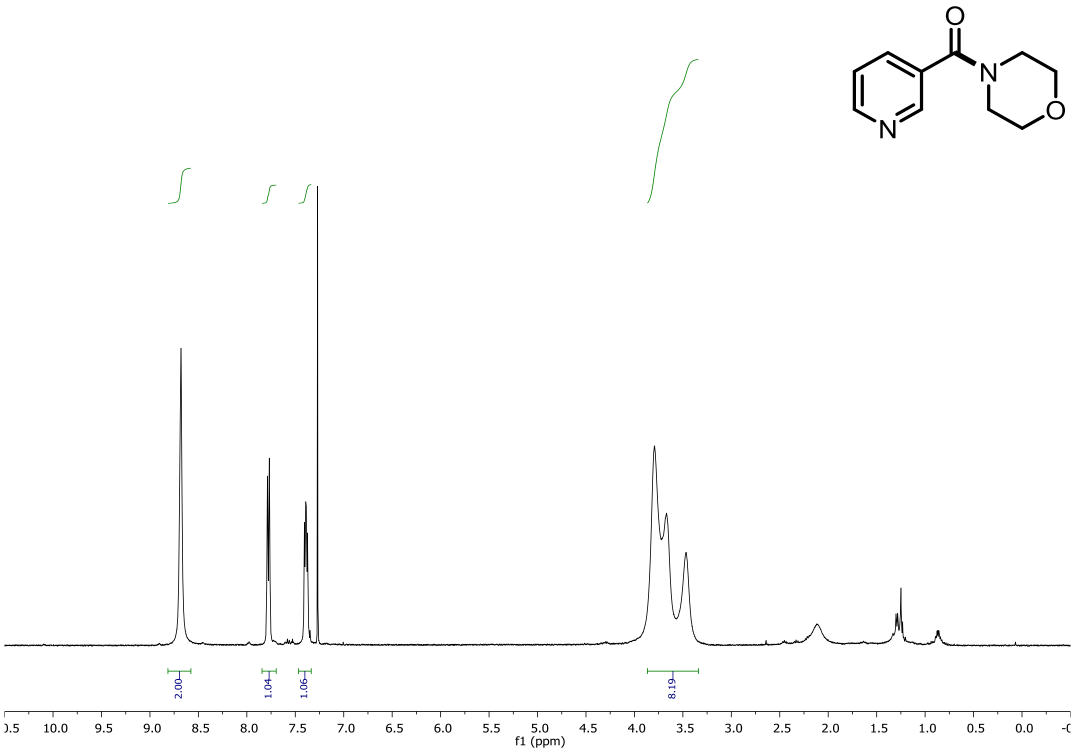


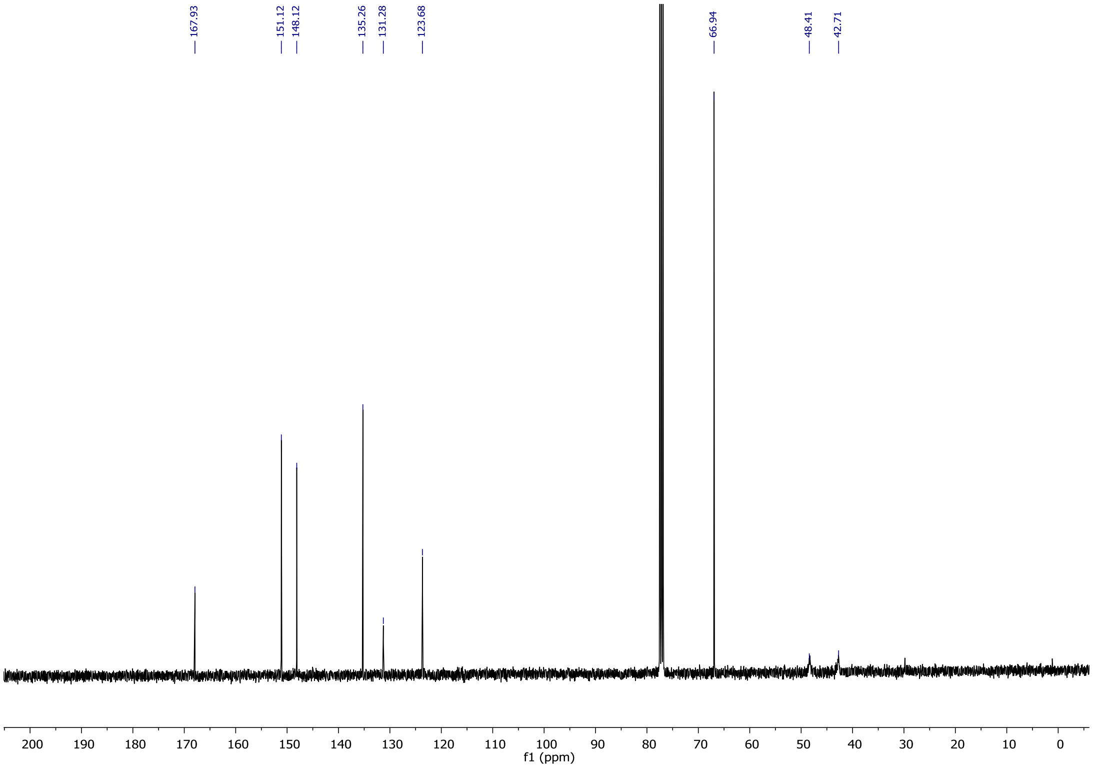
[4-(1,3-Dioxolan-2-yl)phenyl]-morpholin-4-ylmethanone (**3.43**). $CDCl_3$, 400 MHz:



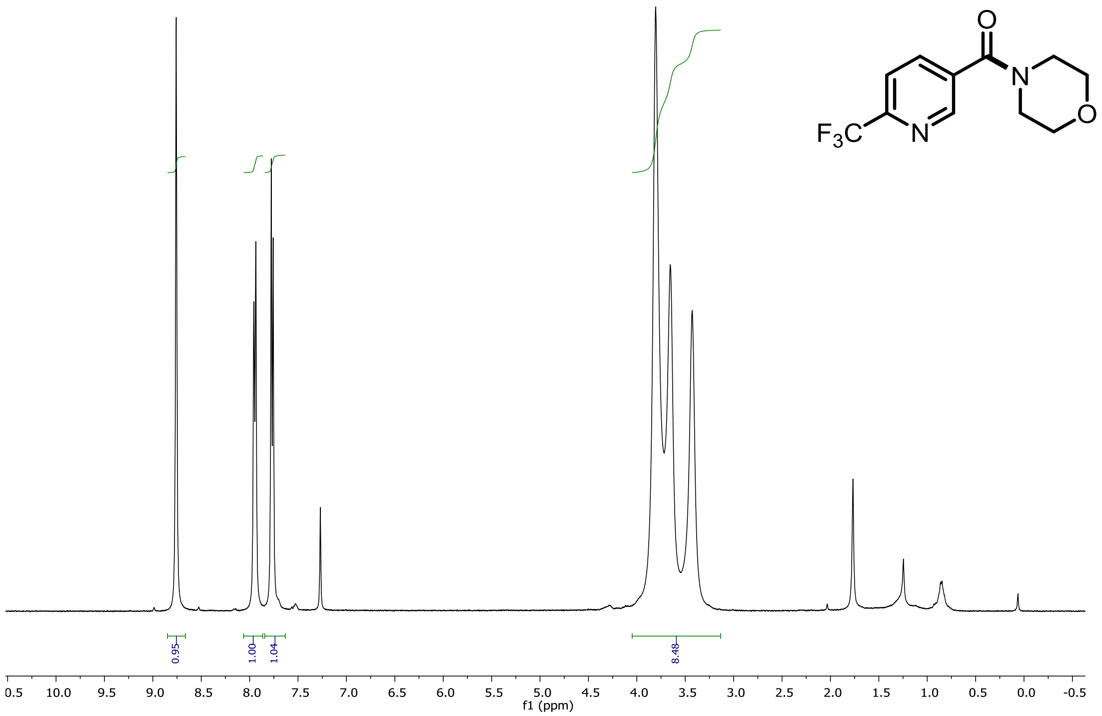


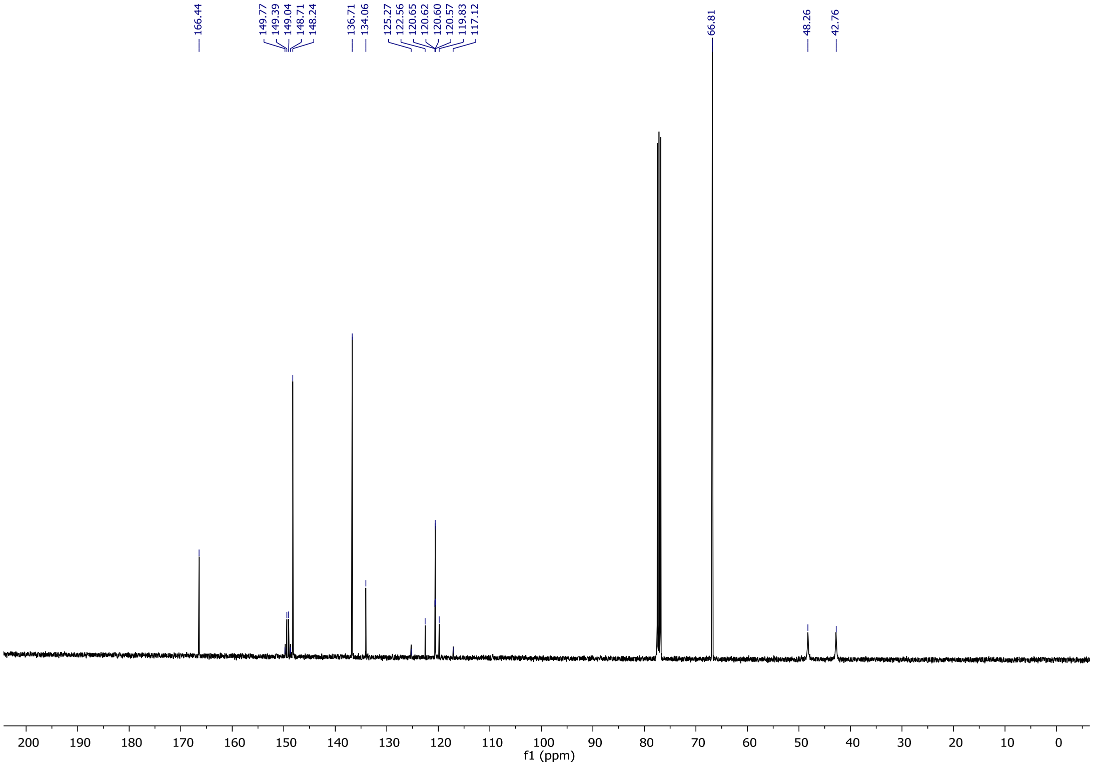
Morpholino(pyridin-3-yl)methanone (**3.44**) $CDCl_3$, 400 MHz:



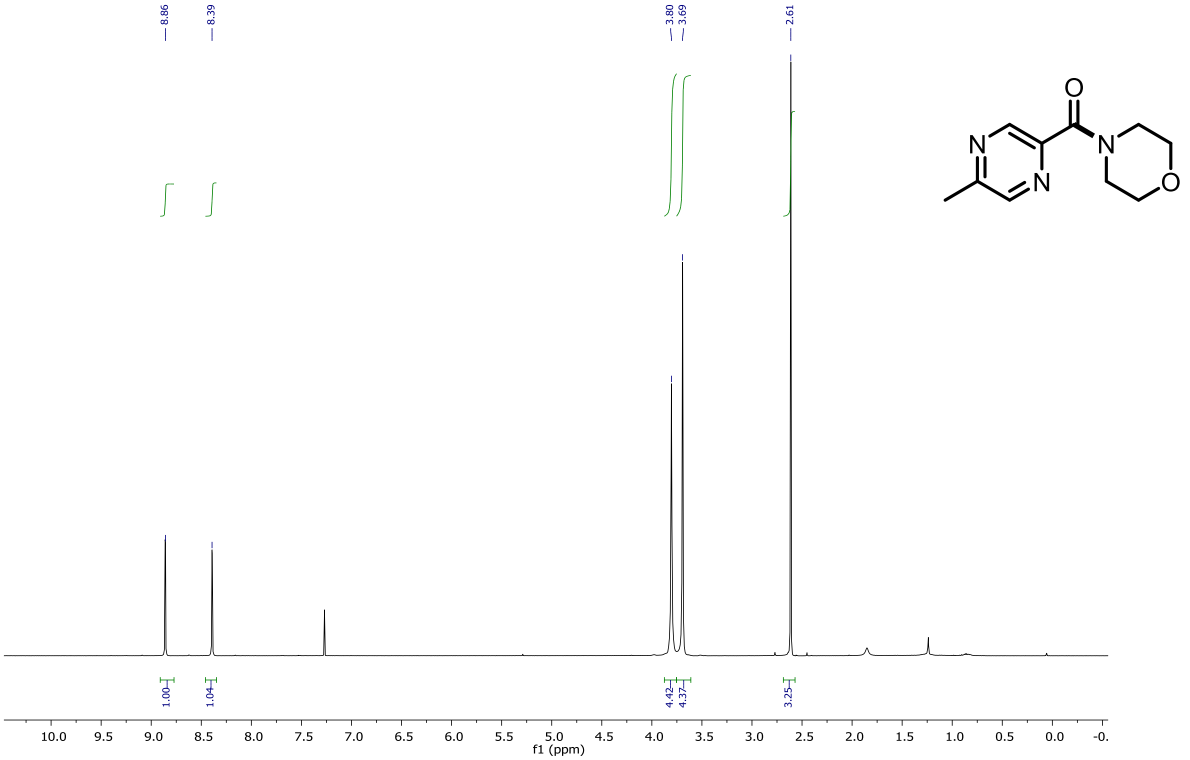


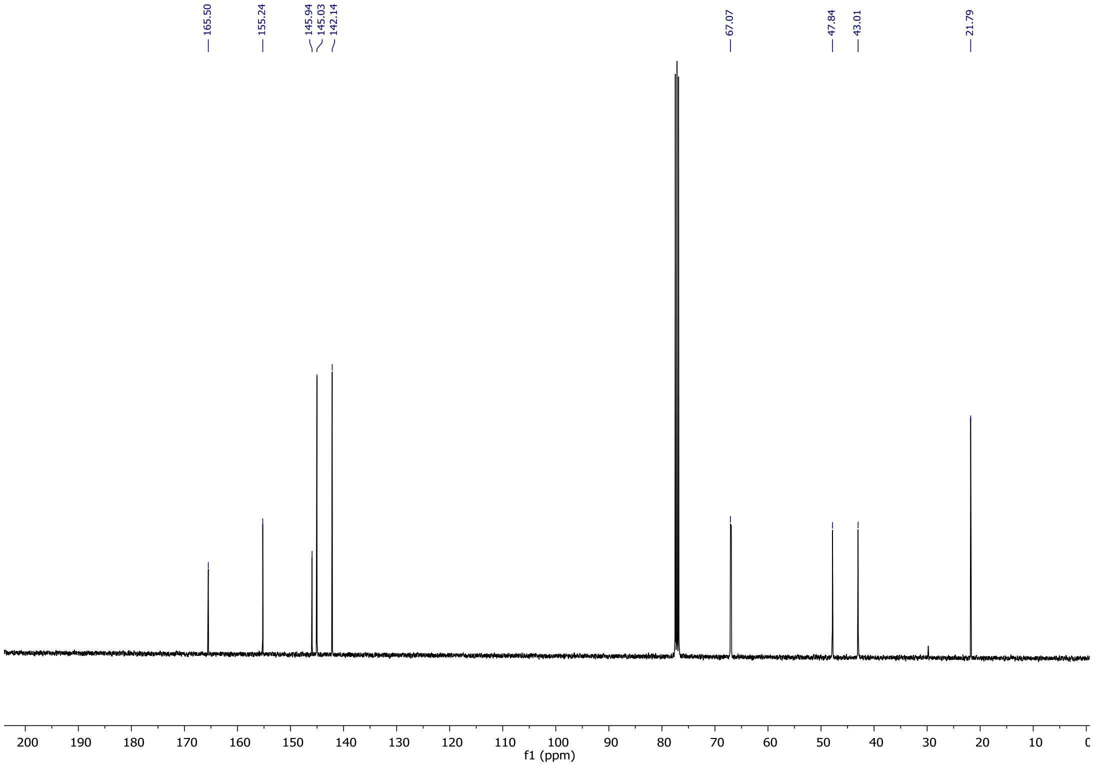
Morpholin-4-yl-[6-(trifluoromethyl)pyridin-3-yl]methanone (**3.45**). $CDCl_3$, 400 MHz :



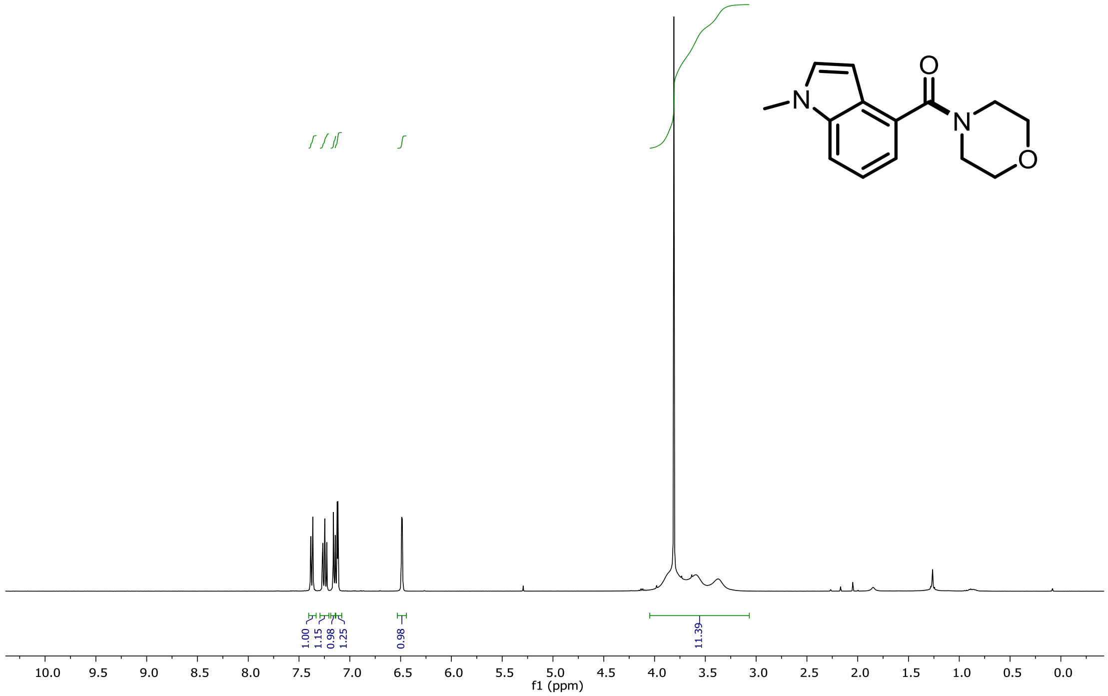


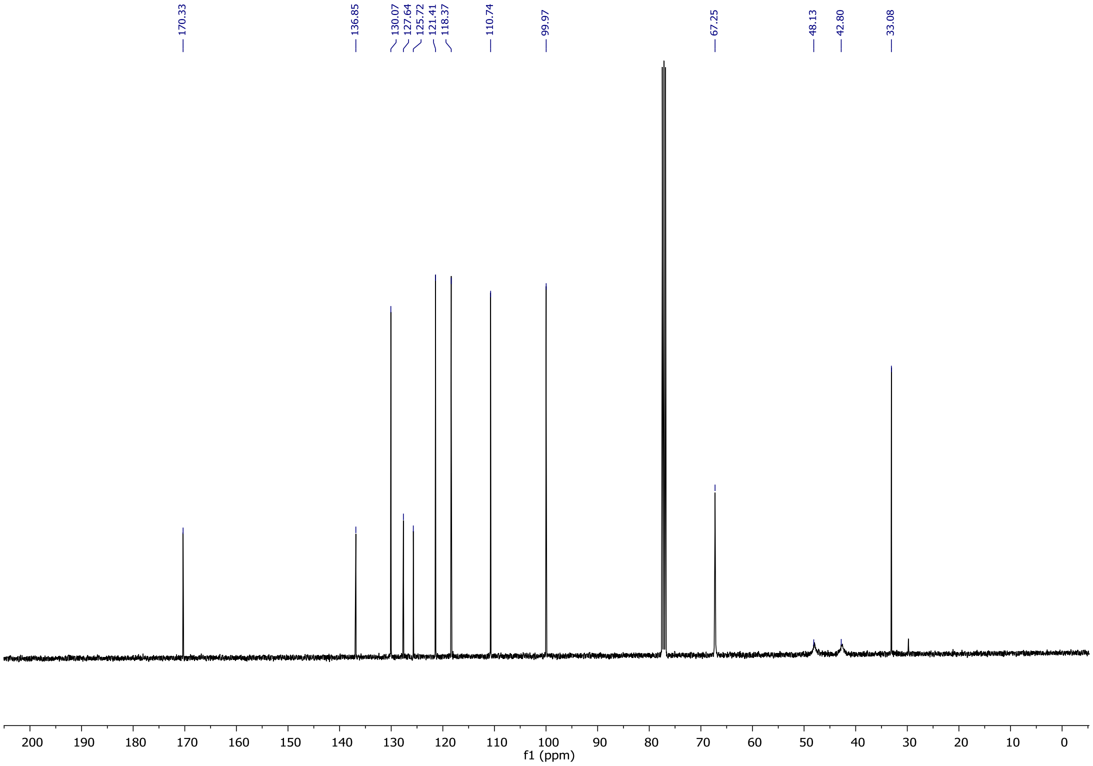
(5-Methylpyrazin-2-yl)(morpholino)methanone (**3.46**). $CDCl_3$, 400 MHz:



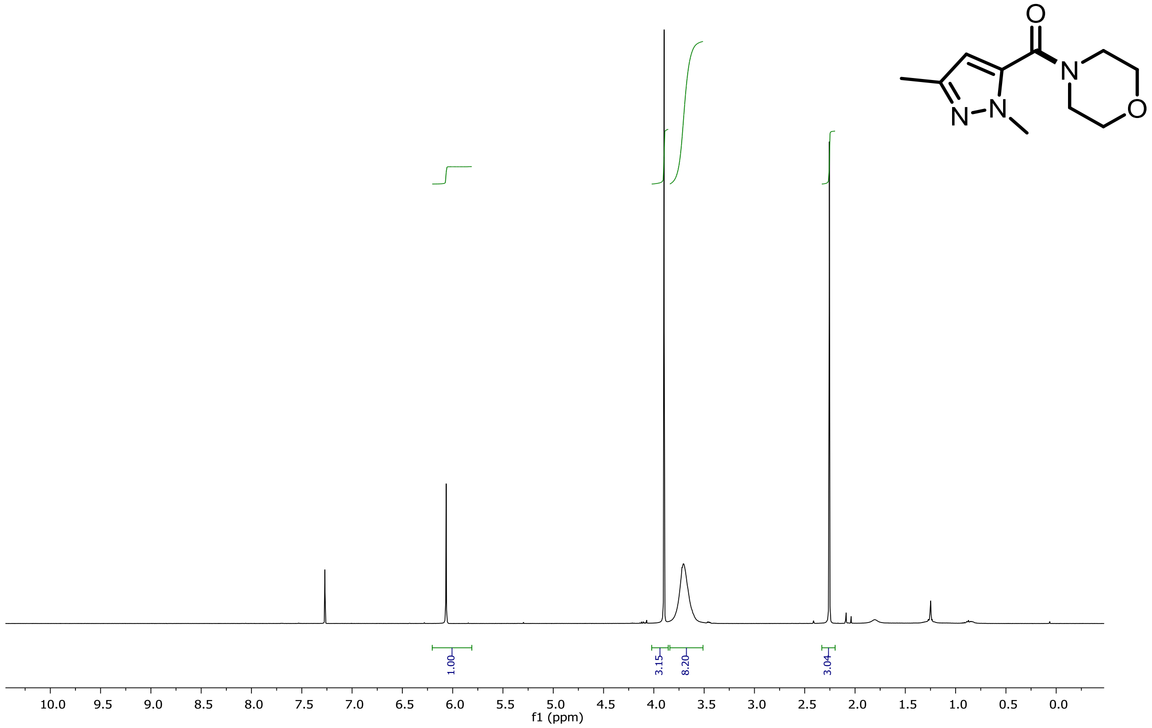


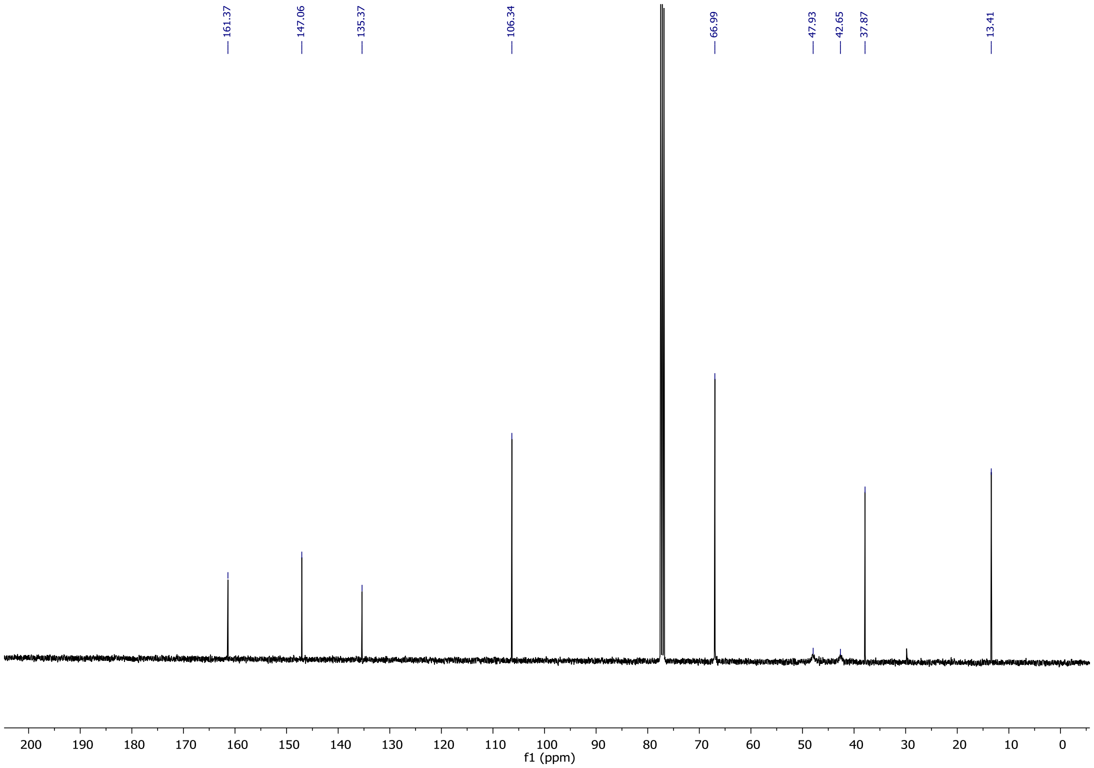
(1-Methyl-1H-indol-4-yl)(morpholino)methanone (**3.47**). $CDCl_3$, 400 MHz:



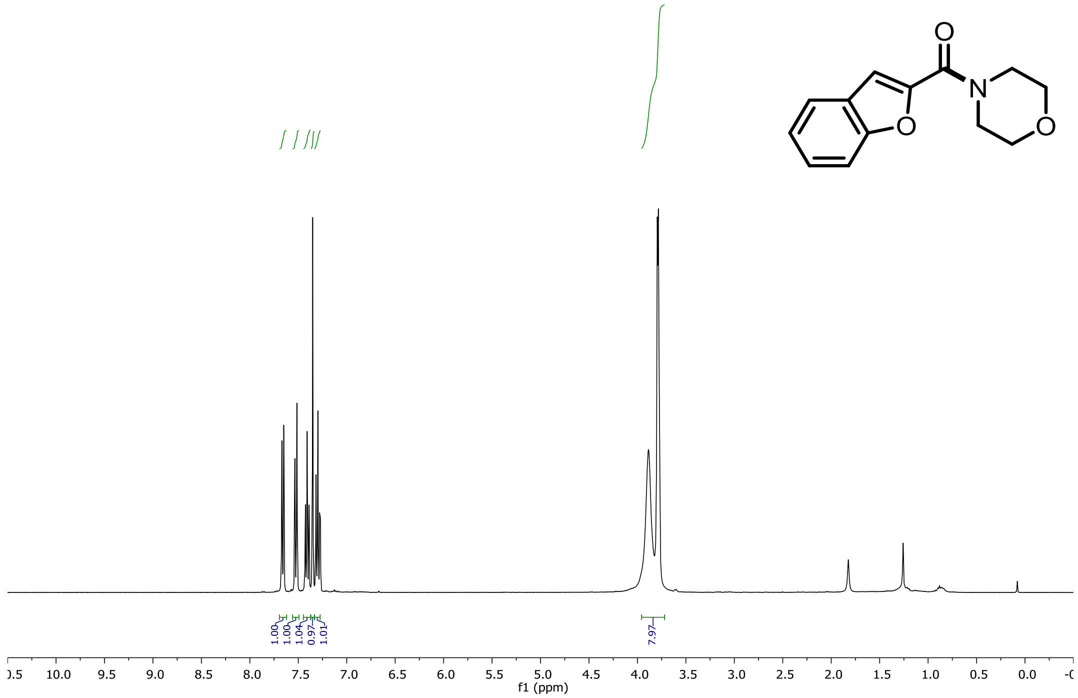


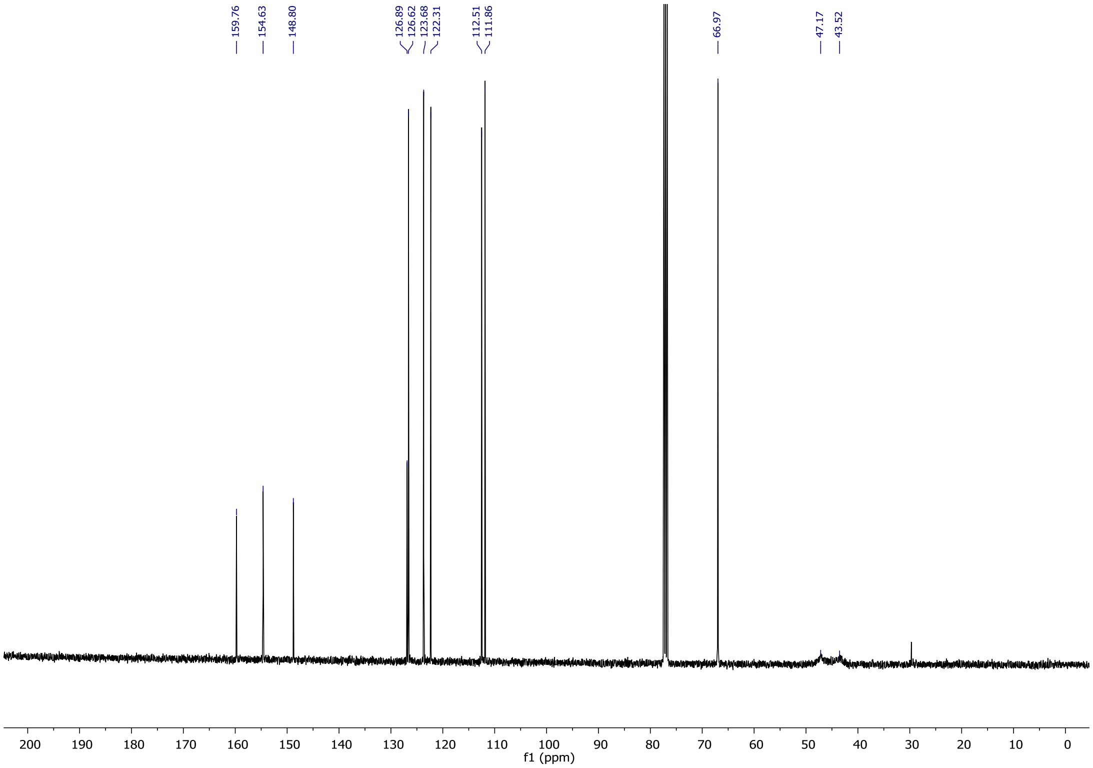
4-(2,5-Dimethyl-2H-pyrazole-3-carbonyl)-morpholine (**3.48**). $CDCl_3$, 400 MHz:



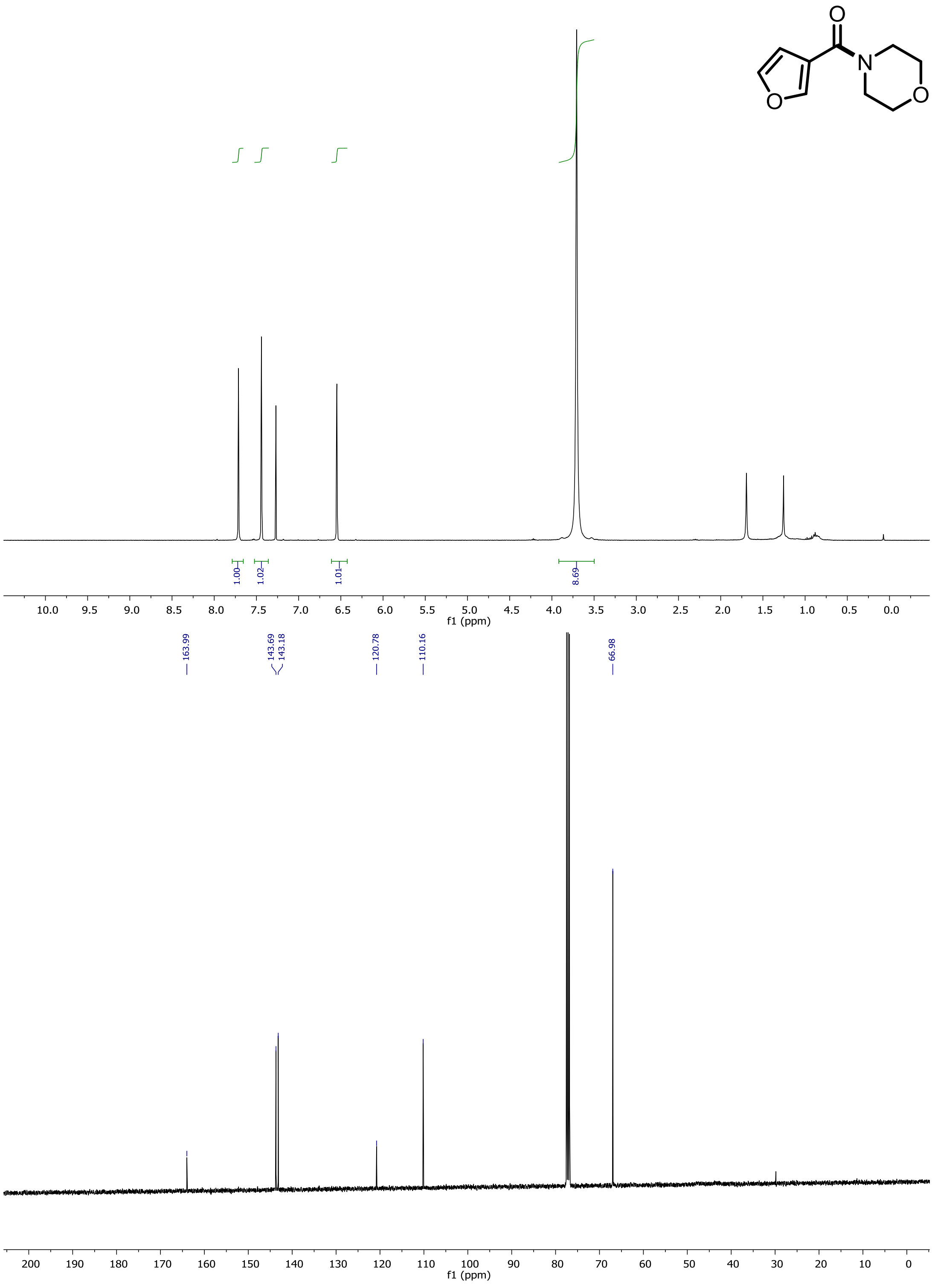


Benzofuran-2-yl(morpholino)methanone (**3.49**). $CDCl_3$, 400 MHz:

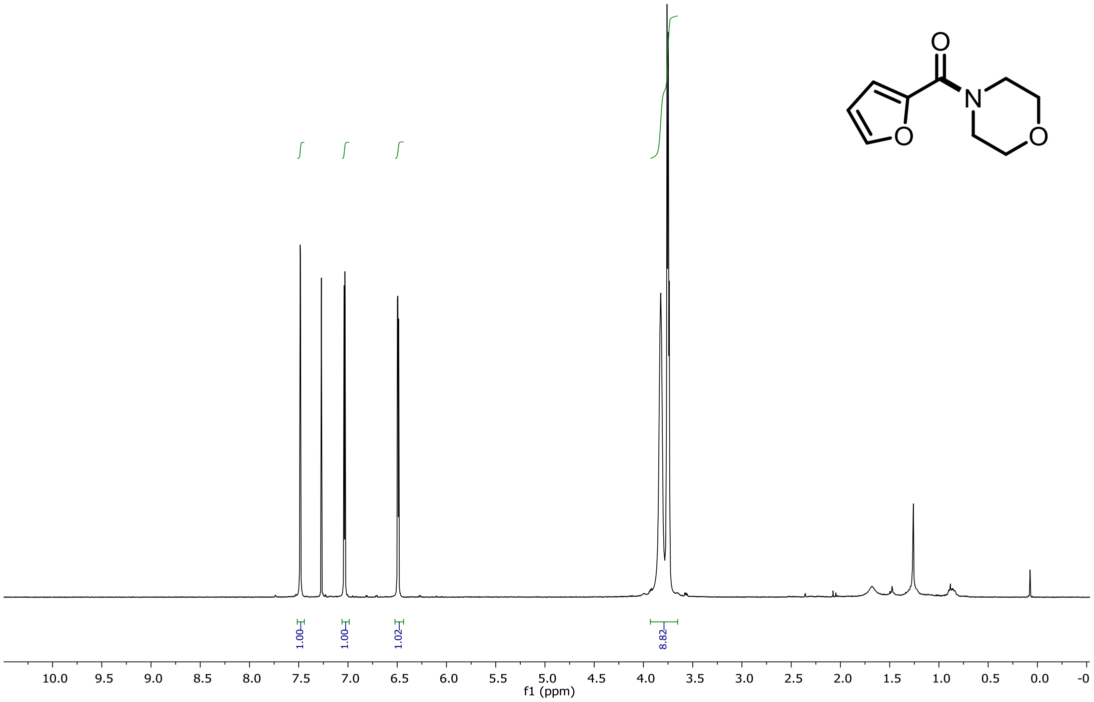


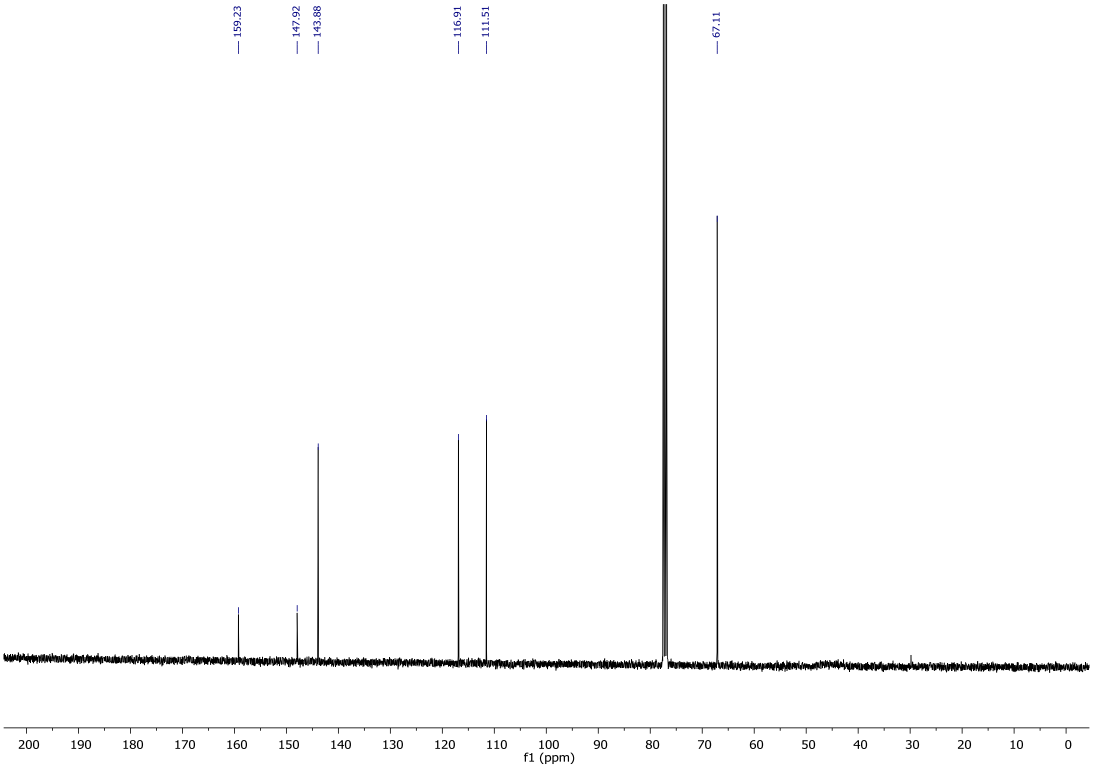


3-Furanyl 4-morpholinyl methanone (**3.50**). $CDCl_3$, 400 MHz:

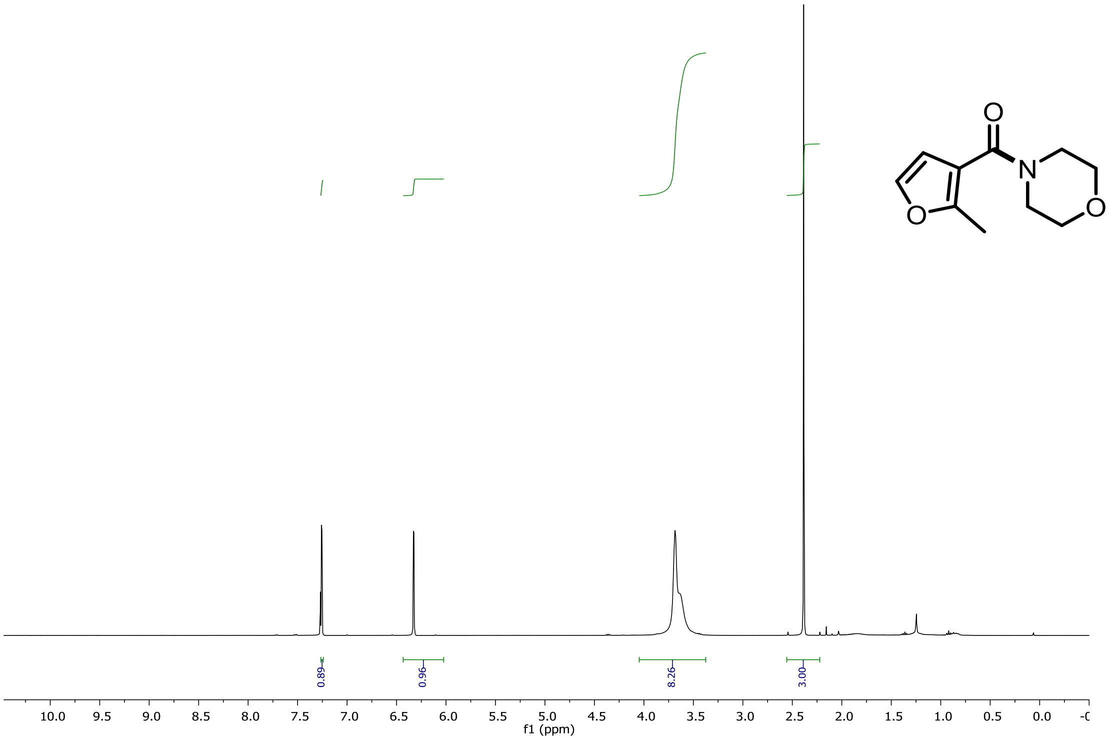


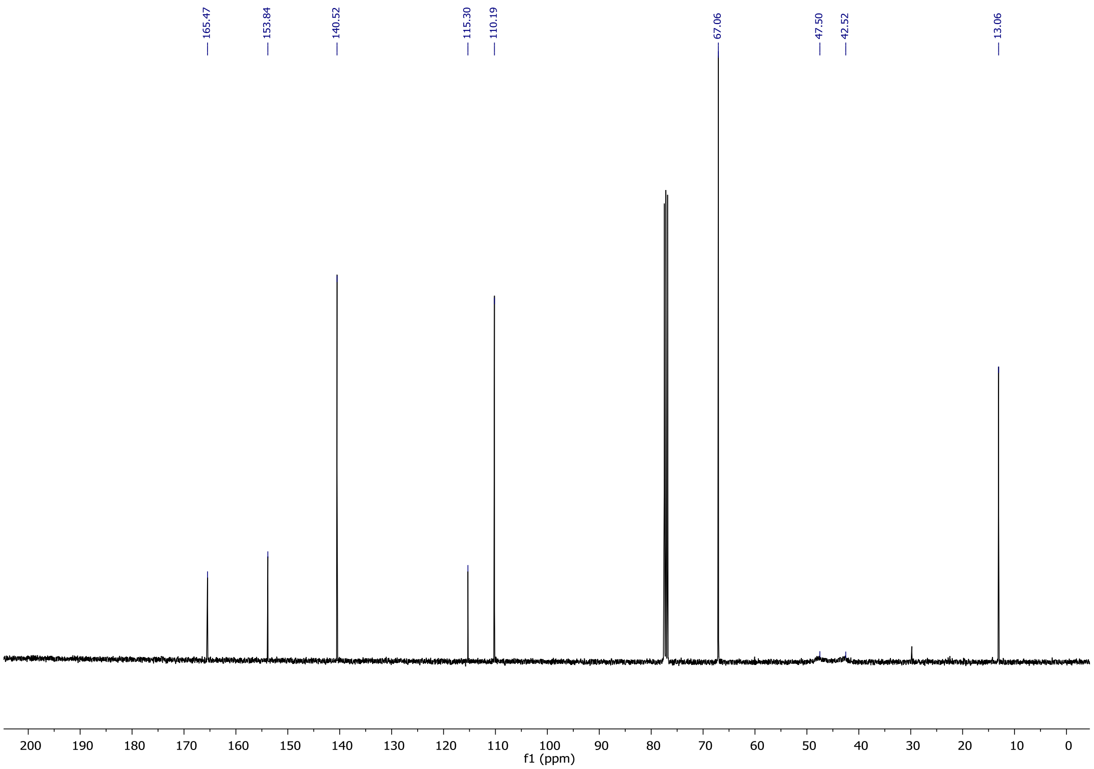
2-Furanyl 4-morpholinyl methanone (**3.51**). $CDCl_3$, 400 MHz:



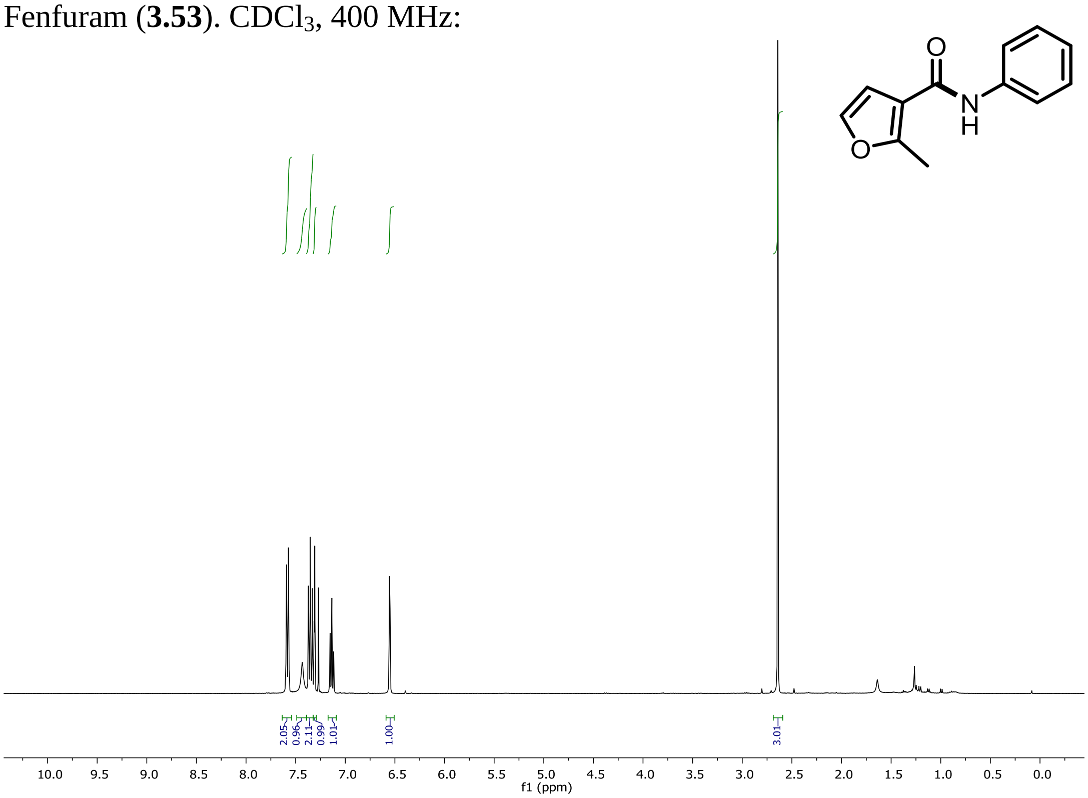


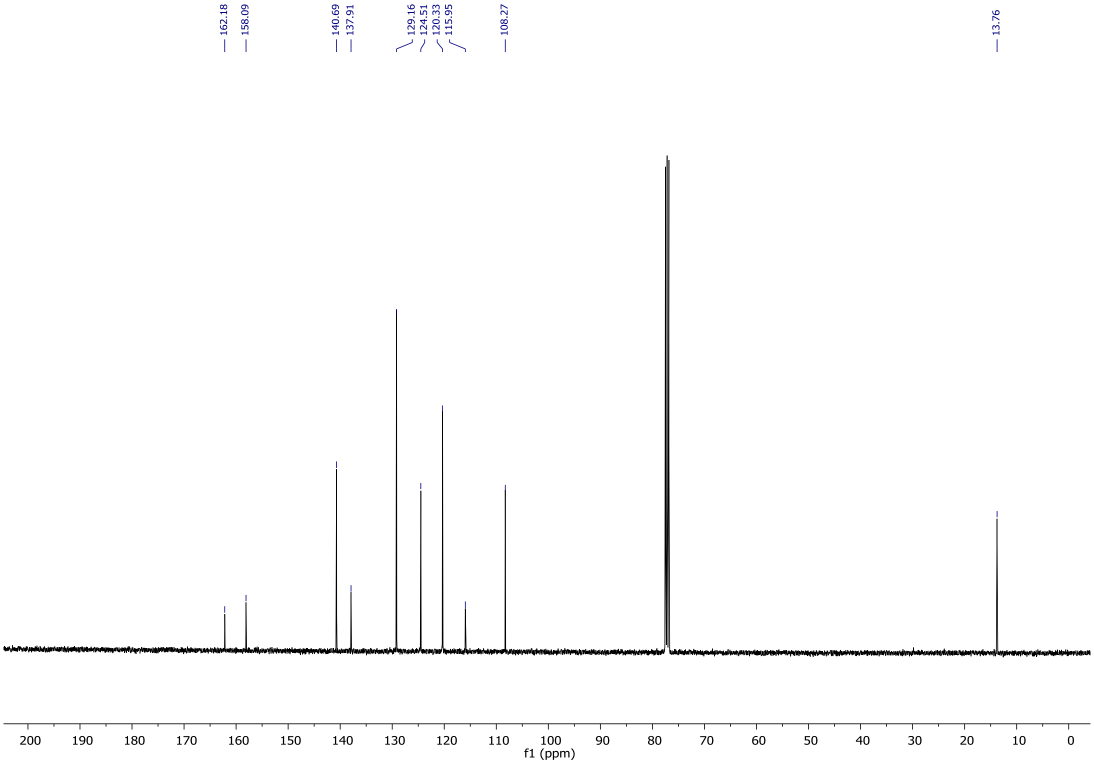
4-(2-Methyl-furan-3-carbonyl)-morpholine (**3.52**). $CDCl_3$, 400 MHz:



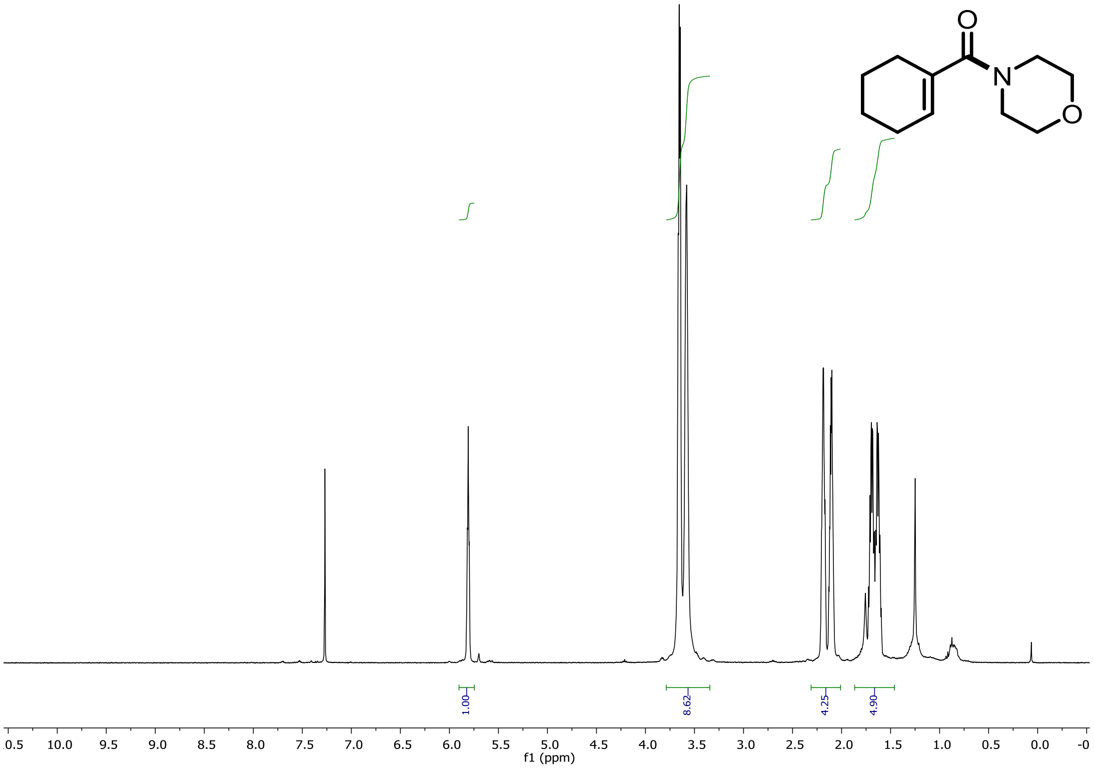


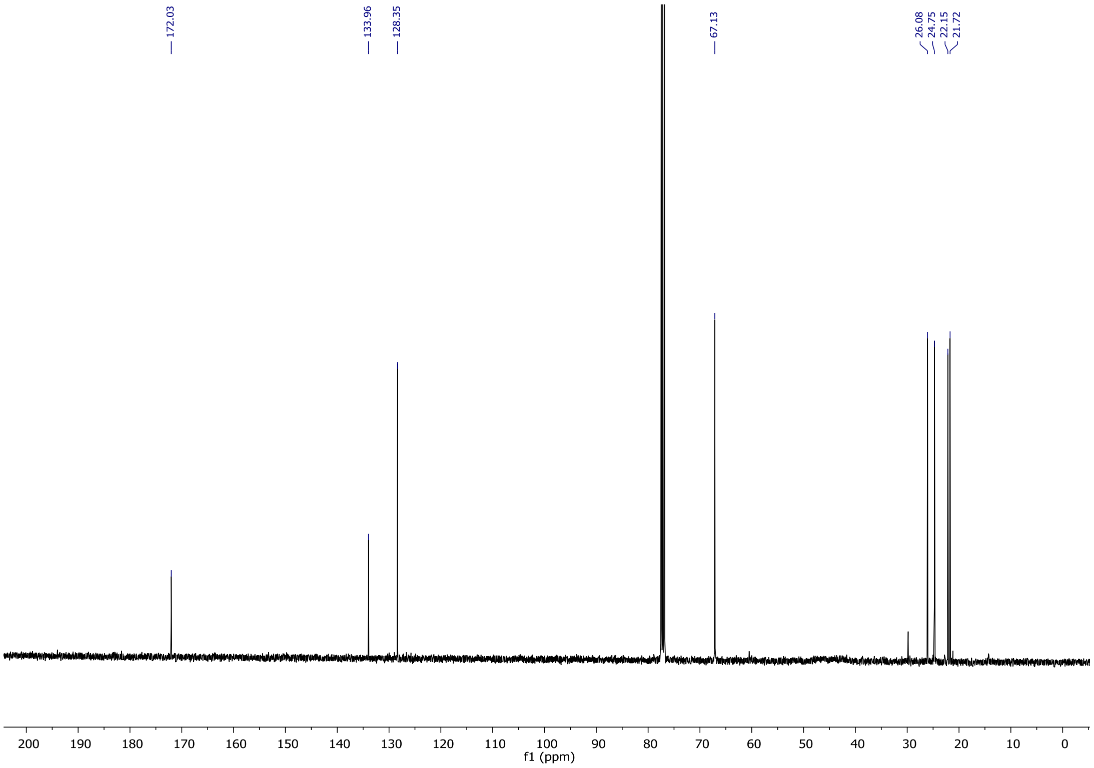
Fenfuram (**3.53**). $CDCl_3$, 400 MHz:



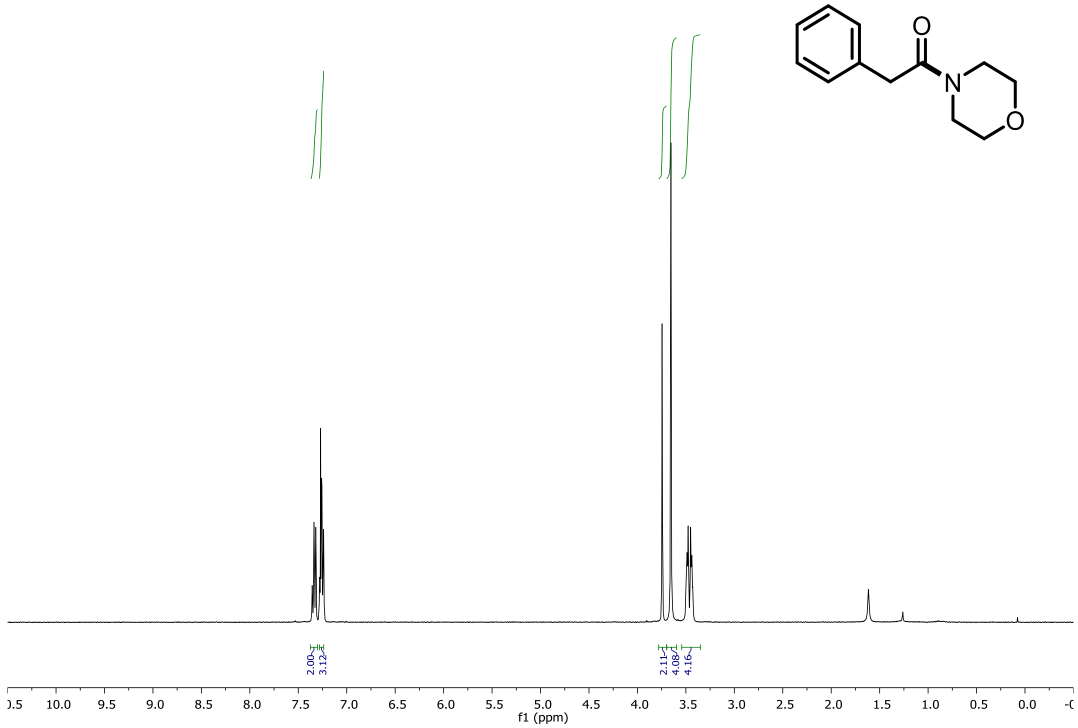


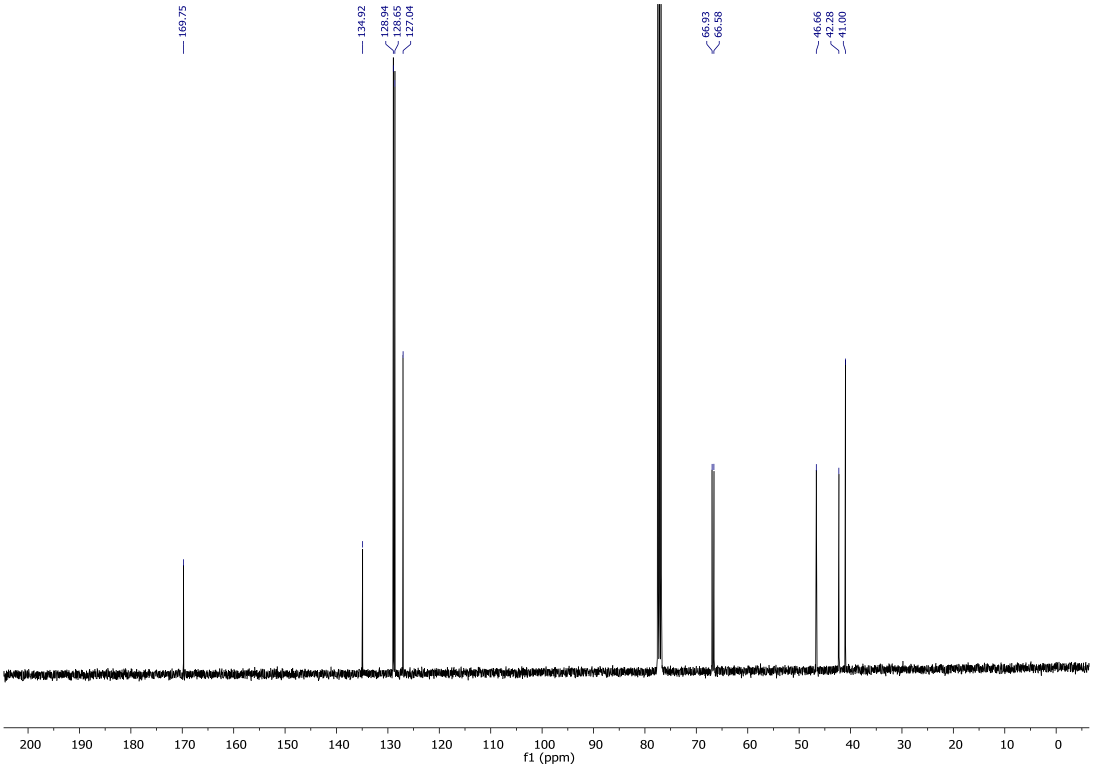
(Cyclohex-1-enyl)(morpholin-4-yl)methanone (**3.54**) $CDCl_3$, 400 MHz:



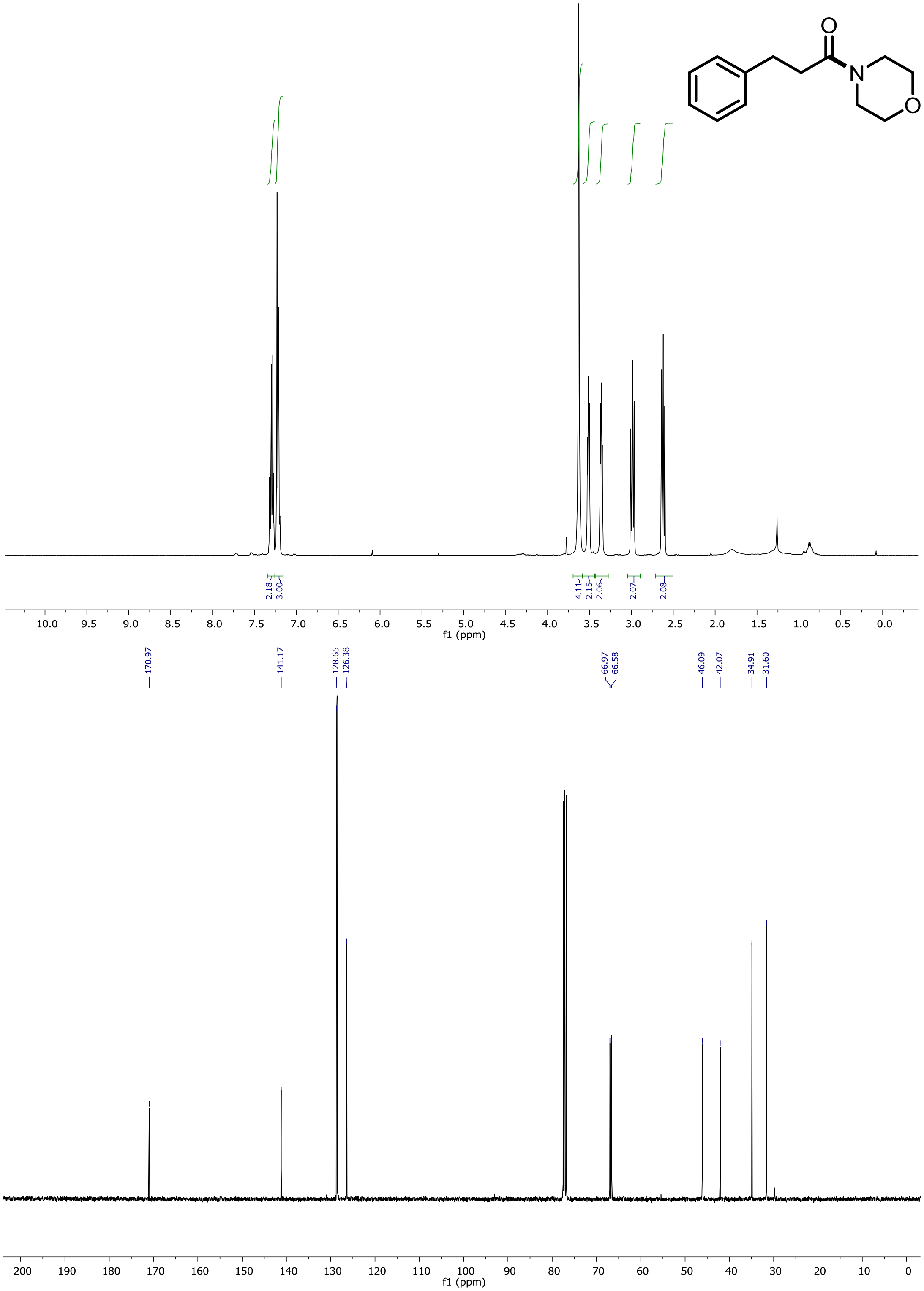


N-(Phenylacetyl)morpholine (**3.55**). $CDCl_3$, 400 MHz:

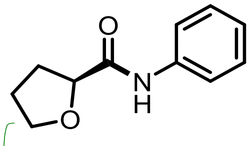


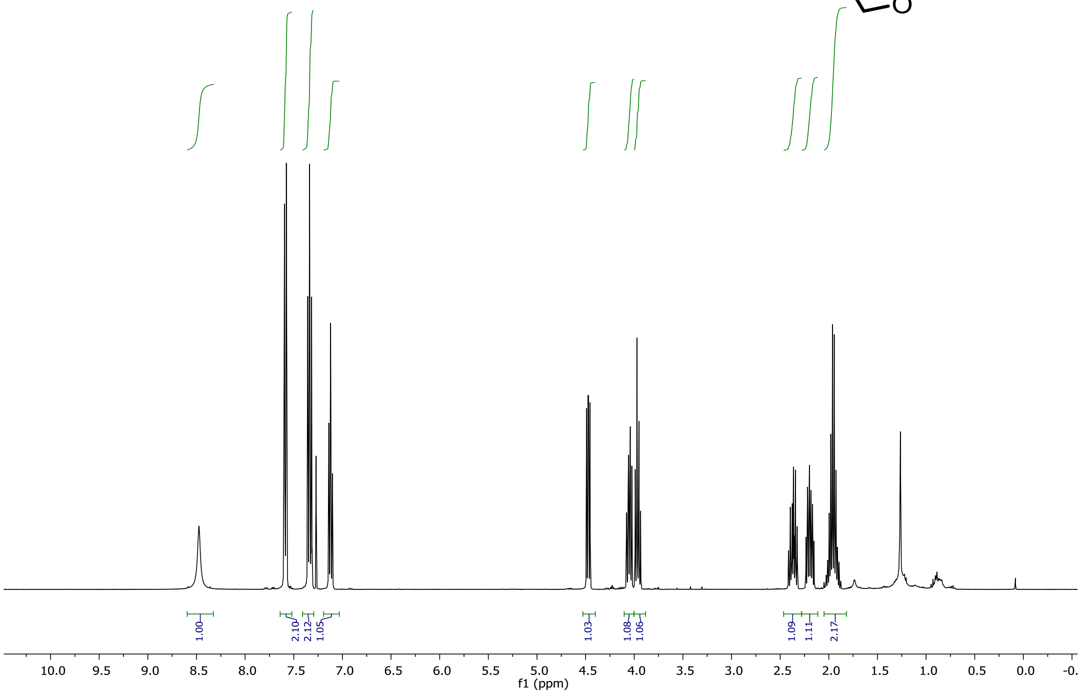


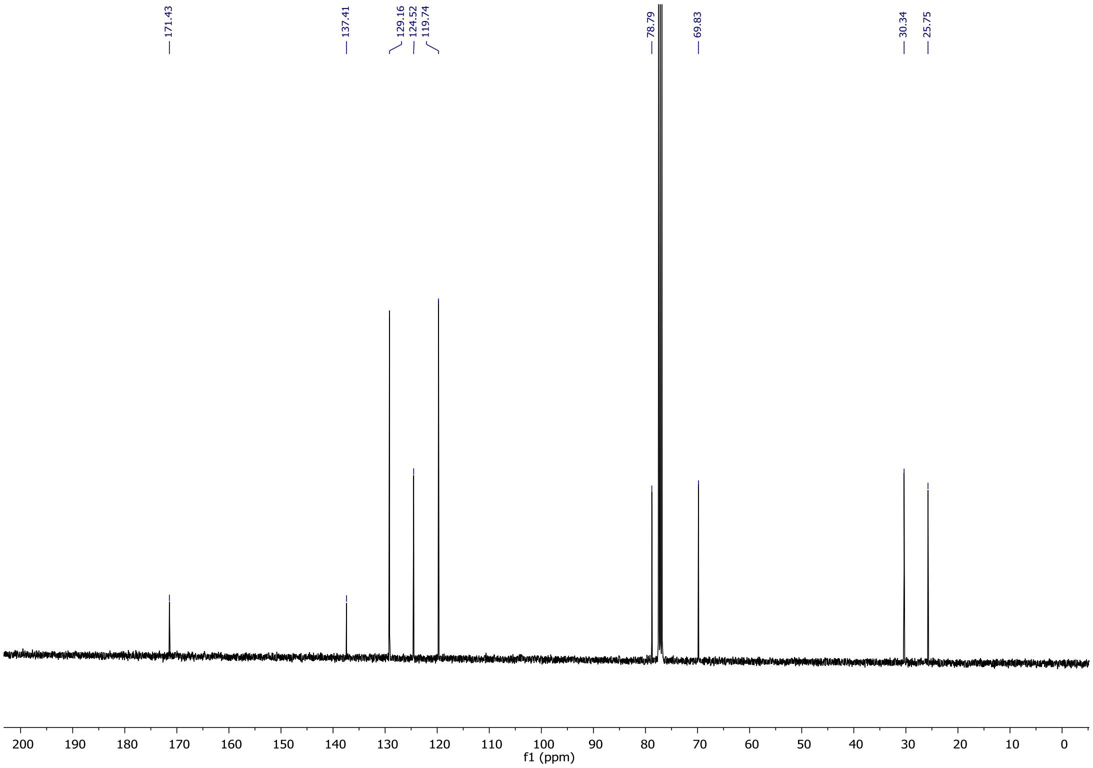
4-(3-Phenyl-propionyl)-morpholine (**3.56**). $CDCl_3$, 400 MHz:



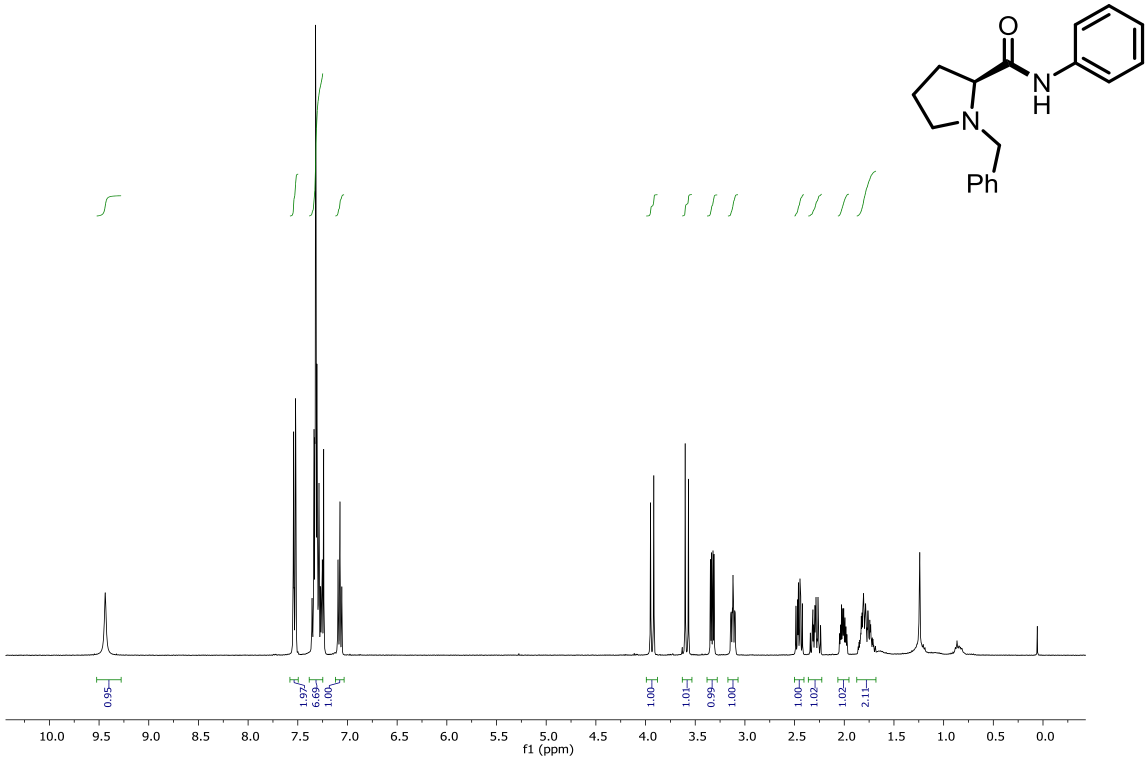
(S)-N-Phenyloxolane-2-carboxamide (**3.58**). $CDCl_3$, 400 MHz:

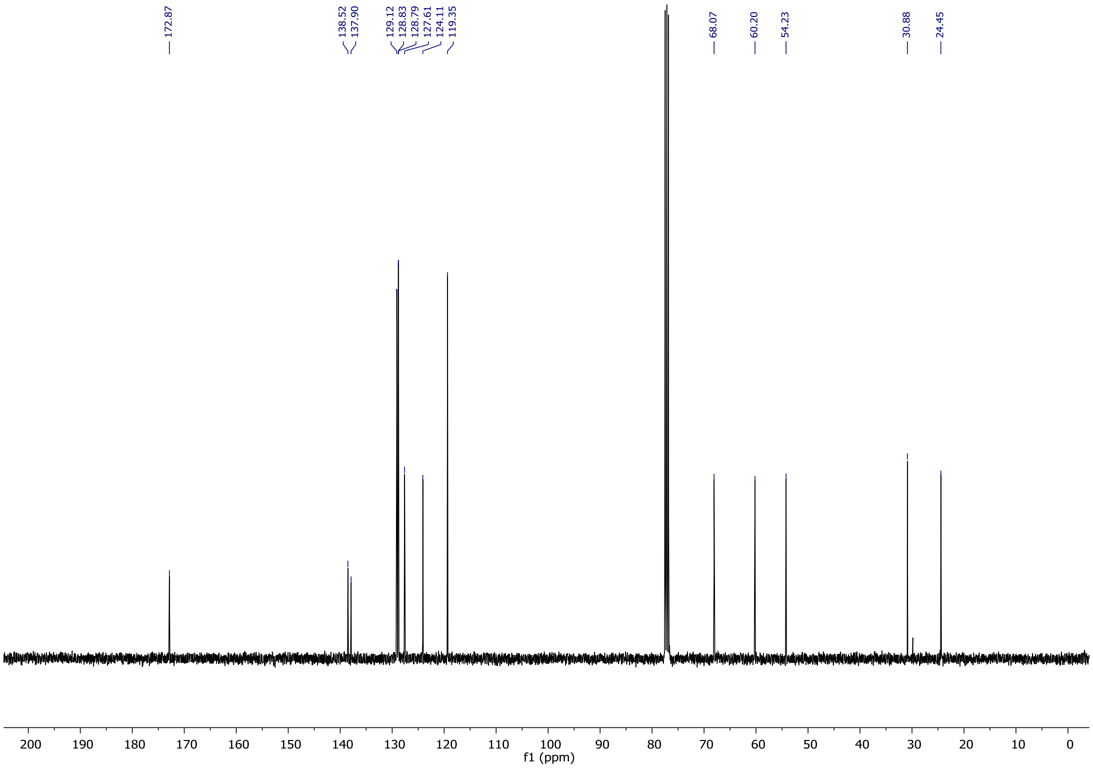




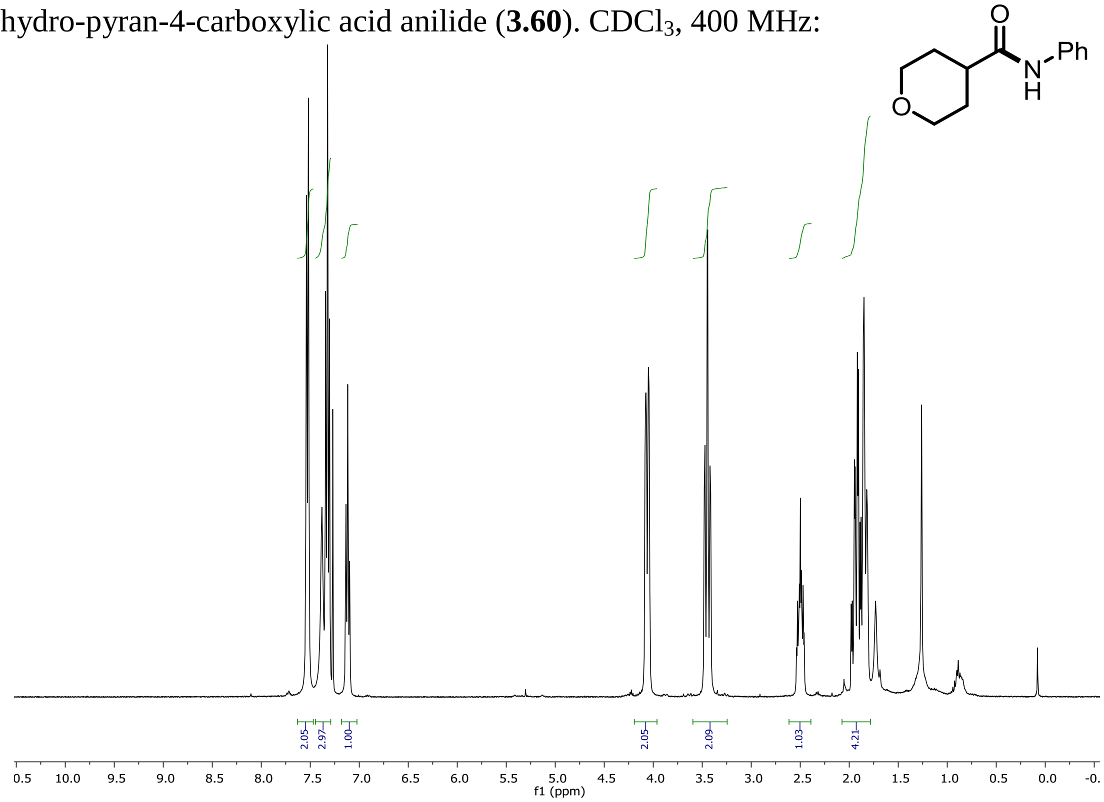


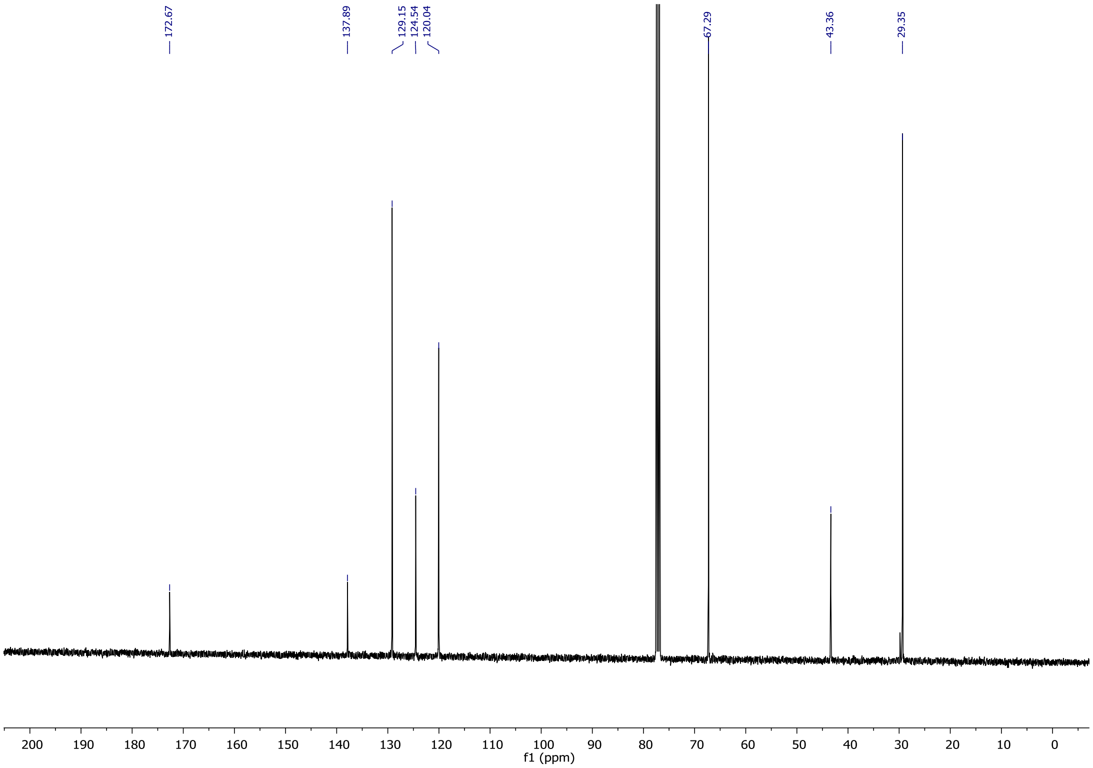
(S)-1-Benzyl-N-phenylpyrrolidine-2-carboxamide (**3.59**) $CDCl_3$, 400 MHz:



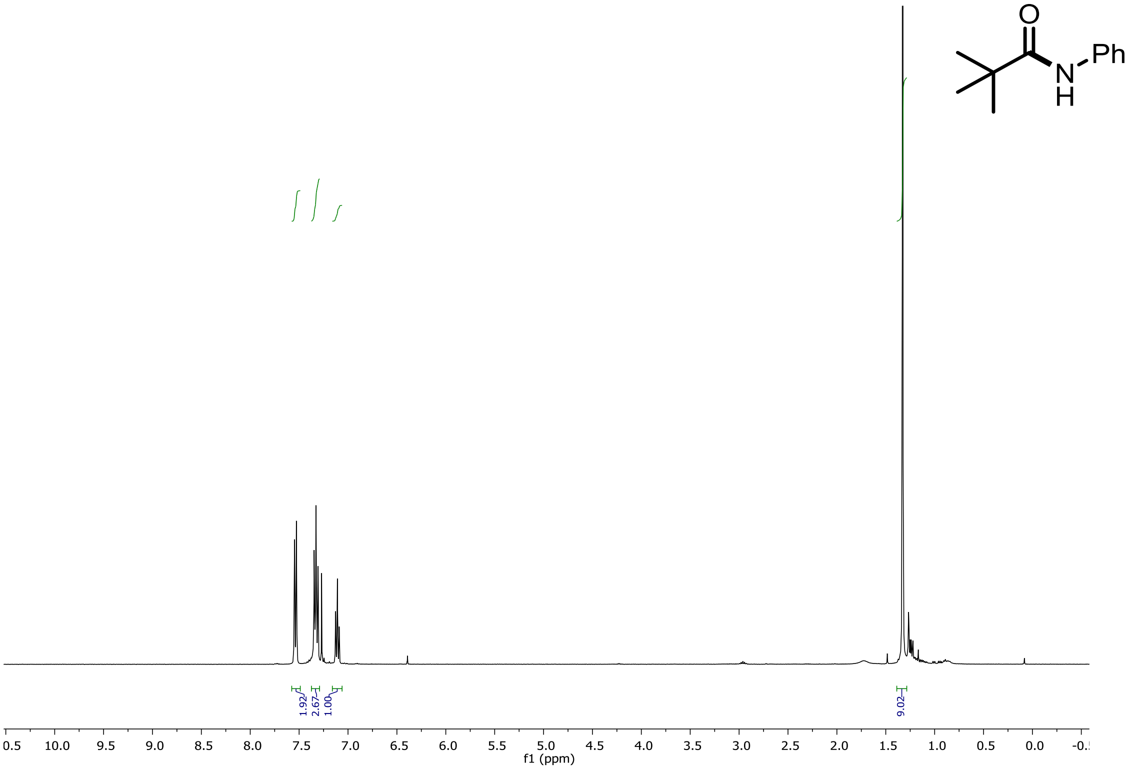


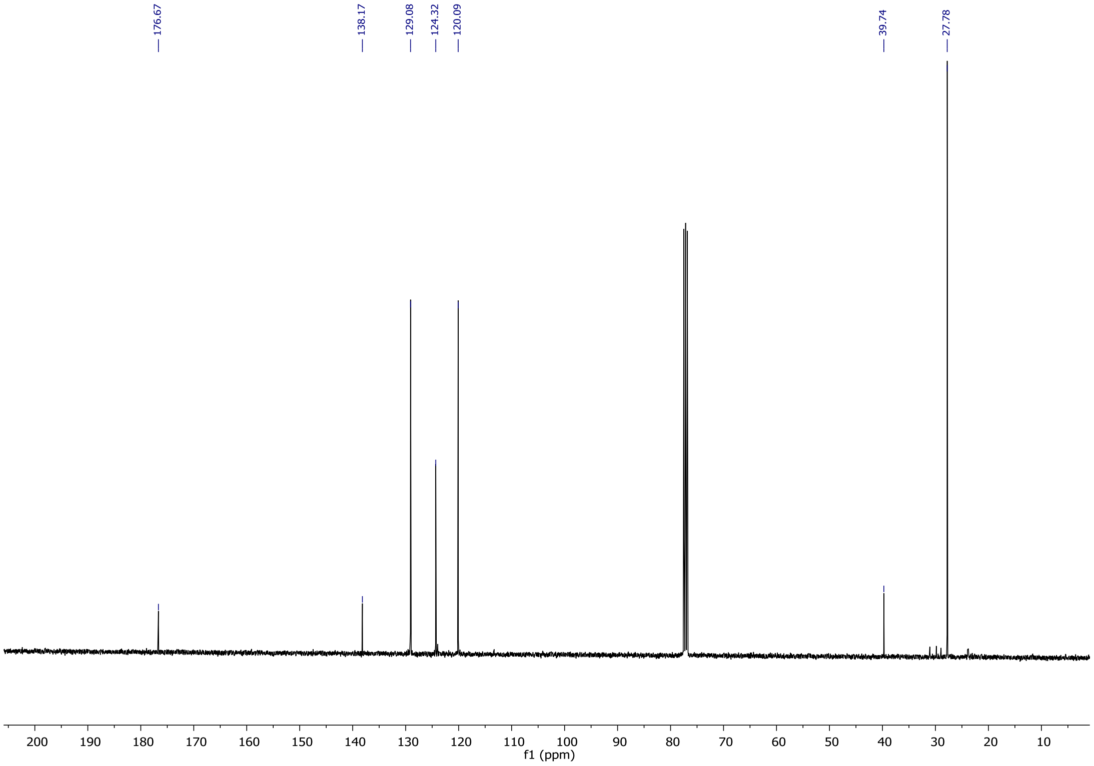
Tetrahydro-pyran-4-carboxylic acid anilide (**3.60**). $CDCl_3$, 400 MHz:



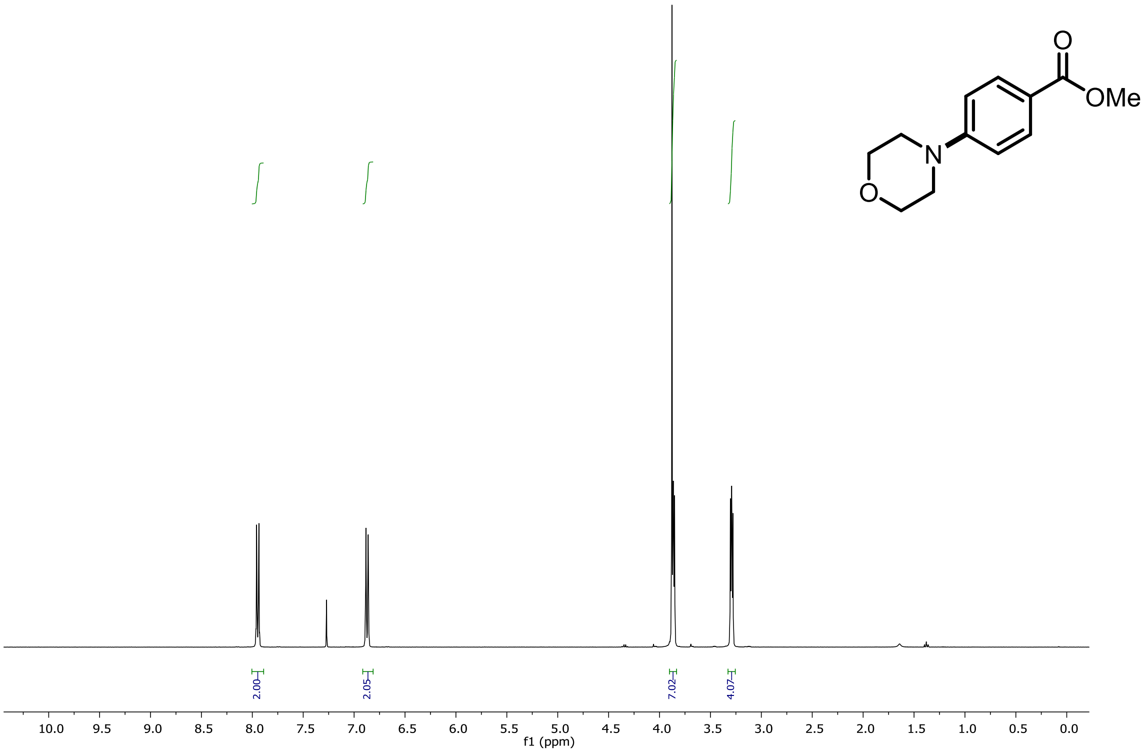


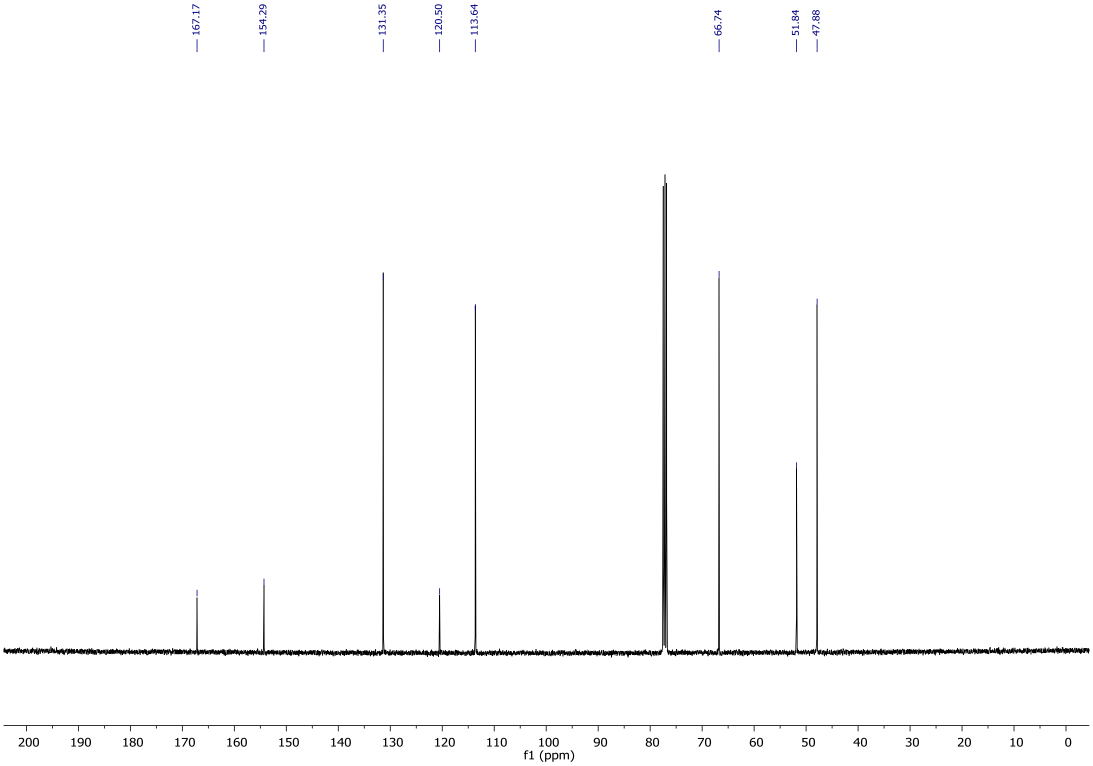
N-Pivaloylaniline (**3.61**). $CDCl_3$, 400 MHz:



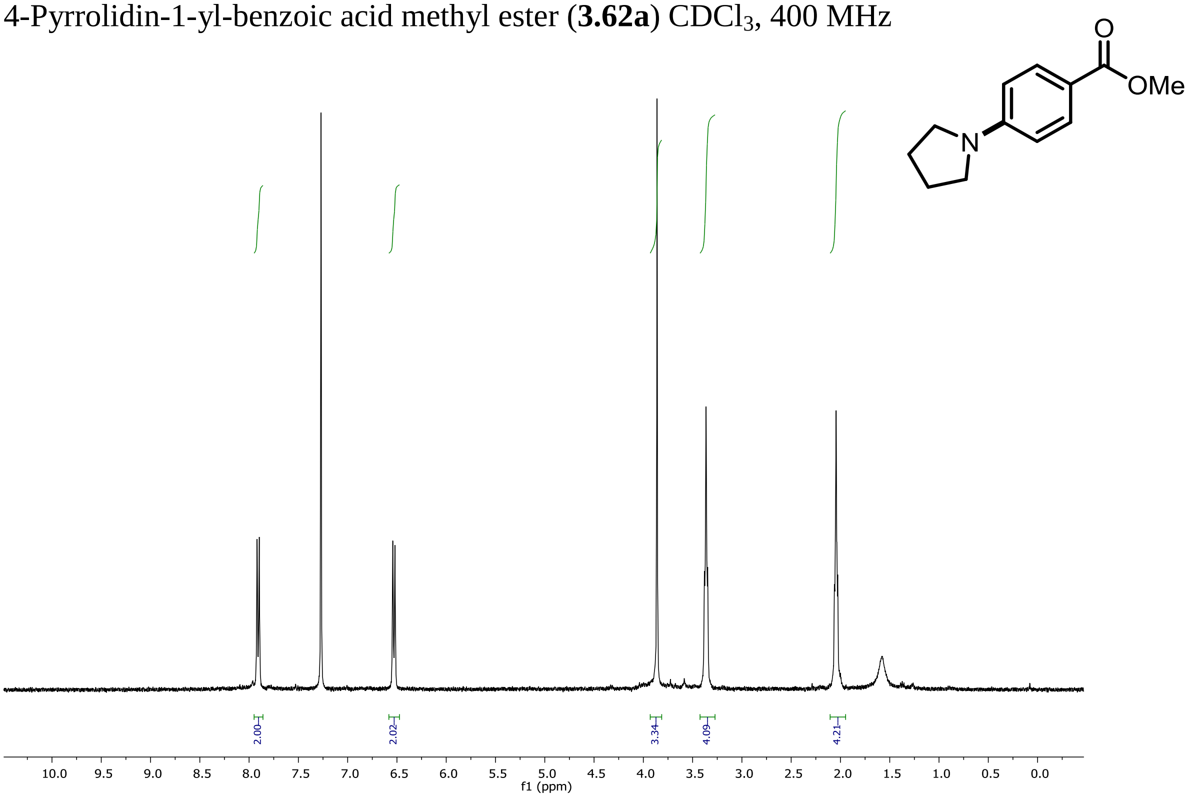


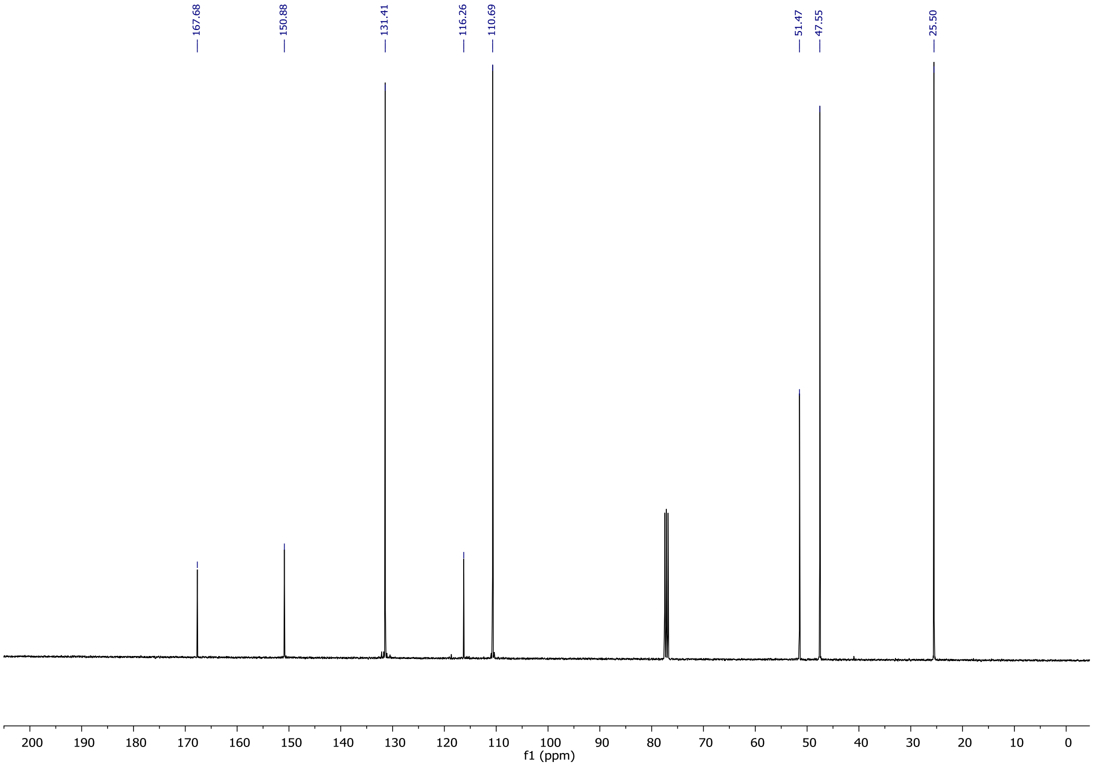
4-Morpholin-4-yl-benzoic acid methyl ester (**3.62b**) $CDCl_3$, 400 MHz



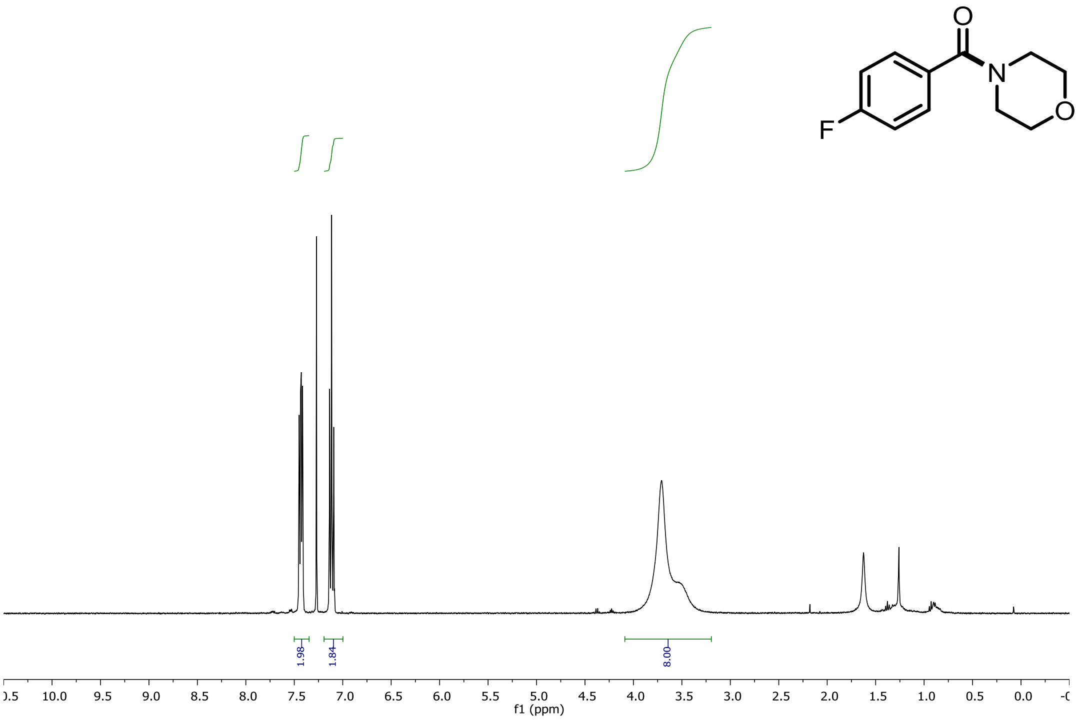


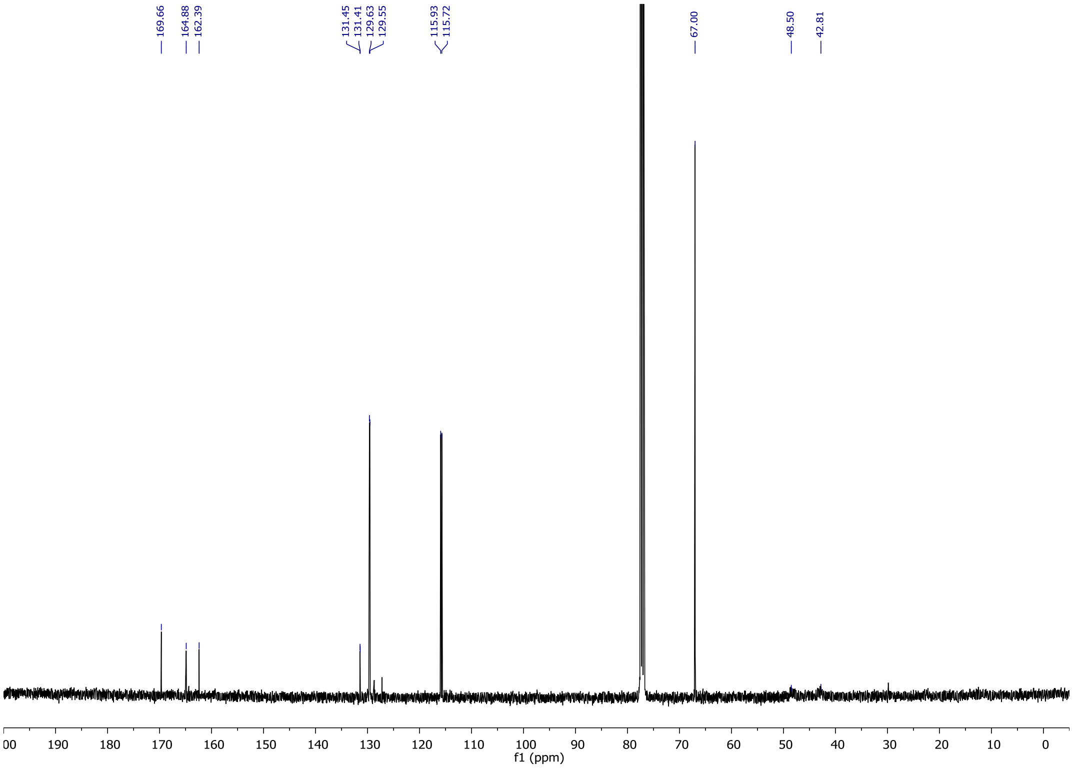
4-Pyrrolidin-1-yl-benzoic acid methyl ester (**3.62a**) $CDCl_3$, 400 MHz



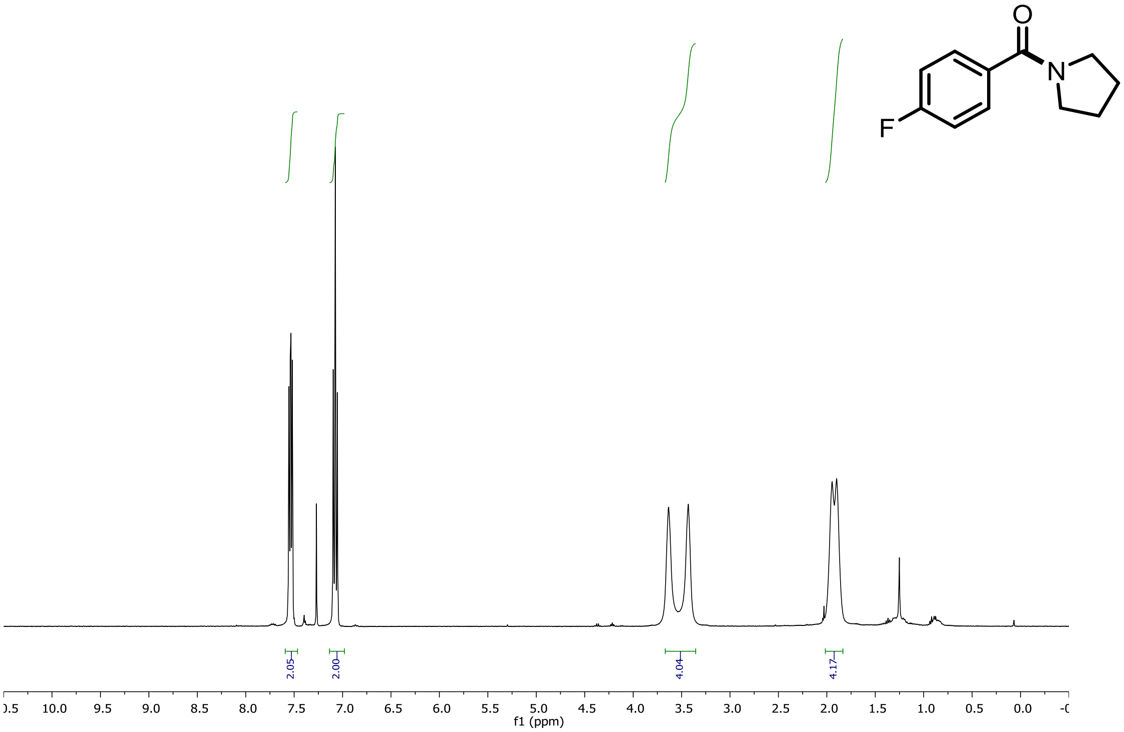


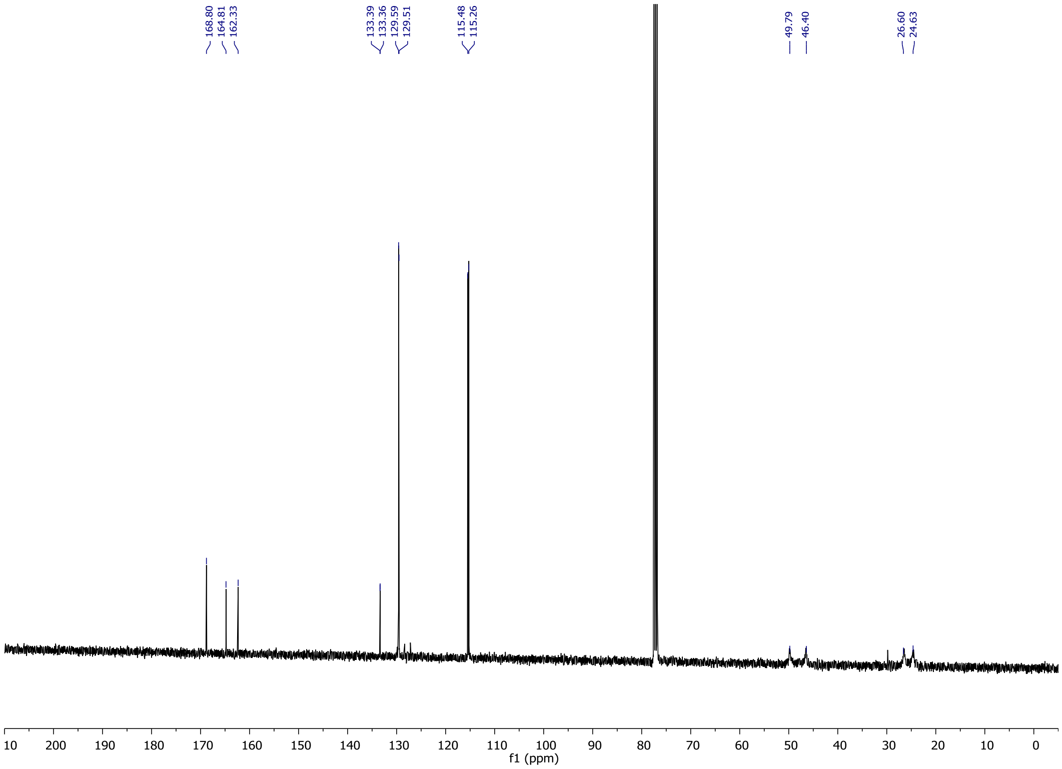
4-(4-Fluorobenzoyl)morpholine (**3.65b**) $CDCl_3$, 400 MHz:



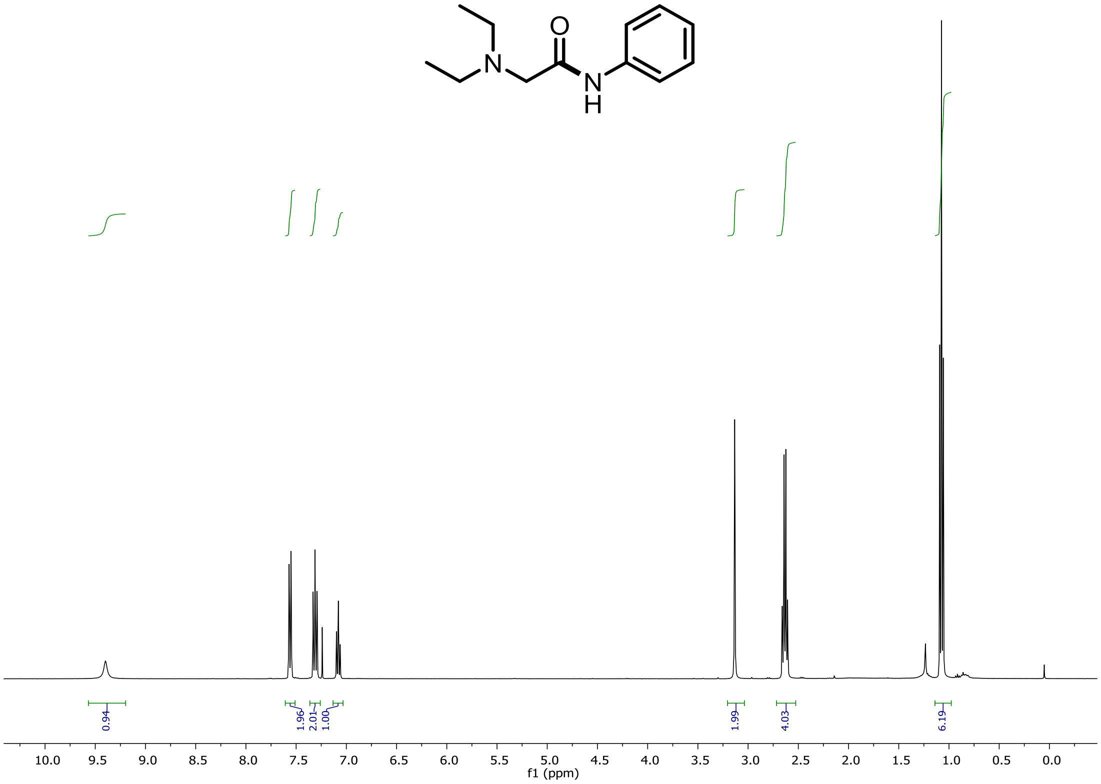


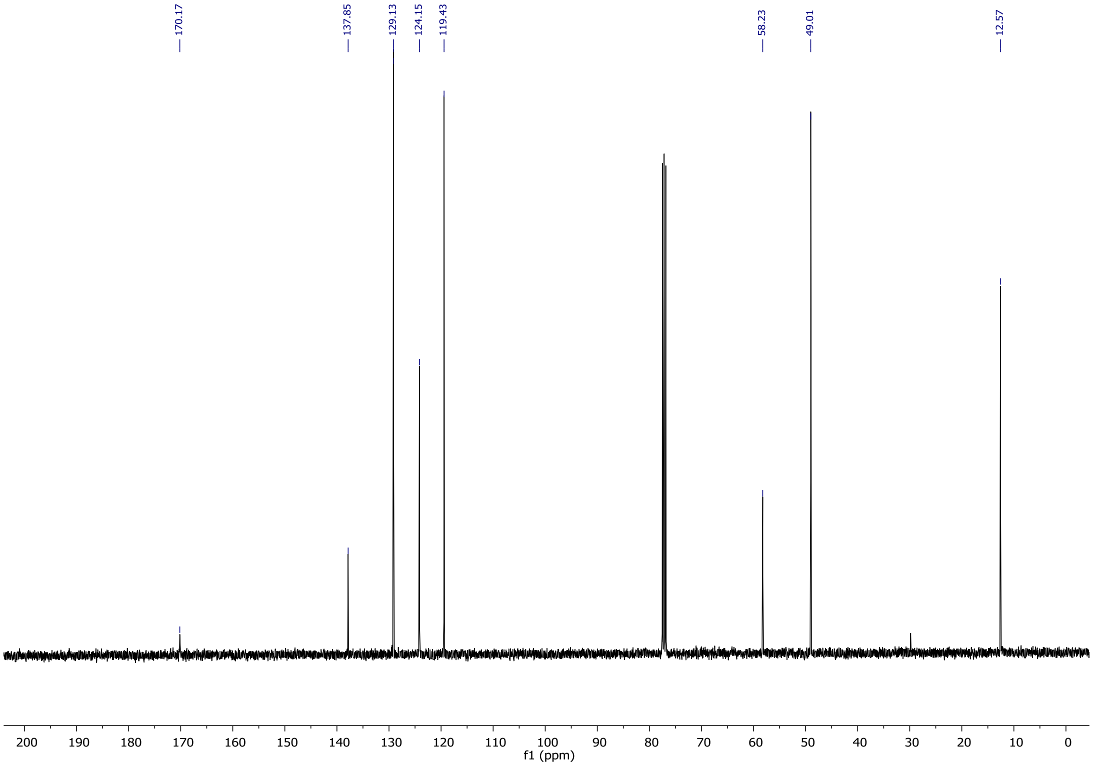
(4-Fluorophenyl)(pyrrolidin-1-yl)methanone (**3.65a**) $CDCl_3$, 400 MHz:



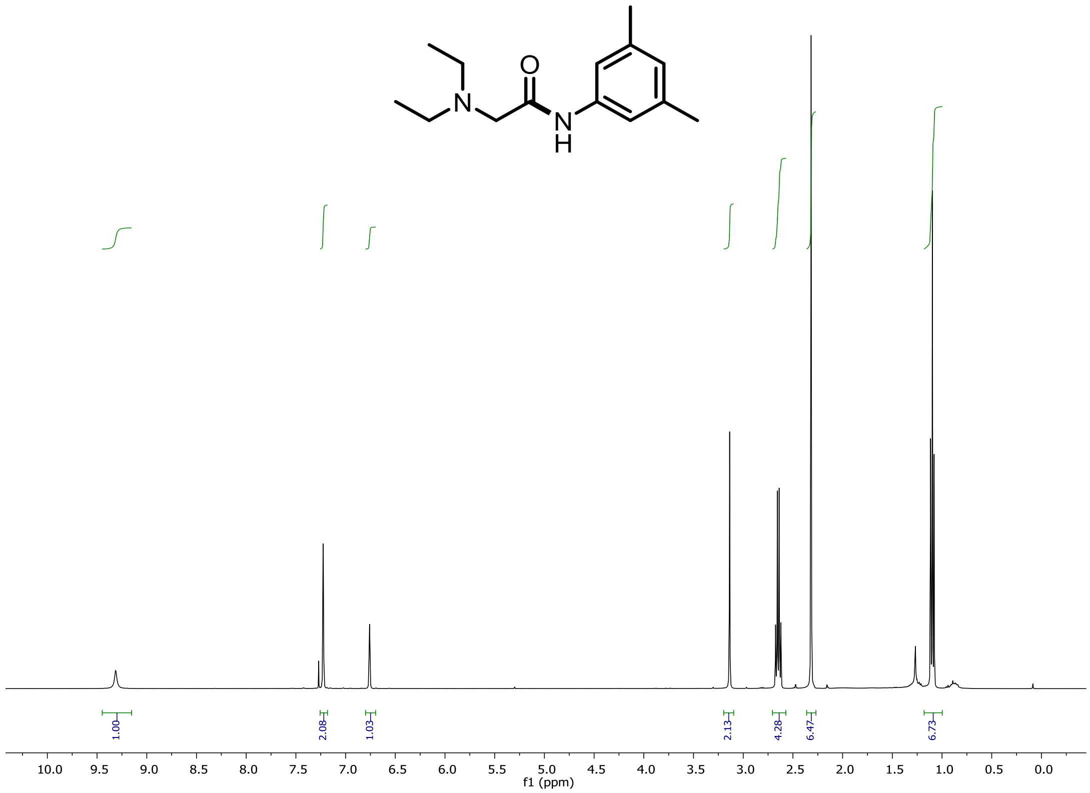


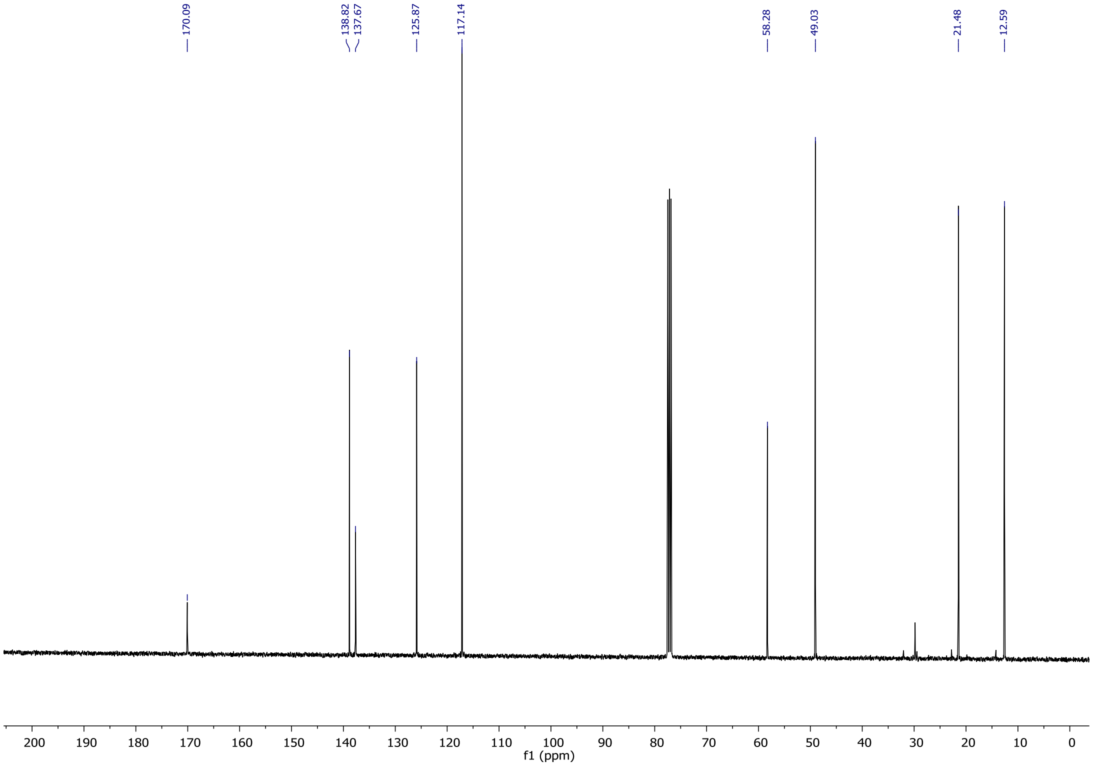
2-Diethylamino-N-phenylacetamide (**3.72a**) $CDCl_3$, 400 MHz:



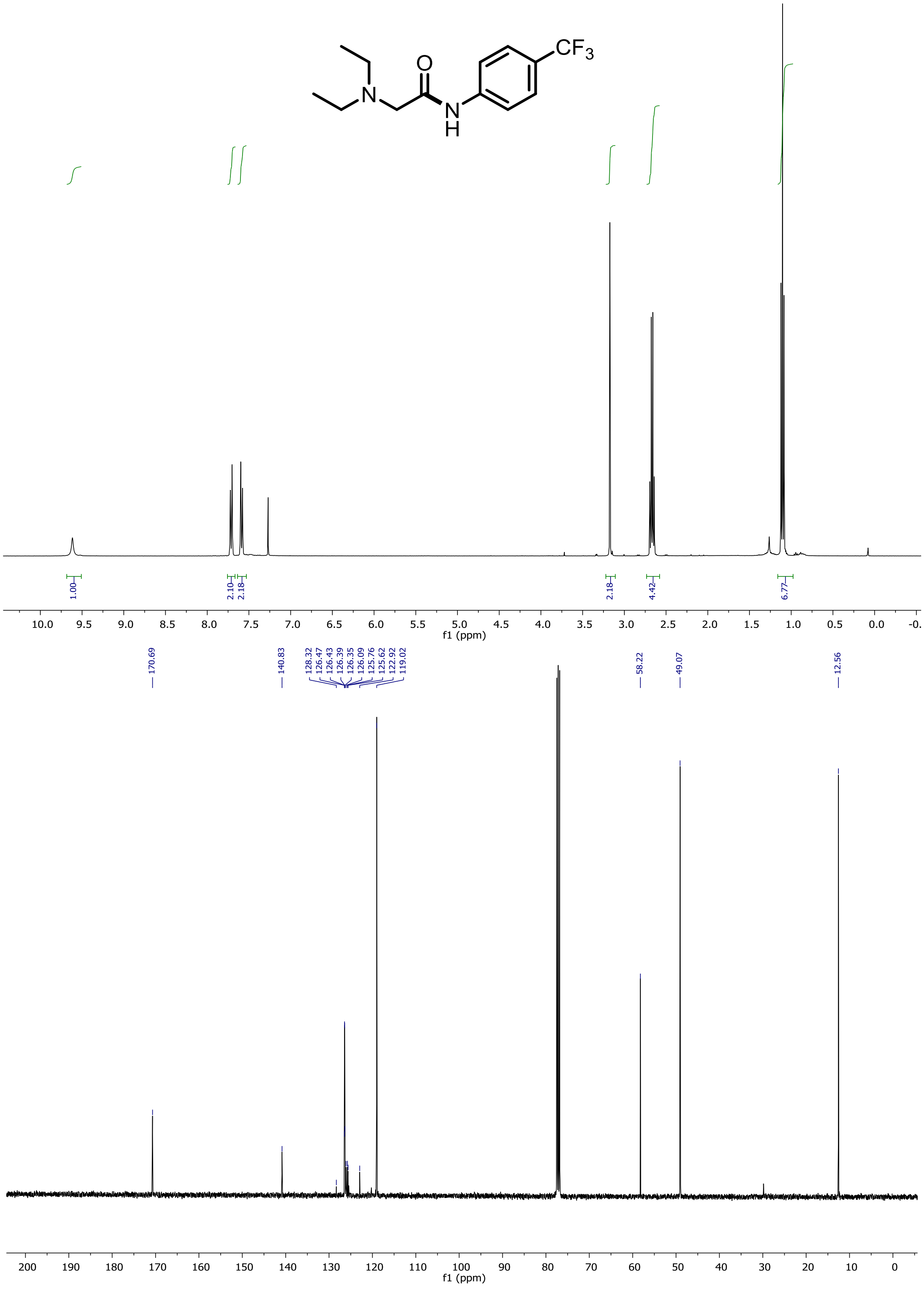


2-(Diethylamino)-N-(3,5-dimethyl-phenyl)acetamide (**3.72c**) $CDCl_3$, 400 MHz:

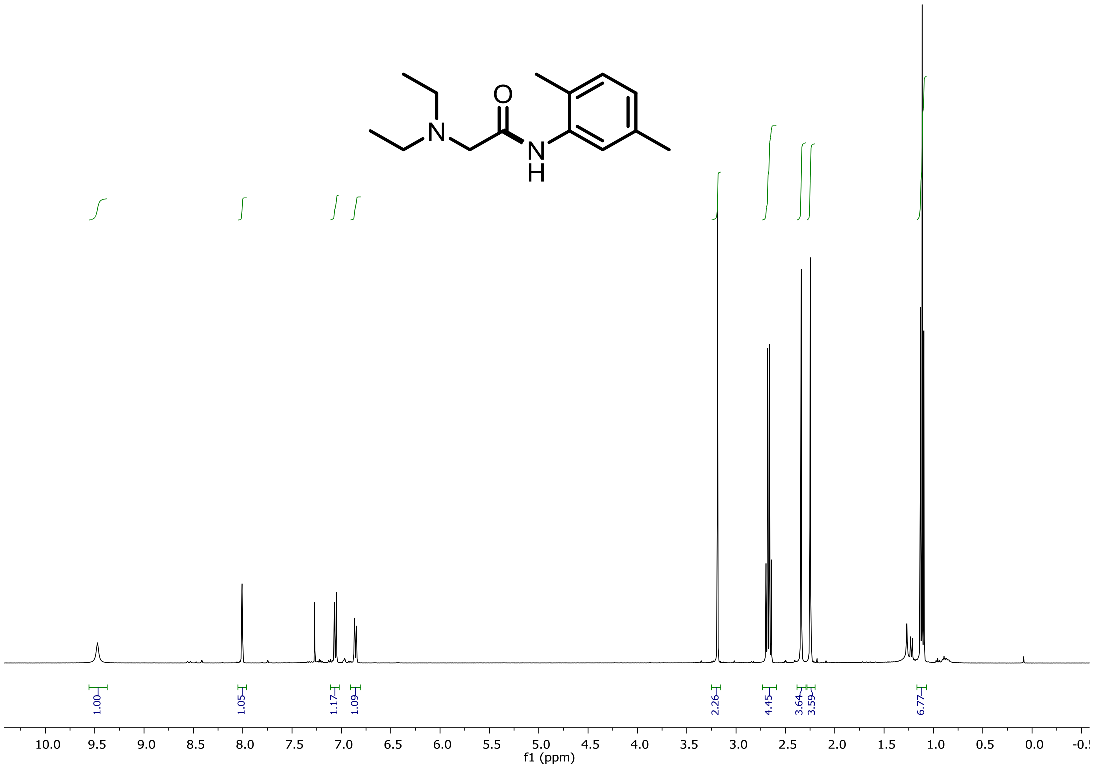


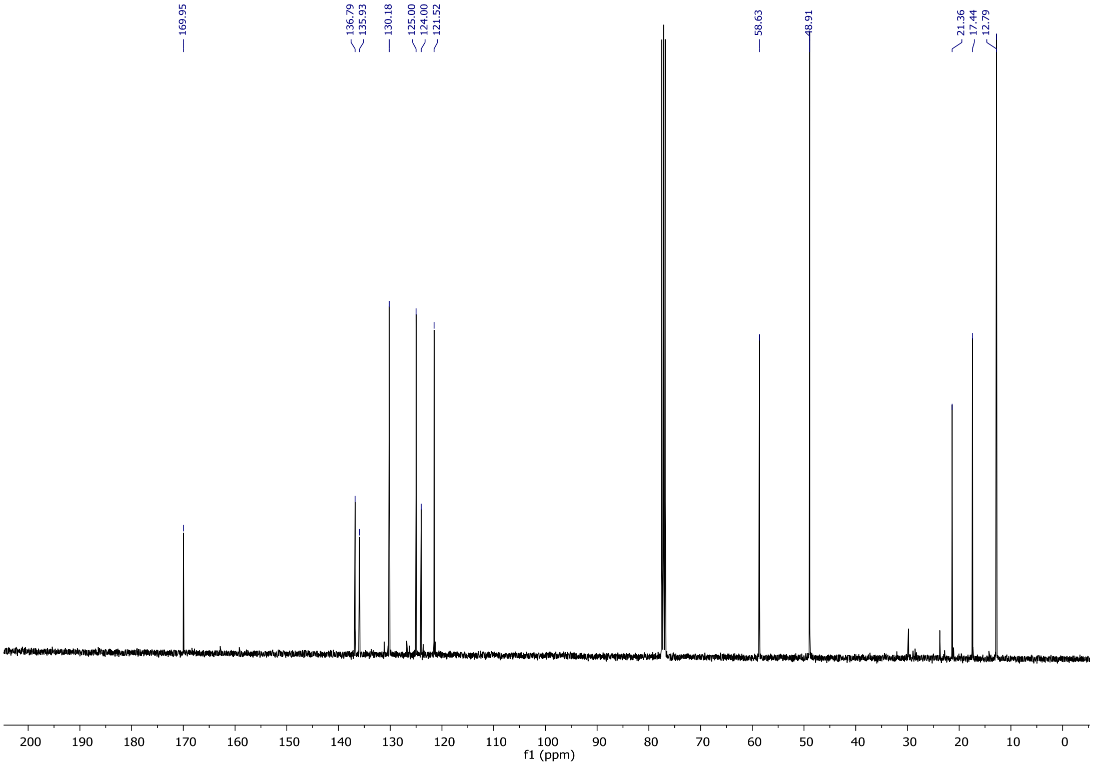


2-(Diethylamino)-N-(4-trifluoromethyl-phenyl)acetamide (**3.72b**) $CDCl_3$, 400 MHz:

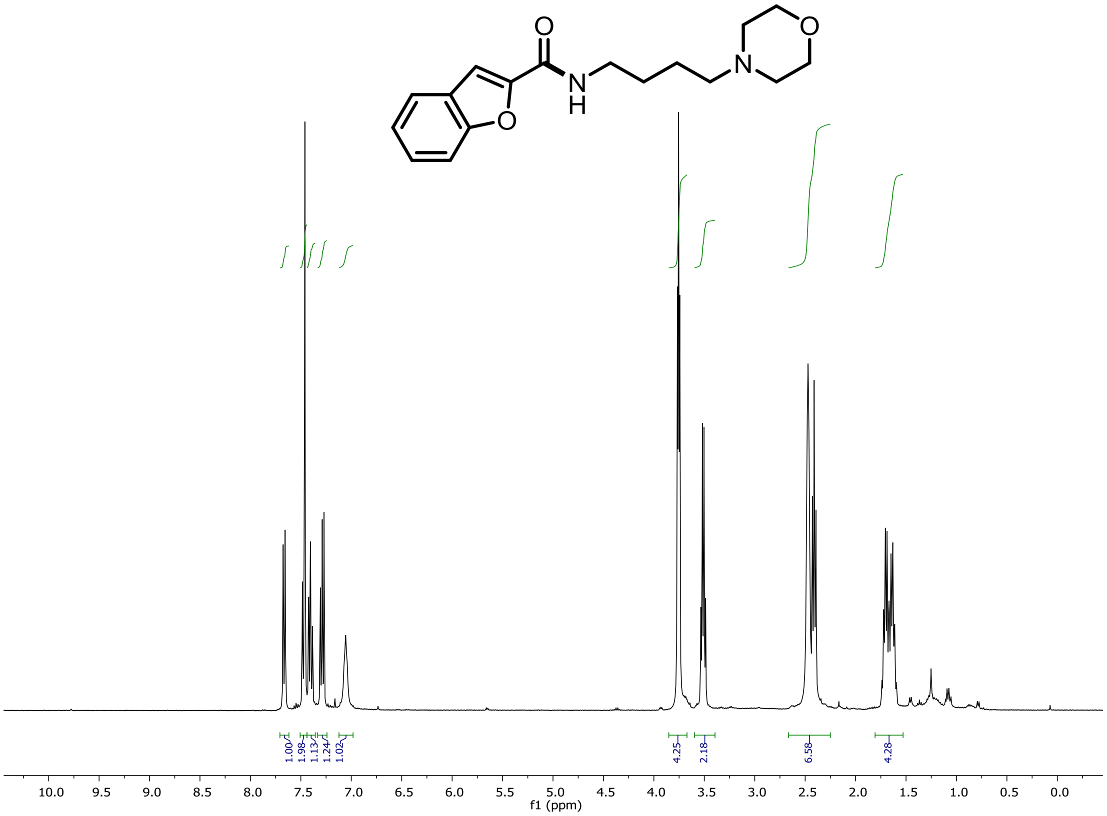


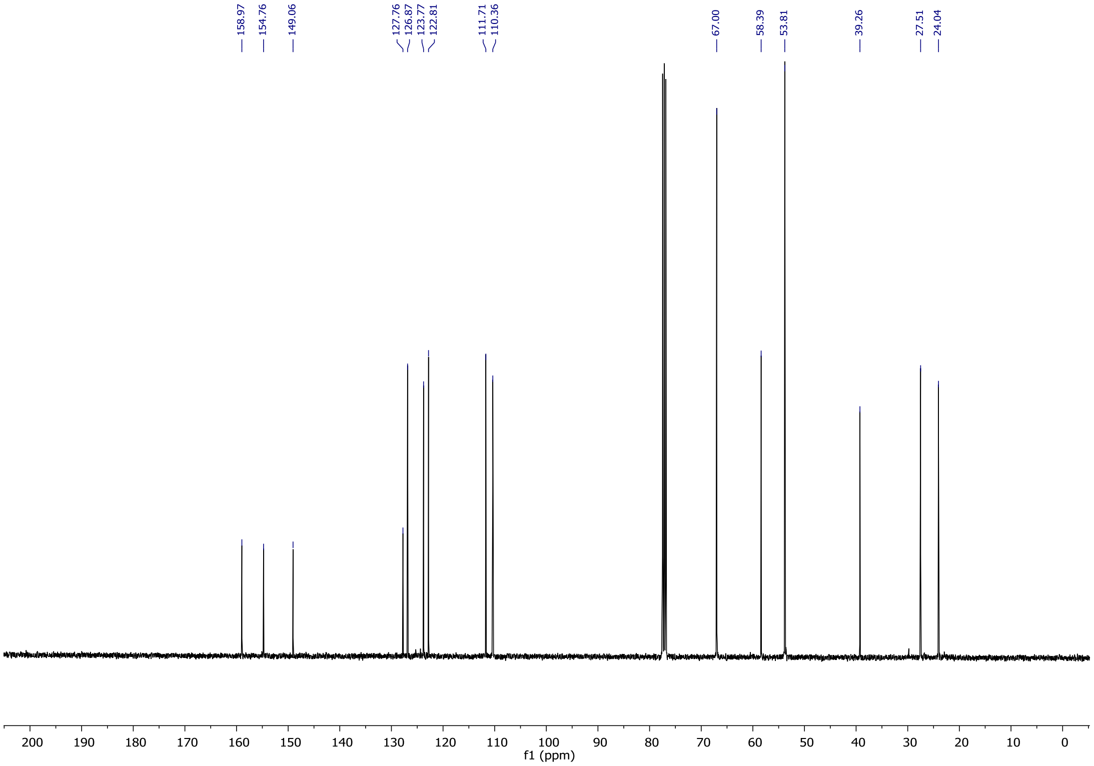
2-(Diethylamino)-N-(2,5-dimethyl-phenyl)acetamide (**JM25-1**). CDCl$_3$, 400 MHz:



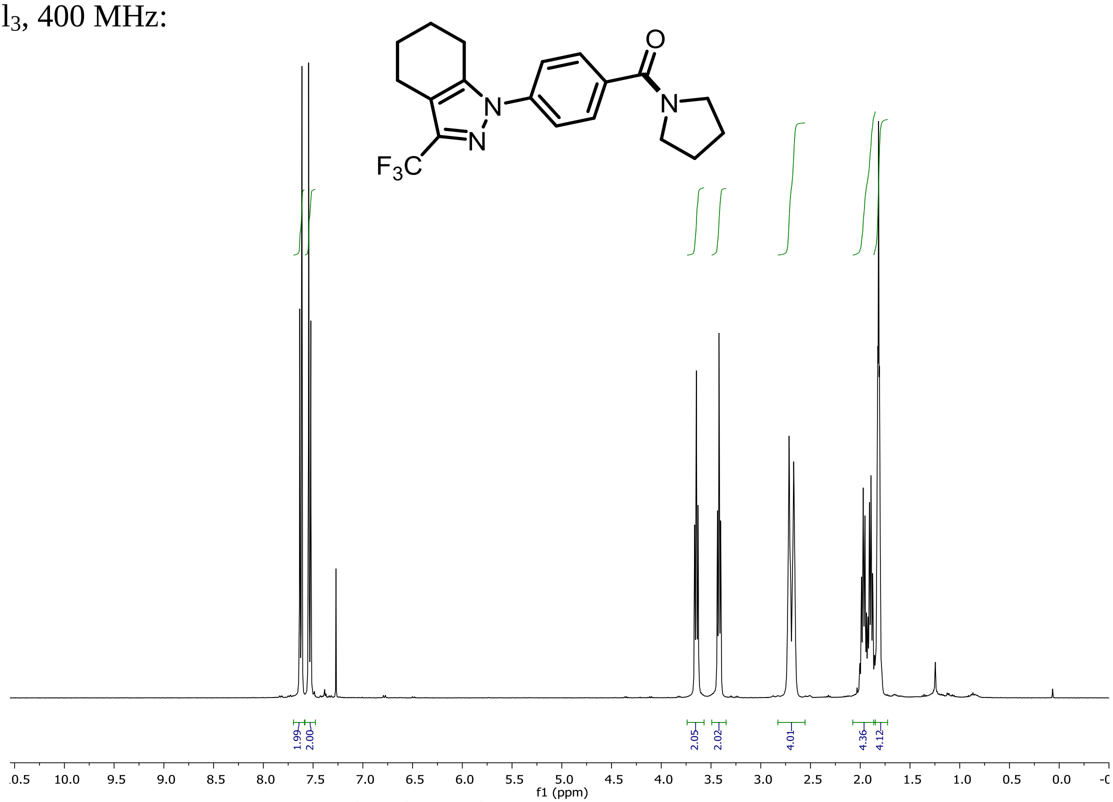


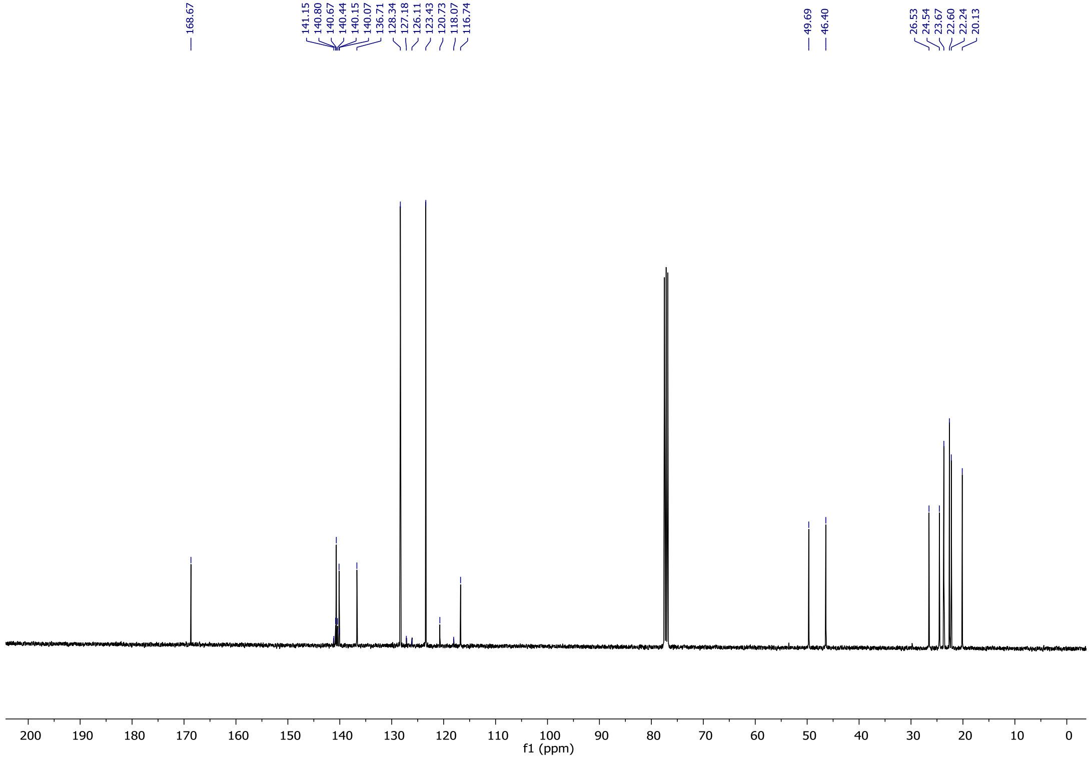
N-[4-(4-Morpholinyl)butyl]-2-benzofurancarboxamide (**CL-82198**). $CDCl_3$, 400 MHz:





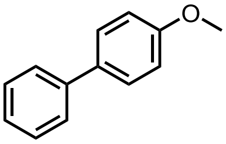
1-[4-(1-Pyrrolidinylcarbonyl)phenyl]-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole (**3.11**). $CDCl_3$, 400 MHz:

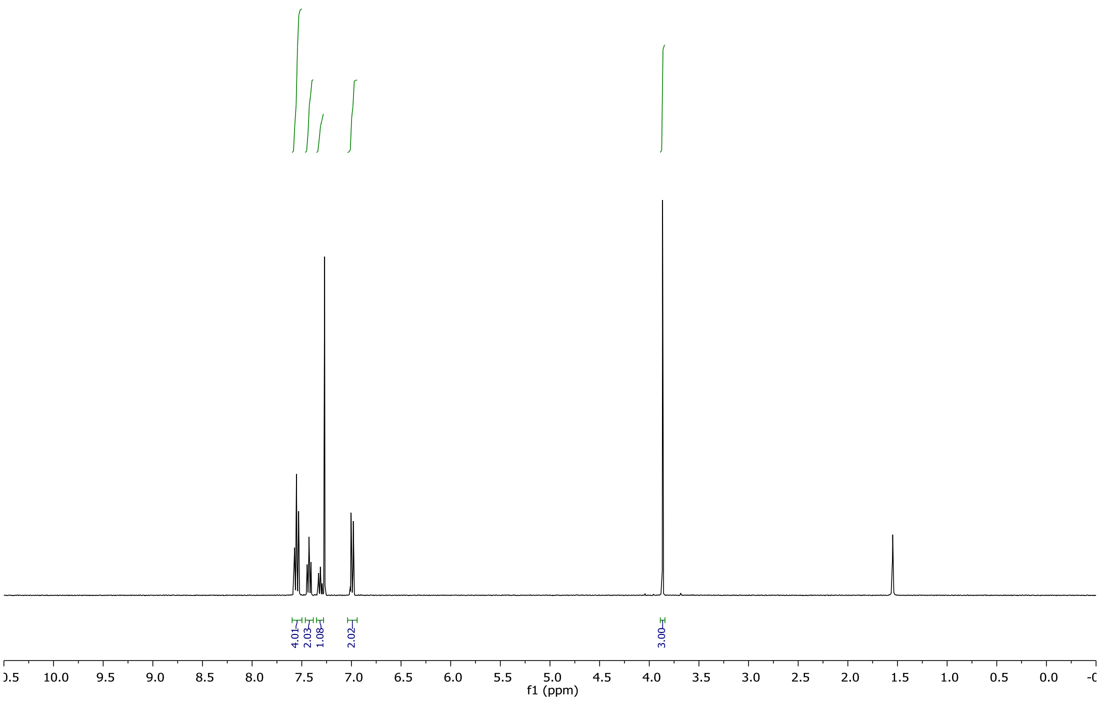


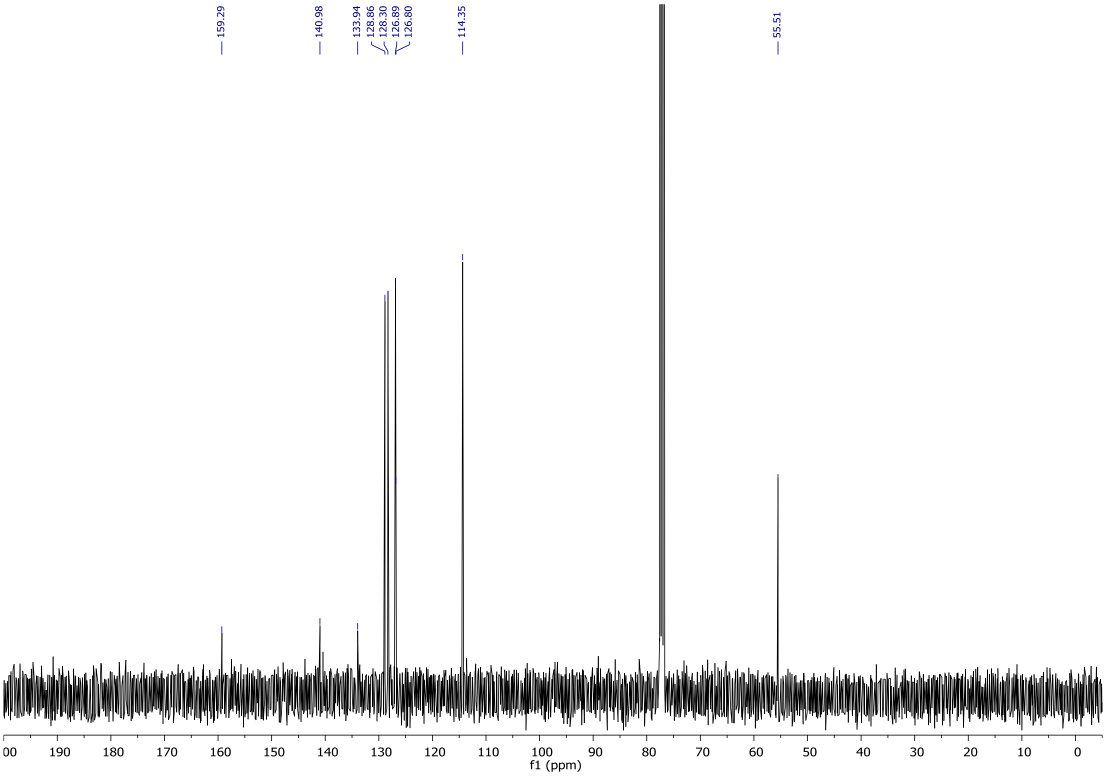


8.3 Appendix3 : ^{1}H and ^{13}C NMR spectra from Chapter 4

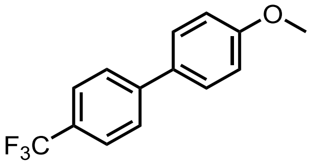
4-Methoxybiphenyl (**4.21**). $CDCl_3$, 400 MHz:

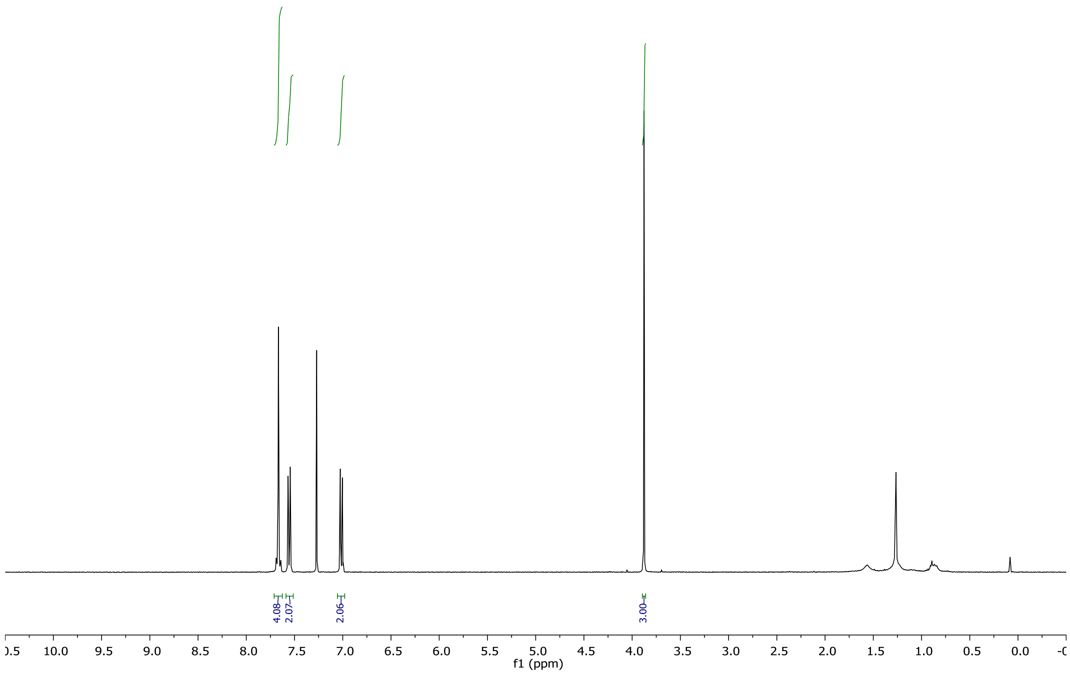


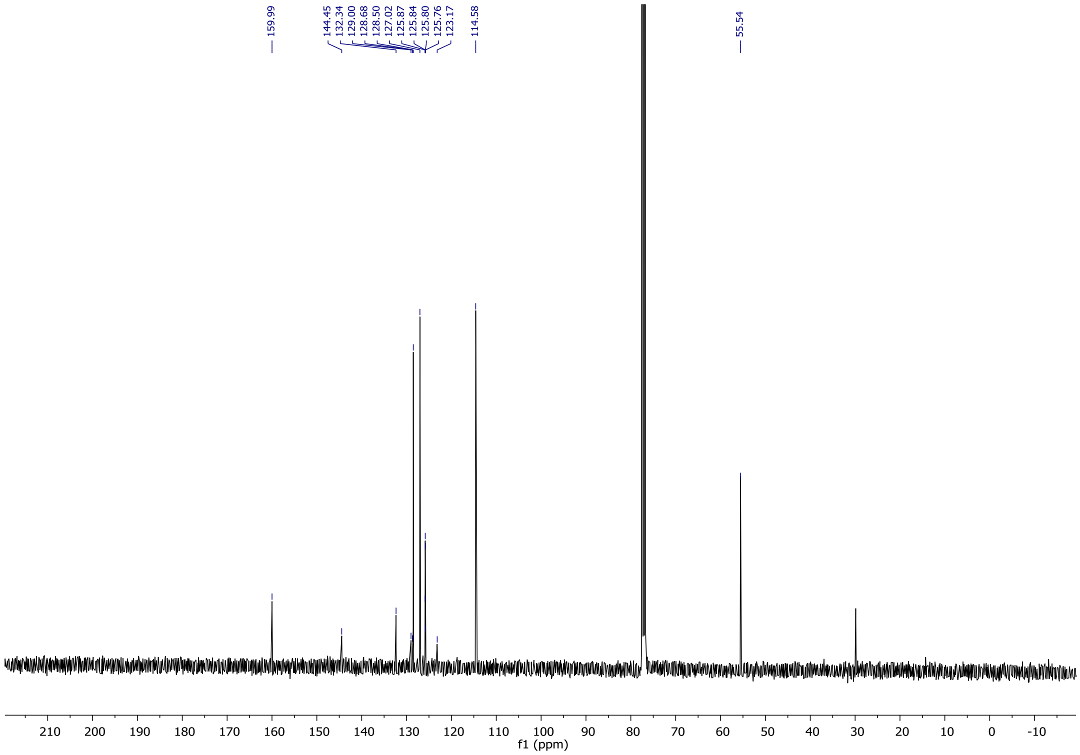




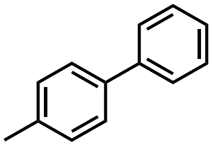
4-Methoxy-4'-(trifluoromethyl)biphenyl (**4.18**). $CDCl_3$, 400 MHz:

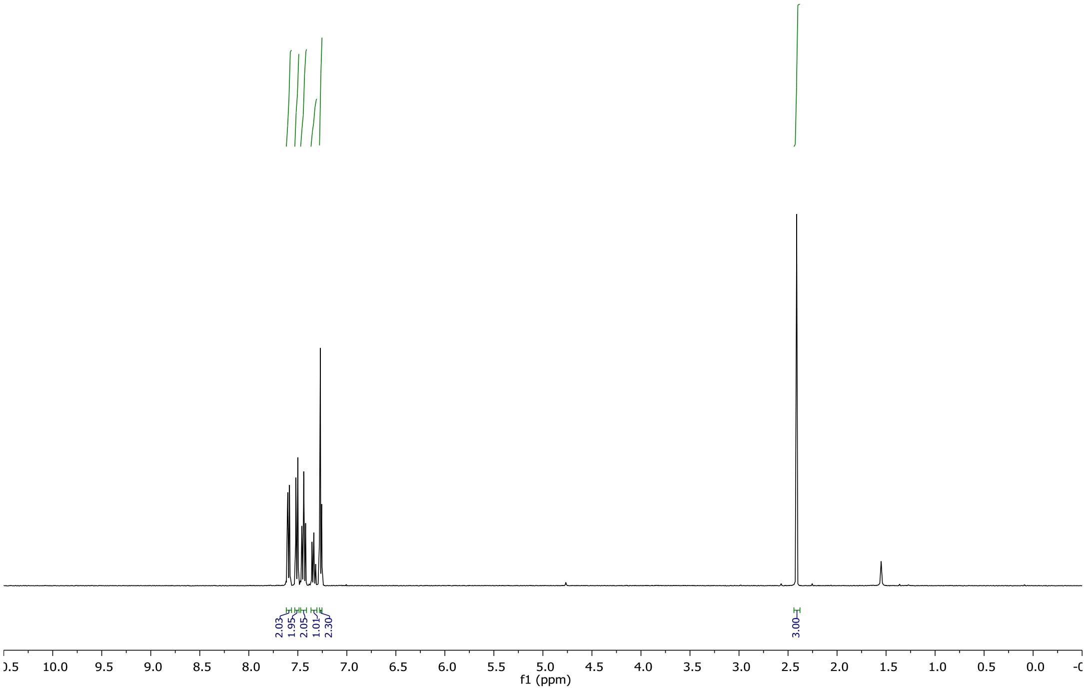


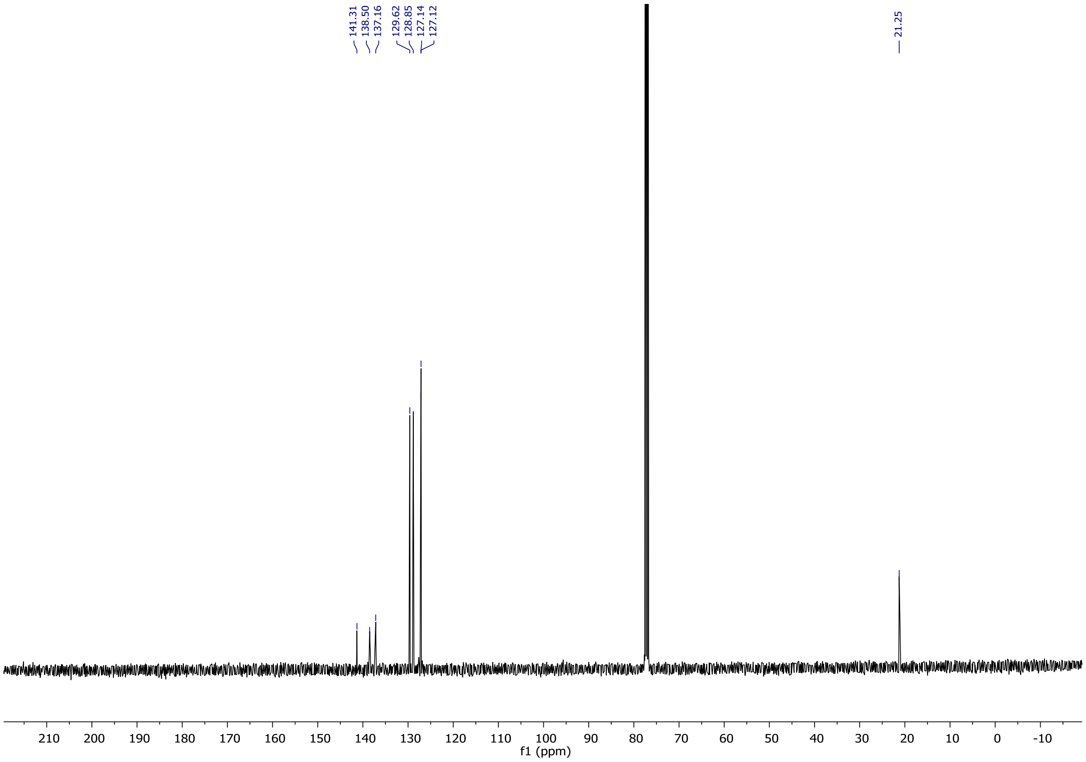


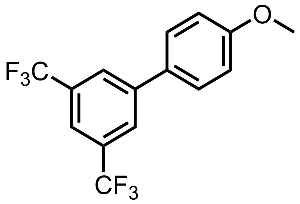


4-Methylbiphenyl (**4.22**). $CDCl_3$, 400 MHz:









4-Methoxy-3′,5′ bis(trifluoromethyl) biphenyl (**4.19**). $CDCl_3$, 400 MHz: