Cross-Coupling Reactions with Methyl Esters as Electrophiles

By

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Abstract:

Constructing C-C and C-heteroatom bonds is of the utmost importance in organic chemistry. Cross-coupling is a reaction where a transition metal catalyst facilitates the formation of a C-C or C-heteroatom bond between two coupling partners. Cross-coupling reactions are often very robust and reliable and thus have established themselves as one of the most powerful and versatile tools for the modern synthetic organic chemist. A great area of modern cross-coupling research has been the expansion of electrophiles that can participate in cross-coupling reactions. By expanding the scope of available electrophiles, one can access a greater variety of products from simpler starting materials. Esters are relatively robust scaffolds and are difficult to engage in cross-coupling reactions due to the substantial double-bond character of the C(acyl)-O bond. Developing methods to functionalize esters via cross-coupling reactions would be highly beneficial as esters are ubiquitous and readily available. The cross-coupling of phenyl esters has been relatively well established throughout the past decade. The cross-coupling of simple methyl esters largely remains elusive in the primary literature.

Chapter 1 of this thesis provides a detailed literature background on the field of carboxylic acid derivative cross-coupling, with a primary focus on esters.

Chapter 2 describes our efforts in discovering new methodologies for methyl ester cross-coupling reactions. We invoked the use of high throughput experimentation (HTE) studies to facilitate our search for novel methyl ester cross-coupling reactivity.

Chapter 3 describes our efforts in developing an additive free, Ni-catalyzed transesterification reaction of methyl esters. The use of alcohols as nucleophilic coupling partners for methyl esters has yet to be reported. We obtained a scope of 20 isolated examples and were able to identify scaffolds that could not be tolerated under our reaction conditions. Lastly, we began preliminary reaction kinetics studies in order to gain useful mechanistic insights for methyl ester cross-coupling reactions.

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I wanted to give a special mention to my dear friend Saeed Kashani of the Newman group. You were tragically taken from us and we all miss you greatly. Rest in peace Saeed.

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9-BBN	9-borabicyclo(3.3.1)nonane
acac	acetylacetonate
Ar	aryl
BDE	bond dissociation energy
cat.	catalytic or catalyst
Cp	cyclopentadienyl
Cy	cyclohexyl
Cyp	cyclopentyl
d	doublet
dcype	1,2-Bis(dicyclohexylphosphino)ethane
dba	dibenzylideneacetone
DFT	density functional theory

DMF	dimethylformamide
dppp	1,3-bis(diphenylphosphino)propane
equiv	equivalent
Et	ethyl
EtOAc	ethyl acetate
FID	flame ionization detector
g	gram(s)
GC	gas chromatography
h	hour(s)
HPLC	high performance liquid chromatography
HTE	high throughput experimentation
Hz	hertz
J	coupling constant
KO^{t}Bu	potassium tert-butoxide
L	ligand
M	generic metal, or molar
m	multiplet
m/z	mass over charge
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mol	mole(s)
MS	mass spectrometry
MSTFA	N-methyl-N-(trimethylsilyl)trifluoroacetamide
OVAT	one variable at a time
NHC	N-heterocyclic carbene

NMR	nuclear magnetic resonance
Nuc	nucleophile
Ph	phenyl
PMHS	polymethylhydrosiloxane
q	quartet
R	generic chemical group
r.t.	room temperature
s	singlet
SM	starting material
t	triplet
^{t}Bu	tert-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet
X	generic halogen/heteroatom

Chapter 1: An Introduction to Esters as Cross-Coupling Electrophiles

1.1: Transition metal-catalyzed cross-coupling reactions

The forefront of organic chemistry lies in the ability to construct carbon-carbon and carbon-heteroatom bonds. Access to valuable organic compounds such as natural products, polymers, and drug candidates is reliant on the various carbon-carbon and carbon-heteroatom bond forming reactions available in the arsenal of the synthetic organic chemist. Although there are many classical methods to synthesize C-C and C-heteroatom bonds, they often differ in their respective reaction conditions. However, a commonality is that they are often stoichiometric in nature. Some of the defining mantras of green chemistry have been the reduction or elimination of chemical waste and the use of renewable resources. When performing stoichiometric chemistry, these two principles of green chemistry are frequently overlooked. Nevertheless, this presents synthetic chemists with the opportunity to develop new catalytic transformations as viable alternatives to the existing stoichiometric reactions. This is a worthwhile goal as more sustainable processes will lessen the impact on the environment.

Substantial research into transition metal-catalyzed cross coupling reactions began in the early 1970's with the discovery of a powerful new carbon-carbon bond forming

reaction, the Mizoroki-Heck coupling.[1] Many related reactions were developed after, including the C-C bond forming Suzuki-Miyaura cross-coupling in 1979 [2] and the C-N bond forming Buchwald-Hartwig amination as recently as 1994.[3] The impact of transition metal-catalyzed cross-couplings has been substantial in industries such as medicinal chemistry, where it is estimated that Suzuki-Miyaura and Buchwald-Hartwig couplings account for approximately 30% of all reactions that are run.[4] It is unsurprising that they represent such a large portion of chemical transformations in the pharmaceutical industry, as transition metal-catalyzed transformations have been shown to be a powerful and reliable method to accessing a variety of different C-C and C-heteroatom scaffolds.[5] Accordingly, the 2010 Nobel-prize in chemistry was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their pioneering efforts in developing powerful palladium-catalyzed cross-couplings.

Cross-coupling reactions differ from many classical transformations as they do not operate via mechanisms that invoke the use of nucleophiles and electrophiles in the traditional sense. Instead, cross-coupling reactions allow for carbon-carbon bond

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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.

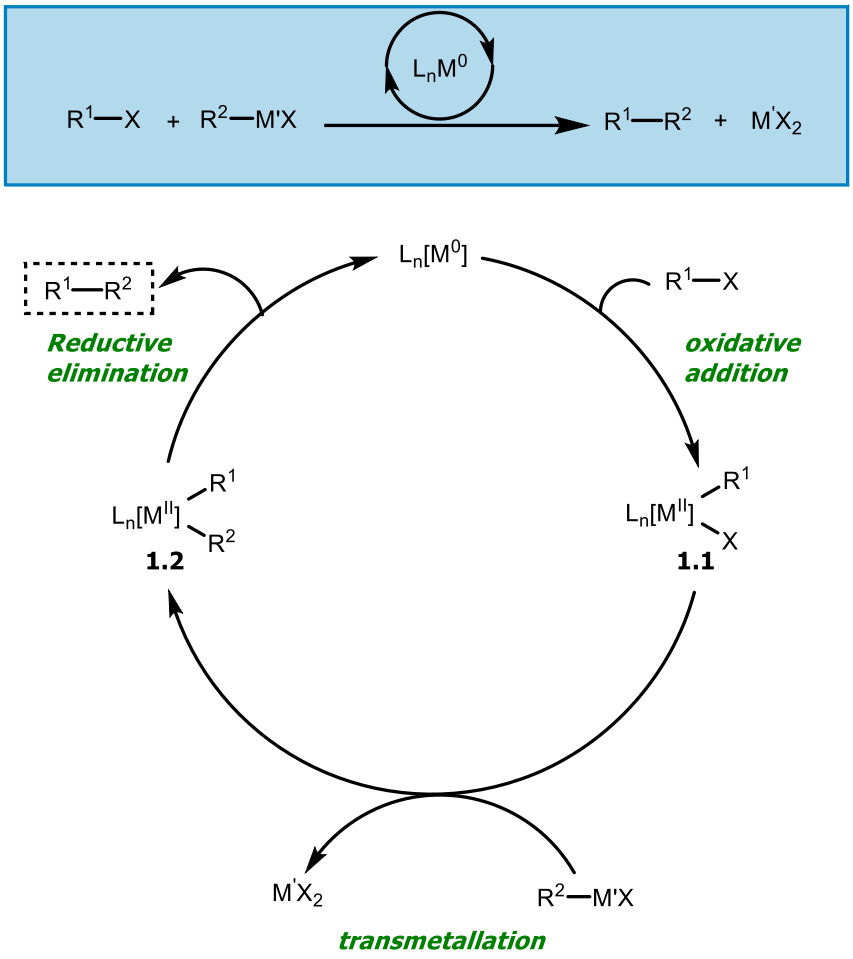
[2] Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett*. **1979**, 20, 3437.

[3] (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.

[4] Brown, D. G.; Boström, J. *Journal of Medicinal Chemistry* **2015**, *59*, 4443.

[5] Meijere, A. de; Diederich, F.; Eds., *Metal-Catalyzed Cross-Coupling Reactions* 2nd ed., Wiley-VCH, Weinheim, **2004**.

formation between seemingly inert aryl halides and organometallic species. Crucial to the success of this process is the use of transition metal catalysts (often nickel and palladium).[5] A simplified mechanism for a general cross coupling reaction is shown below in **Scheme 1**. Cross-coupling reactions usually involve three main steps. The first involves the oxidative addition of a low-valent metal (ex. Pd^0) into the C-halogen bond of the aryl halide to provide intermediate **1.1,** where the oxidation state of the active catalyst has increased by 2. Next, intermediate **1.1** can undergo transmetallation with an organometallic species, furnishing intermediate **1.2**. Reductive elimination is the final step which releases the final product and the active catalyst which can propagate another cycle.

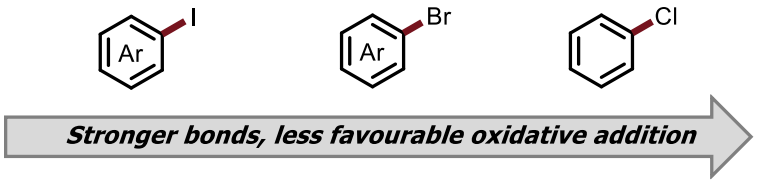


Scheme 1. General scheme and mechanism of a transition metal-catalyzed cross-coupling reaction

These cross-coupling reactions usually feature homogenous catalysts, where ligands play a vital role. Ligands aid in solubilizing the metal as well as altering its electronic properties. The nature of the ligand can drastically alter the reactivity of the metal catalyst and can influence all steps involved in the reaction. Moreover, the ligands influence the sterics around the metal center and thus the catalytic environment. The sterics of the metal center can also have an effect on all steps involved in the reaction.

Oxidative addition

As shown in **scheme 1**, the first step usually involves the transition metal catalyst inserting itself into the C-X bond, giving rise to intermediate **1.1** where the metal centre has increased its oxidation state by 2. As the metal gets oxidized in this step, ligands that render the metal centre more electron rich are favourable. Ligands also play a role with regards to sterics for this step. A less hindered metal centre is preferred for oxidative addition. The nature of the metal itself is also significant. Oxidative addition tends to be more facile with less electronegative transition metals, which is why nickel tends to be better than palladium at oxidative addition.[6] Another important consideration is the strength of the C-X bond itself. Oxidative addition is more facile with weaker C-X bonds (Figure 1).



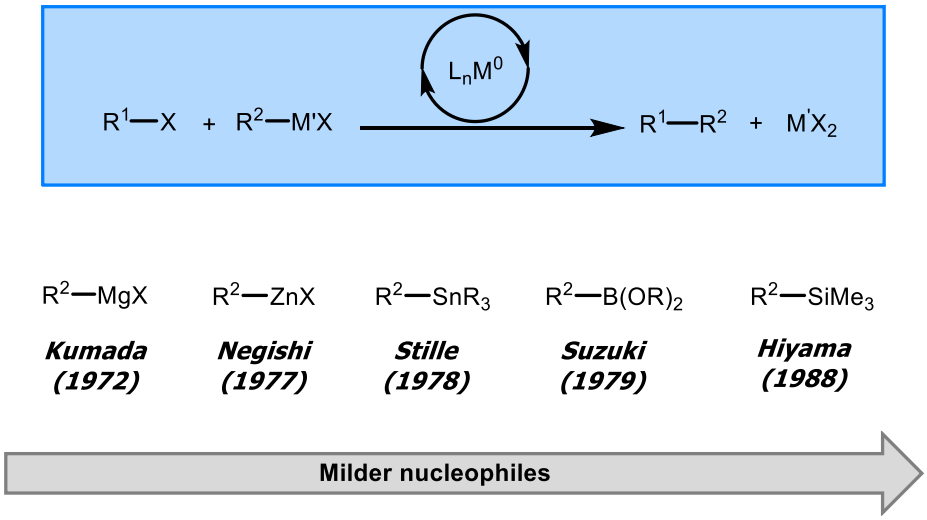
Scheme 2. Relative C-X bond strength of traditional aryl halide coupling partners

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

Transmetallation

Oxidative addition is commonly proceeded by a transmetallation reaction. A transmetallation is when one of the X ligands on the metal centres is exchanged for an R group from an organometallic species (RMX). Many different organometallic reagents have been demonstrated to be viable coupling partners. The first organometallic reagents to be used in modern Pd based cross-coupling reactions were Grignard reagents. This original cross-coupling reaction was discovered by Kumada and Corriu in 1972.[7] Grignard reagents are harsh nucleophiles, thus the scope of suitable coupling partners is limited. This provided researchers with an opportunity to develop novel cross-coupling reactions with milder nucleophilic coupling partners (**Scheme 3**). Organozinc species[8] (Negishi cross-coupling), organotin species[9] (Stille cross-coupling), organoboron[2] (Suzuki cross-coupling) and organosilicon[10] (Hiyama cross-coupling) nucleophiles were all used shortly after. Organoboron and organosilicon species are so mild that they often require activation in situ via base/water or fluoride sources respectively in order to transmetallate.

[7] (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, 94, 4374. (b) Corriu, R. J. P.; Masse, J. P. J. Chem. Soc., *Chem. Comm*. **1972**, 144a.
[8] Negishi, E. -I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, 42, 1821.
[9] Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, 100, 363.
[10] Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, 53, 918.



Scheme 3. The development of milder nucleophiles for cross-coupling reactions

Traditional cross-coupling reactions have been well established as reliable methods of forming new carbon-carbon bonds; however, they are not limited to the formation of carbon-carbon bonds. Other cross-coupling reactions that result in carbon-heteroatom bond formation include but are not limited to carbon-nitrogen[3], carbon-phosphorus[11], carbon-sulfur[12], carbon-oxygen[13], and carbon-boron[14] bond formation.

Reductive elimination

The last step of the cycle is reductive elimination, which releases the desired product and regenerates the catalyst for another turnover. Reductive elimination is the reverse of

[11] Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Synthesis* **1981**, 1981, 56.
[12] (a) Li, G. Y. *Angew. Chem., Int. Ed*. **2001**, 40, 1513. (b) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, 66, 8677. (c) Li, G. Y. *J. Org. Chem.* **2002**, 67, 3643.
[13] Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2006**, 45, 4321.
[14] Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, 60, 7508.

oxidative addition. After reductive elimination, the oxidation state of the metal goes down by 2. Electron-poor metals and the use of electron-deficient ligands can facilitate reductive elimination.[15] For reductive elimination to occur, the bonds must be *cis* to each other on the metal center.[16] If the bonds are trans relative to one another, they will need to isomerize before the metal can perform reductive elimination. Most bidentate ligands tend to force a *cis* configuration on the metal center, alleviating the need for an isomerization to occur.[17]

1.1.1: Application of cross-coupling reactions

The impact of cross-coupling reactions has been substantial in a variety of different fields such as medicinal chemistry, natural product synthesis, and materials chemistry.[18] This is owed to their reliability and efficiency in synthesizing new carbon-carbon or carbon-heteroatoms bonds.

For instance, a nickel-catalyzed Kumada-Corriu reaction was used towards the enantioselective synthesis of (S)-macrostomine, a natural product (**Scheme 4A)**.[19] Suzuki-

[15] Korenaga, T.; Abe, K.; Ko, A.; Maenishi, R.; Sakai, T. *Organometallics* **2010**, 29, 4025.
[16] Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, 102, 4933.
[17] (a) Suseno, S.; Agapie, T. *Organometallics* **2013**, 32, 3161. (b) Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, 38, 1099. (c) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, 41, 581. (d) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, 61, 5405. (e) Barbaro, P.; Bianchini, C.; Giambastiani, G.; Parisel, S. L. Coord. *Chem. Rev.* **2004**, 248, 2131.
[18] (a) M. Iwasaki, Y. Nishihara, *Applied Cross-Coupling Reactions*, Nishihara, Y., Ed.; Lecture Notes in Chemistry, Springer Berlin Heidelberg: Berlin, Heidelberg, 2013; Vol. 80 (b) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev*. **2016**, 116, 12564.
[19] Enamorado, M. F.; Ondachi, P. W.; Comins, D. L. *Org. Lett.* **2010**, *12*, 4513.

Miyaura couplings have been used towards the synthesis of valuable cancer drugs such as Tamoxifen, which is commonly used for treatment of breast cancer (**Scheme 4B)**.[20]

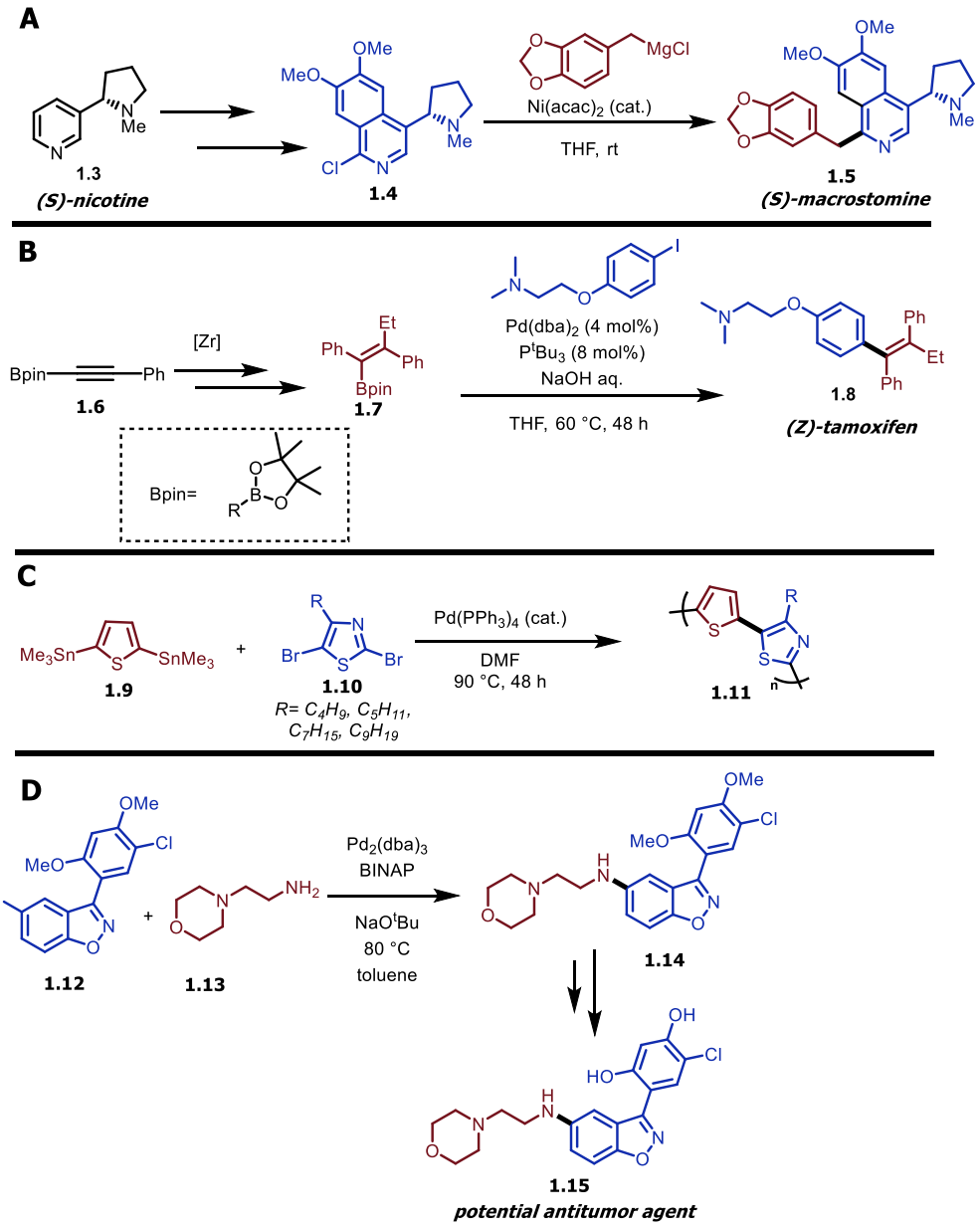
π-conjugated polymers are sought after scaffolds as they display interesting electrochemical qualities and are known to be electrochemically conductive materials.[21] A Stille cross-coupling was successful in accessing a thiophene based π-conjugated polymer with high regioregularity (**Scheme 4C)**.

The applications of cross-coupling in an industrial setting are not limited to carbon-carbon bond formation. Carbon-nitrogen bond formation via the Buchwald-Hartwig amination has seen noteworthy use across a variety of different industries (**Scheme 4D)**.[22]

[20] Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K. *J. Am. Chem. Soc.* **2007**, *129*, 12634.

[21] (a) Zhan, X.; Zhu, D. *Polymer Chemistry* **2010**, *1*, 409. (b) Park, D. H.; Kim, M. S.; Joo, J. *Chem. Soc. Rev.* **2010**, *39*, 2439. (c) Tuncel, D. *Nanoscale* **2011**, *3*, 3545. (d) He, M.; Qiu, F.; Lin, Z. *J. Mater. Chem.* **2011**, *21*, 17039. (e) Pate, R.; McCormick, R.; Chen, L.; Zhou, W.; Stiff-Roberts, A. D. *Appl. Phys. A.* **2011**, *105*, 555.

[22] Gopalsamy, A.; Shi, M.; Golas, J.; Vogan, E.; Jacob, J.; Johnson, M.; Lee, F.; Nilakantan, R.; Petersen, R.; Svenson, K.; Chopra, R.; Tam, M. S.; Wen, Y.; Ellingboe, J.; Arndt, K.; Boschelli, F., *J. Med. Chem.* 2008, 51, 373.



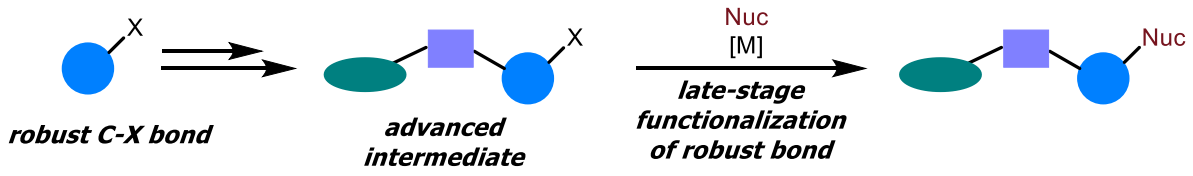
Scheme 4. (A) Synthesis of (S)-macrostomine via a nickel-catalyzed Kumada-Corriu cross-coupling. (B) Synthesis of (Z)-tamoxifen via a palladium-catalyzed Suzuki-Miyaura cross-coupling. (C) Synthesis of a thiophene based polymer via a palladium-catalyzed Stille cross-coupling. (D) Synthesis of potential antitumor agent via palladium-catalyzed Buchwald-Hartwig amination.

1.2: Expanding the scope of viable electrophiles for cross-coupling

As outlined in section 1.1, the first cross-coupling reaction which made use of an organometallic reagent was the Kumada-Corriu coupling. Soon after, research of cross-coupling reactions began to focus on the development of conditions that employed milder coupling partners. This was a valuable advancement as more sensitive functional groups could be tolerated.

Traditional cross-coupling reactions make use of organohalides as the electrophilic coupling partner. Ongoing research efforts have led to the expansion of the types of pseudo-halides that can act as surrogates. Expanding the scope of viable electrophiles for cross-coupling can address some issues that plague organohalides. Firstly, organohalides generate stoichiometric halide salts as by-products, many of which are toxic. By using other electrophiles, this can be mitigated. Secondly, it is possible that the desired organohalide is not commercially available, is exceptionally expensive, or requires elaborate multistep synthesis to access. By expanding the scope of available electrophiles, a wider variety of synthetic pathways become accessible.

Complex molecule synthesis can also greatly benefit by expanding the scope of electrophiles. If the new electrophiles are robust, then that bond can likely be inert to conditions in the early stages, and can then be exploited for late-stage functionalization (**Scheme 5)**.



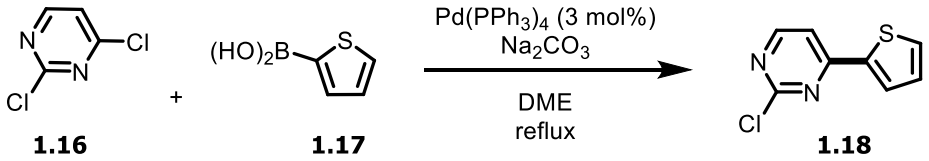
Scheme 5. Using a robust bond for late-stage functionalization

1.2.1: Advancements in strong bond activation for cross-coupling catalysis

1.2.1.1: Engaging difficult electrophiles towards cross-coupling reactions

Aryl electrophiles

Despite significant advancements in the 1970s in the scope of suitable organometallic coupling partners, the electrophiles used were largely limited to organohalides. Most commonly, aryl bromides and iodides. The aryl chloride counterparts are ubiquitous and often more affordable; however, they are challenging substrates to successfully functionalize using traditional cross-coupling reactions. The low reactivity of the aryl chlorides could be attributed to their relatively strong C-X bond (bond dissociation energies for Ph-Cl: 96 kcal mol^{-1}; Ph-Br: 81 kcal mol^{-1}; Ph-I: 65 kcal mol^{-1}), which can impede the key oxidative addition step of traditional catalysts, rendering them largely unreactive under cross-coupling conditions.[23] An exception is very electron poor aryl chlorides. One of the earliest examples of heteroaryl coupling was a Suzuki-Miyaura coupling of 2,4-dichloropyrimidines which could be coupled selectively at the 4 position (**Scheme 6)**.[24]

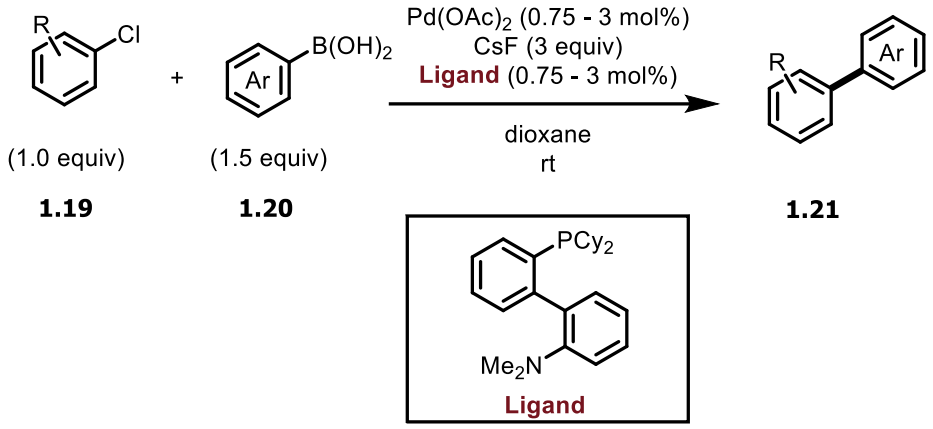


Scheme 6. Selective Suzuki-Miyaura coupling of 2,4-dichloropyrimidines

However, it took until the year 1998 for the discovery of a method that allowed for Suzuki-Miyaura coupling with unactivated aryl chlorides.[25] This breakthrough was

[23] Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, 41, 4176.
[24] S. Gronowitz, A.-B. Hornfeldt, V. Kristjansson, T. Musil, *Chem. Scr.* **1986**, 26, 305.
[25] Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

realized via the use of novel ligands which would make powerful catalyst systems with palladium, capable of promoting the desired reaction at room temperature (**Scheme 7**).



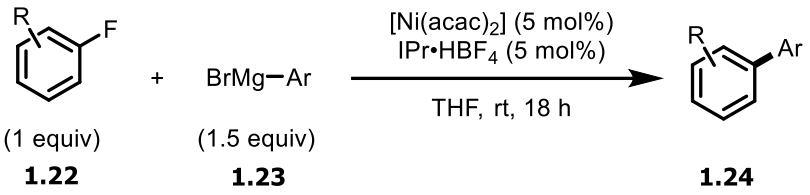
Scheme 7. Suzuki-Miyaura coupling of unactivated aryl chlorides

This discovery was a very meaningful step forward in the research of strong bond activation. A subsequent objective for chemists was to then develop cross-coupling methods for the activation of even stronger electrophiles such as C-F and C-O bond activation.

Some of the pioneering work involving aryl fluorides as cross-coupling electrophiles necessitated the use of highly electron-deficient aryl fluorides such as perfluorinated[26], nitro-substituted [27] and chromium bound [28] aryl fluorides. A sole report of coupling with unactivated aryl fluorides was published in 1973, where they were coupled with organomagnesium reagents.[29] It took until the early 2000s until new methodologies

[26] Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964.
[27] (a) Kim, Y. M.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696. (b) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **2003**, 578. (c) Mikami, K.; Miyamoto, T.; Hatano, M. *Chem. Commun.* **2004**, 2082. (d) Bahmanyar, S.; Borer, B. C.; Kim, Y. M.; Kurtz, D. M.; Yu, S. *Org. Lett.* **2005**, *7*, 1011. (e) Cargill, M. R.; Sandford, G.; Tadeusiak, A. J.; Yufit, D. S.; Howard, J. A.; Kilickiran, P.; Nelles, G. *J. Org. Chem.* **2010**, *75*, 5860.
[28] (a) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **1999**, , 2211. (b) Wilhelm, R.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3808.
[29] Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem*. **1973**, 50, C12.

emerged which utilized simple unactivated aryl fluorides for cross-coupling (**Scheme 8)**.[30]



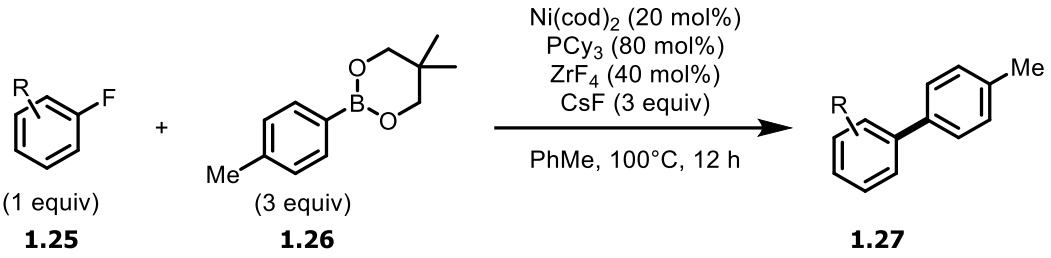
Scheme 8. Kumada-type coupling of unactivated aryl fluorides

Although the work concerning aryl fluoride cross-coupling published up to this point was certainly impactful, it wasn't without drawbacks. These reactions required the use of highly activated aryl fluorides or harsh organometallic species. Both of these issues limited the broad applicability of the methodologies as the substrate scopes would be limited to specific activated scaffolds, or limited to moieties that could survive harsh organomagnesium reagents.

These limitations were overcome by the Chatani group in 2011 when they developed a protocol for the cross-coupling of simple unactivated aryl fluorides with aryl boronic esters (**scheme 9)**.[31] Key to the success of the reaction was the addition of metal fluoride cocatalyst ZrF_4.

[30] Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. *A. Angew. Chem., Int. Ed.* **2001**, 40, 3387

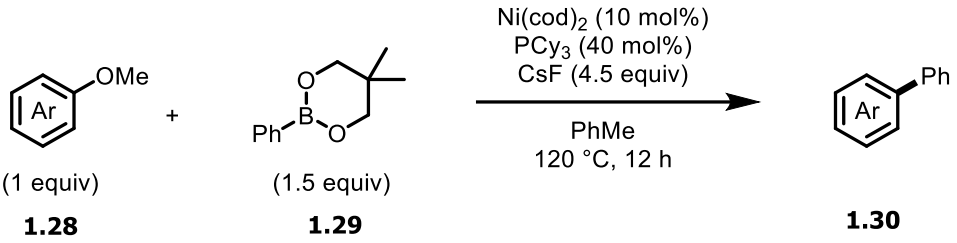
[31] Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 19505.



Scheme 9. Unactivated aryl fluoride cross coupling with mild transmetallating reagent

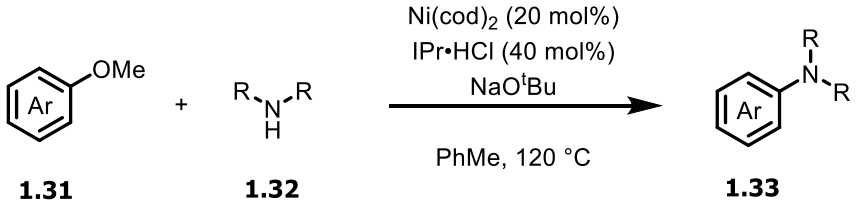
The Chatani group had seen great success with a similar Ni/PCy_3 catalyst system prior to their use in aryl fluoride chemistry. Ni/PCy_3 in conjunction with aryl boronic esters were used to functionalize the C-O bond of aryl methyl ethers, a bond that is relatively inert and unreactive (**Scheme 10)**.[32] Earlier reports of aryl methyl ethers as cross-coupling electrophiles existed; however, much like aryl fluorides, the coupling partners were initially harsh organomagnesium reagents.[33] Thus, in developing a method to functionalize aryl methyl ethers with aryl boronic esters, scaffolds such as carbonyls could be tolerated, once again overcoming the limitations of previous methodologies. However, it is important to note that this novel methodology is largely limited to polyaromatic aryl methyl ethers such as naphthalenes and anthracenes, whereas molecules like anisole were completely unreactive.

[32] Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem.* **2008**, *120*, 4944.
[33] (a) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246. (b) E. Wenkert, E. L. Michelotti, C. S.Swindell, M. Tingoli, *J. Org. Chem.* **1984**, *49*, 4894. (c) Dankwardt, J. W. *Angew. Chem.* **2004**, *116*, 2482.



Scheme 10. Suzuki-Miyaura cross-coupling of aryl methyl ethers

Shortly after, Chatani and co-workers expanded upon this work by developing methods that would allow for amines to serve as cross-coupling nucleophiles **(Scheme 11)**.[34] The crucial change from the existing aryl methyl ether was the use of N-heterocyclic carbene (NHC) ligands. This amination reaction had a broadened scope compared to the aryl boronic ester cross-coupling as electron deficient heteroaryl and phenyl esters could be aminated. The broadened scope could not solely be attributed to the NHC ligand however, as replacing the PCy_3 ligand with IPr furnished no arylated product.[35]



Scheme 11. Amination reaction of aryl methyl ethers mediated by nickel-catalysis

A dedicated ligand study later published by the Chatani group discovered that the low reactivity of anisole derivatives could be overcome when employing a Ni(0)/cyclohexyl-substituted NHC ligand (ICy) catalyst system (**Scheme 12)**.[36] Changing the cyclohexyl groups on the ligand resulted in complete loss of reactivity, which underlines the importance of the specific catalyst system for this transformation.

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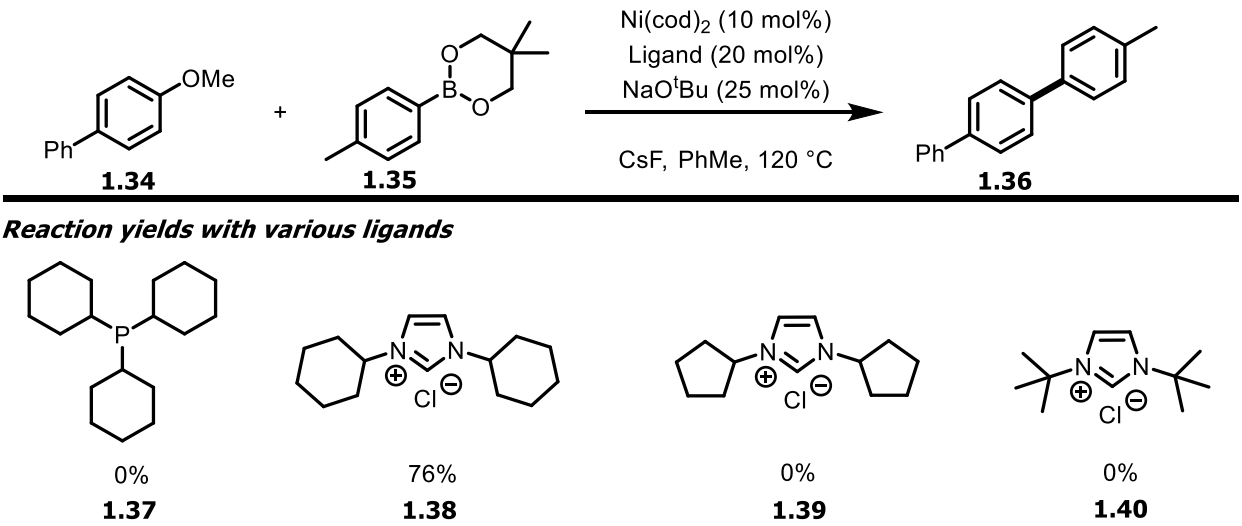
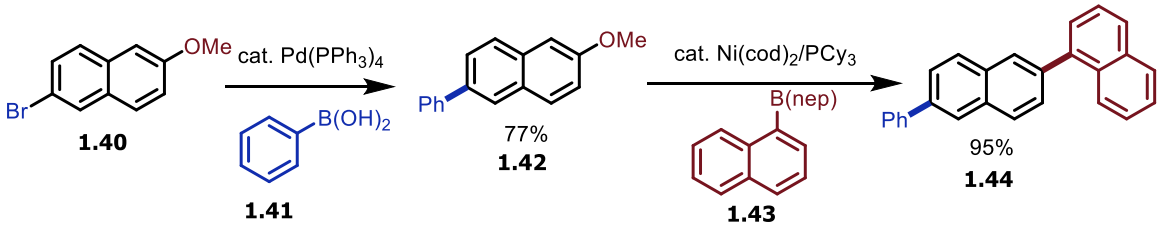
[34] Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett*. **2009**, *38*, 710.
[35] Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48* (6), 1717.
[36] Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K.; Chatani, N. *Org. Lett*. **2014**, *16*, 5572.



Scheme 12. Overcoming scope issues in Ni-catalyzed Suzuki-Miyaura cross-couplings of aryl methyl ethers

To highlight the synthetic utility of strong C-O bond activation, sequential cross coupling reactions have been performed. [35] A molecule bearing two or more reactive sites will undergo a set of reactive conditions that will selectively functionalize one site, leaving the other(s) intact. A different set of reaction conditions will selectively functionalize another reactive site. As shown in **Scheme 13,** a Suzuki-Miyaura coupling can be done selectively with an aryl bromide, leaving the OMe group intact. The OMe group can then be arylated with a boronic ester by taking advantage of a Ni/PCy_3 catalyst system. [32]



Scheme 13. Sequential aryl bromide and aryl methyl ether cross-coupling

1.3: Esters as viable acyl cross-coupling electrophiles

Note: The content of Section 1.3 is taken from a Wiley book chapter on ester cross-coupling chemistry with minor edits made to meet the formatting requirements of the thesis. This book chapter was original work written by myself and my supervisor, with permission given by Wiley to be reproduced herein.[37]

As discussed in the previous sections, transition metal catalyzed cross-coupling reactions are among the most frequently run reactions as they provide an efficient and reliable way to construct C-C and C-heteroatom bonds.[38] Traditionally, these reactions are often run with aryl halides as the electrophilic reaction partner, generating halide salt by-products. Ongoing research efforts have led to the expansion of the types of pseudo-halides that can act as surrogates, avoiding the halide salt waste and enabling a wider variety of synthetic pathways. For example, sulfamates, pivalates, carbamates and aryl ethers have all been engaged in cross-coupling reactions. [32, 33, 34, 36, 39]

In tandem to the expansion of the type of (pseudo)halide leaving groups that could be cleaved, great progress has been made to diversify the carbon scaffolds that can participate. For example, carboxylic acid derivatives can be activated to make a range of product classes. Pioneering work in this area was realized by Yamamoto in 1976, when the stoichiometric reaction between Ni(0) and a phenyl ester was disclosed.[40] Ni(0) was proposed to oxidatively insert into the acyl(C)-O, as evidenced by the decarbonylated ester product and Ni(0)-CO complex that were obtained. Around the same time, acyl

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[37] Daneshfar, O.; Newman, S. G. In *Amide Bond Activation*; Szostak, M., Ed. Wiley **2022**

[38] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Johansson Seechurn, C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (d) Forero-Cortés, P. A.; Haydl, A. M. *Org. Process. Res. Dev.* **2019**, *23*, 1478.

[39] (a) Qiu, Z.; Li, C.-J. *Chem. Rev.* **2020**, *120*, 10454. (b) Campeau, L.-C.; Hazari, N. *Organometallics* **2018**, *38*, 3

[40] (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.

chlorides were first used as cross-coupling electrophiles to give ketones.[41] By the end of the 20th century, anhydrides [42] and thioesters [43] were similarly demonstrated to be viable reaction partners. A key mechanistic step in coupling of these acyl electrophiles is the oxidative addition into the C(acyl)–X bond, which is facilitated by selecting a (pseudo)halide that acts as a good leaving group. More robust carboxylic acid derivatives such as esters and amides can be difficult to engage in cross-coupling because of the relative stability of the C(acyl)-O and C(acyl)-N bonds, which have substantial double bond character. The cross-coupling of amides was ultimately achieved by two key strategies: choosing powerful catalysts capable of cleaving the robust amide bond, or identifying amides that are more readily activated. The cross-coupling of esters shares key similarities along with many distinct differences. The key step involves oxidative addition of a transition metal catalyst into the C(acyl)-O bond (**Scheme 14)**. The complex resulting from oxidative addition can react with nucleophiles in a decarbonylative fashion, or in a carbonyl retentive manner. Two different product classes can arise from the use of a single electrophile. Controlling this process provides access to a wide range of products.

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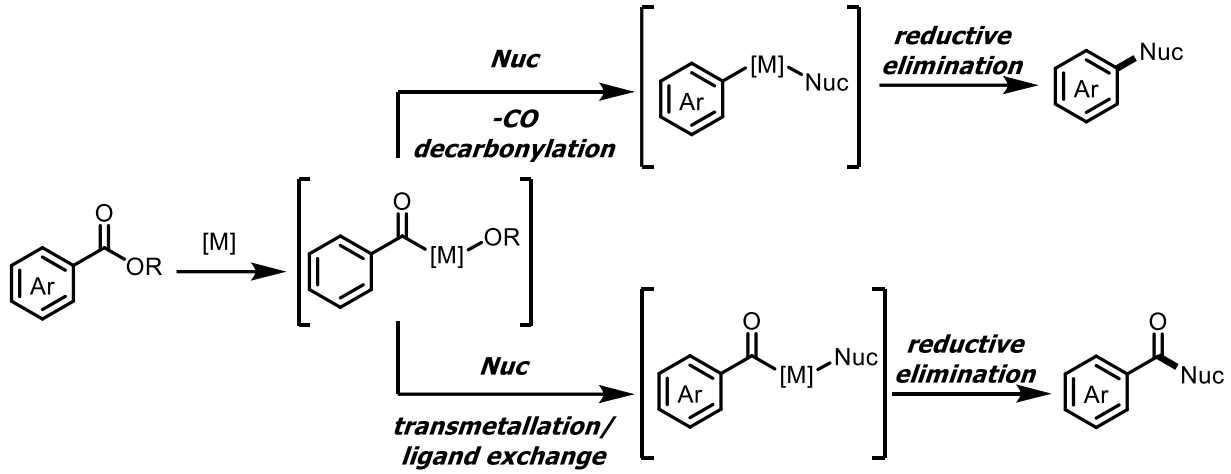
[41] Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, *6*, 1423. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636.

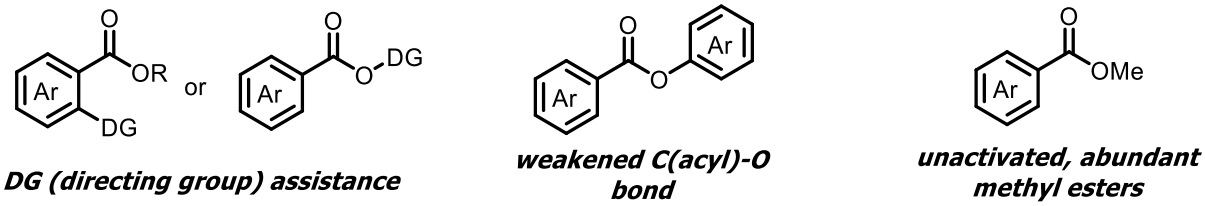
[42] (a) Stephan, M. S.; Teunissen, A. J.; Verzijl, G. K.; de Vries, J. G. *Angew. Chem. Int. Ed.* **1998**, *37*, 662. (b) Gooßen, L. J.; Ghosh, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3458. (c) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 137.

[43] (a) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tett. Lett.* **1998**, *39*, 3189. (b) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (c) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033. (d) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554.



Scheme 14. General mechanism for the cross-coupling of esters.

Section 1.2 of this chapter aims to first provide a very brief overview of the pioneering work in cross-coupling of activated carboxylic acid derivatives–acyl chlorides, anhydrides and thioesters. Afterwards, three main classes of esters that can be engaged in cross-coupling will be discussed. Aryl esters (Sections 1.3-1.4), methyl esters (Sections 1.5-1.6) and esters with directing group assistance (Sections 1.4.1 and 1.6.1) have all been engaged in cross-coupling reactions (**Scheme 15**). Detailed discussion in each section will discuss dates and timelines to provide contextualization.



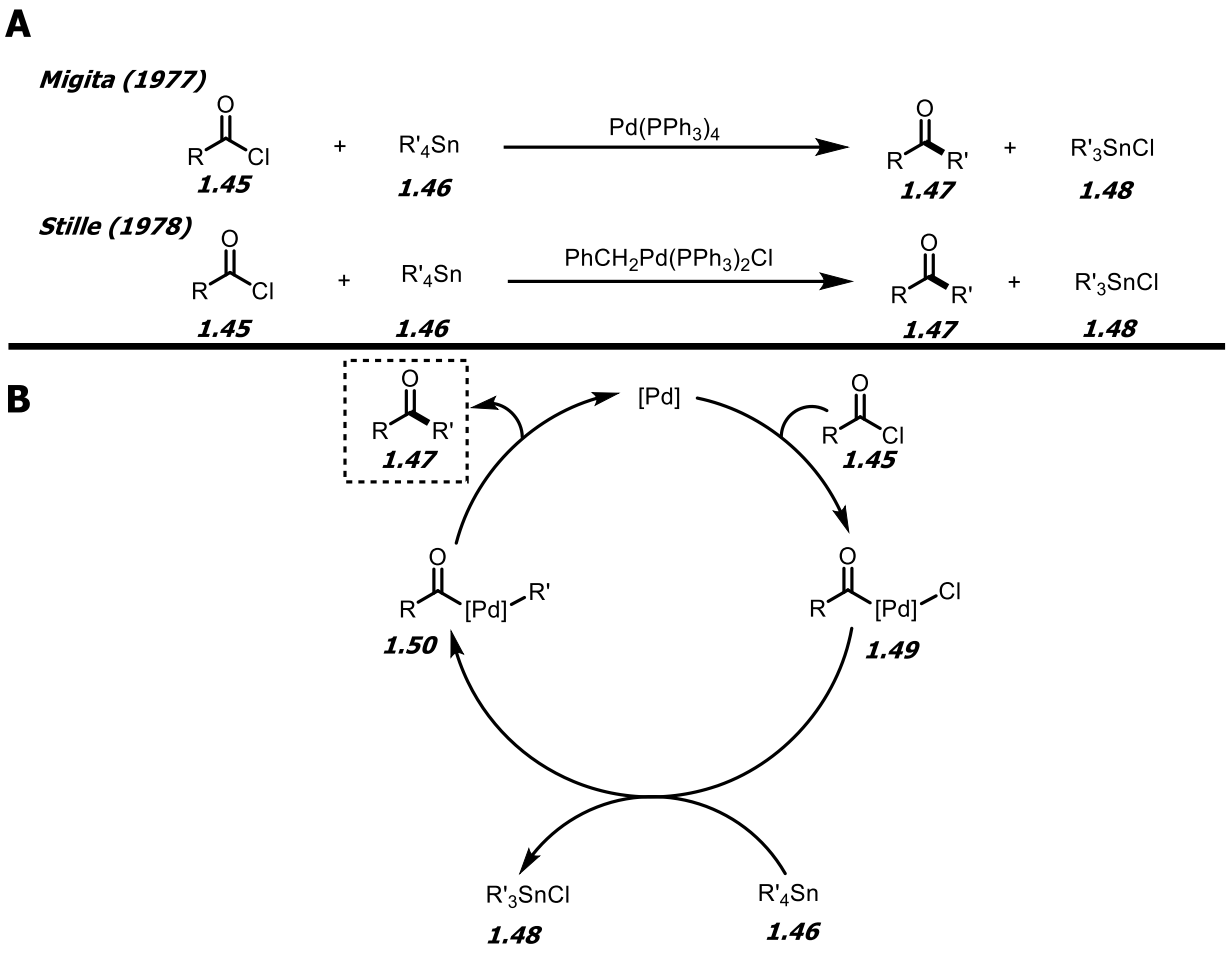
Scheme 15. Various classes of ester activation

1.3.1: Early work in the cross-coupling of carboxylic acid derivatives

This section aims to take a brief look at some of the pioneering examples concerning the cross-coupling of activated carboxylic acid derivatives such as acyl chlorides, anhydrides

and thioesters. This is not an exhaustive list of all work concerning the aforementioned electrophiles, nor does it include all varieties of electrophiles studied before, during and after this field began to make use of esters. Rather, this section seeks to contextualize the early research and follow its natural progression to esters.

Acyl chlorides are highly electrophilic species that readily react with carbon-based nucleophiles (e.g. Grignard or organolithium reagents) in the absence of transition metal catalysts. Ketones are relatively difficult to access this way due to the electrophilicity of the resulting product, which renders them susceptible to a second attack from the organometallic reagent, giving rise to alcohol products. In the late 70's, Migita and Stille independently reported the first cross-coupling reactions that made use of a carboxylic acid derivative as the electrophile.[41] In the presence of Pd catalysts, it was demonstrated that acyl chlorides could undergo cross-coupling reactions with alkyl or aryl organotin reagents, forming a variety of different ketone products **(Scheme 16A)**. The importance of this work was substantial as it demonstrated the power of cross-coupling catalysis by allowing the use of mild nucleophiles, avoiding over-addition of aggressive organometallic nucleophiles, and allowing for the efficient synthesis of ketones. Both reports proposed a similar mechanism which began with Pd oxidatively inserting into the C(acyl)-Cl bond (**Scheme 16B**), generating intermediate **1.49**. This intermediate **1.49** could then undergo transmetallation with the organotin species, yielding intermediate **1.50**. Reductive elimination releases the product and the palladium catalyst, allowing for propagation of the catalytic cycle.

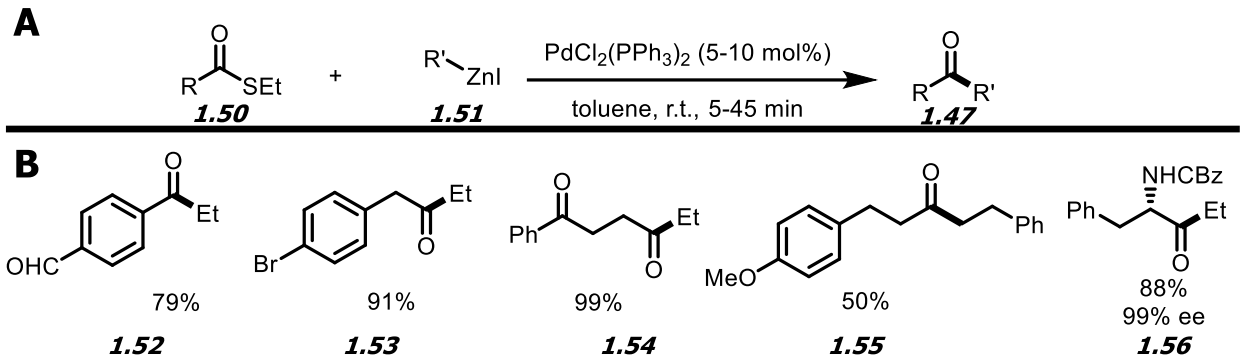


Scheme 16. (A) First examples of acyl electrophiles used for cross-coupling catalysis. (B) Proposed mechanism of the Pd-catalyzed cross-coupling of acyl chlorides with organotin reagents.

Notably, the Weinreb ketone synthesis was developed at approximately the same time as this cross-coupling approach to make ketones, which features carefully chosen amide electrophiles that overcomes the over addition problem.[44] While this method became and has remained powerful in synthetic organic chemistry, the need for harsh organometallic reagents and multi-step preparation of the Weinreb amide electrophile left room for

[44] Nahm, S.; Weinreb, S. M. *Tett. Lett.* **1981**, *22*, 3815.

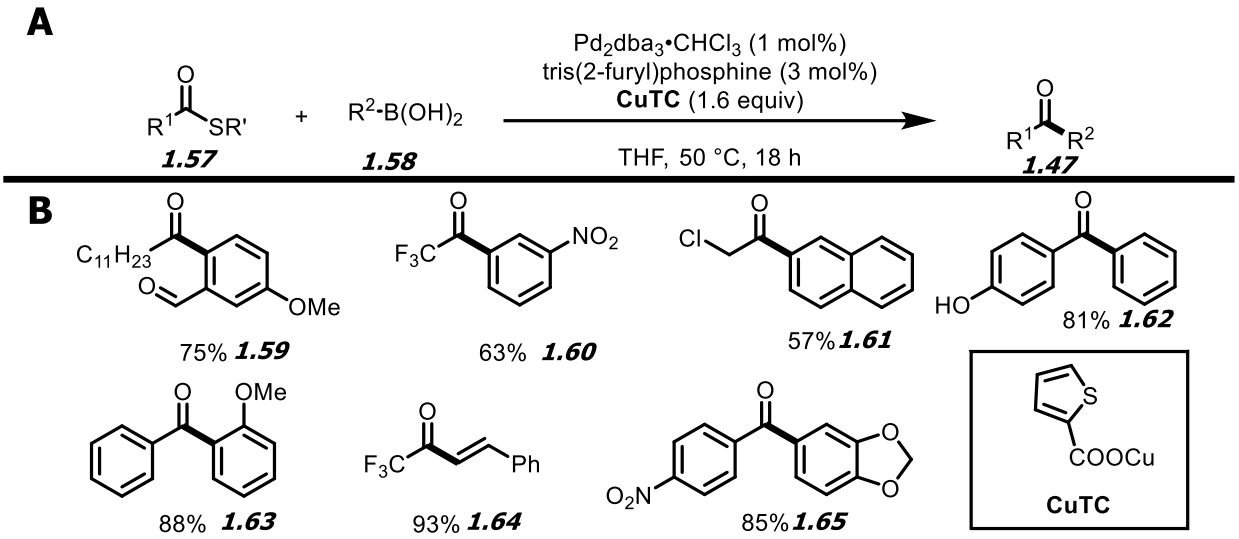
improvement for future coupling methods. In 1998, the Fukuyama group developed coupling of thioesters, providing an advantage over use of acid chlorides due to their robustness (**Scheme 17A)**.[43a] In the so-called Fukuyama coupling, thioesters and organozinc reagents are coupled in the presence of a Pd catalyst to furnish ketone products under mild reaction conditions. Encouragingly, a variety of sensitive functional groups such as ketones, aldehydes, aryl chlorides and bromides were tolerated, demonstrating high chemoselectivity for ketone formation. Within this study, oxidative addition of the Pd catalyst with aryl halides and deleterious nucleophilic addition of the organozinc reagents to other electrophilic functionality were both avoided **(Figure 16B)**.



Scheme 17. (A) Pd-catalyzed carbonyl retentive Negishi-type coupling of thioesters. (B) Representative scope examples

In many ways, boronic acids are ideal cross-coupling nucleophiles due to their stability, commercial availability, and mildness. In 2000, Liebeskind and Srogl developed a ketone-forming reaction via the coupling of thioesters with boronic acids under strictly non-basic conditions **(Scheme 18)**. [43b] This reaction was facilitated by a Pd catalyst. Critically, Cu(I) thiophene-2-carboxylate (CuTC) was used as a stoichiometric additive. Although the mechanism was not fully understood, it was proposed that the transmetallation from boron to palladium was mediated by CuTC, which was bound to the acyl palladium-thiolate complex. This was unique as traditional Suzuki-Miyaura couplings often require

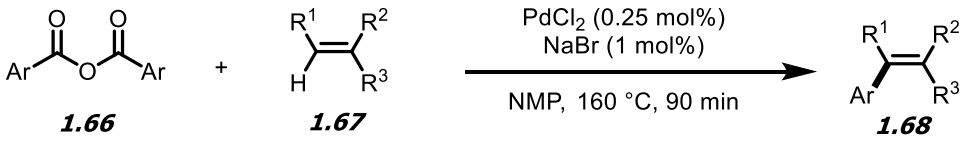
base, while the use of base in this chemistry was detrimental due to binding to boron, blocking the necessary coordination of the Cu(I) carboxylate to the trivalent boron for transmetallation. In 2003, Liebeskind and Srogl reported a similar base free, Cu and Pd mediated ketone synthesis via the coupling of thioesters with organotin reagents. [43c] The following year, this was extended to include alkyl nucleophiles through the use of B-alkyl-9-BBN reagents. [43d] A Pd catalyst was used again, along with a Cu(I) mediator, however this reaction required the use of base.



Scheme 18. (A) Pd-catalyzed carbonyl retentive Suzuki-Miyaura type coupling of thioesters. (B) Representative scope examples

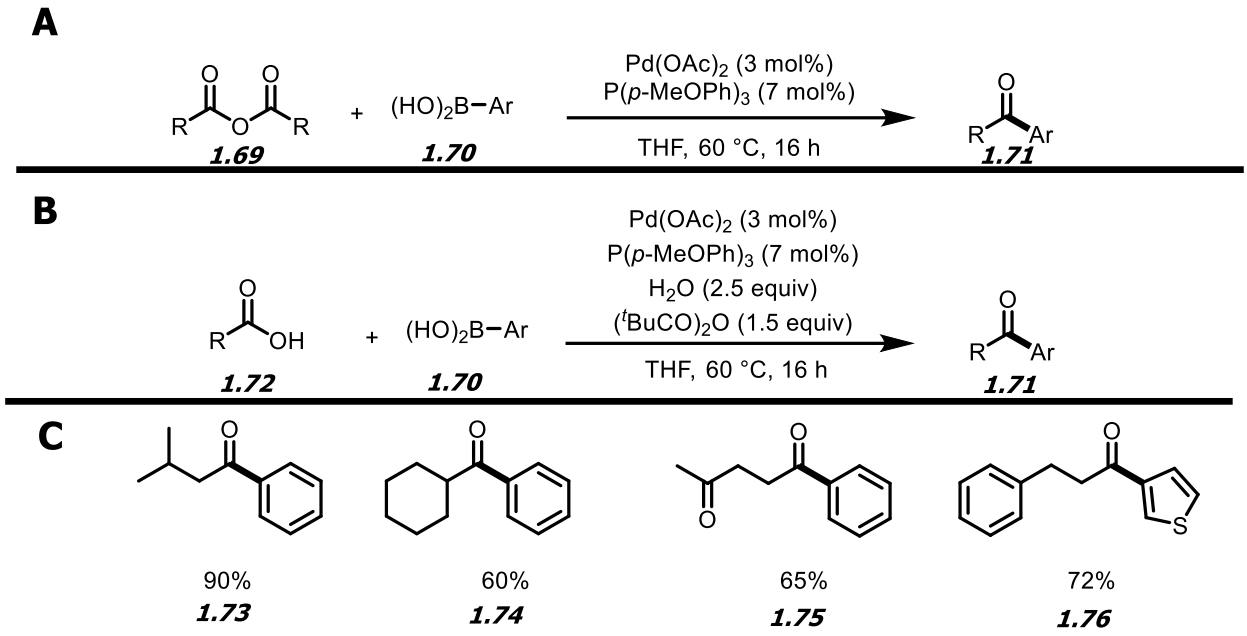
Around the same time as thioesters, cross-coupling reactions of acid anhydrides were developed. The first such report was in 1998 by de Vries and co-workers (**Scheme 19**). [42a] They demonstrated that in the presence of a Pd catalyst, aromatic carboxylic anhydrides could decarbonylate and be used to arylate olefins. In traditional Mizoroki-Heck reactions with aryl halides, a stoichiometric amount of base is required to neutralize the acid generated during the reaction. Furthermore, a stoichiometric amount of halide salt is generated as waste. Both of these drawbacks were circumvented in this report with

anhydrides acting as organohalide surrogates. However, a high reaction temperature was required, ranging from 140-190 °C. As a result, mixtures of olefins isomers were formed. While this issue limited the synthetic usefulness, this seminal work demonstrated both the power of acyl electrophiles to overcome issues associated with existing chemistry and that acyl electrophiles are not limited to ketone-forming coupling reactions.



Scheme 19. Pd-catalyzed decarbonylative Mizoroki-Heck type cross-coupling of aromatic carboxylic anhydrides

Gooßen and co-workers envisioned that ketone products could be accessed from anhydrides via a mechanistic pathway that mirrors the cross-coupling of acid chlorides (**Scheme 16B**). In 2001, Gooßen reported the first Pd-catalyzed coupling of aromatic carboxylic anhydrides with boronic acids in a carbonyl retentive manner (**Scheme 20A**). [42b] In contrast to the decarbonylative reactions developed by de Vries and co-workers described above, the carbonyl group was retained to provide the ketone product. Free carboxylic acids were also converted to acid anhydrides in situ with the use of stoichiometric pivalic anhydride (**Scheme 20B**) to form various ketone products (**Scheme 20C**). A similar anhydride cross-coupling reaction was also reported by Yamamoto and co-workers in 2002. [42c]



Scheme 20. (A) Pd-catalyzed carbonyl retentive Suzuki-Miyaura coupling of acid anhydrides. (B) In situ formation and coupling of acid anhydrides. (C) Representative scope of in situ anhydride coupling

Although the coupling reactions with acyl electrophiles discussed thus far are of both fundamental and practical importance, they are not without their drawbacks. Acid chlorides and anhydrides are reactive species, and thus are seldom useful in late stage functionalization. Relative to acyl chlorides and anhydrides, thioesters are much more robust; however, they too need to be prepared prior to coupling, and they often require the use of stoichiometric copper salts to be activated. Continued progress in this field calls for the ability to functionalize more abundant and, more importantly, more robust electrophiles. Esters have the potential to satisfy both of these demands. The acyl cross-coupling reactions described thus far paved the way for future achievements with esters that will be described throughout the proceeding sections. In particular, the power of esters to form both decarbonylative and carbonyl retentive products will be highlighted.

1.3.2: Decarbonylative coupling of aryl esters

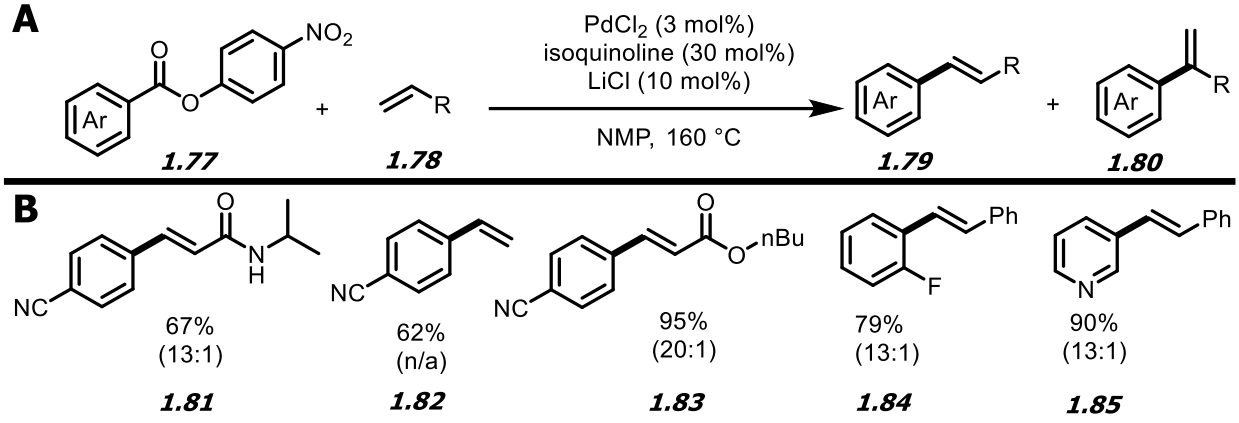
Cross-coupling reactions of esters that selectively form decarbonylated products provides an alternative route to more traditional reactions with aryl halides. Beyond providing a distinct synthetic disconnection, these reactions avoid the formation of halide salt waste products and display useful chemoselectivity. Furthermore, esters are a common, relatively robust motif that make them useful in complex molecule synthesis. The majority of these decarbonylative couplings feature esters that are modestly activated by a phenyl ring on oxygen. These so-called aryl esters feature a weaker C(acyl)–O bond than alkyl esters, rendering them more susceptible to cleavage. Leading examples of these transformations are given below.

1.3.2.1: Mizoroki-Heck type coupling

Since its discovery, the Mizoroki-Heck reaction has been demonstrated as a reliable way to arylate olefins efficiently and often regioselectively.[45] Decarbonylative couplings using acid anhydrides as aryl halide surrogates were described above (**Scheme 19**), which obviate the need for a stoichiometric base. The first example using aryl esters was reported by Gooβen and co-workers, who coupled *p*-nitrophenyl esters with olefins using a palladium catalyst (**Scheme 21A**).[46] As was the case in the work of de Vries, $PdCl_2$ was identified as the optimal precatalyst, and the addition of alkali metal halides, most notably LiCl, helped to increase the effectiveness of the catalyst. To diminish catalyst deactivation, nitrogen ligands, particularly isoquinoline, were identified as useful stabilizing additives. A strongly coordinating phosphine ligand like PPh_3 led to diminished yields of product. The *p*-nitro group on the arene was critical; in contrast to the high yields obtained, use of a simple phenyl ester gave trace product formation.

[45] Heck, R. F. *Org. React.* **1982**, 345.
[46] Gooßen, L. J.; Paetzold, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1237.

Linear products were formed preferentially using a range of terminal olefin coupling partners (**Scheme 21B**). A 'waste free' procedure was also demonstrated, with formation of the aryl ester by condensation and recovery of the *p*-nitrophenol after coupling enabling a closed recycle loop.



Scheme 21. (A) Mizoroki-Heck type reaction of *p*-nitrophenyl esters. (B) Representative scope examples where ratio in brackets represent linear:branched selectivity

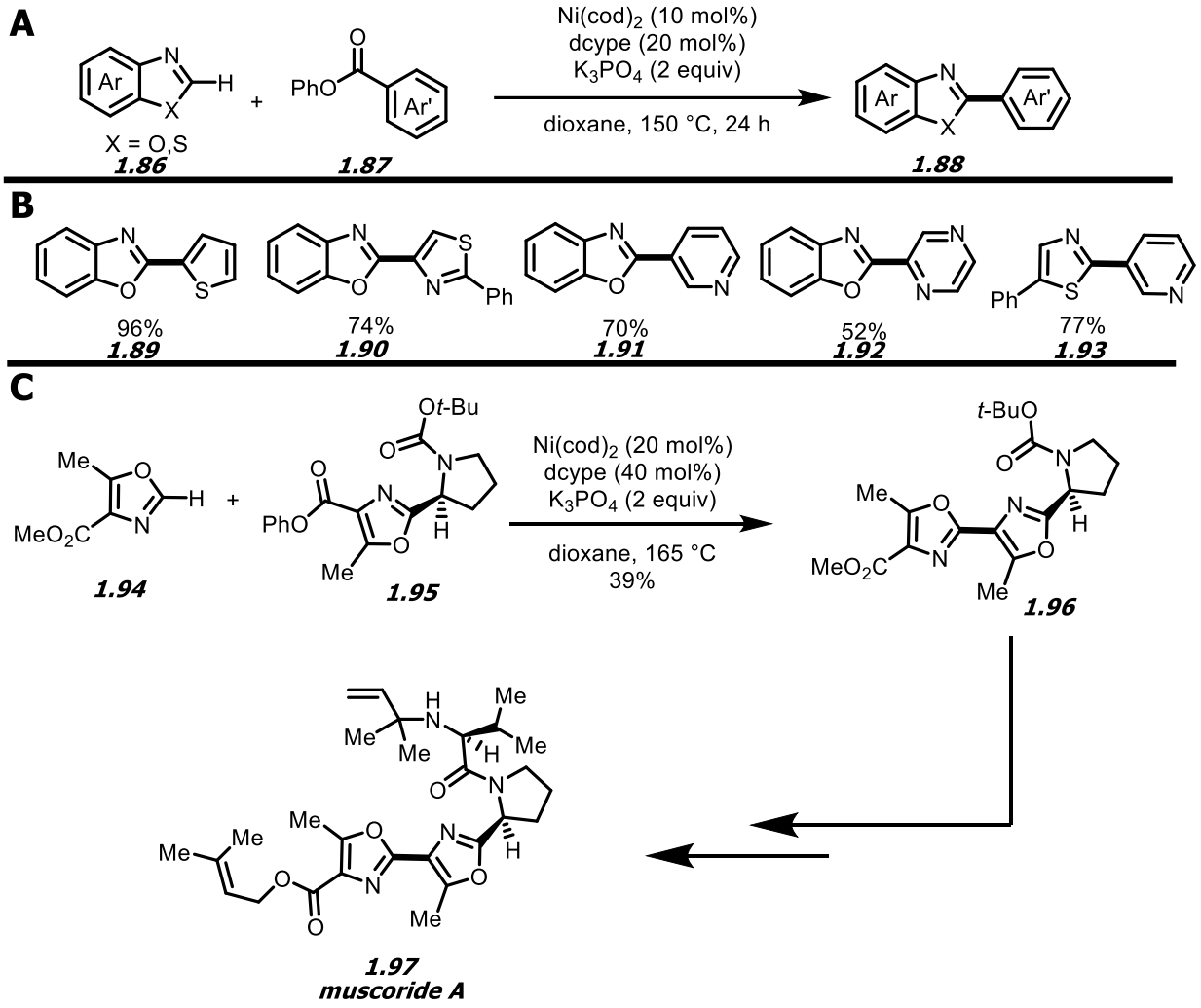
1.3.2.2: C-H biaryl coupling

The cross-coupling reactions described thus far feature traditional nucleophilic coupling partners, including olefins, boronic acids, and organozincs. The use of unfunctionalized arenes provides an appealing alternative for C-C bond construction, but adds the additional challenge of necessitating a C-H activation step. Towards this goal, Itami and Yamaguchi reported the first decarbonylative C-H arylation of phenyl esters in 2012 (**Scheme 22A**).[47] This involved a nickel catalyst system in a net redox-neutral transformation. The authors were particularly interested in investigating the coupling of heteroaromatic esters as they would lead to the formation of heteroarylated azoles

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

(**Scheme 22B**), which are important scaffolds in pharmaceutically relevant compounds and natural products. This method was applied towards the formal synthesis of muscoride A, using the decarbonylative C-H coupling for access to a key intermediate (**Scheme 10C**). Under similar conditions a decarbonylative alkenylation of azoles with α,β-unsaturated esters has also been demonstrated.[48] While the use of Ni/dcype was limited to the coupling of benzoxazoles and benzothiazoles, Itami and Yamaguchi later expanded the reaction to include benzothiazoles and benzimidazoles by switching to a Pd/dcypt or dcype catalyst system.[49]

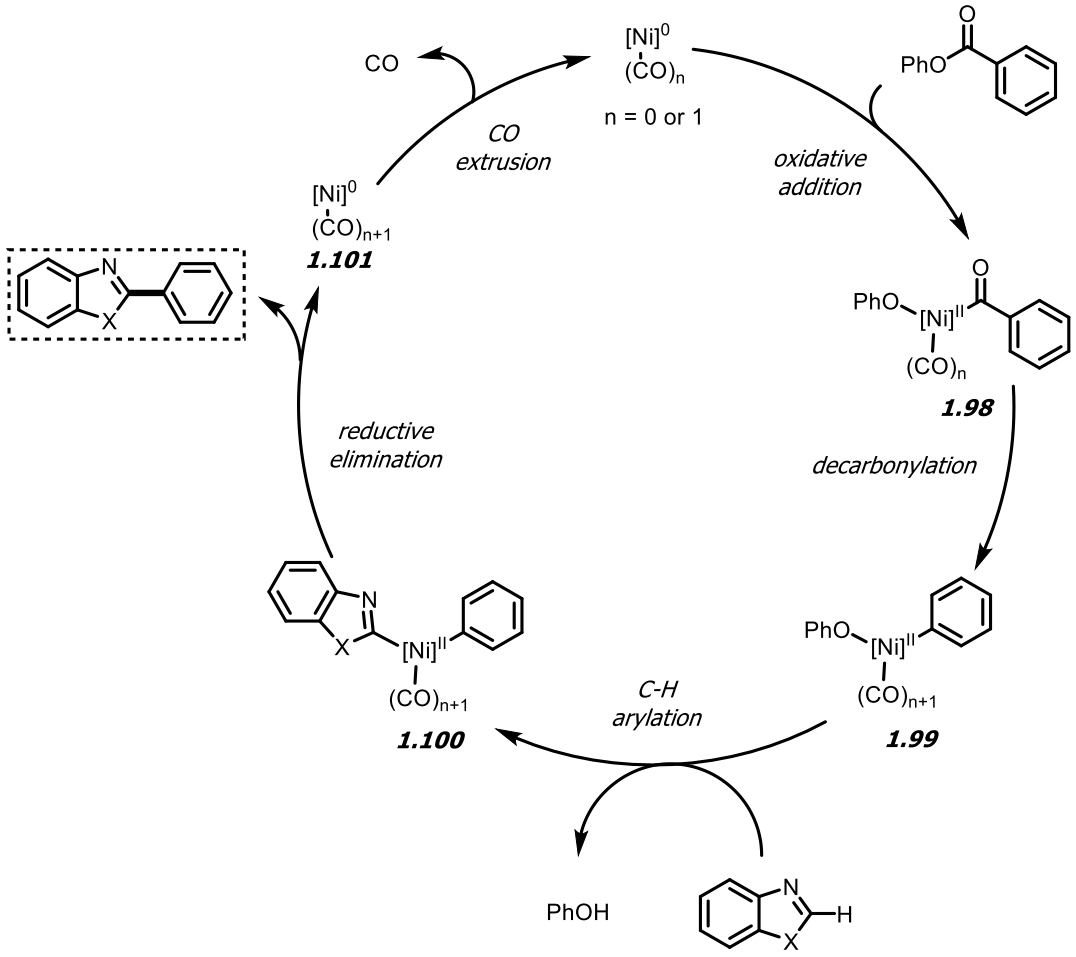
[48] Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem.* **2013**, *125*, 10232.
[49] Matsushita, K.; Takise, R.; Hisada, T.; Suzuki, S.; Isshiki, R.; Itami, K.; Muto, K.; Yamaguchi, J. *Chem. Asian. J.* **2018**, *13*, 2393.



Scheme 22. (A) Ni-catalyzed decarbonylative C-H coupling of azoles with phenyl esters. (B) Representative scope examples. (C) Formal synthesis of muscoride A.

A Ni(0)/Ni(II) catalytic cycle was proposed for this C-H functionalization, which starts with Ni(0) oxidatively adding into the phenyl ester C-O bond to form complex **1.98** (**Scheme 23**). Decarbonylation occurs to generate intermediate **1.99**, followed by the key C-H arylation to give intermediate **1.100**. This Ni(II) intermediate then reductively eliminates the product and generates Ni(0) species **1.101**, which can finally be turned over via thermal extrusion of CO. Ni(dcype)$(CO)_2$ was prepared and demonstrated to be an effective catalyst, suggesting that CO extrusion is a viable step. Lastly, more user-friendly

conditions for this arylation were demonstrated with $NiCl_2$ and Zn powder replacing air-sensitive $Ni(COD)_2$, albeit in lower yields.

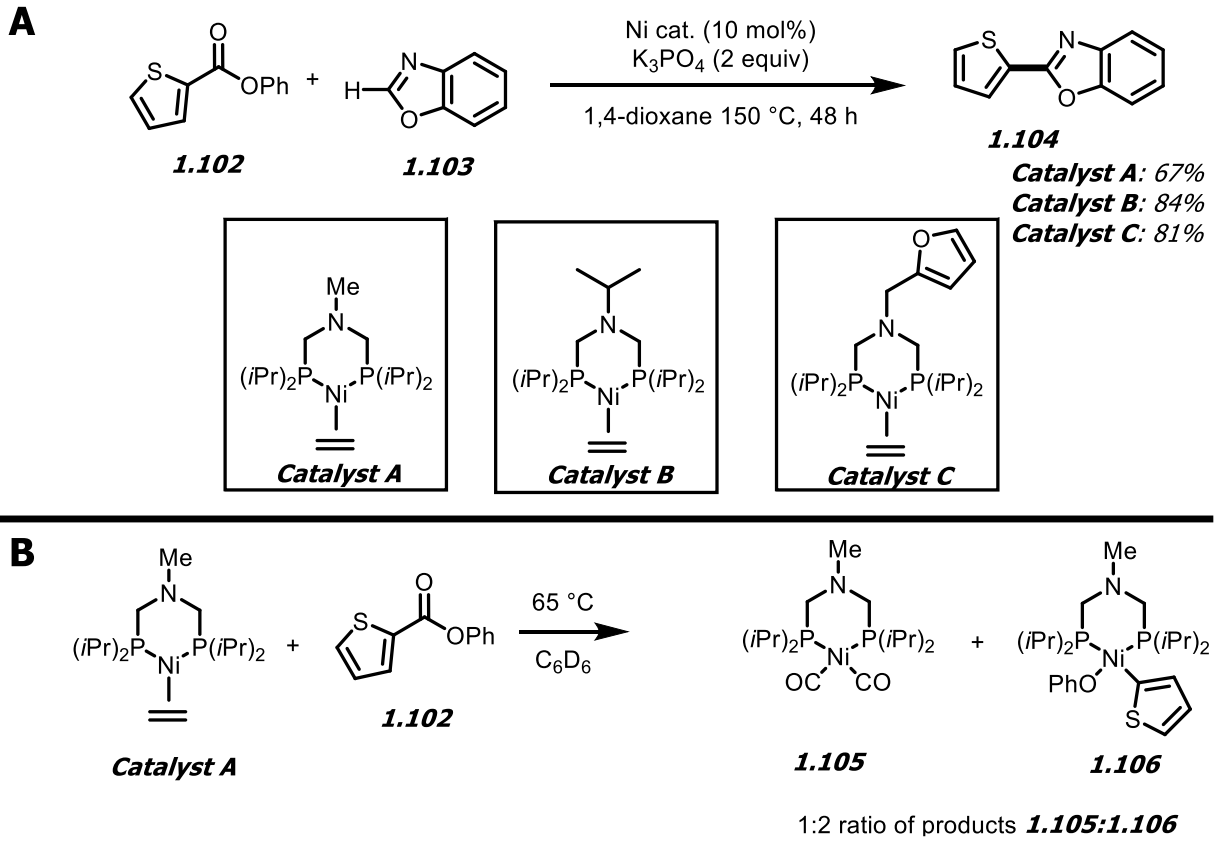


Scheme 23. Proposed mechanism for decarbonylative C-H coupling of azoles with phenyl esters

In 2013, Gade and co-workers investigated new Ni complexes for application in the decarbonylative C-H arylation of phenyl esters with azoles (**Scheme 24A**).[50] At the time of this report, there had been no detailed mechanistic studies for this transformation. The

[50] Kruckenberg, A.; Wadepohl, H.; Gade, L. H. *Organometallics* **2013**, *32*, 5153.

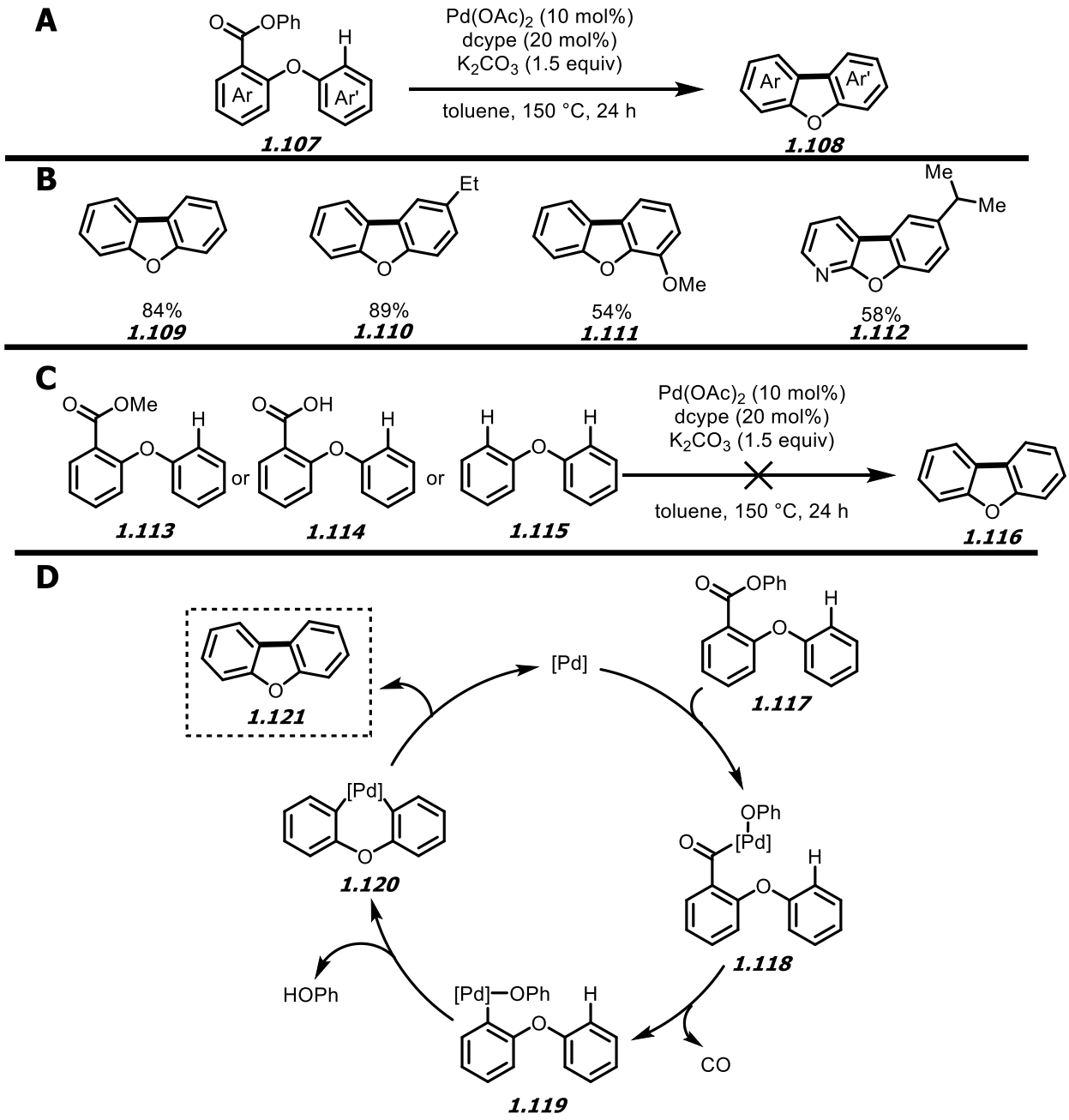
authors were interested in the synthesis of potential intermediates in the proposed catalytic (**Scheme 23**). With this goal in mind, a novel nickel Ni(0) catalyst **A** was treated with phenyl-2-thiophenecarboxylate (**Scheme 24B**). NMR was used to monitor consumption of the Ni complex while tracking the gradual formation of products **1.105** and **1.106** in a 1:2 ratio. Product **1.106** arises from the oxidative addition of the Ni complex into the C(acyl)-O bond of the ester, resulting in the formation of an acyl-Ni(II) intermediate, which was not observed spectroscopically. Instead, the acyl-Ni(II) intermediate undergoes a rapid decarbonylation directly to product **1.106**. The CO that is liberated in the process can react with Ni complex **A**, which leads to the formation of product **1.105** as Ni(0) can take on two CO ligands**.**



Scheme 24. (A) New Ni complexes for application in C-H arylation reactions. (B) Isolation of Ni complexes following oxidative addition and decarbonylation

In 2018, Yamaguchi and co-workers extended their decarbonylative C-H arylation of phenyl esters beyond reaction with 1,3-azoles.[51] Attempts at intermolecular C-H arylation of simple arenes had thus far proven unsuccessful, so intramolecular reactions were explored towards accessing dibenzofurans (**Scheme 25**). While nickel-catalyzed conditions could not be identified, palladium was very successful for the desired transformation, in particular with $Pd(OAc)_2$/dcype. Control experiments determined that the phenyl ester was necessary for reactivity (**Scheme 25C**); methyl ester activation, decaboxylative coupling, and C-H/C-H coupling were all ineffective. Although a precise mechanism is not known, the authors proposed a mechanism analogous to their Ni-catalyzed C-H arylations, with Pd oxidatively inserting into the C(acyl)-O bond followed by subsequent decarbonylation, intramolecular C-H activation, and reductive elimination to release the final product (**Scheme 25D**).

[51] Okita, T.; Komatsuda, M.; Saito, A. N.; Hisada, T.; Takahara, T. T.; Nakayama, K. P.; Isshiki, R.; Takise, R.; Muto, K.; Yamaguchi, J. *Asian. J. Org. Chem.* **2018**, *7*, 1358.



Scheme 25. (A) Pd-catalyzed decarbonylative intramolecular C-H arylation of phenyl esters. (B) Representative scope examples. (C) Control experiments. (D) Proposed mechanism.

1.3.2.3: Suzuki-Miyaura coupling

In modern organic synthesis, the Suzuki-Miyaura coupling has streamlined the synthesis of many important compounds, establishing itself as one of the most frequently used reactions.[52] Some of the earliest reports of the Suzuki-Miyaura coupling of esters led to ketone products, particularly with the use of a directing group [53], and are described in Section 1.3.3.1 (see also section 1.3.5.1). Decarbonylative Suzuki-Miyaura coupling of phenyl esters was not reported until 2015, when Itami, Musaev and co-workers disclosed a Ni(0) catalyzed procedure for this transformation (**Scheme 26A**).[54] In their work, extensive ligand screening showed that monodentate ligands were particularly effective with $Ni(OAc)_2/P^nBu_3$ serving as the optimized catalyst. A broad substrate scope was demonstrated for both the ester and the boronic acid coupling partners (**Scheme 26B**). $C(sp^3)$-$C(sp^2)$ bond formation was also possible when arylacetic acid phenyl esters were treated with boronic acids, although this necessitated the use of catalytic DMAP. The use of moderately activated phenyl esters was critical, with unactivated alkyl esters being unsuccessful. Interestingly, the reaction provided product (albeit in lower yields) in the absence of an exogenous base, which is usually necessary for Suzuki-Miyaura reactions that implement aryl halides as the electrophile. A one-pot protocol was also developed, which involved making the phenyl ester in situ via the corresponding carboxylic acid and diphenyliodonium triflates (**Scheme 26 C**). A by-product of the esterification was iodobenzene, which was subsequently removed under reduced pressure.

DFT calculations were conducted in order to gain a stronger appreciation for the key mechanistic features associated with the reaction (**Scheme 26D**). π-Complexation

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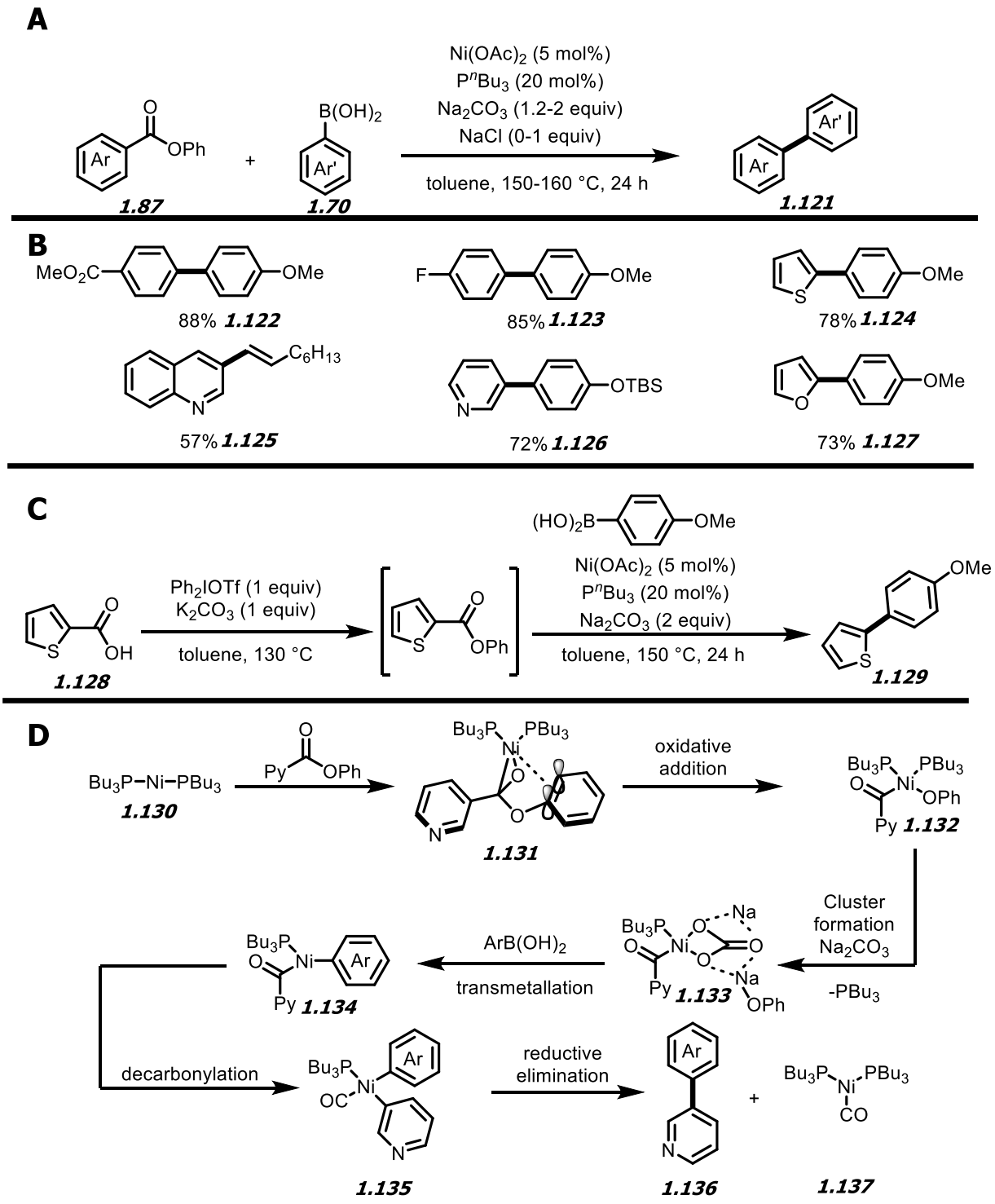
[52] Miyaura, N. ed. *Cross-coupling reactions: A practical guide*; Springer: Berlin, 2002.
[53] Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, *6*, 3597.
[54] Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508.

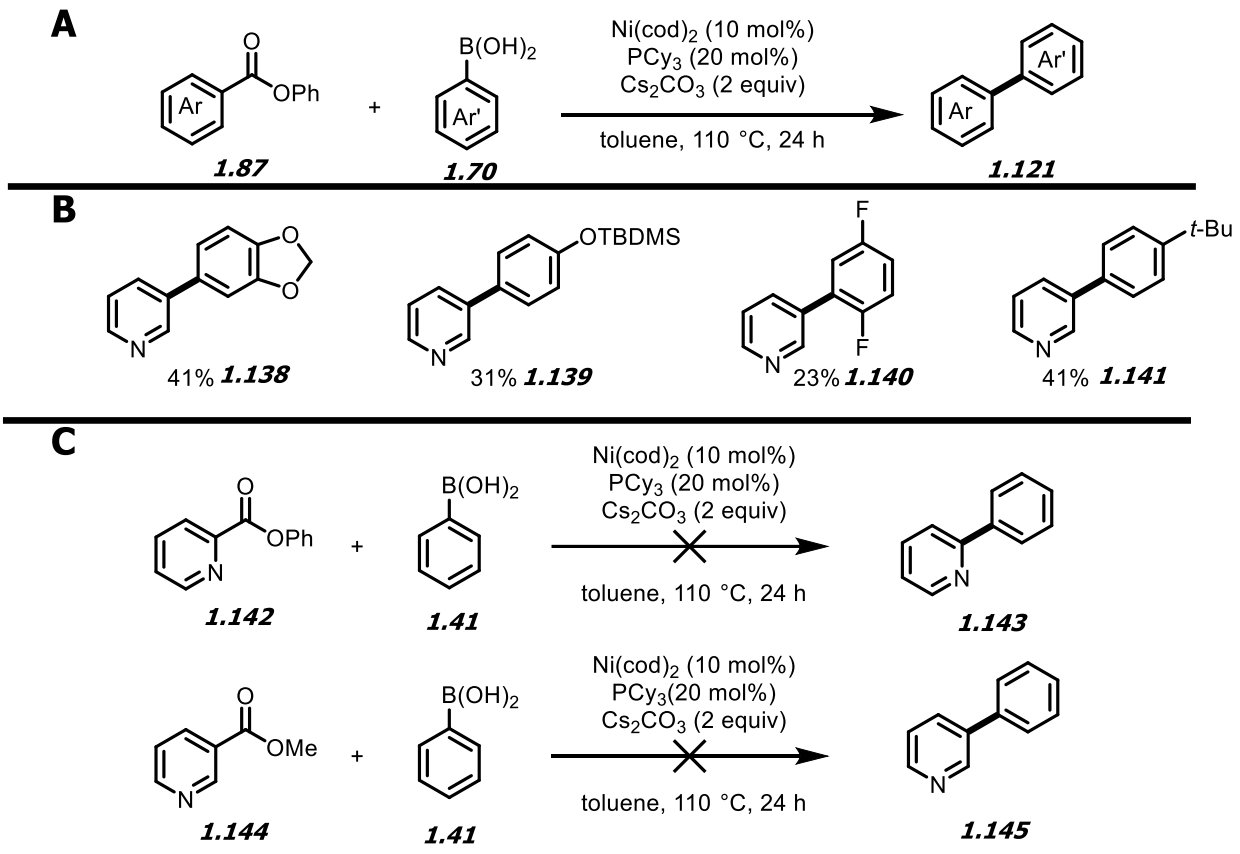
between the aryl ester moiety and the empty d-orbitals of Ni was proposed as the first step. This interaction was predicted to be important for a subsequent oxidative addition into the C(acyl)-O bond, as alkyl esters were unreactive under the reaction conditions. Na_2CO_3 reacts with the oxidative addition intermediate to form a cluster complex, which lowers the energy barrier for transmetallation. Following transmetallation is a decarbonylation step, which was proposed to be rate-determining. A slightly higher energy pathway in the absence of base was possible, where the transmetallation was the rate-determining step, explaining why the reaction occurs without base in lower yields.



Scheme 26. (A) Ni/P^{n}Bu$_3$ catalyzed decarbonylative Suzuki-Miyaura cross-coupling of phenyl. esters. (B) Represenative scope examples. (C) One-pot protocol using carboxylic acids. (D) Important intermediates identify by DFT studies.

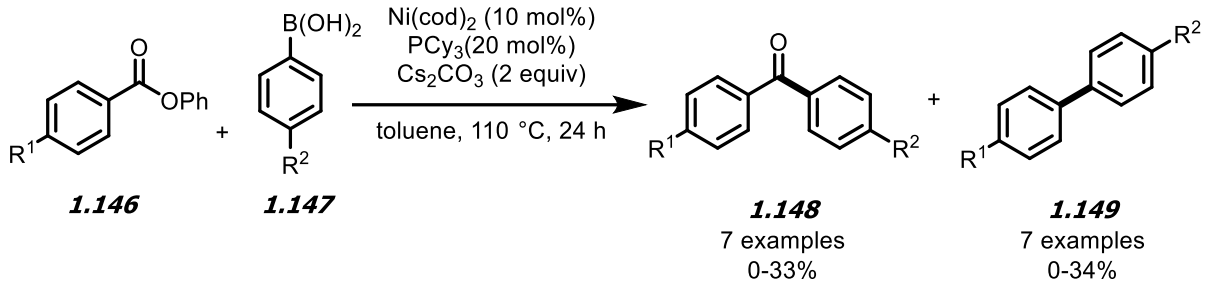
The same year, the Love group reported a similar transformation making use of a $Ni(cod)_2$ and PCy_3 catalyst system (**Scheme 27A**).[55] By running the reaction under a constant flow of N_2, the authors could mitigate the catalyst poisoning effect of CO in the flask. Phenyl esters could be coupled with arylboronic acids to form biaryl products (**Scheme 27B**). These reaction conditions were mostly limited to heterophenyl esters. Methyl nicotinate was not tolerated under the reaction conditions, demonstrating that this chemistry could not be extended to simple methyl esters. While 3- and 4-pyrididine carboxylates could be coupled effectively under the reaction conditions, aryl 2-pyridinecarboxylates and methyl esters were not tolerated (**Scheme 27C**).

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



Scheme 27. (A) Ni/PCy_3 catalyzed decarbonylative Suzuki-Miyaura coupling of heterophenyl esters. (B) Representative scope examples. (C) Scope limitations

Under Love's standard conditions, non-heteroaryl esters could also be coupled, albeit in low yields (**Scheme 28**). A mixture of biaryl and ketone products were obtained with non-heteroaryl esters. The authors proposed that the ketone products stemmed from transmetallation with the boronic acid prior to decarbonylation.

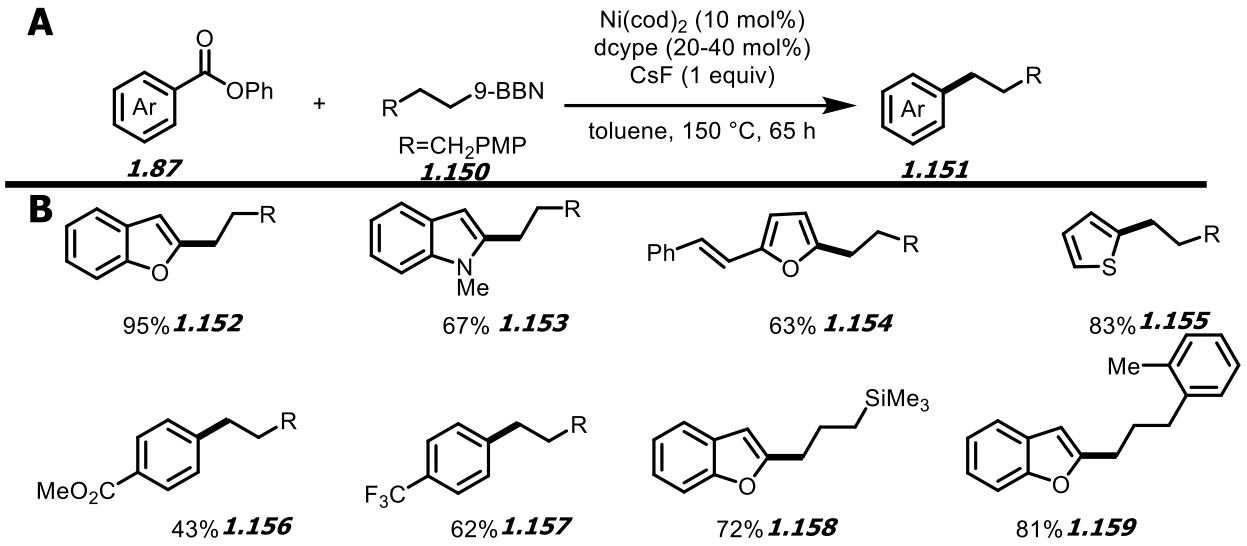


Scheme 28. Coupling of non-heterophenyl esters under Ni/PCy$_3$ catalysed Suzuki-Miyaura conditions

In 2016, the Yamaguchi group developed a method to functionalize aryl 2-pyridinecarboxylates using Suzuki-Miyaura coupling with Pd catalysis.[56] Application of this method was later demonstrated through a decarbonylative aryl 2-pyridinecarboxylate coupling [55], decarbonylative C-H coupling [47], and a decarboxylative [4+2] cycloaddition to access triarylpyridines towards the formal synthesis of antibiotic compounds [57]. Although the Suzuki-Miyaura coupling is a powerful transformation, it is often used to make C-C bonds between two C(sp^2) fragments. [38a] C(sp^2)-C(sp^3) bond formation is less common, largely due to issues associated with synthesis and use of alkyl boron nucleophiles. For example, they are prone to protodeboration, are more reluctant to transmetalate relative to their aryl nucleophile counterparts, and may undergo β-hydride elimination after transmetallation with a transition metal catalyst.[58] In 2018, the Rueping group expanded the decarbonylative Suzuki-Miyaura type couplings to include C(sp^3)-hybridized organoboron nucleophiles (**Scheme 29A**; also see **Scheme 36** for organozincs C(sp^3)-hybridized nucleophiles).[59] Interestingly, it was observed that the outcome of the reaction was ligand controlled. When dcype was used, an alkylated arene

[56] Muto, K.; Hatakeyama, T.; Itami, K.; Yamaguchi, J. *Org. Lett.* **2016**, *18*, 5106.
[57] Amaike, K.; Itami, K.; Yamaguchi, J. *Chem. Eur. J.* **2016**, *22*, 4384.
[58] Lennox, A. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412.
[59] Chatupheeraphat, A.; Liao, H.-H.; Srimontree, W.; Guo, L.; Minenkov, Y.; Poater, A.; Cavallo, L.; Rueping, M. *J. Am. Chem. Soc.* **2018**, *140*, 3724.

was obtained selectively. When P^{n}Bu$_3$ or PCy$_3$ was used, ketones were formed (see Section 1.3.3.1). DFT studies suggested that the Ni/dcype system favours oxidative addition into the C(aryl)-C bond, which ultimately decarbonylates and thus leads to the formation of alkylated arenes. A variety of aryl and heteroaryl esters were demonstrated to participate smoothly in the reaction (**Scheme 29B**). Substitutions on the organoborane could also be tolerated, including silyl groups and esters. While the B-alkyl-9-BBN reagents were prepared in situ, commercially available BEt$_3$ was also shown to be a suitable alkylating agent. Although not extensively investigated, it was also shown that amides were also capable of undergoing a similar decarbonylative alkylation reaction.

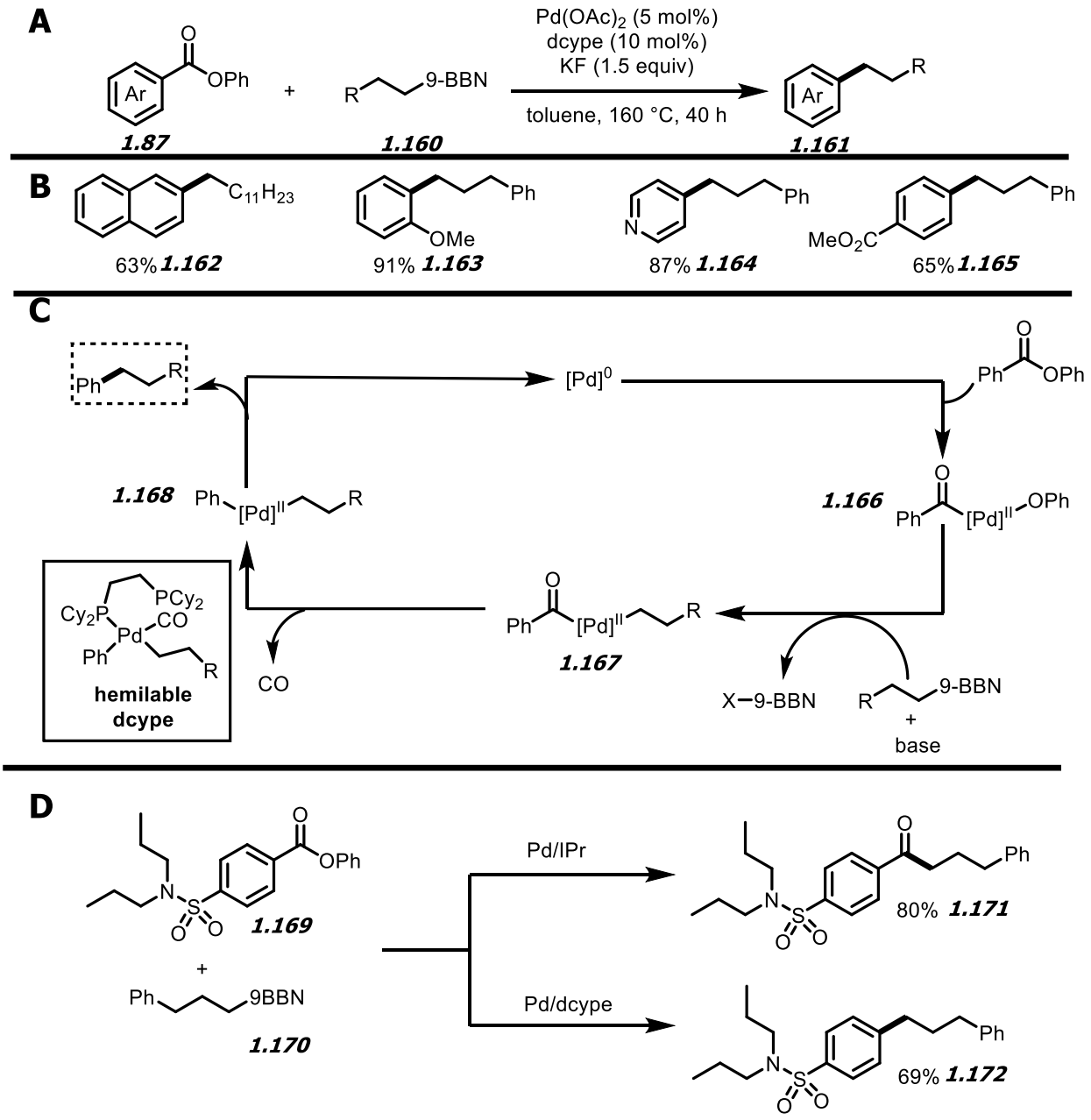


Scheme 29. (A) Ligand controlled decarbonylative alkylation of phenyl esters. (B) Representative scope examples.

In the same year, the Newman lab disclosed a Pd-catalyzed coupling of phenyl esters with B-alkyl-9-BBN reagents (**Scheme 30A**).[60] Several aryl and heteroaryl esters were well tolerated (**Scheme 30B**). Under these conditions, the formation of the products also

[60] Masson-Makdissi, J.; Vandavasi, J. K.; Newman, S. G. *Org. Lett.* **2018**, *20*, 4094.

depended on the choice of ligand. A bulky NHC catalyst favoured the formation of alkylated ketones (see Section 1.3.3.1). The use of the bidentate phosphine dcype instead led to the formation of alkylated arenes. The authors proposed that dcype acts as a hemilable ligand, capable of opening coordination sites on the metal that allow decarbonylation to occur; a key step that is prevented by bulky monodentate NHCs (**Scheme 30C**). The ability to functionalize a single starting material into different classes of products was also demonstrated by transforming the hyperuricemia treatment Probnecid into either an alkyl arene or alkyl ketone by changing the choice of ligand (**Scheme 30D**).



Scheme 30. (A) Pd-catalyzed decarbonylative alkyl Suzuki-Miyaura coupling of phenyl esters. (B) Representative scope examples. (C) Proposed mechanism. (D) Bioactive molecule derivatization

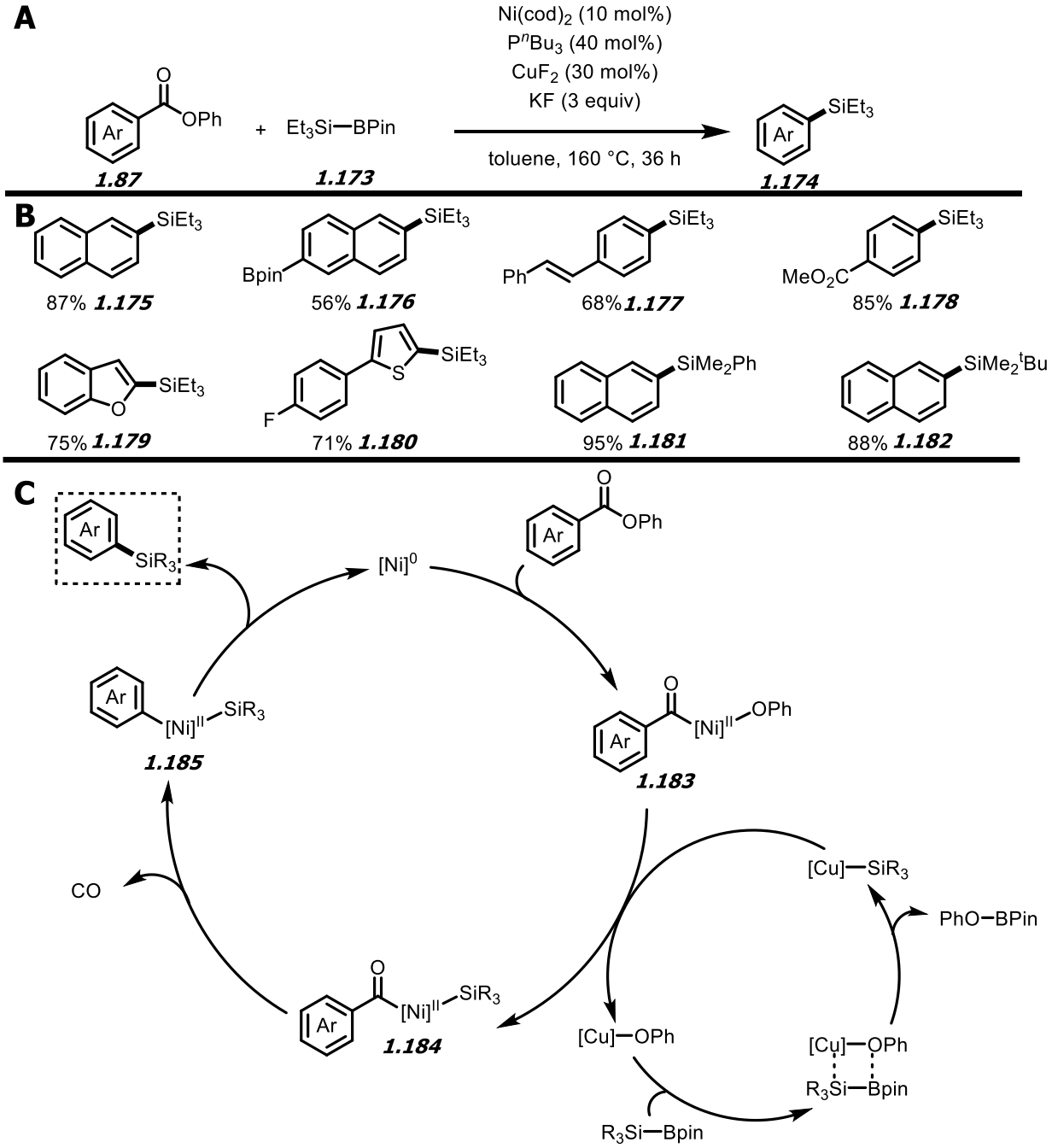
1.3.2.4: Silylation and borylation

Organosilicon reagents are important as they can be used towards the synthesis of valuable natural products as well as being incorporated into pharmaceutical compounds.[61] Routes to organosilanes often use aggressive organometallic nucleophiles [62] or necessitate the cross-coupling between organohalides and disilanes.[63] Organoboron compounds are also highly useful, particularly as the nucleophilic reactant in the Suzuki-Miyaura coupling. Like organosilanes, they can be prepared by reaction of an organometallic nucleophile with an electrophilic boron source [64] or by cross-coupling of aryl halides and diborons.[65] Constructing C–Si and C–B bonds by decarbonylative coupling reactions of esters provides similar advantages to the C–C forming reactions discussed above, including a distinct synthetic route, avoidance of metal halide salts, and potential chemoselectivity advantages.

In 2016, the Rueping group developed a decarbonylative silylation of aromatic phenyl esters with silylboranes in the presence of nickel/copper co-catalysis (**Scheme 31A**).[66] The authors demonstrated a wide substrate scope for tolerated functionalities on the ester (**Scheme 31B**). The reaction was not limited to Et_3Si-Bpin, as a variety of silylborane coupling partners could be used. The first step in this transformation was proposed to be an oxidative addition of Ni(0) into the C(acyl)-O bond of the ester, yielding an acyl nickel(II) intermediate **1.183**. Intermediate **1.183** undergoes transmetallation with the copper silane species that is generated in situ, forming complex **1.184**. Complex **1.184** then undergoes decarbonylation to form nickel complex

[61] (a) Denmark, S. E.; Liu, J. H.-C. *Angew. Chem. Int. Ed.* **2010**, *49*, 2978. (b) Ramesh, R.; Reddy, D. S. *J. Med. Chem.* **2017**, *61*, 3779.
[62] Manoso, A. S.; Ahn, C.; Soheili, A.; Handy, C. J.; Correia, R.; Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 8305.
[63] Denmark, S. E.; Kallemeyn, J. M. *Org. Lett.* **2003**, *5*, 3483.
[64] Pintaric, C.; Olivero, S.; Gimbert, Y.; Chavant, P. Y.; Duñach, E. *J. Am. Chem. Soc.* **2010**, *132*, 11825.
[65] Molander, G. A.; Trice, S. L.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701.
[66] Guo, L.; Chatupheeraphat, A.; Rueping, M. *Angew. Chem.* **2016**, *128*, 11989.

1.185. Reductive elimination releases the silylated product and regenerates Ni(0) to further propagate the catalytic cycle (**Scheme 31C**).

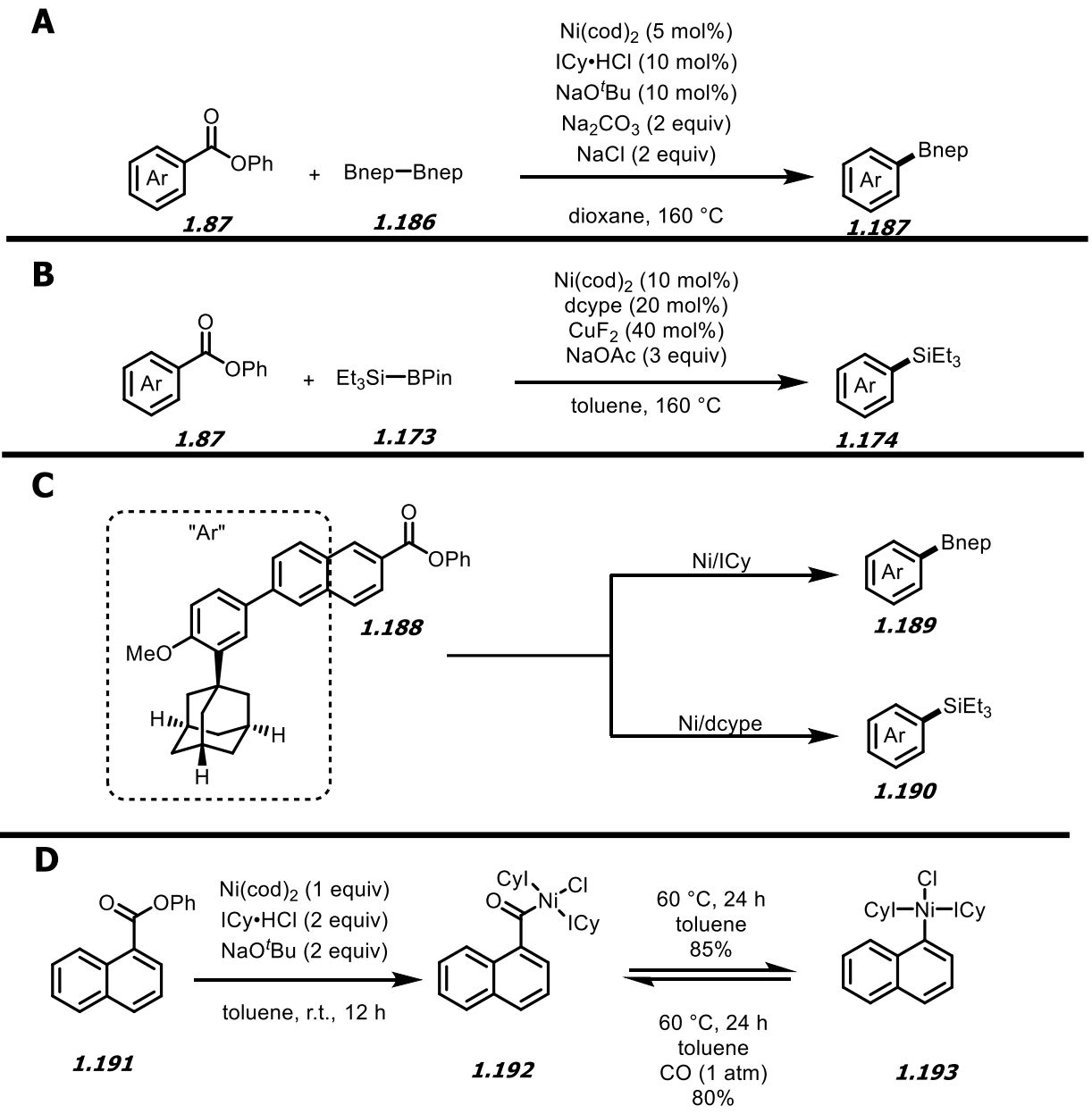


Scheme 31. (A) Ni-catalyzed decarbonylative silylation of phenyl esters. (B) Representative scope examples. (C) Proposed mechanism.

In the same year, the Shi group reported a similar decarbonylative silylation reaction of aromatic phenyl esters (**Scheme 32A**).[67] This reaction also made use of nickel/copper co-catalysis using dcype as the ligand. The silylation reaction exhibited tolerance for diverse functional groups and heteroaromatic compounds. In the same publication, a decarbonylative borylation of aromatic phenyl esters using B_2nep_2 was also reported (**Scheme 32B**). Key to the success of the borylation reaction was the use of the NHC ligand ICy. To demonstrate the synthetic utility of these methods, a phenyl ester analogue of a complex molecule was shown to be capable of being borylated or silylated selectively (**Scheme 32C**).

Although significant advances had been made in the field of ester cross-coupling, at the time of these publications, the isolation of an acyl nickel(II) species remained an elusive goal. The Shi group were the first to synthesize and isolate an acyl nickel(II) species derived from a phenyl ester (**Scheme 32D**). Phenyl 1-naphthoate was treated with a stoichiometric amount of $Ni(cod)_2$, NHC ligand, and NaO^tBu, yielding the corresponding nickel(II) oxidative addition adduct **1.192**. By heating the complex at 60 °C, decarbonylation occurred to yield nickel (II) complex **1.193**. When complex **1.193** was heated at 60 °C under 1 atm of CO, it reverted back to the acyl nickel (II) complex **1.192**. These results suggest that the decarbonylation process is fast and reversible. It was also found that both the aryl complex **1.193** and acyl complex **1.192** were capable of catalyzing the standard reaction in near identical yields, indicating that both species can enter catalytic cycle.

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

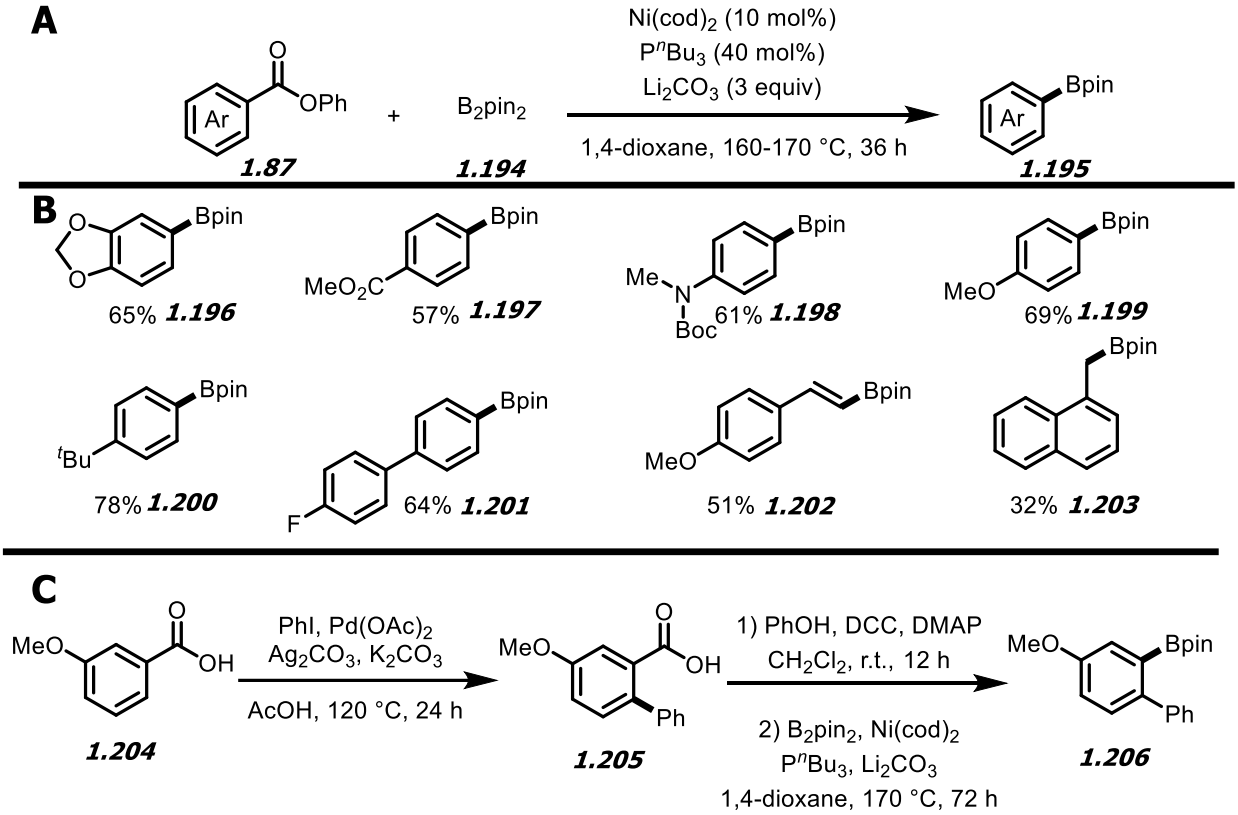


Scheme 32. (A) Standard conditions A: Ni-catalyzed decarbonylative borylation of phenyl esters. (B) Standard conditions B: Ni-catalyzed decarbonylative silylation of phenyl esters. (C) complex molecule derivatization. (D) isolation of nickel intermediates

Rueping also reported a decarbonylative borylation reaction of aromatic phenyl esters with B_2pin_2 by making use of a $Ni(cod)_2/P^nBu_3$ catalytic system (**Scheme 33A**).[68] This

[68] Guo, L.; Rueping, M. *Chem. Eur. J.* **2016**, *22*, 16787.

reaction demonstrated a wide substrate scope and was additionally shown to be capable of functionalizing some α-alkenyl and α-alkyl esters (**Scheme 33B**). Gram scale synthesis was also demonstrated. The synthetic utility of such a transformation was demonstrated when performing sequential couplings, using a carboxylate as a directing group prior to installing and activating a phenyl ester for borylation (**Scheme 33C**).



Scheme 33. (A) Ni/P^{n}Bu$_3$ catalyzed decarbonylative borylation of phenyl esters. (B) Representative scope examples. (C) Sequential cross-couplings.

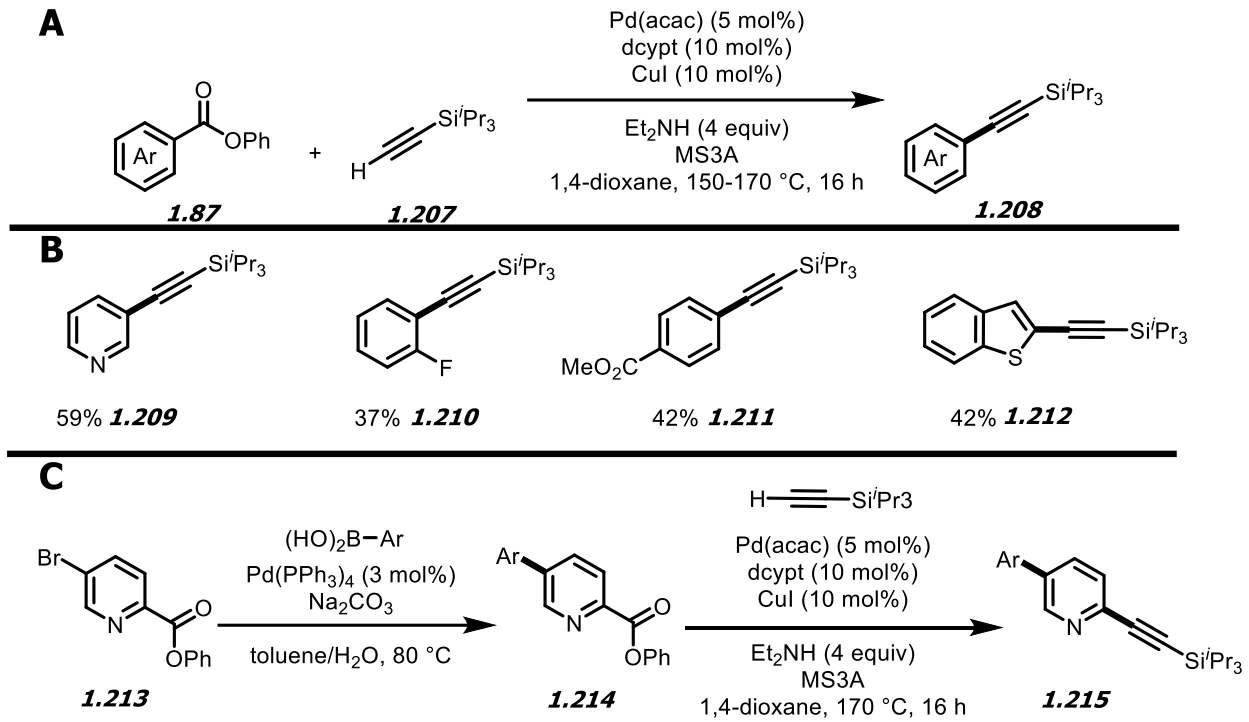
1.3.2.5: Other C-C/C-H bond forming reactions

This section describes miscellaneous impactful phenyl ester cross-couplings that forge C-C or C-H bonds using nucleophilic coupling partners not captured in the prior sections.

Sonogashira-type couplings

Arylalkynes are important scaffolds that are commonly used as versatile intermediates towards the synthesis of valuable organic compounds.[69] The Sonogashira coupling is an efficient transformation that accesses arylalkynes, traditionally from aryl halides and terminal alkynes.[70] Leading up to 2017, substantial progress was made in research concerning ester cross-coupling. However, decarbonylative C-C bond forming reactions of esters were still limited to $C(sp^2)$- $C(sp^2)$ bond formation at that time. In 2017, the first example of decarbonylative $C(sp^2)$-C(sp) bond formation was reported by Itami and Yamaguchi by coupling aromatic phenyl esters with alkynes in the presence of palladium/copper co-catalysts to furnish a variety of alkynylated arene products (**Scheme 34A and B**).[71] This protocol was limited to the use of silylacetylenes, as aryl and alkylacetylenes were not applicable for this reaction. To demonstrate the synthetic utility of such a transformation, sequential cross-couplings were conducted. Notably, traditional Suzuki-Miyaura couplings with aryl halides were shown to leave phenyl esters untouched, which allowed further derivatization (**Scheme 34C**).

[69] Chinchilla, R.; Nájera, C. *Chem. Rev.* **2014**, *114*, 1783.
[70] Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.
[71] Okita, T.; Kumazawa, K.; Takise, R.; Muto, K.; Itami, K.; Yamaguchi, J. *Chem. Lett.* **2017**, *46*, 218.



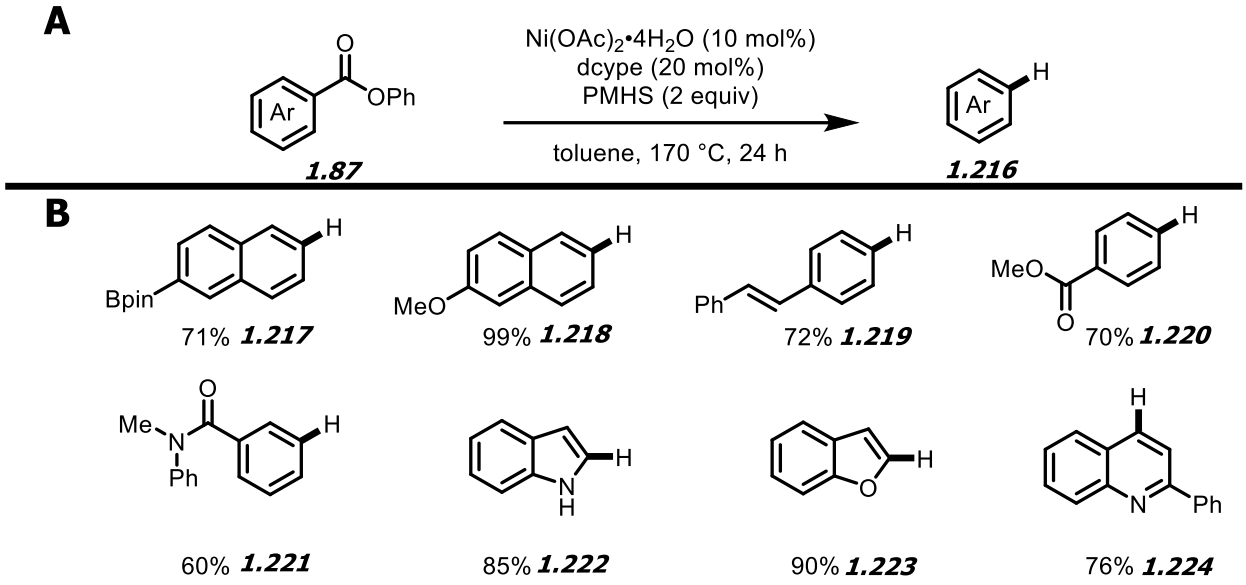
Scheme 34. (A) Pd-catalyzed decarbonylative Sonogashira type cross-coupling. (B) Representative scope examples. (C) Sequential cross-coupling sequence.

Reduction

The reduction of carboxylic acid derivatives such as esters is a staple transformation in organic synthesis, often achieved by the use of metal hydrides [72] or via hydrosilylation.[73] In contrast, the replacement of an ester with a hydrogen atom ($RCO_2R' \rightarrow$ R-H) is an interesting alternative reduction product. Rueping and coworkers were the first to develop a reductive defunctionalization of phenyl esters (**Scheme 35A**).[74] This was the first of such reports to achieve this without the use of directing groups (see section 1.3.5.1). The catalyst was an inexpensive combination of $Ni(OAc)_2 \bullet 4H_2O$ and dcype,

[72] Seyden-Penne, J. *Reductions by the alumino- and Borohydrides in organic synthesis*; Wiley-VCH: New York, 1997.
[73] Marciniec, B. *Hydrosilylation: A comprehensive review on recent advances*; Springer: Heidelberg, 2009.
[74] Yue, H.; Guo, L.; Lee, S.-C.; Liu, X.; Rueping, M. *Angew. Chem.* **2017**, *129*, 4030.

and made use of polymethylhydrosiloxane (PMHS) as the reducing agent. Under the reaction conditions, the authors were capable of reducing a variety of aryl and heterophenyl esters (**Scheme 35B**). The reaction was also readily extended to aryl and heteroaryl amides. As for other reduction protocols, triazine esters have also been shown to reduce down to aldehydes in the presence of a Pd-catalyst and a silane.[75]



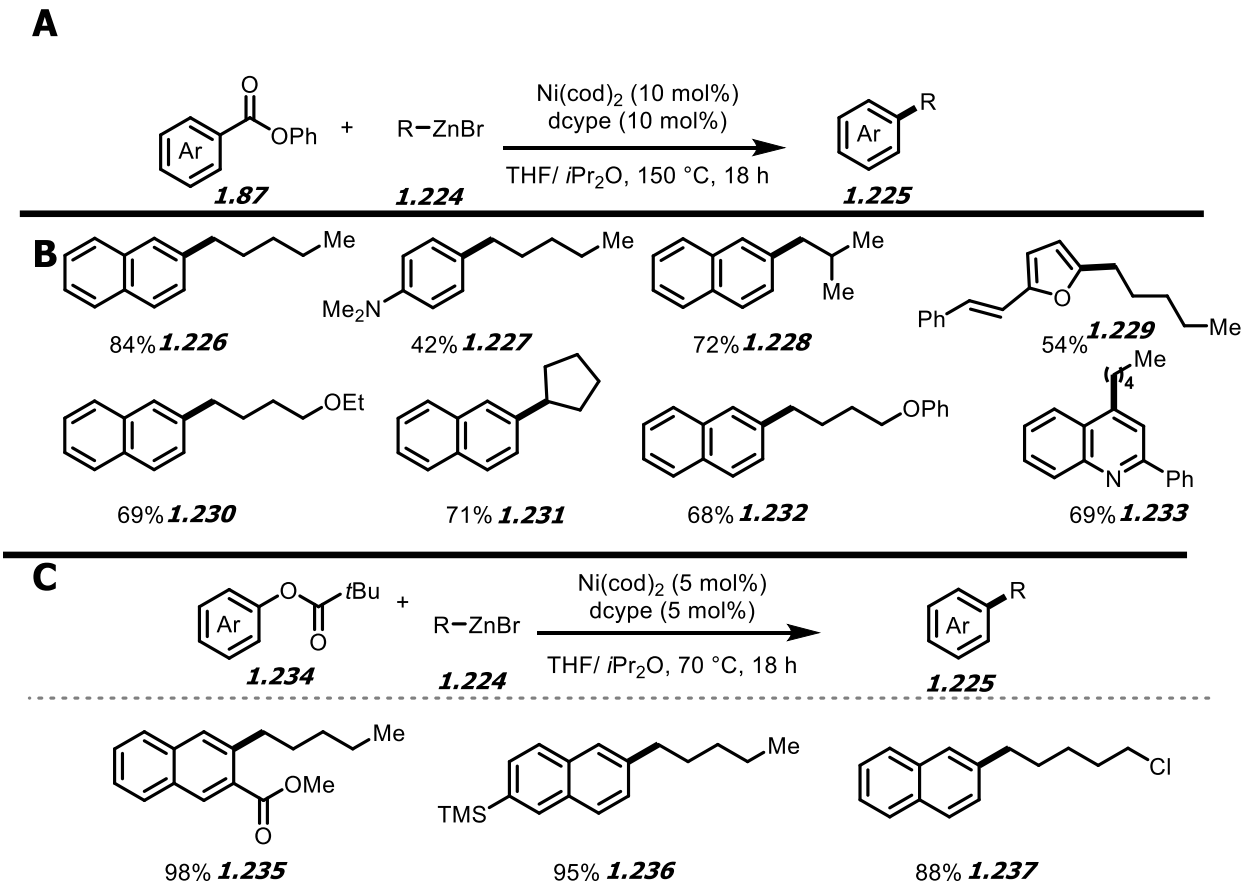
Scheme 35. (A) Ni-catalyzed decarbonylative reduction of phenyl esters using PMHS. (B) Representative scope examples

Negishi type coupling

Up until 2017, several different nucleophiles have been demonstrated to undergo coupling with esters. Some of these include 1,3-azoles, alkynes, boronic acids and silylboranes. Yet to be reported was a decarbonylative aryl-alkyl cross-coupling of esters. Rueping and co-workers were the first to develop a decarbonylative alkylation of

[75] He, Z.; Wang, Z.; Ru, J.; Wang, Y.; Liu, T.; Zeng, Z. *Adv. Synth. Catal.* **2020**, *362*, 5794.

phenyl esters using organozinc reagents (**Scheme 36A**).[76] As is often seen in ester activation, the choice of ligand was particularly important, with the bidentate phosphine ligand dcype being ideal. Under the optimized reaction conditions, a variety of aryl and heterophenyl esters could be coupled efficiently with alkyl organozinc reagents (**Scheme 36B**). Interestingly, the reaction was not limited to the use of phenyl esters. Pivaloyl esters could be converted to the same alkylated products via cleavage of the C(aryl)–O bond (**Scheme 36C**).



Scheme 36. (A) Ni-catalyzed decarbonylative Negishi type coupling. (B) Representative scope examples. (C) Pivalate ester cleavage and scope examples.

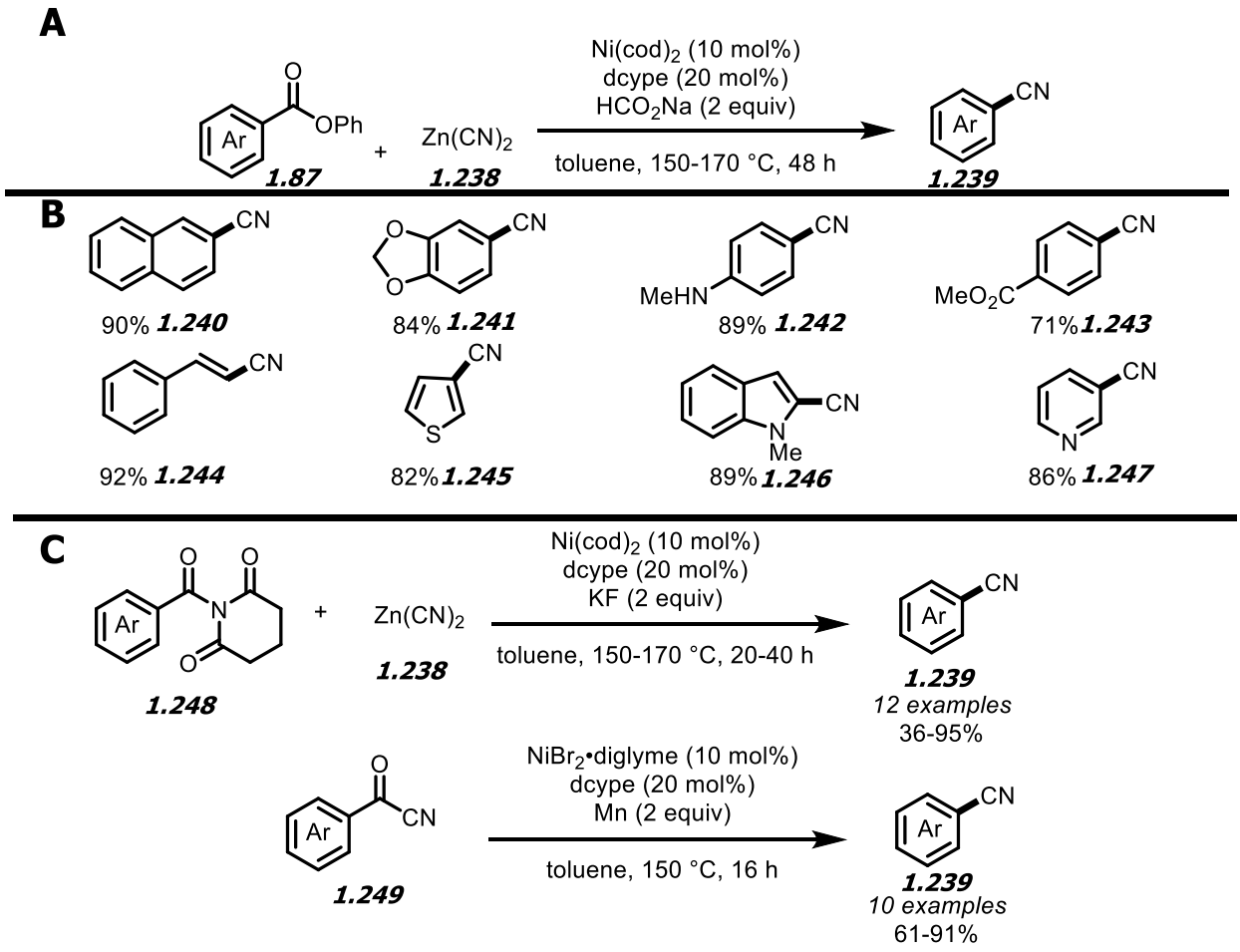
[76] Liu, X.; Jia, J.; Rueping, M. *ACS Catal.* **2017**, *7*, 4491.

Chen and co-workers also described the Ni-catalyzed cross-coupling of 2-pyridyl esters with alkyl zinc reagents, followed by Ni-H reduction of the corresponding ketones to yield benzylic alcohols in a single step.[77]

Cyanation

Traditionally, the introduction of cyano groups into aromatic compounds is achieved either by the Sandmeyer [78] or Rosenmund von Braun reactions.[79] Unfortunately, both of these methods suffer from relatively limited substrate scopes. The Rueping group were the first to report the nickel catalyzed decarbonylative cyanation of phenyl esters with zinc cyanide, which seeks to address the substrate scope issue associated with the existing protocols (**Scheme 37A**).[80] Ligand screening with $Ni(cod)_2$ determined that monodentate phosphines and NHC ligands were not useful for this transformation. Instead, success was realized with a $Ni(cod)_2$/dcype catalyst system. A variety of aryl and heterophenyl esters were demonstrated to undergo coupling with zinc cyanide smoothly (**Scheme 37B**). The authors also demonstrated that their protocol was capable of being extended to amide bond activation. Decarbonylative cyanation could also be done in an intramolecular fashion, with acyl cyanides directly furnishing the desired aryl nitrile products (**Scheme 37C**). The Yamaguchi group have also reported the decarbonylative synthesis of aryl nitriles by coupling phenyl esters with non-metal cyanating reagents.[81]

[77] Wu, X.; Li, X.; Huang, W.; Wang, Y.; Xu, H.; Cai, L.; Qu, J.; Chen, Y. *Org. Lett.* **2019**, *21*, 2453.
[78] Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. *J. Organomet. Chem.* **2004**, *689*, 3810.
[79] Rosenmund, K. W.; Struck, E. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 1749.
[80] Chatupheeraphat, A.; Liao, H.-H.; Lee, S.-C.; Rueping, M. *Org. Lett.* **2017**, *19*, 4255.
[81] Yamaguchi, J.; Iizumi, K.; Kurosawa, M. B.; Isshiki, R.; Muto, K. *Synlett* **2020**, *32*, 1555.



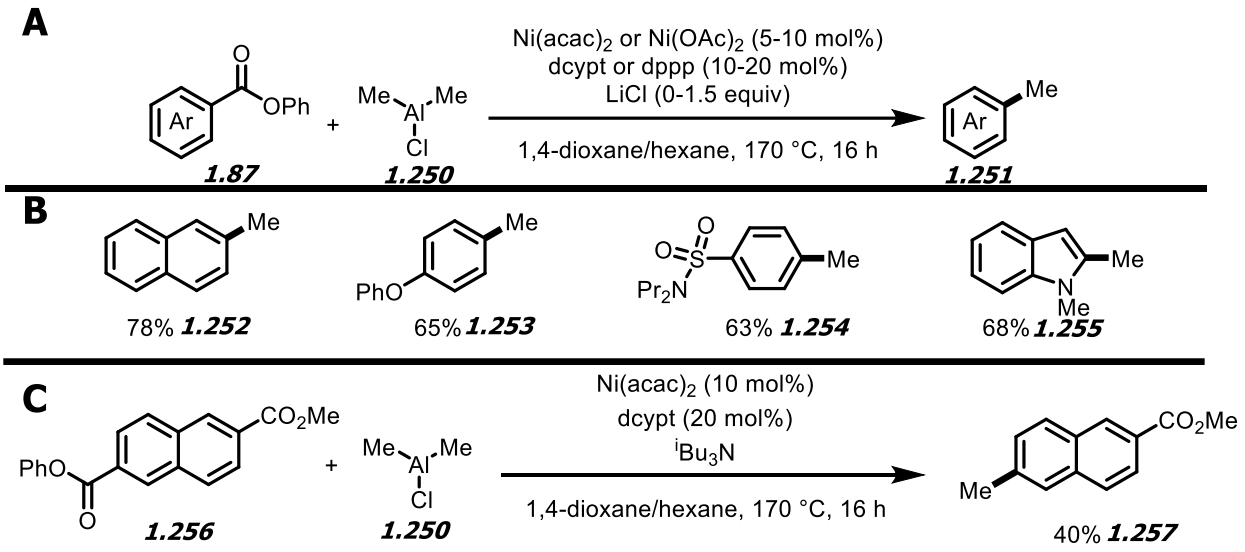
Scheme 37. (A) Ni-catalyzed decarbonylative aryl nitrile synthesis. (B) Representative scope examples. (C) Cyanation of amides and acyl cyanides.

Methylation

The majority of decarbonylative coupling reactions discussed this far feature formation of $C(sp^2)$-$C(sp^2)$ bonds. Towards developing new ester alkylation methods, Yamaguchi and co-workers described a Ni-catalyzed decarbonylative methylation of aromatic esters using methylaluminum reagents (**Scheme 38A**).[82] Dimethylaluminum chloride was particularly effective. Interestingly, this reagent was suggested to play a dual role,

[82] Okita, T.; Muto, K.; Yamaguchi, J. *Org. Lett.* **2018**, *20*, 3132.

acting both as a source of alkyl nucleophile and simultaneously acting as a Lewis acid, allowing for the functionalization of seemingly inert methyl esters (see Section 1.3.5.2 for further details). Ultimately, $Ni(acac)_2$/dcypt or dppp were determined to be optimal catalyst systems, which allowed for the functionalization of several aryl and heterophenyl esters (**Scheme 38B**). The authors also demonstrated that a phenyl ester could be functionalized selectively in the presence of a methyl ester, which is achieved when a tertiary amine is used in the reaction to suppress the Lewis acidity of the methylating agent (**Scheme 38C**). In the absence of the tertiary amine, both the phenyl ester and methyl ester were functionalized.



Scheme 38. (A) Ni-catalyzed decarbonylative methylation of phenyl esters. (B) Representative scope examples. (C) Chemoselective alkyl coupling.

1.3.2.6:Other C-heteroatom bond forming reactions

This section will describe miscellaneous impactful phenyl ester cross-coupling that make C-heteroatom bonds using nucleophilic coupling partners not captured in the prior sections.

Etherification

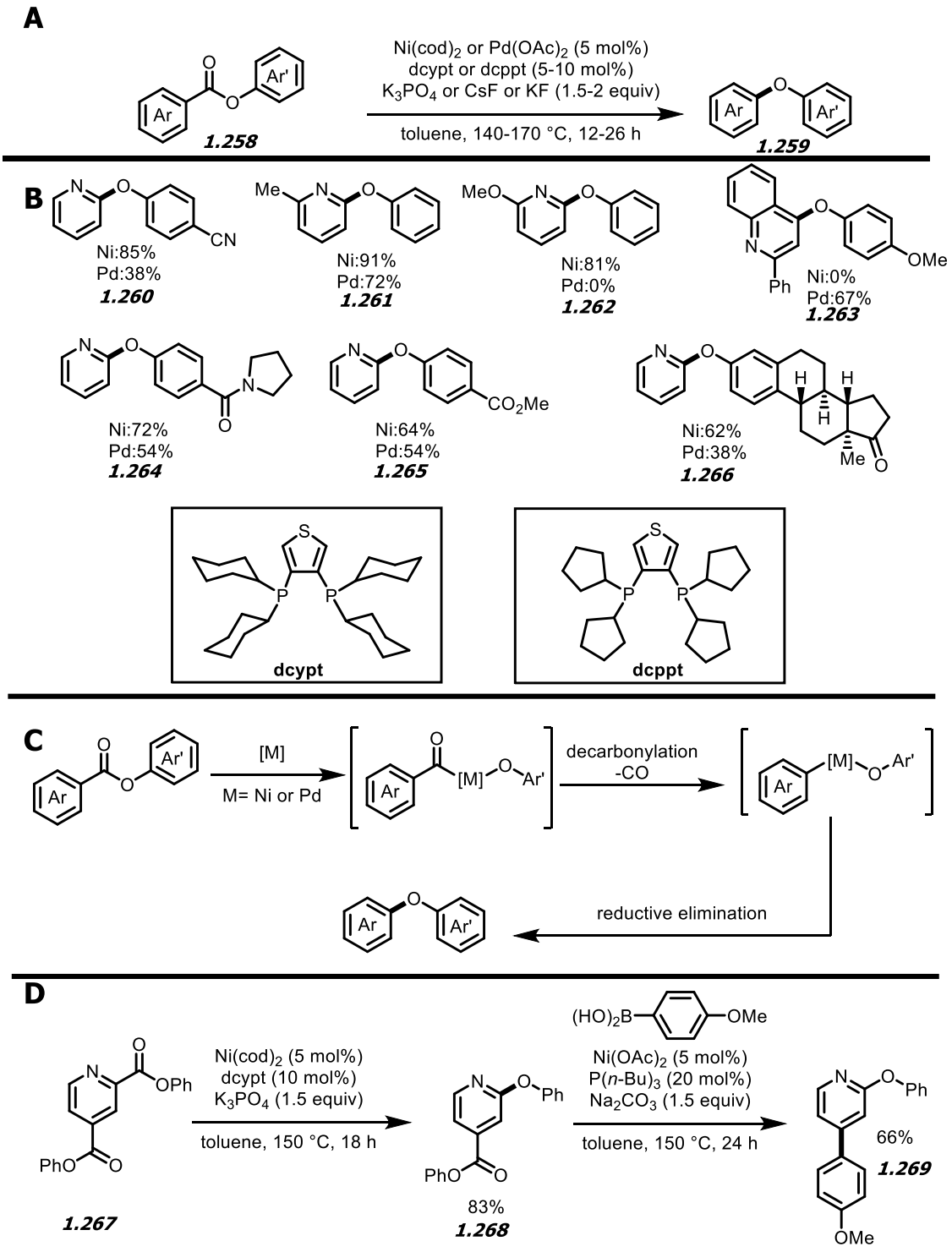
Diaryl ethers are scaffolds commonly seen in pharmaceuticals and natural products. Due to their importance, several methods have been developed for the synthesis of diaryl ethers, including the use of Pd [83] or Cu [84] catalysts to bring together aryl halides and phenols. Although the established protocols are powerful, extending the work to enable ester derivitizaiton would be synthetically useful particularly when late stage molecule functionalization is concerned.

Itami and Yamaguchi demonstrated that aryl esters such as **1.258** can be use to form diaryl ethers (**Scheme 39A and B**).[85] This C(acyl)–O bond activation was achieved by either Ni or Pd catalysis without need for an external nucleophile. Mechanistically, an oxidative addition, decarbonylation, reductive elimination sequence was proposed (**Scheme 39C**). The ligands dcypt and dcppt were found to be optimal, regardless of which metal they were paired with. While both Ni and Pd were effective for most substrates, some were observed to only work with one of the two. The reaction conditions were mostly limited to 2-azinecarboyxlates as the ester substrates. The selectivity of this catalyst system was demonstrated when a molecule bearing two phenyl esters was subjected to sequential cross-couplings (**Scheme 39D**). First a decarbonylative etherification was achieved on at the pyridine 2-position followed by a decarbonylative Suzuki-Miyaura coupling at the 4-position.

[83] (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369. (b) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4321.

[84] (a) Maiti, D.; Buchwald, S. L. *J. Org. Chem.* **2010**, *75*, 1791. (b) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284.

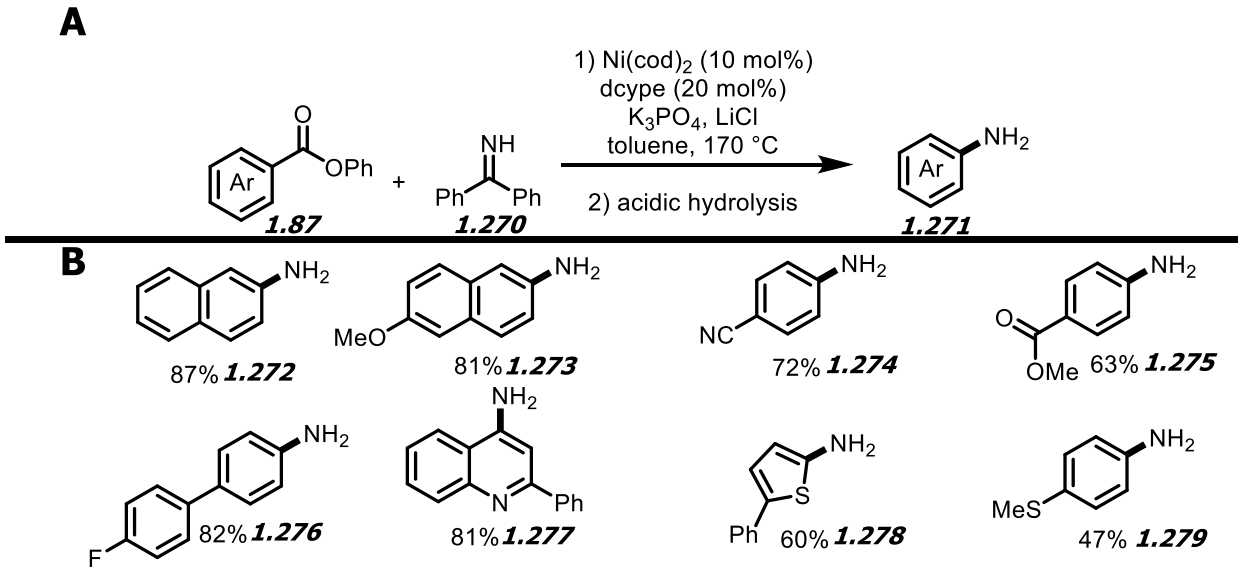
[85] Takise, R.; Isshiki, R.; Muto, K.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2017**, *139*, 3340.



Scheme 39. (A) Decarbonylative etherification of heterophenyl esters. (B) Representative scope examples. (C) Mechanistic hypothesis. (D) Chemoselectivity/sequential cross-coupling study.

Amination

Aryl amines are often found in pharmaceuticals, natural products and other important organic compounds such as dyes.[86] An efficient way of accessing C(sp^2)-N bonds is the Buchwald-Hartwig amination between aryl halides and amines. Given the value of these products, new protocols that can access C(sp^2)-N scaffolds are still sought, particularly without use of precious metals such as Pd. In 2017, the Rueping group developed a new aryl amine synthesis via the decarbonylative cross-coupling of phenyl esters with imines (**Scheme 40A**).[87] A Ni/dcype catalyst system, as well as the use of K_3PO_4 were crucial to the success of the reaction. After decarbonylative amination to form the arylated imine, the intermediate was treated with acid to hydrolyse the imine and release the aniline product.



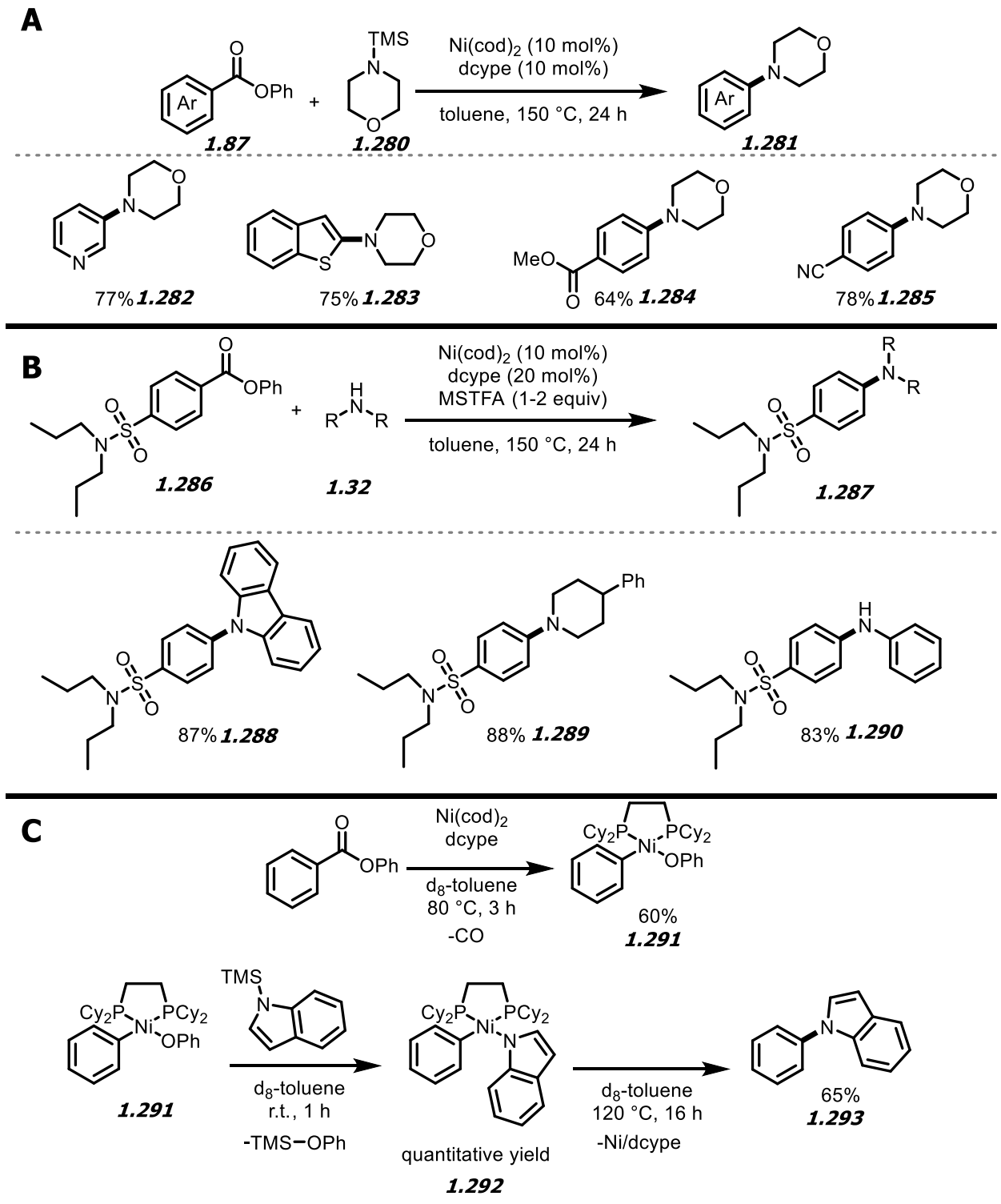
Scheme 40. (A) Ni-catalyzed decarbonylative aryl amine synthesis. (B) Representative scope examples

[86] (a) Liang, M.; Chen, J. *Chem. Soc. Rev.* **2013**, *42*, 3453. (b) Ricci, A. *Amino group chemistry from synthesis to the Life Sciences*; Wiley-VCH: Weinheim, Germany, 2008.

[87] Yue, H.; Guo, L.; Liao, H.-H.; Cai, Y.; Zhu, C.; Rueping, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 4282.

In 2020, the Sanford group developed a protocol for aryl amine synthesis via a decarbonylative cross-coupling between phenyl esters and silylated amines (**Scheme 41A**).[88] By masking the amine with a main group element, these nucleophiles would not react directly with the phenyl ester to form the amide, and would instead selectivity interact with the catalyst by transmetallation with Ni(II), after a decarbonylation event. In the presence of free amines, low yields of amide products would be obtained as transmetallation with free amines was faster than decarbonylation. By using N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA), the amines could be silylated in situ (**Scheme 41B**). A variety of primary and secondary aryl and alkyl amines were demonstrated to be effective coupling partners. It was also demonstrated that $Ni(CO)_2(PPh_3)_2$, a commercial and air stable source of Ni(0), could be utilized in place of $Ni(cod)_2$. Mechanistic investigation of the reaction led to the isolation of Ni(II) complex **1.291** formed by oxidative addition and subsequent decarbonylation. No acyl Ni(II) complexes were observed during the studies, likely indicating that decarbonylation occurs rapidly under the reaction conditions. The treatment of **1.291** with TMS-indole resulted in transmetallation to form Ni(II) complex **1.292**, which was stable and isolable at room temperature. Once complex **1.292** was heated at 120 °C, it allowed the formation of the corresponding aryl amine product **1.293** (**Scheme 41C**).

[88] Malapit, C. A.; Borrell, M.; Milbauer, M. W.; Brigham, C. E.; Sanford, M. S. *J. Am. Chem. Soc.* **2020**, *142*, 5918.

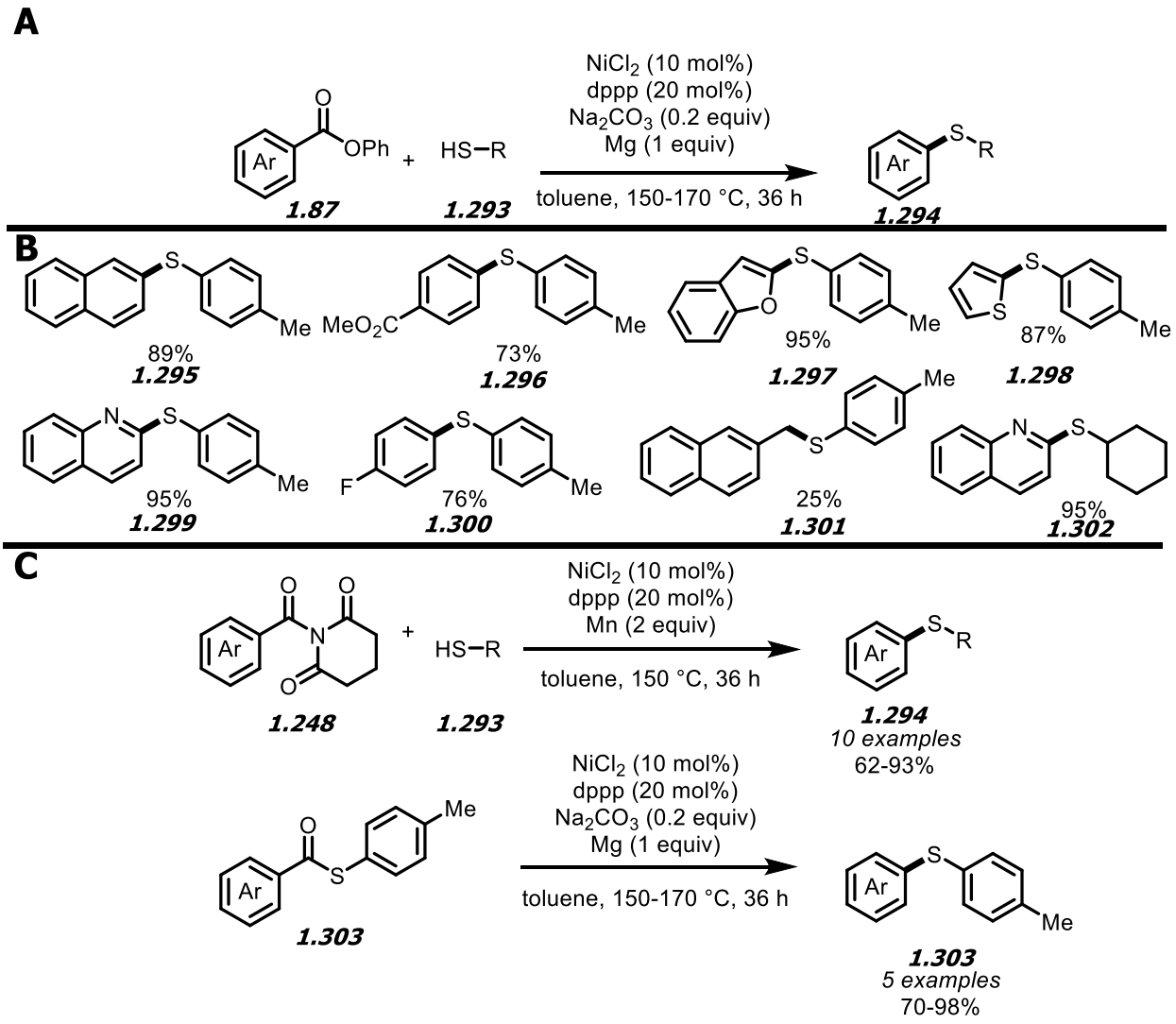


Scheme 41. (A) Representative silyl amine scope. (B) Representative scope of in situ amine silylation. (C) Isolation of nickel intermediates.

Thioetherification

Thioethers are important scaffolds [89] that can be synthesized via the Chan-Evans-Lam, Ullmann and related transition metal couplings.[90] In 2018, Rueping and co-workers investigated a decarbonylative thioetherification reaction, with the added goal of developing a glovebox free protocol (**Scheme 42A**).[91] Investigation of air and moisture stable catalysts and ligands identified $NiCl_2$/dppp as the optimal catalyst system. A range of aromatic and heteroaromatic esters could be coupled with thiols to provide the corresponding sulfanes (**Scheme 42B**). Non-aromatic thiols were also demonstrated to be viable coupling partners. Prompted by their success with esters, the authors also investigated other classes of electrophiles for decarbonylative thioetherification. With their own respective optimized conditions, aryl amides and thioesters could also be viable cross-coupling electrophiles (**Scheme 42C**).

[89] Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832.
[90] Bichler, P., Love, J.A. *Organometallic Approaches to Carbon–Sulfur Bond Formation.* Topics in Organometallic Chemistry, vol 31. Springer, Berlin, Heidelberg, 2010.
[91] Lee, S.-C.; Liao, H.-H.; Chatupheeraphat, A.; Rueping, M. *Chem. Eur. J.* **2018**, *24*, 3608.



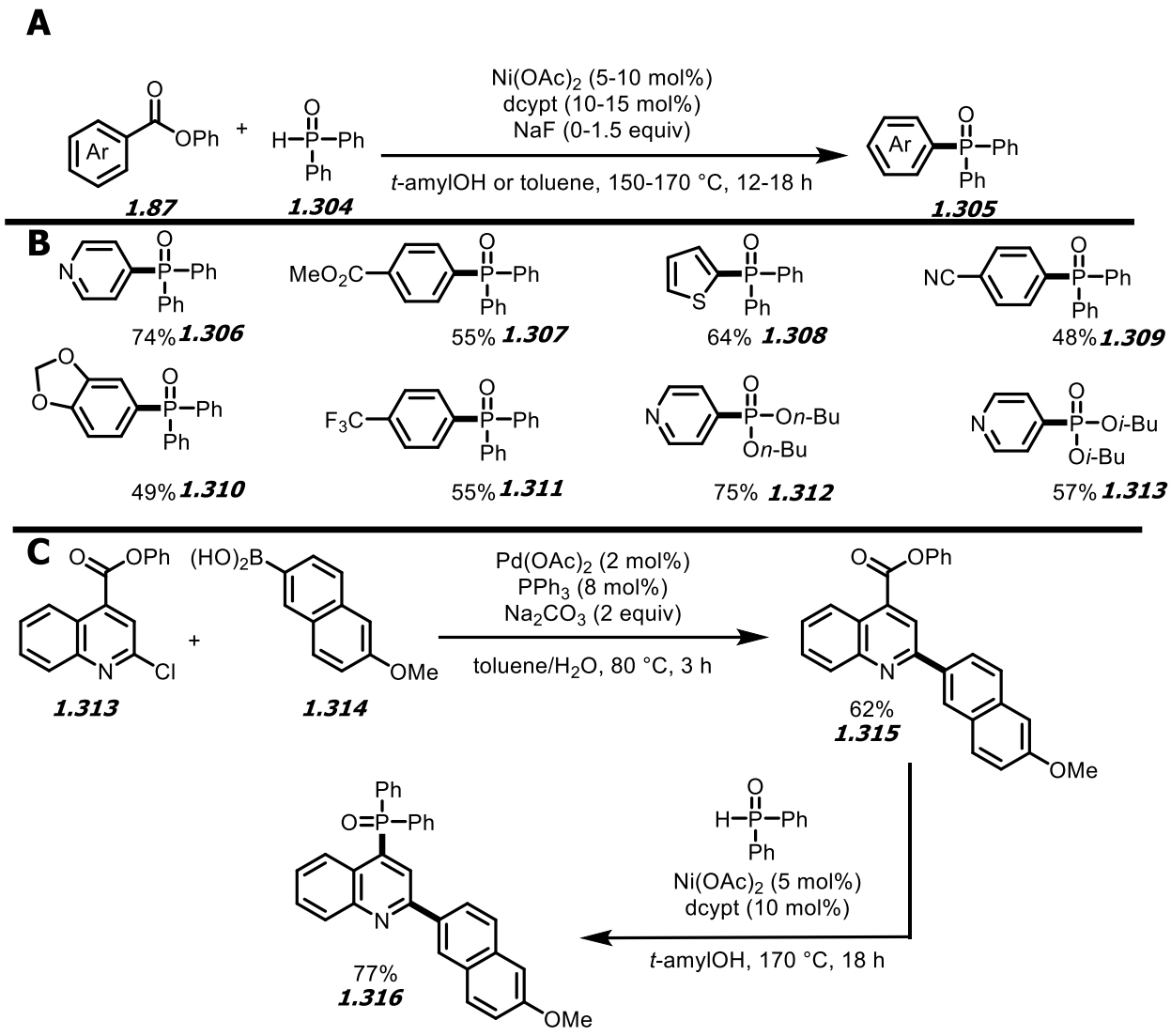
Scheme 42. (A) Ni-catalyzed decarbonylative thioetherification. (B) Representative scope examples. (C) Amide and thioester thioetherification.

1.3.2.7: Carbon-phosphorus bond formation

The use of organophosphorous nucleophiles in cross-coupling is less common than more traditional coupling partners, but can provide a useful route to access useful derivatives. The Yamaguchi group were the first to develop a catalytic decarbonylative C-P bond

forming reaction using phenyl esters as the electrophile (**Scheme 43A**).[92] Initial studies of the phosphorus containing nucleophile used diphenyl phosphine oxide. Robust ligands were screened to avoid the possibility that diphenyl phosphine oxide would poison the catalyst. Common ligands for ester activation, particularly PCy_3 and bulky NHCs, were found to be completely ineffective. Ultimately, a $Ni(OAc)_2$/dcypt catalytic system was most successful. Under the reaction conditions, a variety of aryl and heteroaryl esters were tolerated in modest to good yields (**Scheme 43B**). Different phosphates could be used as a nucleophilic coupling partner by using NaF as in additive in toluene. To demonstrate the synthetic utility of this transformation, a sequential cross-coupling was conducted where molecule **1.313** was first functionalized via Suzuki-Miyaura conditions, followed by C-P bond formation (**Scheme 43C**).

[92] Isshiki, R.; Muto, K.; Yamaguchi, J. *Org. Lett.* **2018**, *20*, 1150.



Scheme 43. (A) Ni-catalyzed decarbonylative C-P bond formation. (B) Representative scope examples. (C) Sequential cross-coupling.

1.3.3: Carbonyl retentive coupling of phenyl esters

Section 1.3.2 described numerous instances where esters act as aryl halide surrogates, losing the carbonyl group in the process. While mechanistically more analogous to traditional cross-couplings, reactions where the carbonyl group is retained are somewhat less common. These so-called carbonyl-retentive couplings allow for the formation of various ketone products when using carbon-based nucleophiles. Ketones are highly

desirable scaffolds to access via cross-coupling due to challenges associated with synthesizing them from traditional nucleophile-electrophile chemistry. Organometallic reagents can attack carboxylic acid derivatives; however, due to the harsh nature of these nucleophiles, the ketone products are still susceptible to further attack. To address this issue, the Weinreb ketone synthesis was developed which pre-functionalizes the desired carbonyl fragment into a stable species referred to as a Weinreb amide. [44] By exploiting a transition metal catalyst, pre-functionalization of the molecule can be avoided and the catalyst can directly activate the acyl electrophile. In doing so, milder organometallic nucleophiles can be used to access the desired ketones, which will not react with the products. If the nucleophile is an amine, amide products can be obtained. The two common streategies for preparing amides from esters rely either on activation of the electrophile with Lewis acids [93] or activation of the amine nucleophile with harsh organometallic base.[94] Both methods suffer from significant scope limitations. Novel methods of synthesizing amides will also be valuable, given the prevalence of nitrogen in so many bioactive molecules.[95] This section describes routes that maintain the carbonyl group to provide access to ketones and amides.

1.3.3.1: Suzuki-Miyaura coupling

The use of phenyl ester electrophiles in acyl Suzuki cross-coupling is advantageous given that they are highly stable species. Their inherent stability can be exploited for the purpose of orthogonal cross coupling strategies. One of the earliest breakthroughs was

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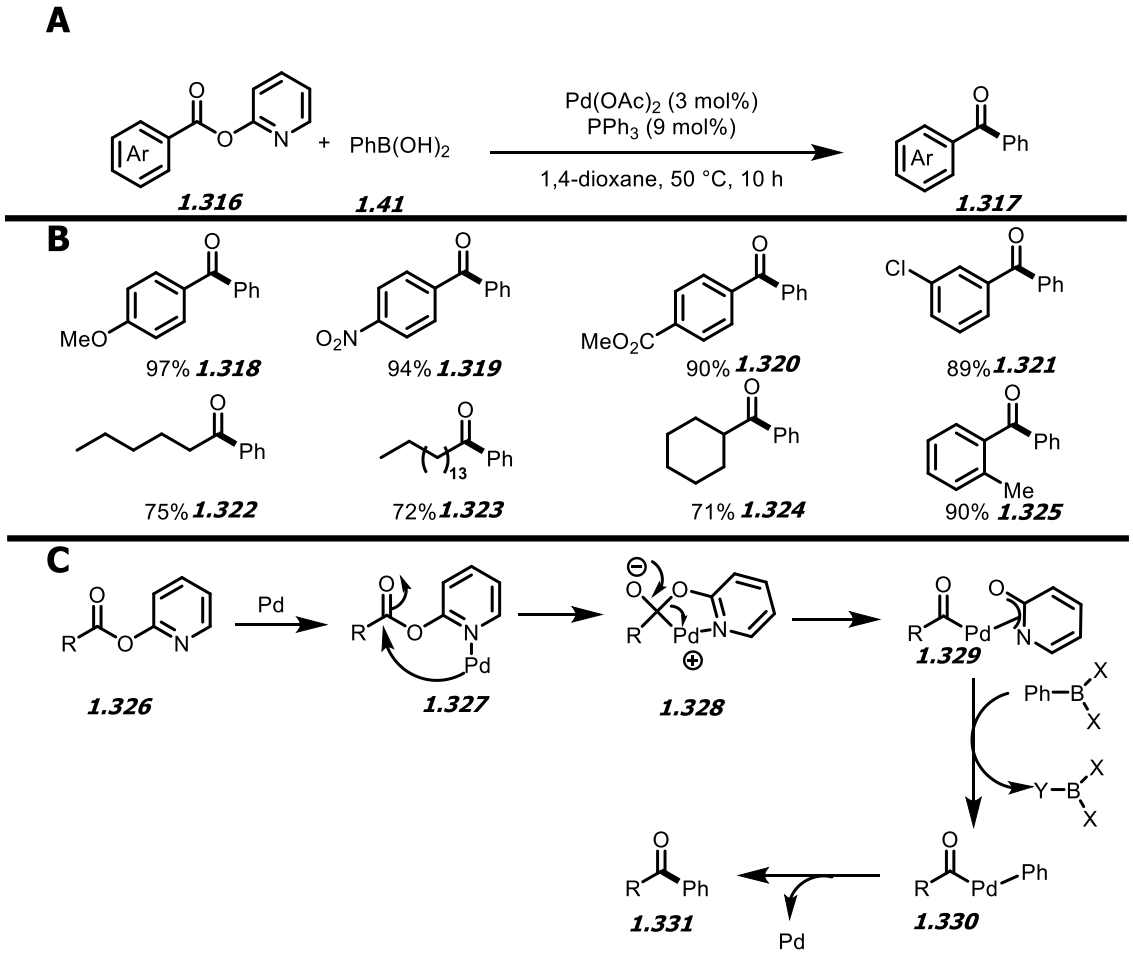
[93] (a) Ishihara, K.; Kuroki, Y.; Hanaki, N.; Ohara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 1569. (b) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 10039. (c) Tsuji, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2016**, *138*, 14218. (d) Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. *Org. Lett.* **2014**, *16*, 2018.

[94] (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tett. Lett.* **1977**, *18*, 4171. (b) Wang, W. B.; Roskamp, E. J. *J. Org. Chem.* **1992**, *57*, 6101. (c) Ohshima, T.; Hayashi, Y.; Agura, K.; Fujii, Y.; Yoshiyama, A.; Mashima, K. *Chem. Commun.* **2012**, *48*, 5434.

[95] (a) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564. (b) Bariwal, J.; Van der Eycken, E. *Chem. Soc. Rev.* **2013**, *42*, 9283. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.

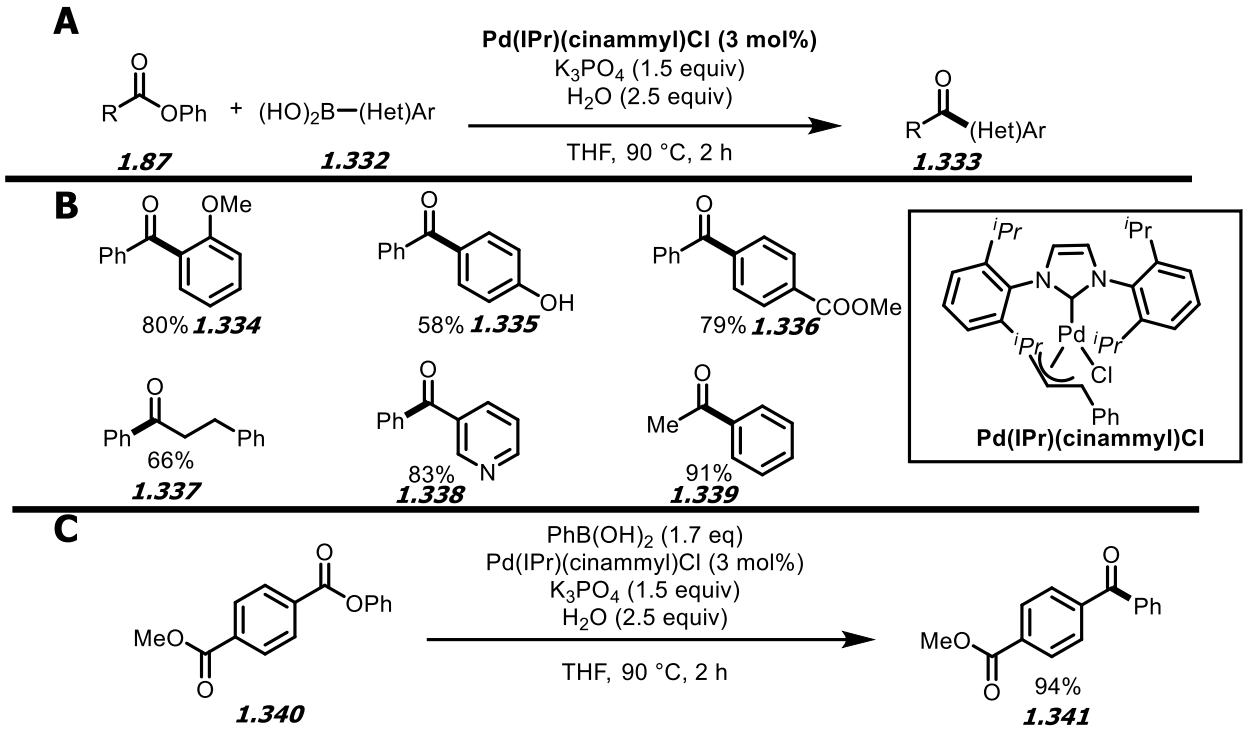
realized by the Chatani group in 2004, who exploited the reactivity of 2-pyridyl esters (**Scheme 44A**) (see also section 1.3.5.1). [53] Extensive screening of potential chelating groups was conducted, with 2-pyridyl esters determined to be the most efficient. A Pd/PPh_3 catalyst system allowed for the efficient coupling of aryl and alkyl 2-pyridyl esters under relatively mild reaction conditions (**Scheme 44B**). Although not extensively studied, it was also demonstrated that under slightly modified reaction conditions, benzylic B-alkyl-9-BBN reagents could also be coupled, giving rise to alkylated ketone products.



Scheme 44. (A) Pd-catalyzed carbonyl retentive Suzuki-Miyaura coupling of 2-pyridyl esters. (B) Representative scope examples. (C) Proposed chelation assistance mechanism.

Towards the goal of carbonyl retentive ester coupling, in 2017 the Newman lab developed the first catalytic method of aryl phenyl ester activation to provide ketone products selectively and in high yields (**Scheme 45A**).[96] Crucial to the success of this transformation was the use of a Pd catalyst and a bulky NHC ligand. A variety of aryl and heteroaryl substituents were tolerated (**Scheme 45B**). Chemoselectivity studies demonstrated the synthetic utility of such a method, as selective functionalization of the phenyl esters could occur in the presence of other bonds susceptible to cleavage (**Scheme 45C**). Prior to this study, most reported cross-couplings of phenyl esters followed a decarbonylative pathway. Mechanistic investigation provided an explanation for this stark contrast in reactivity. The bulky NHC ligand hinders decarbonylation by blocking open coordination sites on the acyl-Pd(II) intermediate, leaving the carbonyl-retentive pathway as the only accessible mechanism.

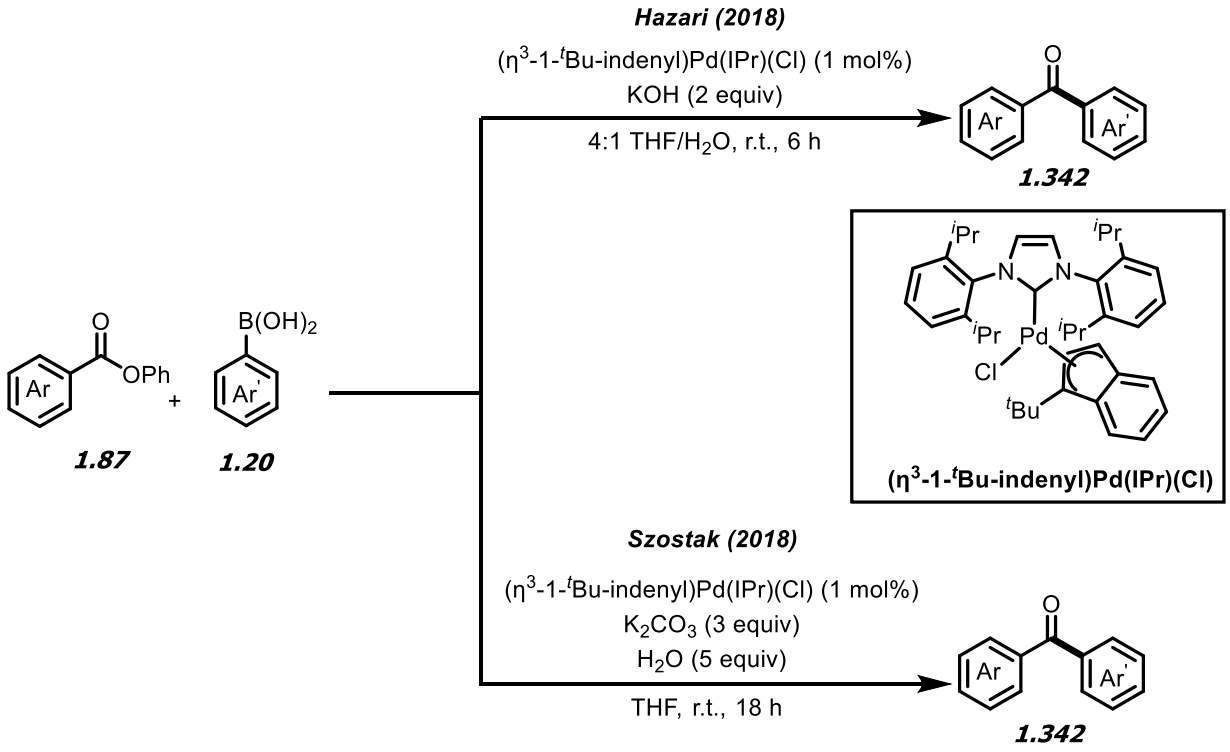
[96] Ben Halima, T.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Newman, S. G. *J. Am. Chem. Soc.* **2017**, *139*, 1311.



Scheme 45. (A) Pd-catalyzed carbonyl retentive Suzuki-Miyaura coupling of phenyl esters. (B) Representative scope examples. (C) Chemoselective C-O cleavage.

An ongoing challenge in catalysis is to enable reactions to occur under mild conditions using low catalyst loading. Towards achieving this goal, the groups of Hazari and Szostak independently demonstrated the use of bench stable Pd precatalysts capable of activating phenyl esters under mild conditions (**Scheme 46**). These precatalysts feature 1-^{t}Bu-indenyl groups and activate to form monoligated L1-Pd(0) species without forming inactive Pd(I) dimers. Using 1 mol% of these precatalysts, Suzuki-Miyaura reactions of phenyl esters and N-Boc protected amides can occur at room temperature. It was also demonstrated that the precatalysts were useful for Buchwald-Hartwig type couplings of

phenyl esters, which could occur near room temperature (See Section 1.3.3.2, below).[97, 98, 99, 100] Szostak and co-workers also demonstrated that Pd-PEPPSI-IPr [101] and [Pd(NHC)(acac)Cl] [102] catalyst systems were capable of coupling phenyl esters under similarly mild conditions. Catalyst design was not the sole method of achieving milder conditions. The green solvent 2-methyltetrahydrofuran was also demonstrated to be substantially effective for amide and ester Suzuki-Miyaura coupling.[103]



Scheme 46. Pd catalysts for mild phenyl ester activation

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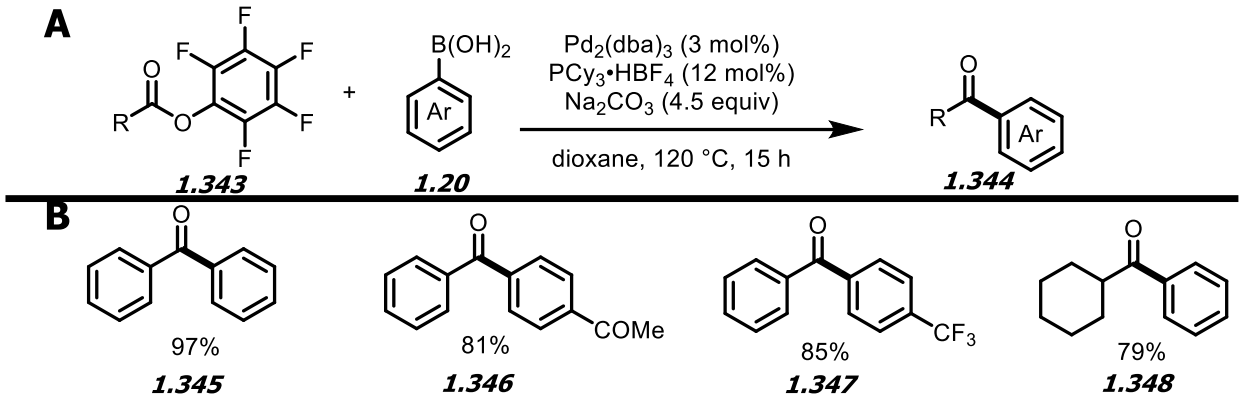
[97] Dardir, A. H.; Melvin, P. R.; Davis, R. M.; Hazari, N.; Mohadjer Beromi, M. *J. Org. Chem.* **2017**, *83*, 469.
[98] Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; Tudge, M. T. Design of a Versatile and Improved Precatalyst Scaffold for Palladium-Catalyzed Cross-Coupling: (η3-1-tBu-Indenyl)2(μ-Cl)2Pd2. *ACS Catal.* **2015**, *5*, 3680.
[99] Lei, P.; Meng, G.; Shi, S.; Ling, Y.; An, J.; Szostak, R.; Szostak, M. *Chem. Sci.* **2017**, *8*, 6525.
[100] Shi, S.; Szostak, M. *Chem. Commun.* **2017**, *53*, 10584.
[101] (a) Shi, S.; Lei, P.; Szostak, M. *Organometallics* **2017**, *36*, 3784. (b) Li, G.; Shi, S.; Lei, P.; Szostak, M. *Adv. Synth. Catal.* **2018**, *360*, 1538.
[102] Zhou, T.; Li, G.; Nolan, S. P.; Szostak, M. *Org. Lett.* **2019**, *21*, 3304.
[103] Lei, P.; Ling, Y.; An, J.; Nolan, S. P.; Szostak, M. *Adv. Synth. Catal.* **2019**, *361*, 5654.

Thus far, all work concerning carbonyl retentive coupling of phenyl esters had made use of NHC ligands. The Szostak group demonstrated in 2018 that phosphine ligands could also be applied to this chemistry successfully (**Scheme 47**). Critical to the success of Pd/phosphine catalyst systems was the use of electronically activated pentafluorophenyl esters.[104]

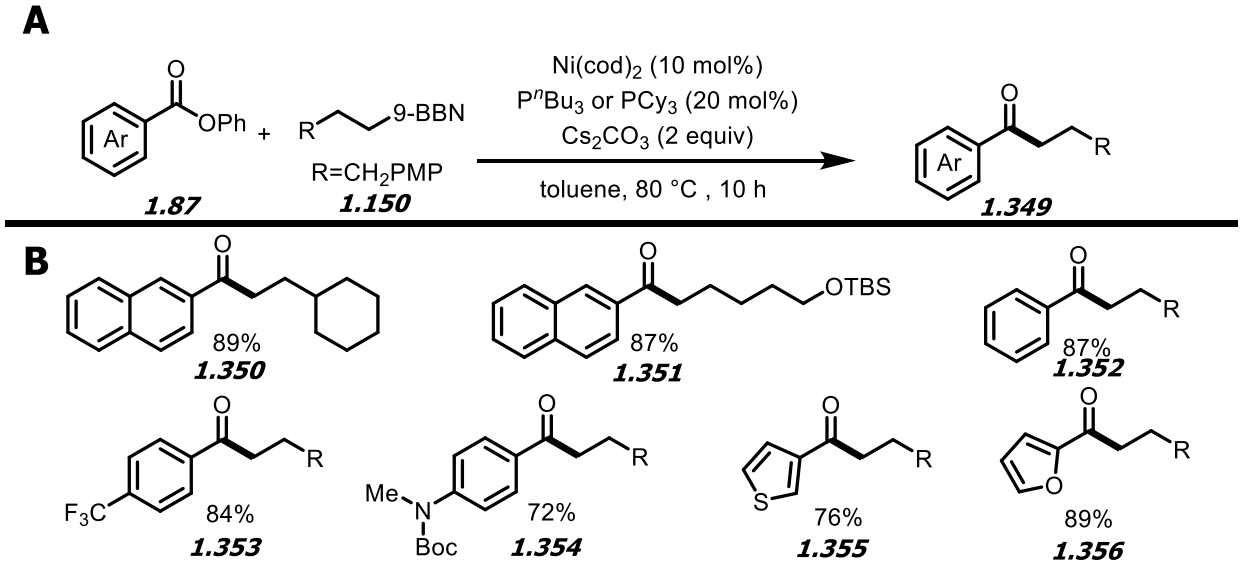


Scheme 47. (A) Pd-catalyzed carbonyl retentive Suzuki-Miyaura coupling of pentafluorophenyl esters. (B) Representative scope examples.

Accessing $C(sp^2)$-$C(sp^3)$ bonds in Suzuki-Miyaura cross-coupling is relatively challenging because of the sensitivity of alkylboranes to protodeboration as well as the potential for undesired β-hydride elimination to occur from key intermediates. The Rueping group expanded the scope of nucleophiles capable of performing Suzuki-Miyaura type couplings with phenyl esters by developing a method to selectively form alkyl ketones using B-alkyl-9-BBN reagents by utilizing Ni catalysts. The selectivity for ketone product formation was reliant on the choice of ligand and reaction conditions (**Scheme 48A**). The use of elevated temperatures and the bidentate ligand dcype leads to the formation of decarbonylated products (See **Scheme 29**). DFT studies suggested that the use of

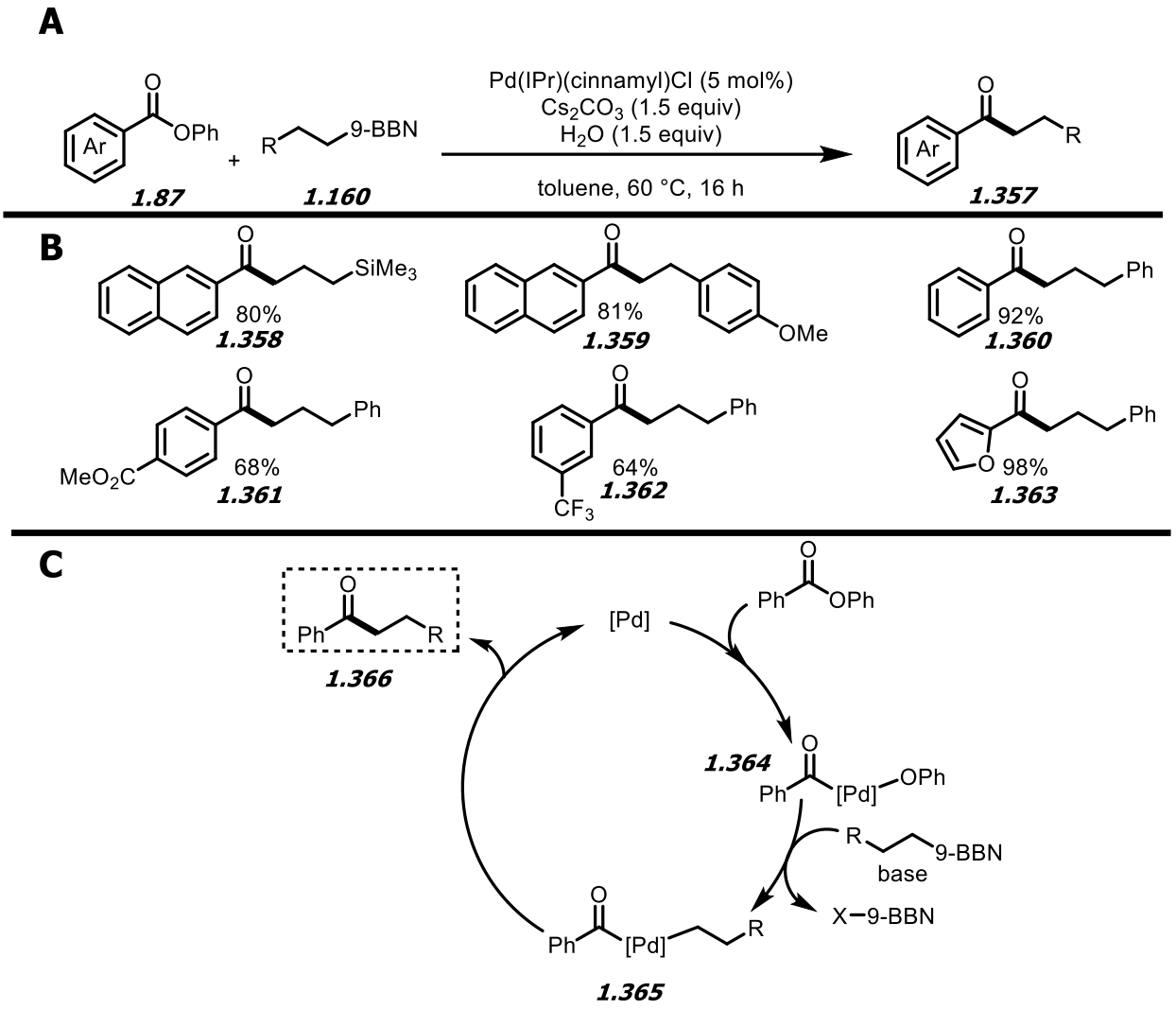
[104] Buchspies, J.; J. Pyle, D.; He, H.; Szostak, M. *Molecules* **2018**, *23*, 3134.

monodentate PCy_3 or P^nBu_3 ligands would lead to the cleavage of the C(acyl)-O bond, allowing formation of the ketone products. Under a Ni/PCy_3 or P^nBu_3 catalyst system, a variety of aryl and heteroaryl products could be synthesized efficiently (**Scheme 48B**). [59]



Scheme 48. (A) Ligand controlled carbonyl retentive Suzuki-Miyaura coupling of phenyl esters. (B) Representative scope examples.

Concurrently, the Newman lab reported a similar alkylative transformation which was a Pd-catalyzed process (**Scheme 49A**). [60] Again, crucial to the success of this reaction was the careful selection of reaction parameters. Elevated temperatures and a Pd/dcype catalyst system led to the formation of decarbonylated products (see **Scheme 30**). In contrast, the use of a bulky Pd-IPr catalyst led to the formation of carbonyl-retentive alkylated ketones. Under the reaction conditions, aryl and heteroaryl esters could be coupled smoothly (**Scheme 49B**). Using a bulky ligand was proposed to block the decarbonylation of the acyl-Pd intermediate, favouring the transmetallation and thus the formation of ketones (**Scheme 49C**).



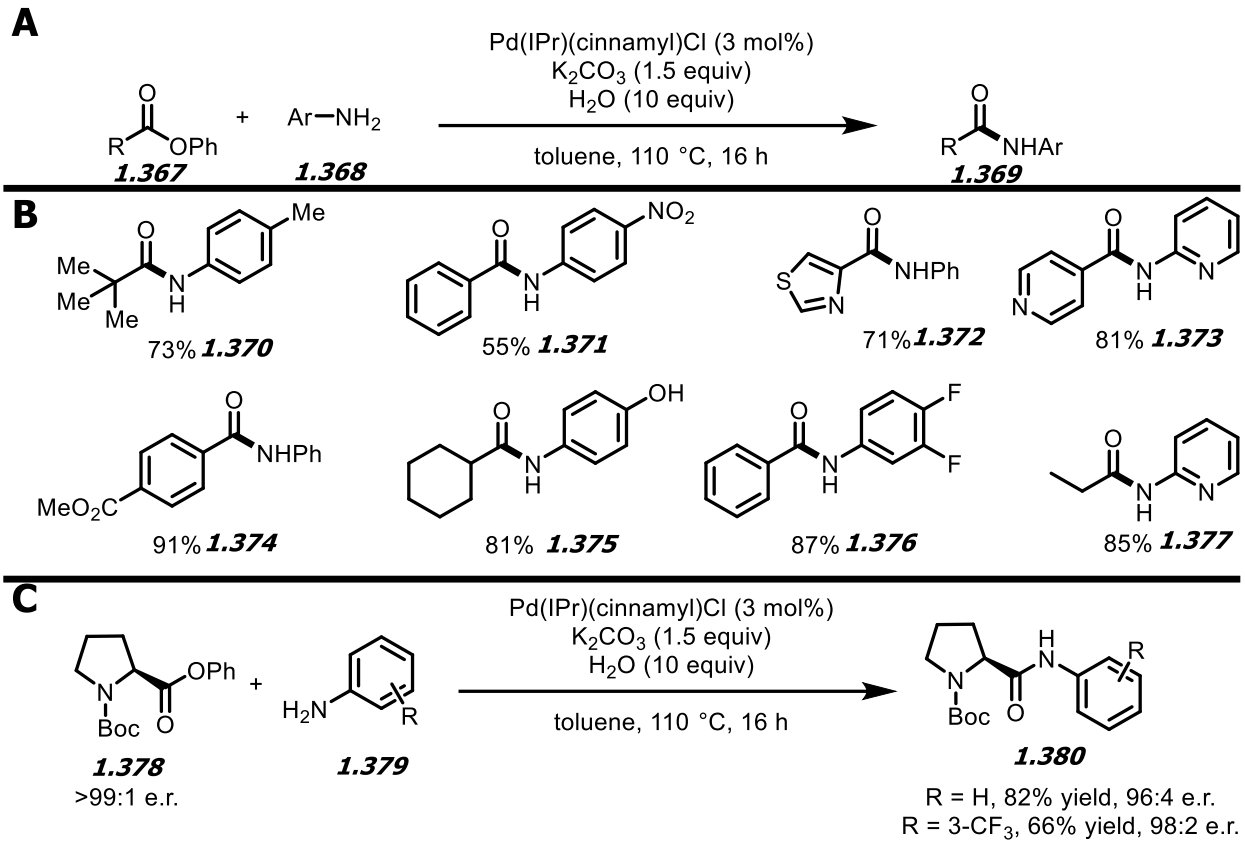
Scheme 49. (A) Pd-catalyzed carbonyl retentive alkyl Suzuki-Miyaura coupling of phenyl esters. (B) Representative scope examples. (C) Proposed mechanism.

1.3.3.2: Amidation

Cross-coupling catalysis has opened the door towards accessing new heteroatom containing molecules. [95] The Buchwald-Hartwig reaction is particularly important, bringing together aryl halides and amines, allowing access to new C-N bonds. The strength of such a reaction is demonstrated by its ability to functionalize two molecules that would otherwise be inert to each other. While both acylative cross-coupling reactions

and Buchwald-Hartwig amination reactions are independently important, the overlap between these two families is not obvious. For instance, acid chlorides require a Pd catalyst to react with organotin nucleophiles, but not with amines. Phenyl esters, however, are only modestly electrophilic, and do not react with aniline derivatives in the absence of strong base. With this in mind, the Newman lab developed a Pd-catalyzed amide bond formation from phenyl esters and anilines (**Scheme 50A**).[105] A variety of aryl, heteroaryl and alkyl amide products were obtained (**Scheme 50B**). This method did not require deprotonation of the aniline derivative, so the use of potassium carbonate was sufficient for the coupling. As a result, enantiopure esters did not undergo significant racemization under the reaction conditions (**Scheme 50C**).

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



Scheme 50. (A) Pd-catalyzed amide bond formation from phenyl esters. (B) Representative scope examples. (C) Enantiopure ester coupling.

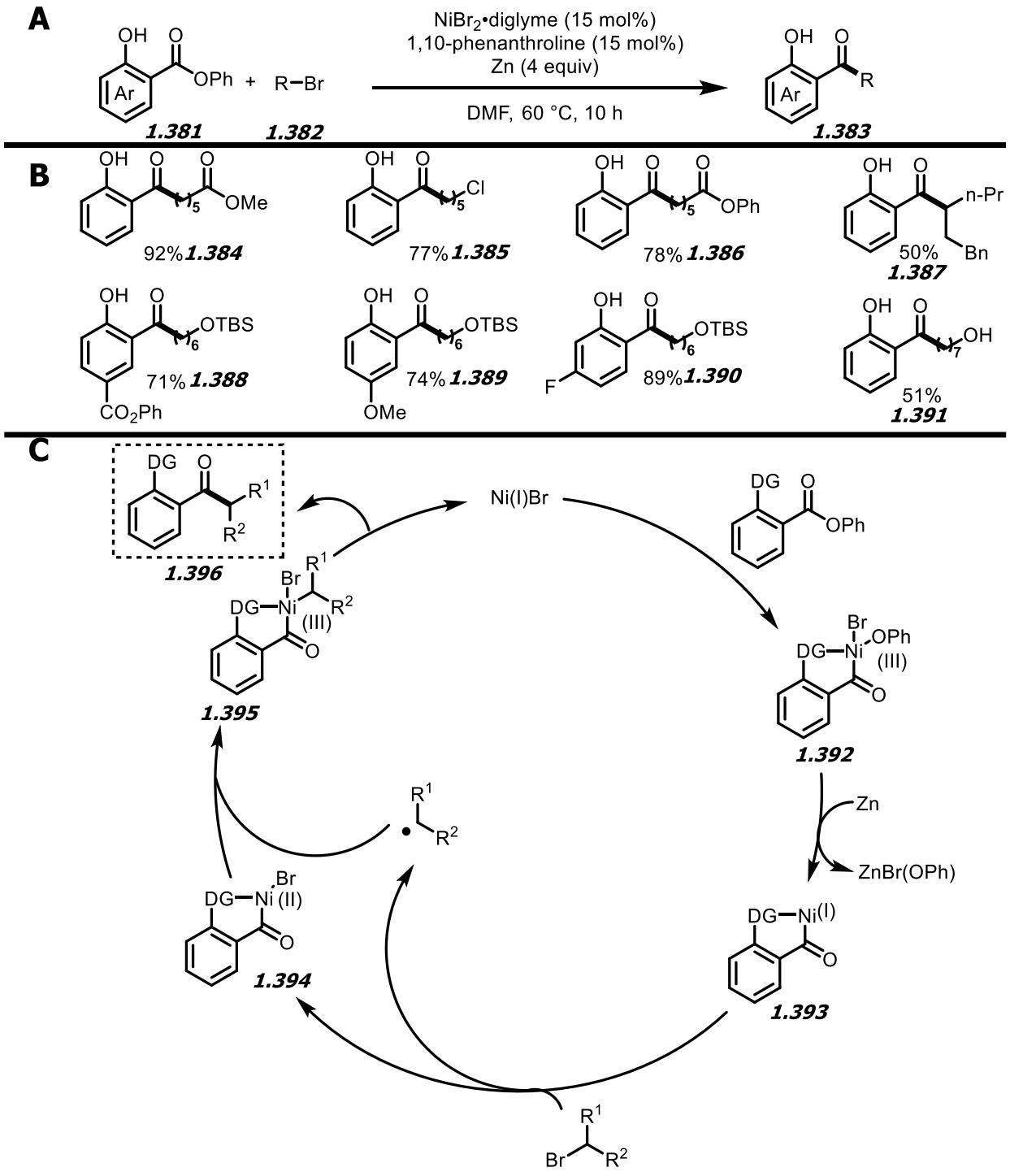
1.3.3.3:Cross-electrophile coupling

Ni-catalyzed cross-electrophile coupling between acylating agents and aryl or alkyl halides has become a very useful method for preparing ketones while avoiding the use of stoichiometric organometallic reagents.[106] Thus far, the cross-coupling reactions of phenyl esters discussed are net redox neutral. In 2020, Wang and co-workers

[106] (a) Everson, D. A.; Weix, D. J. *J. Org. Chem.* **2014**, *79*, 4793. (b) Moragas, T.; Correa, A.; Martin, R. *Chem. Eur. J.* **2014**, *20*, 8242. (c) Gu, J.; Wang, X.; Xue, W.; Gong, H. *Org. Chem. Front.* **2015**, *2*, 1411. (d) Weix, D. J. *Acc. Chem. Res.* **2015**, *48*, 1767. (e) Correa, A. *Ni- and Fe-based cross-coupling reactions*; Springer International Publishing: Cham, 2017. (f) Richmond, E.; Moran, J. *Synthesis* **2018**, *50*, 499. (g) Poremba, K. E.; Dibrell, S. E.; Reisman, S. E. *ACS Catal.* **2020**, *10*, 8237.

hypothesized that the lack of phenyl esters in cross-electrophile coupling chemistry is due to the difficulty associated with the activation of the C(acyl)-O bond. They reported the first cross-electrophile coupling of phenyl esters by exploiting the presence of an ortho directing group (**Scheme 51A**).[107] Esters were coupled with primary and secondary alkyl bromides with a Ni/1,10-phenanthroline catalyst system to give a wide variety of ketone products (**Scheme 51B**). Tertiary alkyl halides, benzyl halides and aryl halides were all incompatible with the reaction. The authors demonstrated that the hydroxyl directing group could be substituted for sulfonamides and a similar outcome with regard to scope would be achieved, albeit with lower yields. The presence of the directing group was absolutely necessary for reactivity, as when the hydroxyl group is methylated or moved to the para position, the phenyl ester remains unreactive. Control reactions also ruled out the possibility of in situ organozinc formation, thus excluding a Negishi cross-coupling pathway. Even using stoichiometric $Ni(cod)_2$, the authors did not find any product formation, signifying that a catalytic cycle initiated by Ni(0) without an intermediate reduction is not possible. Thus, the authors proposed a mechanism featuring oxidative addition of Ni(I) into the C(acyl)–O bond, facilitated by the directing group, to give complex **1.392**. This intermediate is reduced by Zn to afford a Ni(I) species **1.393**, which can interact with the alkyl bromide to generate a free radical and complex **1.394**. Recombination with the alkyl radical generates Ni complex **1.395**, and releases the product **1.396** and regenerates the Ni(I) catalyst after reductive elimination (**Scheme 51C**).

[107] Yang, F.; Ding, D.; Wang, C. *Org. Lett.* **2020**, *22*, 9203.

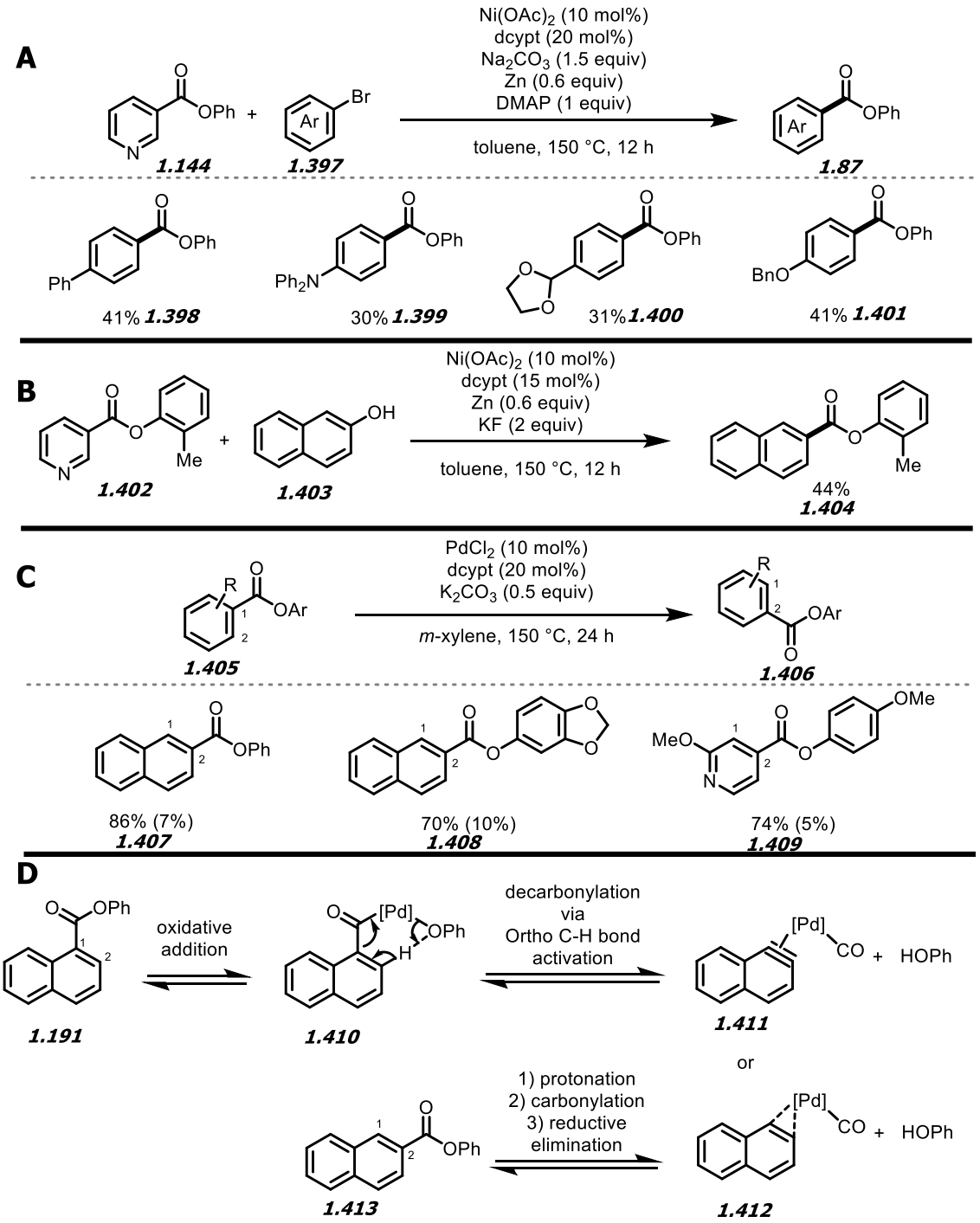


Scheme 51. (A) Ni-catalyzed cross-electrophile coupling of phenyl esters. (B) Representative scope examples. (C) Proposed mechanism.

1.3.3.4: Ester transfer and ester dance

Substitution reactions on aromatic substrates are incredibly important reactions in organic chemistry. To extend this chemistry to phenyl esters, the Yamaguchi group have developed ester transfer [108] and ester dance reactions.[109] The ester transfer reaction used Ni/dcypt catalysis to transfer aryl groups between aryl halides and aromatic esters (**Scheme 52A**). Aryl chlorides and bromides were suitable for this chemistry, whereas aryl iodides were not. As an alternative to aryl halides, phenol based aryl electrophiles could also form ester transferred product (**Scheme 52B**). The ester dance reaction was catalyzed by Pd/dcypt (**Scheme 52C**), and the nature of the base played an important role as the reactions were almost shut down when bases other than K_2CO_3 were used. The nature of the base was proposed to be important for an ortho C-H bond activation step (**Scheme 52D**). A variety of aryl and heteroaryl substrates could undergo this ester dance reaction, generating good yields of the product along with relatively small quantities of recovered starting material due to the modest thermodynamic driving force of this equilibration.

[108] Isshiki, R.; Inayama, N.; Muto, K.; Yamaguchi, J. *ACS Catal.* **2020**, *10*, 3490.
[109] Matsushita, K.; Takise, R.; Muto, K.; Yamaguchi, J. *Sci. Adv.* **2020**, *6*.

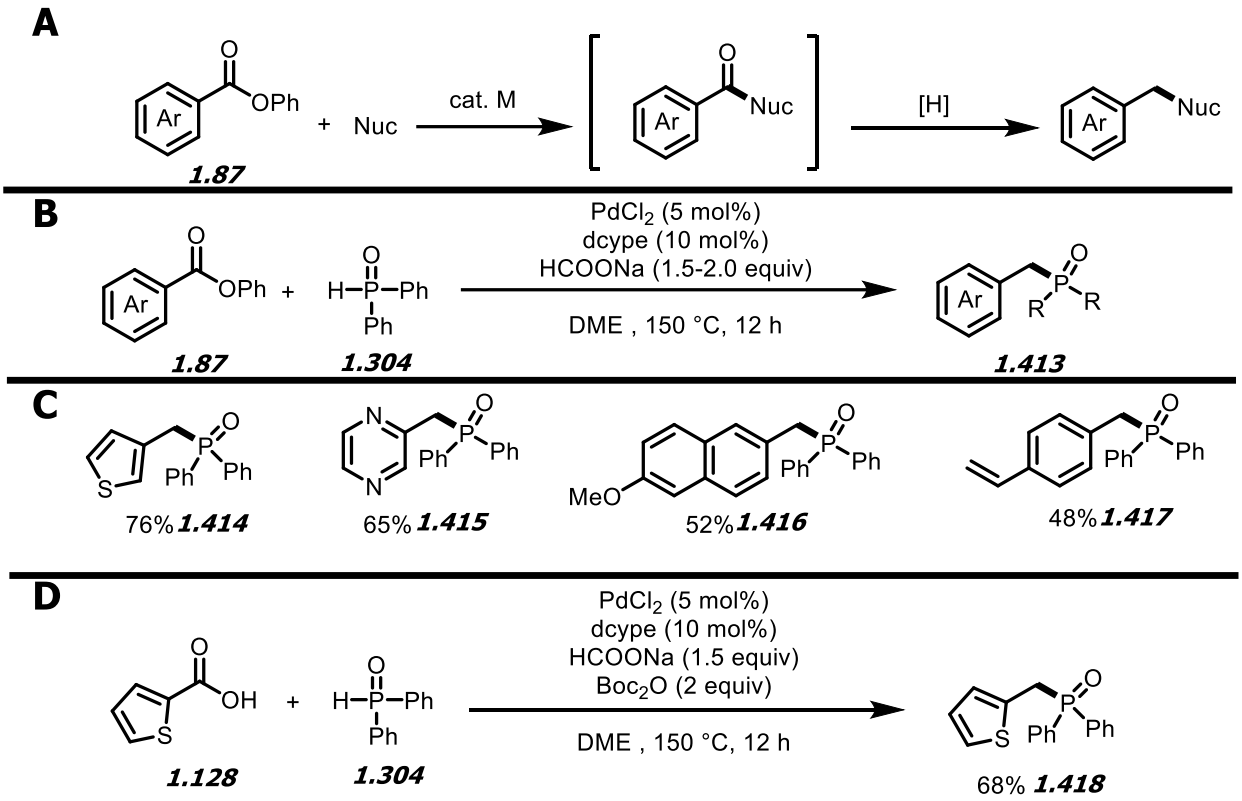


Scheme 52. (A) Ester transfer reaction with representative scope examples. (B) Ester transfer with phenol based electrophile. (C) Ester dance reaction from position 1 to position 2 with representative scope examples. Yields in brackets represent starting material recovery (D) Proposed mechanism of ester dance reaction.

1.3.3.5: Deoxygenative organophosphorus coupling

Cross-coupling reactions with esters most commonly form either carbonyl retentive or decarbonylative products (see **Scheme 14**). Yamaguchi and co-workers hypothesized that the combination of carbonyl-retentive cross-coupling and carbonyl reduction could lead to unusual deoxygenative coupling products (**Scheme 53A**). With this challenge in mind, the authors reported a C–P bond-forming reaction using a Pd/dcype catalyst and HCOONa as a stoichiometric reducing agent to give benzyl phosphine oxides (**Scheme 53B**).[110] A wide variety of aryl and heteroaryl compounds were tolerated under the reactions (**Scheme 53C**). Control experiments demonstrated that the carbonyl-retentive product was an intermediate in the reaction, suggesting that the carbonyl is reduced to the corresponding methylene via a Pd/HCOONa catalytic system. This reaction could also be applied to carboxylic acids thanks to in-situ formation of an anhydride that can react similarly to a phenyl ester (**Scheme 53D**).

[110] Kurosawa, M. B.; Isshiki, R.; Muto, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2020**, *142*, 7386.



Scheme 53. (A) Hypothesis for carbonyl retentive coupling followed by reduction. (B) Pd-catalyzed deoxygenative coupling with organophosphorus compounds. (C) Representative scope examples. (D) Deoxygenative coupling of carboxylic acids.

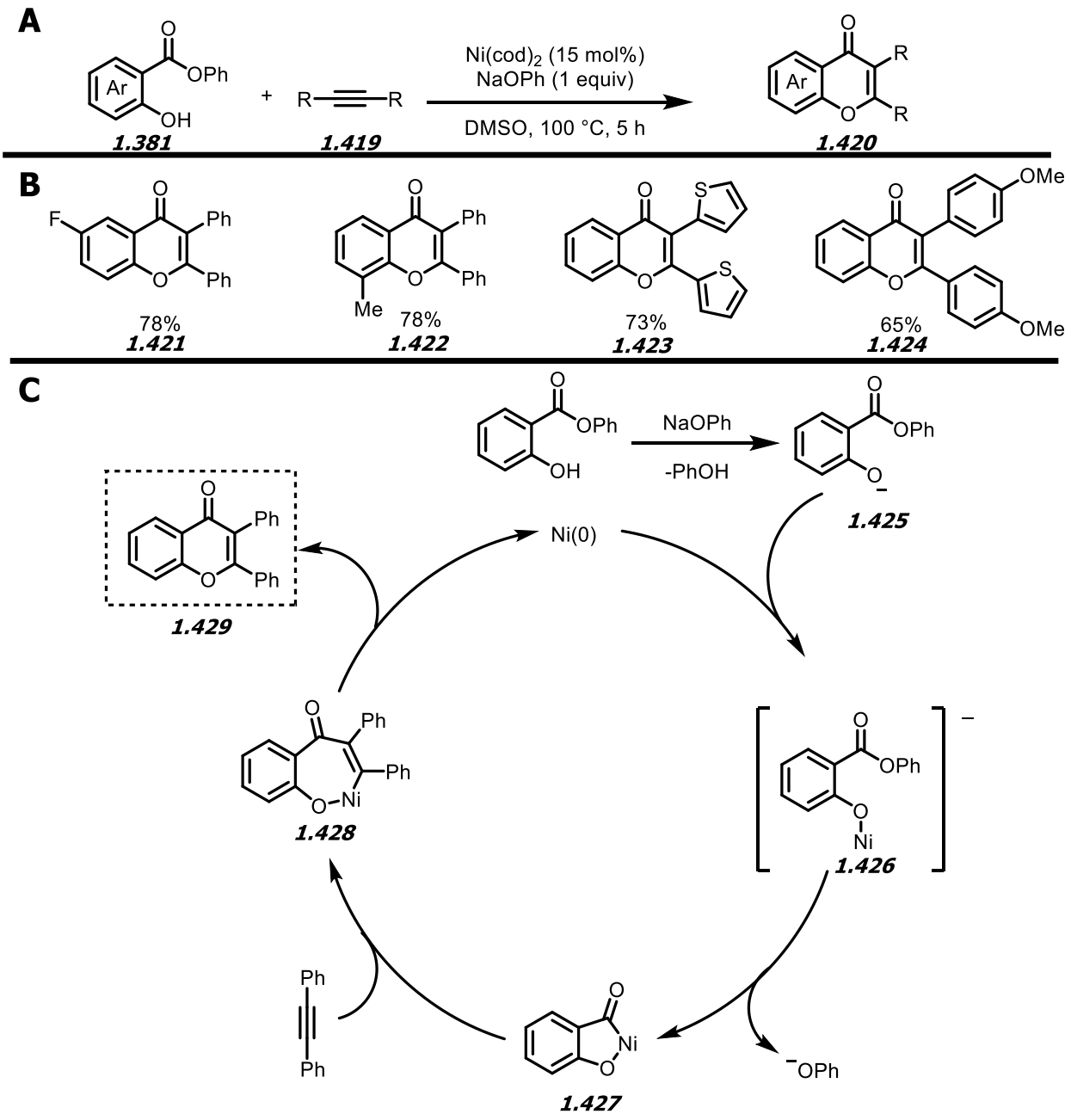
1.3.3.6: Alkyne insertion

In 2008, Matsubara and Kurahashi reported a Ni-catalyzed alkyne insertion/addition reaction of phthalic anhydrides and internal alkynes.[111] This reaction was decarbonylative in nature and formed isocoumarin products. In 2021, the Chatani group reported analogous reactivity between salicylate phenyl esters and alkynes using

[111] Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 17226.

a nickel catalyst (**Scheme 54A**).[112] Unlike the alkyne insertion of phthalic anhydrides, alkyne insertion of salicylate phenyl esters was found to be carbonyl retentive. C-O bond activation was achieved with $Ni(cod)_2$ in the absence of ligand. The presence of base was necessary for reactivity. The ester was proposed to react with NaOPh to generate the anion **1.425** (**Scheme 54C**). This intermediate can react with the Ni catalyst to give the anionic nickel complex **1.426**. Oxidative addition into the C(acyl)-O bond gives complex **1.427**, followed by insertion into the alkyne, forming intermediate **1.428**. Reductive elimination forms the product **1.429** and regenerates the catalyst.

[112] Iyori, Y.; Chatani, N. *Chem. Lett.* **2021**, *50*, 510.



Scheme 54. (A) Ni-catalyzed annulation reaction of salicylate phenyl esters with alkynes. (B) Representative scope examples. (C) Proposed mechanism.

1.3.4: Carbonyl retentive coupling of alkyl esters

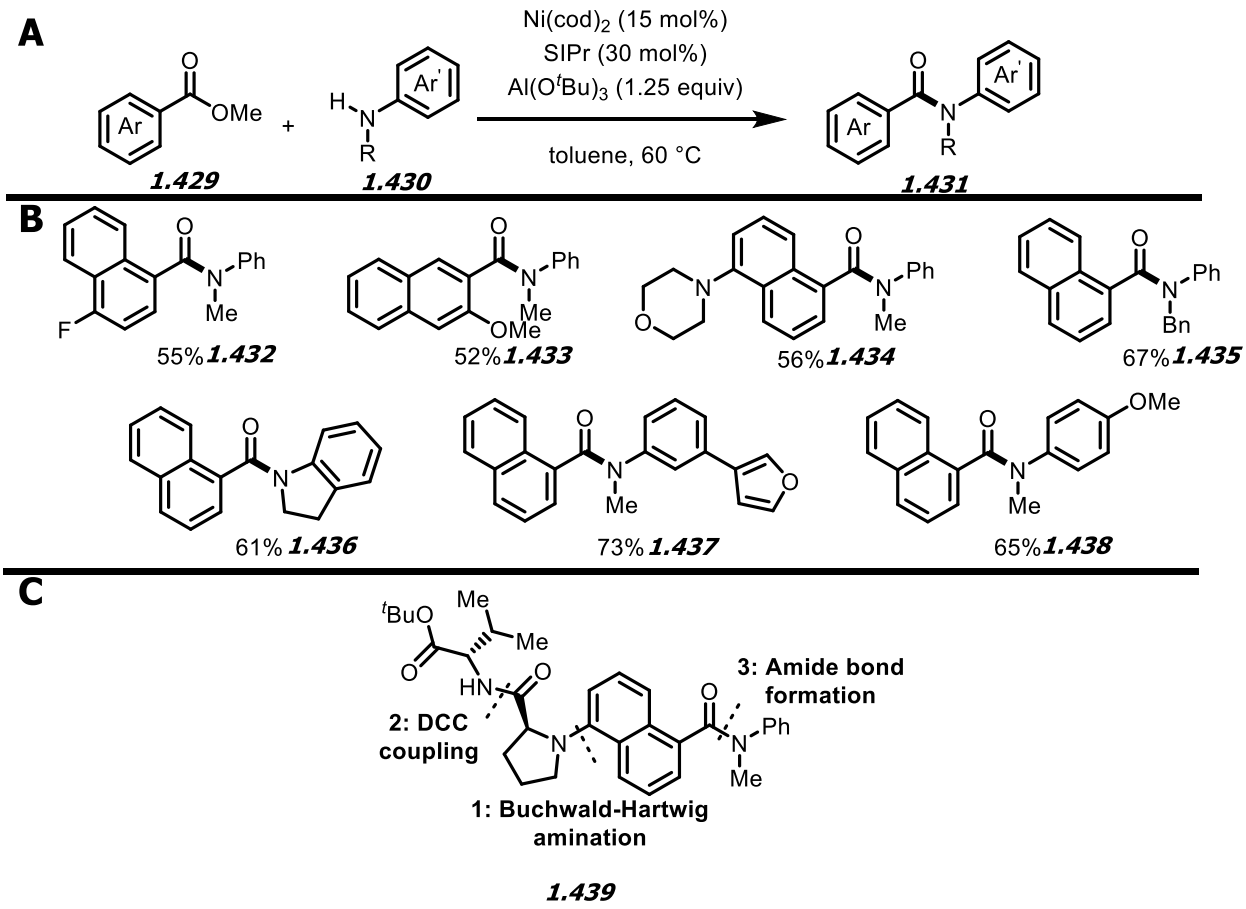
In the past two decades, significant advances have been made in the field of ester cross-coupling through the use of phenyl esters and related compounds as the electrophile. However, these substrates are seldom commercially available and thus need to be synthesized, often from the corresponding carboxylic acid or other acyl electrophiles such as acyl chlorides. In contrast, direct derivatization of unactivated esters via cross-coupling can potentially obviate the need for multistep processes for preparing, e.g., ketones, amides, and aldehydes. However, alkyl esters are much less activated compared to their phenyl ester counterparts and they lack any significant coordinating ability. Furthermore, unactivated esters are generally left untouched in traditional coupling reactions of aryl halides. As a result, oxidative addition of metal catalysts into the strong C(acyl)-O bond of alkyl esters was not a commonly considered pathway. In this section, transformations of simple alkyl esters will be described.

1.3.4.1: Amidation

Despite amides being among the most frequently synthesized molecules, converting simple esters to amides can be problematic. Existing methods rely on activation of the electrophile with Lewis acids [93] or activation of the amine nucleophile with harsh organometallic bases. [94] Due to these scope limitations of both these methods, esters are often converted to amides by first hydrolizing to the corresponding carboxylic acid, followed by subsequent activation with species such as thionyl chloride or peptide coupling reagents. Direct activation of alkyl esters for amide bond formation via cross-coupling has the potential to shortcut this pathway and provide an acid- and base-free alternative to other direct methods.

In 2016, Garg and Houk were the first to demonstrate methyl esters can be viable cross-coupling electrophiles in Ni-catalyzed amidation reactions (**Scheme 55A**), marking a significant milestone in the field.[113] Using a Ni/SIPr catalyst system, amide products were obtained, although the scope was largely limited to 1-napthyl esters (**Scheme 55B**). Vital to this reaction was the addition of $Al(O^tBu)_3$ as a stoichiometric Lewis acid additive. DFT studies suggested that $Al(O^tBu)_3$ was capable of coordinating to the carbonyl group of the ester, lowering the kinetic barrier of the rate-determining oxidative addition step. 1-Naphtyl esters were more successful compared to their 2-naphtyl and methyl benzoate counterparts. The exceptional reactivity of 1-naphthyl esters was also attributed to $Al(O^tBu)_3$. The complex resulting from Lewis acid coordination causes steric repulsion from the bulky 1-naphthyl group, leading to a distortion which makes ester cleavage more thermodynamically favourable. Theoretically, a decarbonylation could occur at steps proceeding oxidative addition. However, it was shown that both the ligand exchange and the reductive elimination are much more energetically favourable than decarbonylation, explaining why amide bond formation takes place. To demonstrate the powerful synthetic utility of this method, orthogonal cross-couplings via DCC, Buchwald-Hartwig and methyl ester cross-couplings were performed (**Scheme 55C**).

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

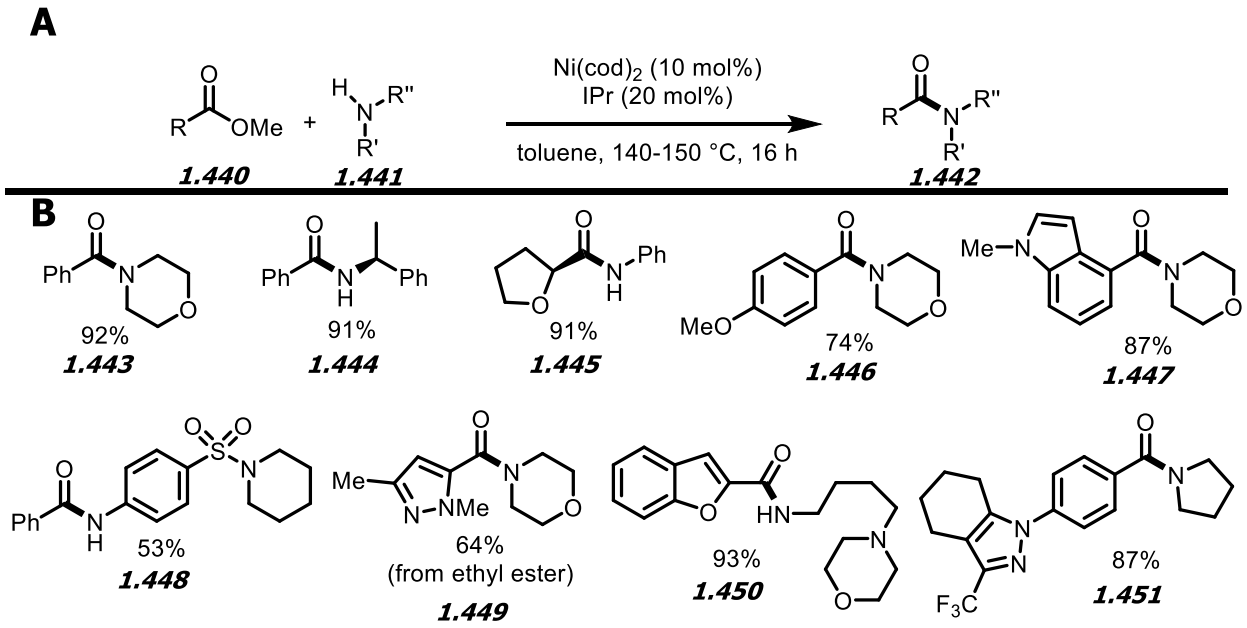


Scheme 55. (A) Ni-catalyzed activation of methyl naphthoates. (B) Representative scope examples. (C) Sequential cross-couplings.

In 2018, the Newman lab expanded the scope of ester and amine functionalities that could be tolerated in Ni-catalyzed amide bond formation.[114] Using only a Ni/IPr catalyst, methyl esters were activated towards amide bond formation in the absence of stoichiometric activating agents, with methanol being the sole stoichiometric by-product (**Scheme 56A**). The use of elevated temperatures that drive methanol out of solution were found to be critical, both to prevent catalyst deactivation and to drive the equilibrium forward. A wide variety of aryl, heteroaryl and alkyl esters were

[114] Ben Halima, T.; Masson-Makdissi, J.; Newman, S. G. *Angew. Chem. Int. Ed.* **2018**, *57*, 12925.

demonstrated to couple smoothly with aniline derivatives as well as aliphatic amines (**Scheme 56B**). This method was also shown to be capable of efficiently accessing several bioactive molecules. In all cases, amides were formed selectively, likely due to the role of the bulky NHC ligand which may prevent decarbonylation. Notably, the Hu group published a mechanistically distinct Ni-catalyzed approach to amide bond formation using nitrobenzene derivatives that are reduced in situ with stoichiometric Zn.[115] A similar reaction has also been realized using Cr catalysis.[116]



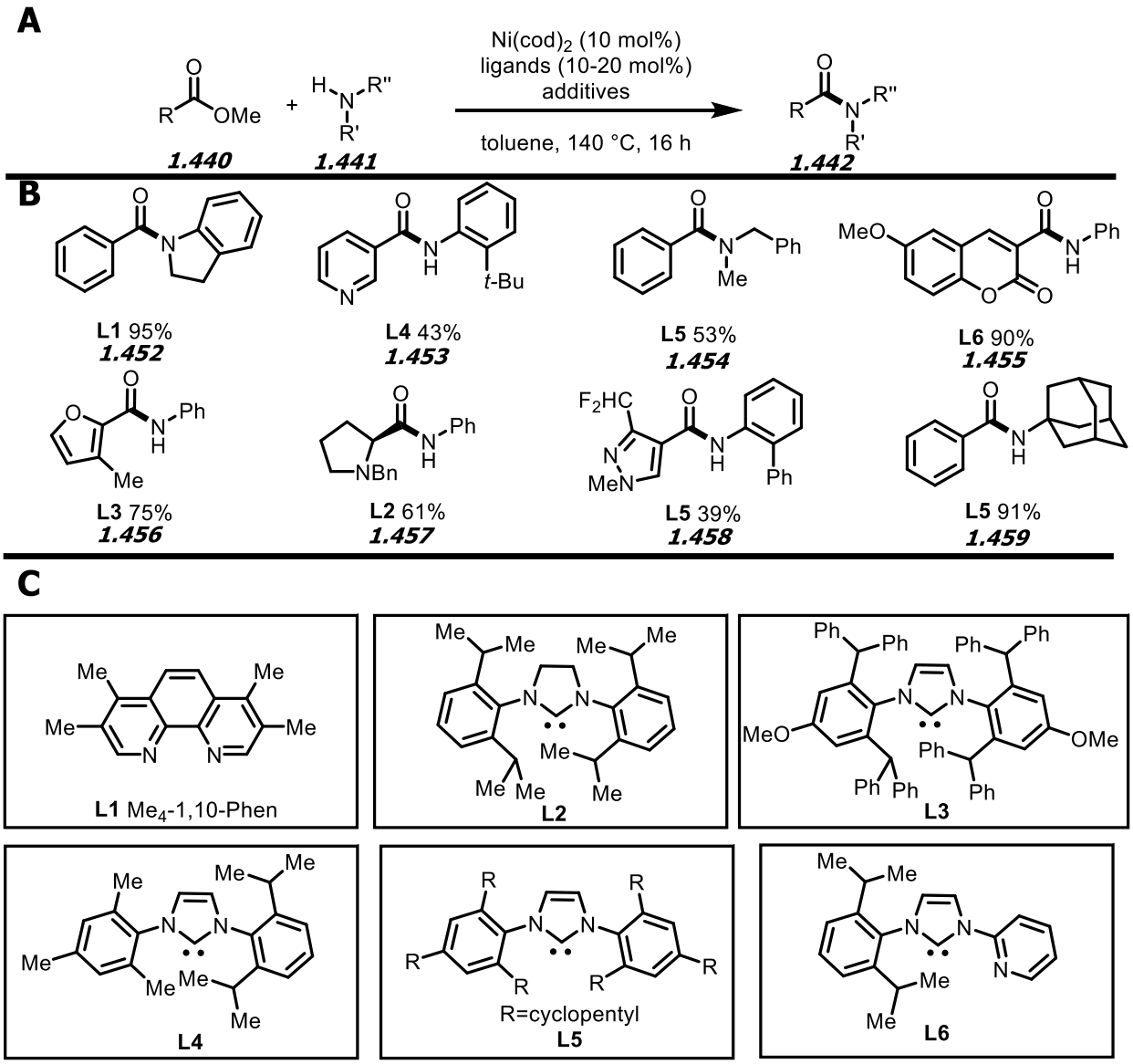
Scheme 56. (A) Additive free Ni-catalyzed methyl ester activation towards amide synthesis. (B) Representative scope examples.

Mechanistic studies by Hong and co-workers suggest that all key steps involved in the Ni-catalyzed amide bond formation from esters and amines - oxidative addition, proton transfer and reductive elimination - have similar transition state energies.[117] These

[115] Cheung, C. W.; Ploeger, M. L.; Hu, X. *Nat. Commun.* **2017**, *8*, 14878.
[116] Ling, L.; Chen, C.; Luo, M.; Zeng, X. *Org. Lett.* **2019**, *21*, 1912.
[117] Ji, C.-L.; Xie, P.-P.; Hong, X. *Molecules* **2018**, *23*, 2681.

findings suggest that any of these three elementary steps could be turnover-limiting, which implies that different ester and amine pairs may benefit from different conditions. With this in mind, the Newman lab re-investigated several coupling reactions that proved difficult using the conditions described in Figure 55, including sterically hindered substrates, certain heterocycles (e.g. furans and coumarins), and dialkylamines. An extensive substrate dependent ligand optimization study was conducted (**Scheme 57A**) in order to couple these challenging substrates.[118] The ligand screening demonstrated that most phosphine ligands were entirely ineffective except for select bidentate phosphine ligands such as dcype. A bidentate nitrogen ligand, Me_4-1,10-Phen was also shown to be effective for the transformation. Several classes of privileged NHC ligands were also identified (**Scheme 57C**). Interestingly, selectivity studies demonstrated that esters bearing α-aryl groups react preferentially to those bearing α-alkyl groups, with the exception of α-benzylic esters which are the most reactive of the three. In 2021, Szostak and co-workers demonstrated that [CpNi(IPr)Cl] complexes were also capable of coupling amines with phenyl and methyl esters in a carbonyl-retentive fashion to provide amides.[119]

[118] Zheng, Y.-L.; Newman, S. G. *ACS Catal.* **2019**, *9*, 4426.
[119] Buchspies, J.; Rahman, M. M.; Szostak, M. *Molecules* **2021**, *26*, 188.



Scheme 57. (A) Extensive ligand optimization to overcome issues in Ni-catalyzed amide bond formation from methyl esters. (B) Representative examples of expanded scope. (C) Examples of privileged ligands.

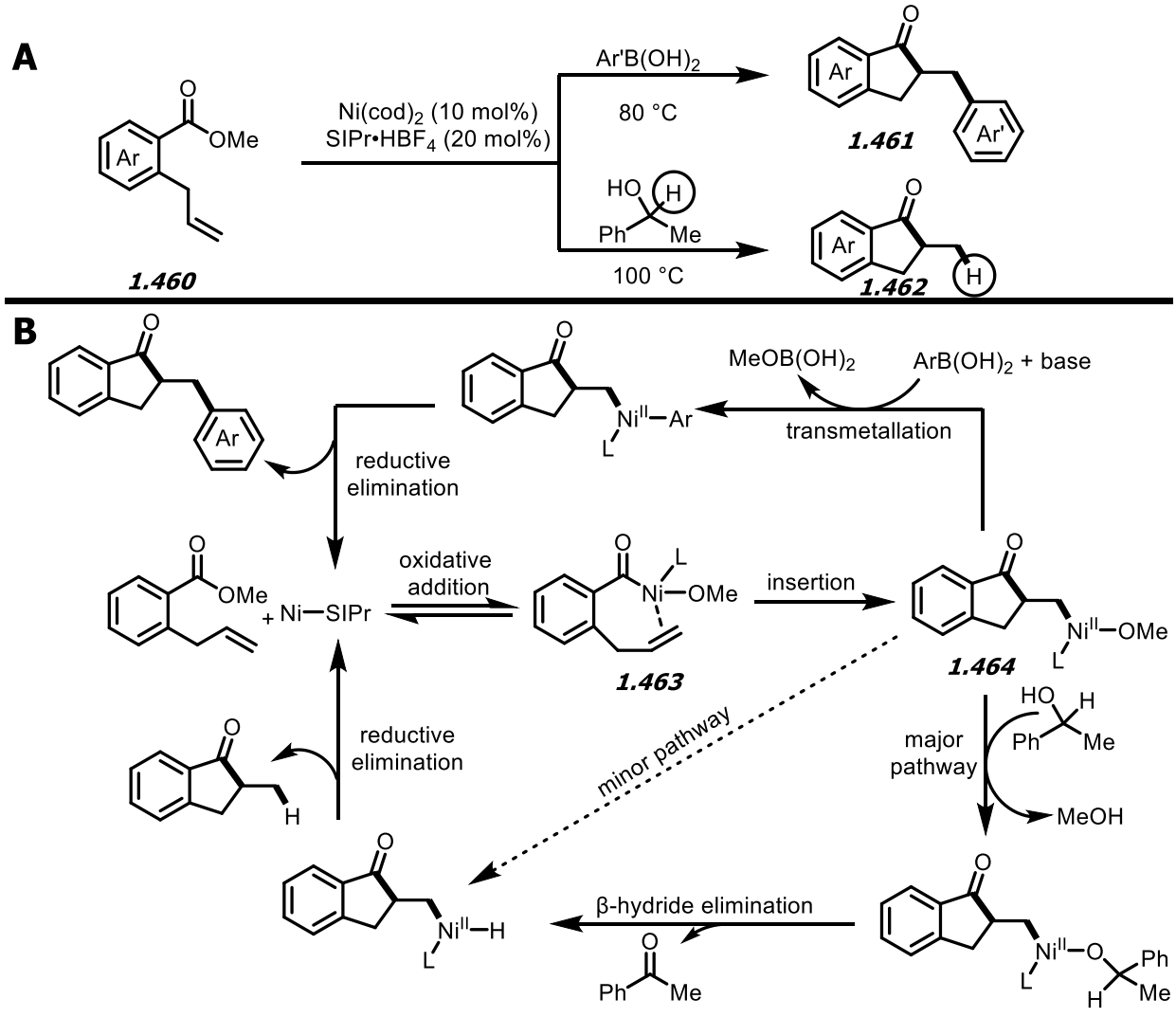
1.3.4.2: Mizoroki-Heck type domino reactions

With the exception of the initial report of methyl ester activation by Garg and co-workers that required specific substrates, cross-couplings of methyl esters generally requires highly elevated temperatures (see also section 1.3.5). DFT studies performed by Hong and co-workers [117] suggest that Ni(0) catalysts are capable of oxidatively adding into the C(acyl)-O bond of a methyl ester with reasonable activation energy, making the use of milder temperatures feasible. However, the formation of the acyl-Ni complex is calculated to be thermodynamically uphill and reversible, complicating intermolecular couplings as the concentration of the reactive Ni(II) species will be extremely low at any given time.

In 2017, the groups of Garg [120] and Stanley [121] independently reported the trapping of N-boc amide derived acyl-Ni intermediates with tethered allyl fragments. Using these reports as inspiration, the Newman lab hypothesized that trapping the oxidative addition complex of a methyl ester with a tethered allyl coupling partner would be thermodynamically favourable and could lead to synthetically valuable products. In comparison to their N-boc amide counterparts, methyl esters are often commercially available and their methyl 2-allylbenzoate derivatives necessary for intramolecular coupling can be easily accessed in a single step via allylation from the organohalide. With this in mind, a Ni-catalyzed cyclization with tethered allyl groups was developed to prepare formal carboacylation or hydroacylation products (**Scheme 58A**).[122] A Ni/SIPr system was found to activate the methyl ester, which was proposed to generate acyl-Ni species **1.463**. This complex inserts the alkene of the tethered allyl group, generating

[120] Medina, J. M.; Moreno, J.; Racine, S.; Du, S.; Garg, N. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 6567.
[121] (a) Walker, J. A.; Vickerman, K. L.; Humke, J. N.; Stanley, L. M. *J. Am. Chem. Soc.* **2017**, *139*, 10228. (b) Kadam, A. A.; Metz, T. L.; Qian, Y.; Stanley, L. M. *ACS Catal.* **2019**, *9*, 5651.
[122] Zheng, Y. L.; Newman, S. G. *Angew. Chem. Int. Ed.* **2019**, *58*, 18159.

intermediate **1.464**. Subsequent transmetallation with an arylboronic acid forms a domino Mizoroki-Heck/Suzuki-Miyaura coupling product. Alternatively, addition of an alcohol in the reaction leads to a domino Mizorki-Heck/reduction product (**Scheme 58B**). This cyclization was successful at 80 °C, which is significantly lower than most other reports on similar transformations, suggesting the intramolecular trapping of the acyl-Ni(II) species may overcome challenges with intermolecular trapping.

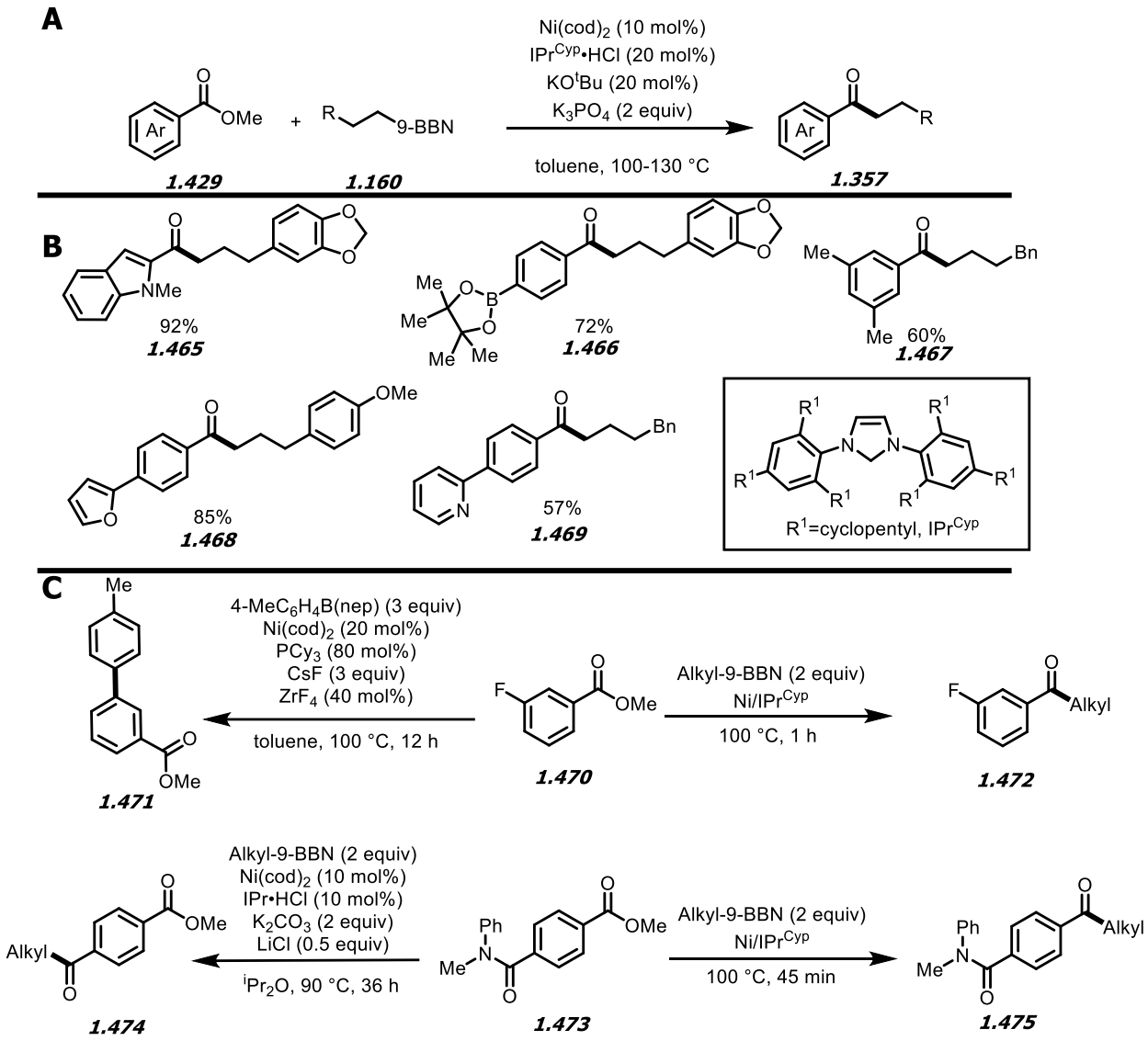


Scheme 58. (A) Ni-catalyzed domino Mizoroki-Heck type reactions using methyl esters. (B) Proposed mechanism.

1.3.4.3: Suzuki-Miyaura coupling

The coupling of methyl esters with carbon-based nucleophiles can in principle occur in a carbonyl-retentive fashion to provide ketone products, circumventing the need to use a multi-step approach such as the Weinreb ketone synthesis. [44] However, such intermolecular couplings have proven more challenging than the previously described amidation and cyclization reactions. In 2021, the Newman lab identified a Ni-catalyzed synthesis of ketones from methyl esters and alkyl-9-BBN reagents (**Scheme 59A**).[123] Crucial to the success of the reaction was the use of a 2,4,6-tricyclopentylaniline-derived N-heterocyclic carbene, IPr^{Cyp}, which in conjunction with Ni, provided access to a wide variety of ketone products (**Scheme 59B**). The use of alkylboranes was necessary, as arylboronic acids and other boron nucleophiles were unsuccessful. This reaction also showed impressive orthogonality to other Ni-catalyzed cross-coupling reactions (**Scheme 47C**). DFT studies were conducted to gain understanding into the challenges of this reaction. With the particularly bulky NHC catalyst, oxidative addition was calculated to be relatively facile, making transmetallation the rate-determining step. The aryl substituents found on the alkyl-9-BBN nucleophiles were found to interact with the para-cyclopentyl ring on the NHC ligand in this step, explaining the non-intuitive importance of these two remote groups.

[123] Zheng, Y. L.; Xie, P. P.; Daneshfar, O.; Houk, K. N.; Hong, X.; Newman, S. G. *Angew. Chem.* **2021**, *133*, 13588.



Scheme 59. (A) Ni-catalyzed synthesis of ketones from methyl esters and alkyl-9-BBN reagents. (B) Representative scope examples. (C) Chemoselectivity studies.

1.3.5: Decarbonylative couplings of alkyl esters

Most reports on the cross-coupling of simple alkyl esters thus far have given carbonyl-retentive products. This contrasts sharply with the coupling of phenyl esters, which have

been primarily used for decarbonylative coupling. In this final section, the few examples of decarbonylative alkyl ester coupling are described.

1.3.5.1: Directing group assistance

The first example of a catalytic reaction involving ester C(acyl)-O bond cleavage followed by decarbonylation was reported in 2001 by the Murai group (**Scheme 60A**).[124] For this reaction, the authors opted to use Ru-catalysis. At the time, Yamamoto and co-workers had reported the first Pd-catalyzed Suzuki-Miyaura coupling of electronically activated esters to form ketone products.[125] The decision to use Ru was driven based on earlier studies from their lab.[126] Pyridylmethyl esters were used, with the pyridine acting as a directing group to render the Ru more nucleophilic. In the presence of ammonium formate, it was demonstrated that the esters could be reduced. Related work in 2004 from the Chatani lab demonstrated the ability of these substrates to give both carbonyl-retentive and decarbonylative products.[127]

In 2012, Wang and co-workers reported a related chelation-assisted decarbonylative Suzuki-Miyaura cross-coupling of ethyl esters (**Scheme 60B**).[128] Chatani has also reported the reduction of alkyl esters in the absence of an external reductant by using a directing group.[129] These early reports on ester activation with carefully selected directing groups were seminal towards future developments in the activation of simpler, more accessible alkyl esters.

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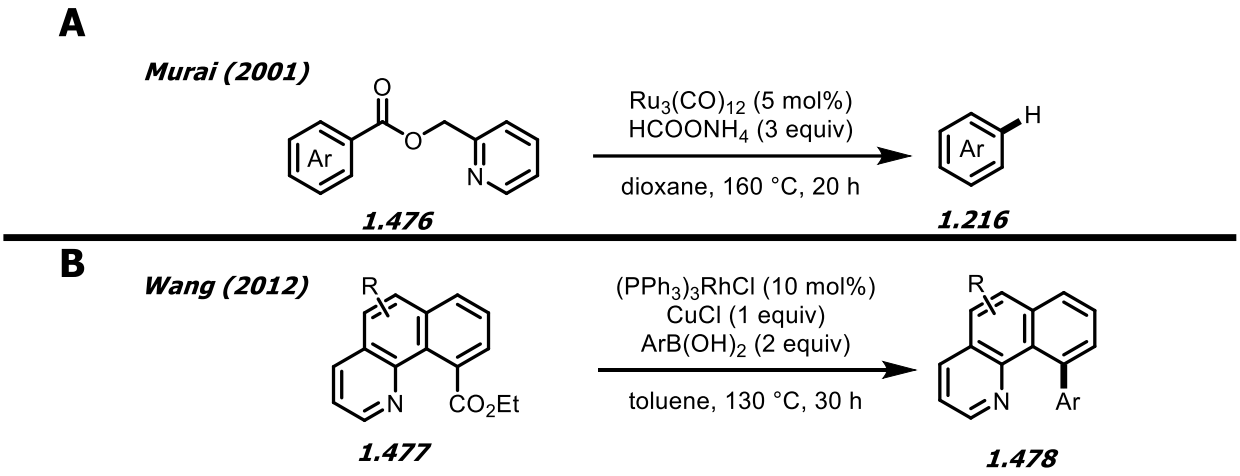
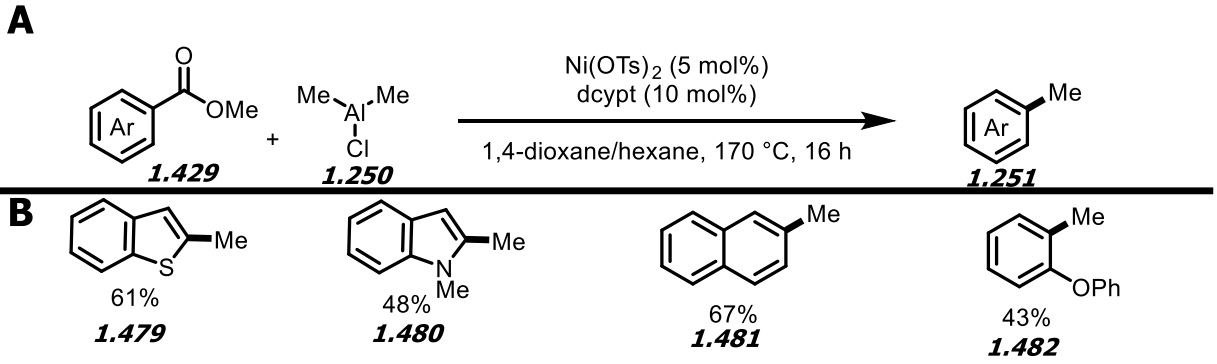
[124] Chatani, N.; Tatamidani, H.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 4849.
[125] (a) Nagayama, K.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 799. (b) Kakino, R.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 371.
[126] (a) Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4039. (b) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 8645. (c) Ishii, Y.; Chatani, N.; Yorimitsu, S.; Murai, S. *Chem. Lett.* **1998**, *27*, 157.
[127] Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 5615.
[128] Wang, J.; Liu, B.; Zhao, H.; Wang, J. *Organometallics* **2012**, *31*, 8598.
[129] Iyori, Y.; Takahashi, K.; Yamazaki, K.; Ano, Y.; Chatani, N. *Chem. Commun.* **2019**, *55*, 13610.



Scheme 60. (A) Alkyl ester cross-coupling achieved via chelation assistance. (B) Rh-catalyzed ethyl ester activation mediated by chelation assistance.

1.3.5.2: Methylation

The decarbonylative methylation of aryl esters via Ni catalysis was outlined in **Scheme 38**. [82] The methylating agent used was dimethylaluminum chloride, which may also act as a Lewis acid to render the ester more reactive. In the same report, a selection of simple alkyl esters were also shown to be amenable using slightly modified conditions (**Scheme 61**). While a mechanism was not proposed, formation of an acyl-Ni intermediate may be occurring.



Scheme 61. (A) Ni-catalyzed decarbonylative methylation of methyl esters. (B) Representative scope examples.

1.3.5.3: Organostannane formation

Arylstannanes are very valuable compounds due to the role they play in the Stille coupling, which allows access to complex molecules.[130, 131] In 2018, the Rueping group developed a decarbonylative stannylation reaction of methyl esters, which could also be extended to ethyl, cyclohexyl, benzyl and phenyl esters (**Scheme 62A**).[132] In the presence of a Ni/dppp catalyst system, methyl esters were coupled with trimethyl(tributylstannyl)silane to give a range of arylstannanes (**Scheme 62B**). If both a methyl and phenyl ester are present, selective reaction occurs at the more reactive phenyl ester (**Scheme 62C**). Monostannylation of substrates bearing two methyl ester groups was also demonstrated, with the resulting product **1.491** being capable of further derivatization by Stille coupling (**Scheme 62D**). No mechanism was proposed, but one possible pathway may involve formation of a Ni-acyl intermediate followed by transmetallation, decarbonylation, and reductive elimination.

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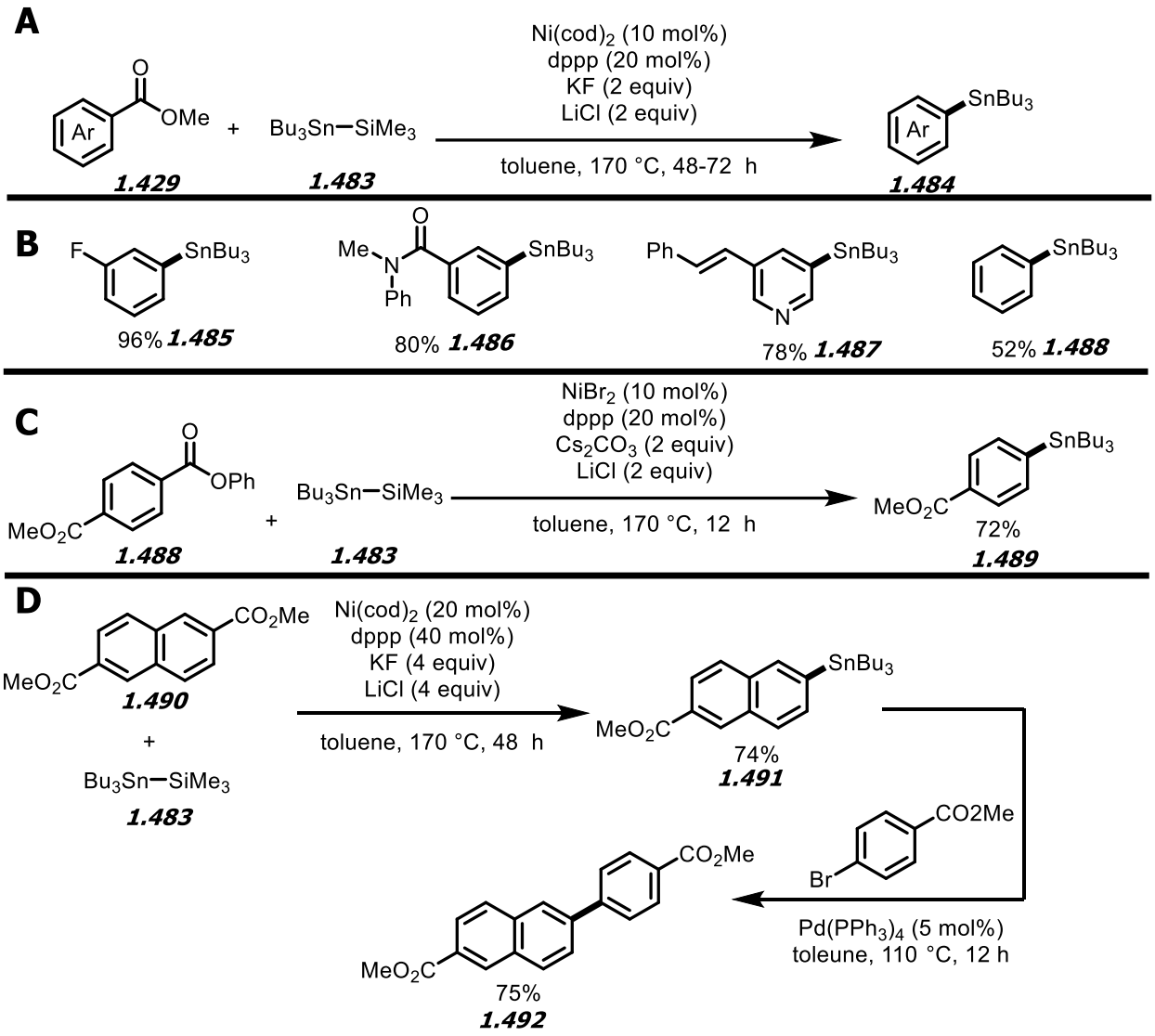
[130] (a) Ragan, J. A.; Raggon, J. W.; Hill, P. D.; Jones, B. P.; McDermott, R. E.; Munchhof, M. J.; Marx, M. A.; Casavant, J. M.; Cooper, B. A.; Doty, J. L.; Lu, Y. *Org. Process Res. Dev.* **2003**, *7*, 676. (b) Alonso, E.; Fuwa, H.; Vale, C.; Suga, Y.; Goto, T.; Konno, Y.; Sasaki, M.; LaFerla, F. M.; Vieytes, M. R.; Giménez-Llort, L.; Botana, L. M. *J. Am. Chem. Soc.* **2012**, *134*, 7467. (c) Valot, G.; Regens, C. S.; O'Malley, D. P.; Godineau, E.; Takikawa, H.; Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9534. (d) Li, J.; Yang, P.; Yao, M.; Deng, J.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 16477. (e) Mailhol, D.; Willwacher, J.; Kausch-Busies, N.; Rubitski, E. E.; Sobol, Z.; Schuler, M.; Lam, M.-H.; Musto, S.; Loganzo, F.; Maderna, A.; Fürstner, A. *J. Am. Chem. Soc.* **2014**, *136*, 15719. (f) Logan, M. M.; Toma, T.; Thomas-Tran, R.; Du Bois, J. *Science* **2016**, *354*, 865.

[131] (a) Soderquist, J. A.; Hassner, A. *J. Am. Chem. Soc.* **1980**, *102*, 1577. (b) Gosmini, C.; Périchon, J. *Org. Biomol. Chem.* **2005**, *3*, 216.

[132] Yue, H.; Zhu, C.; Rueping, M. *Org. Lett.* **2018**, *20*, 385.



Scheme 62. (A) Ni-catalyzed decarbonylative ester to stannane conversion. (B) Representative scope examples. (C) Selective stannylation. (D) Monostannylation and sequential cross-coupling.

1.3.6: Conclusion and outlook

The use of esters for cross-coupling reactions has numerous benefits. They are robust functional groups capable of being carried through multi-step synthesis and used in late

stage functionalization. They are ubiquitous and, in the case of simple alkyl esters, are often commercially available. Their reactions avoid the generation of halide salt waste formed in the coupling of aryl halides. Most importantly, these coupling reactions can serve as appealing alternatives to traditional routes based on the availability of the starting material or the efficiency by which they can be converted into the desired products. Generally speaking, the cross-coupling of esters proceeding via metal-acyl intermediates can provide two classes of products – those that retain the carbonyl, and those that lose the carbonyl. In some cases, control of these two pathways is possible, further highlighting the synthetic utility of esters as cross-coupling electrophiles. Initial reports in ester activation relied on directing groups to facilitate the difficult oxidative addition into the C(acyl)-O bond. Shortly after, ester chemistry was then directed towards the coupling of phenyl esters, as the aromatic ring weakened the C(acyl)-O bond, rendering them modestly activated towards oxidative addition. Most recently, progress has been made in the activation of abundant methyl esters. In contrast, more abundant esters feature stronger bonds that necessitate the use of more aggressive and carefully tuned conditions, which may result in more limited substrate scopes. In the future, we expect further mechanistic understanding and catalyst design enables the continued expansion of acylative and decarbonylative cross-coupling reactions to provide complementarity to traditional organohalide coupling reactions.

1.4: Research goals

As described, influential work spanning the past two decades has seen the emergence of esters as powerful alternatives to more traditional cross-coupling electrophiles. The utilisation of esters as cross-coupling electrophiles has several key advantages. Most

often, alcohol by-products are formed thus circumventing the formation of halide salt by-products. Esters are also relatively robust scaffolds due to the substantial double-bond character of the C(acyl)-O bond. The robustness of esters can be exploited in the context of multi-step synthesis as well as late stage functionalization. Through careful selection of the reaction parameters, one can control the classes of product that arise when using esters as cross-coupling electrophiles. In theory it would be possible to select for products that retain the carbonyl, or products that lose the carbonyl, which underlines the synthetic utility of esters in cross-coupling. Lastly, esters are rather ubiquitous moieties, and in the case of simple methyl esters, are often commercially available. In spite of this, the vast majority of work accomplished thus far concerning ester cross-coupling has been with phenyl esters. Phenyl esters remain less common than their alkyl ester counterparts. Widespread methodologies that make use of simple methyl esters as cross-coupling electrophiles would be significantly more practical. Unfortunately, the relative inertness of methyl esters has made them difficult to engage successfully towards cross-coupling reactions, as there are still limited reports of methyl ester cross-coupling.

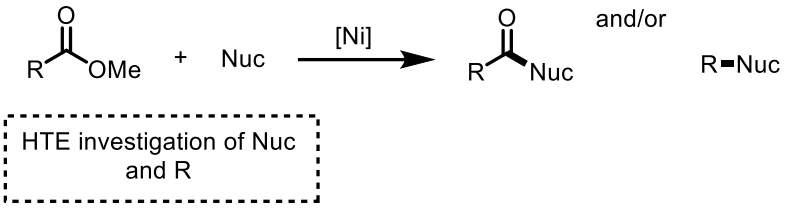
As reports of methyl ester cross coupling remain rare, we determined a worthwhile goal to be the investigation of ester cross-coupling in the context of high throughput experimentation (HTE). HTE is an extremely powerful technique for reaction discovery as it allows for the exploration of several reaction parameters concurrently. The HTE approach explores a wide area of chemical space and can identify conditions of interest that may have been overlooked had a more traditional one variable at a time (OVAT) approach been taken. Reports of intermolecular methyl ester cross-couplings are largely limited to amines, with reports of carbon nucleophiles exclusively limited to dimethylaluminum chloride and alkyl-9-BBN species. We hypothesize that the aforementioned nucleophiles are not the sole coupling partners that can react with methyl esters. We also believe that the investigation of privileged methyl esters could be

key to unlocking more general reactivity, allowing them to be engaged in various types of coupling reactions. Chapter 2 will concern the HTE investigations of novel nucleophilic coupling partners in the context of methyl ester cross-coupling, as well as the investigation of privileged methyl ester scaffolds.

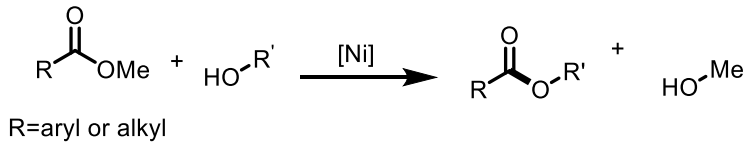
Chapter 3 describes a Ni-catalyzed transesterification reaction of methyl esters. Alcohols have yet to be reported as viable cross-coupling partners with methyl esters. Although transesterification reactions have been well developed with Brønsted acids, bases and Lewis acids, a Ni-catalyzed variant can overcome some of the shortcomings with existing protocols. In this chapter, an additive free, Ni/dcype catalyzed transesterification reaction of methyl esters is disclosed, representing broadening of the the scope of available nucleophiles that can participate in cross-coupling reactions with methyl esters. Specifically, Chapter 3 describes efforts of identifying the optimized conditions for the transformation, a scope of 20 molecules, the identification of scaffolds that cannot be tolerated, and lastly, preliminary kinetics experiments with the goal of providing experimental evidence to support the proposed mechanisms for methyl ester cross-couplings.

A brief summary of the research topics and chapter contents can be found below in **Scheme 63**.

Chapter 2



Chapter 3



Scheme 63. Brief overview of research projects

Chapter 2: Using high-throughput experimentation as a tool for the discovery of new methyl ester reactivity

2.1: Background on high-throughput experimentation:

For the modern chemist, high-throughput experimentation (HTE) has emerged as an extremely powerful technique. Its use has facilitated the optimization of individual steps in total synthesis as well as the discovery of novel methodologies.[134] Applications of HTE are not limited to reaction optimization and discovery, it has also seen use in building libraries of diverse products in the fields of medicinal chemistry [135] and materials science.[136]

HTE is particularly useful because it allows for the exploration of several reaction parameters concurrently. This approach authorizes a wide exploration of chemical space and can permit the investigation of conditions that may have otherwise been unexplored via a more traditional one variable at a time (OVAT) approach.

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[134] (a) Friedfeld, M. R.; Shevlin, M.; Hoyt, J. M.; Krska, S. W.; Tudge, M. T.; Chirik, P. J. *Science* **2013**, *342*, 1076. (b) Li, H.; Belyk, K. M.; Yin, J.; Chen, Q.; Hyde, A.; Ji, Y.; Oliver, S.; Tudge, M. T.; Campeau, L.-C.; Campos, K. R. *J. Am. Chem. Soc.* **2015**, *137*, 13728. (c) Molinaro, C.; Scott, J. P.; Shevlin, M.; Wise, C.; Ménard, A.; Gibb, A.; Junker, E. M.; Lieberman, D. *J. Am. Chem. Soc.* **2015**, *137*, 999. (d) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 4802.

[135] Cernak, T.; Gesmundo, N. J.; Dykstra, K.; Yu, Y.; Wu, Z.; Shi, Z.-C.; Vachal, P.; Sperbeck, D.; He, S.; Murphy, B. A.; Sonatore, L.; Williams, S.; Madeira, M.; Verras, A.; Reiter, M.; Lee, C. H.; Cuff, J.; Sherer, E. C.; Kuethe, J.; Goble, S.; Perrotto, N.; Pinto, S.; Shen, D.-M.; Nargund, R.; Balkovec, J.; DeVita, R. J.; Dreher, S. D. *J. Med. Chem.* **2017**, *60*, 3594.

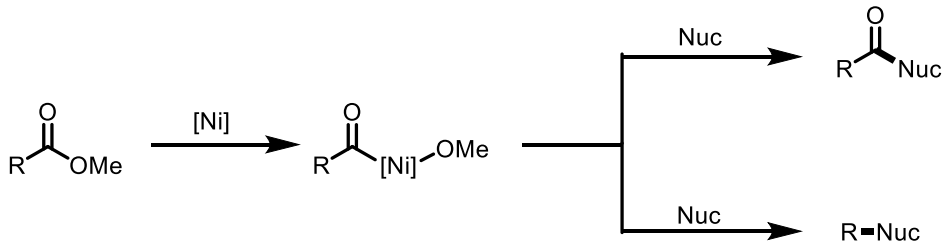
[136] Green, M. L.; Takeuchi, I.; Hattrick-Simpers, J. R. *J. Appl. Phys.* **2013**, *113*, 231101.

The HTE process is more streamlined than its OVAT counterpart, as it takes advantage of tools such as multi-well plates, liquid transfer tools, multi-well filtration plates and GC-MS analysis to analyze the reactions. HTE also has the benefit of quickly generating large data sets. With this newly generated data, one can attempt to identify and extrapolate trends between the many variables of a given chemical transformation. Once a "hit" has been established under HTE conditions, it should be validated. Once validated, the chemist can turn to OVAT optimization to improve the hit, potentially with the aid of the large data set initially generated.

2.2: High-throughput experimentation in the context of novel nucleophiles for methyl ester cross-coupling

The past two decades have seen significant progress in the field of ester cross-coupling. However, the majority of the advancements realized were concerning phenyl esters which are moderately activated and often need to be prepared. Their methyl ester counterparts are much more robust and accessible, thus a method to functionalize them via cross-coupling means would be of great use. The first report of methyl ester cross-coupling was by the Garg group in 2016[113], where they disclosed an amidation reaction of methyl esters (see chapter 1). Since that time, the nucleophiles used in the intermolecular cross-couplings of methyl esters have been limited to amines and trimethyl(tributylstannyl)silanes, with the carbon nucleophiles being limited to dimethylaluminum chloride and alkyl-9-BBN species.

Given the practicality and importance of developing novel methyl ester cross-coupling reactions, we deemed it appropriate to take an HTE approach in investigating novel nucleophilic coupling partners in the hopes of discovering new reactivity (**Scheme 64)**.



Scheme 64. HTE investigation of novel nucleophiles for methyl ester cross-coupling

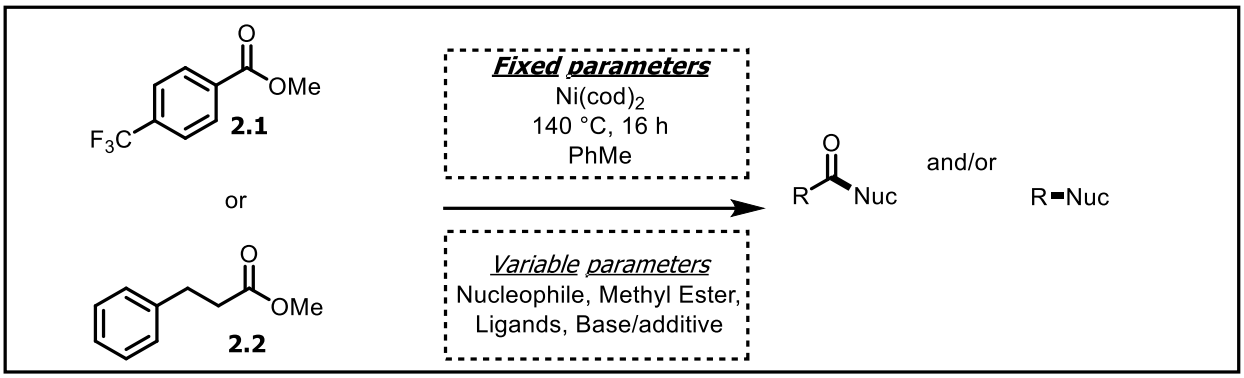
2.2.1: Plate design in the investigation of novel nucleophiles for methyl ester cross-coupling

As detailed above, methyl esters are quite robust. This innate robustness has made them difficult to engage in cross-coupling reactions. Reports of intermolecular methyl ester cross-coupling remain rare, with only 4 different classes of nucleophiles demonstrated as viable coupling partners.

We hypothesized that by taking an HTE approach to reaction discovery, we increase our chances of finding success. A range of variables and hypotheses are tested all at once. A hit can also potentially be obtained from non-intuitive reaction conditions that may otherwise have been missed had the more traditional OVAT approach been taken.

2.2.2: Choice of the fixed parameters

The limited reports of methyl ester activation all make use of Ni catalysts (See chapter 1, section 1.3.4). Several phenyl ester transformations are Pd-catalyzed (see chapter 1), however Pd catalysts may be unable to oxidatively insert into the strong C-O bonds of methyl esters, which may explain their absence in the existing literature of methyl ester activation. For these reasons, Ni catalysts were deemed most appropriate for our HTE investigations (**Scheme 65**). The solvent of choice was toluene, with time and temperature respectively chosen as 140 °C and 16 h.

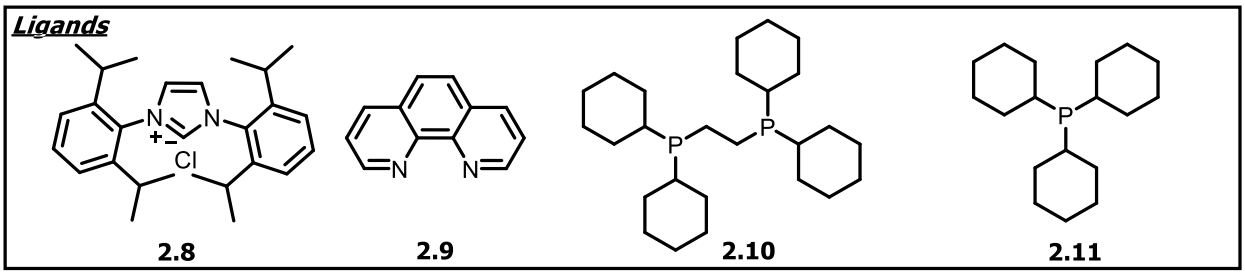


Scheme 65. Fixed parameters for HTE plates 1 and 2

2.2.3: HTE plate design

Aside from amidation reactions, scope examples of methyl ester cross-coupling reactions are largely limited to α-sp^2 hybridized esters. For this project, it was deemed equally important to screen α-sp^3 hybridized esters alongside α-sp^2 hybridized esters (**Scheme 65**).

As outlined in chapter 1, the choice of catalyst system can be of great importance in ensuring the success of ester cross-coupling reactions. Existing protocols often employ NHCs as their ideal ligand. Thus it was deemed imperative that NHCs be screened in this project (**scheme 66**). For reasons of availability and cost, IPr was chosen as the NHC to be screened for this project. It is important to note that the IPr used for HTE discovery projects was in the HCl salt form, and thus required catalytic amounts of KO^{t}Bu to release the free ligand in situ.



Scheme 66. Ligands to be screened on HTE plates 1 and 2

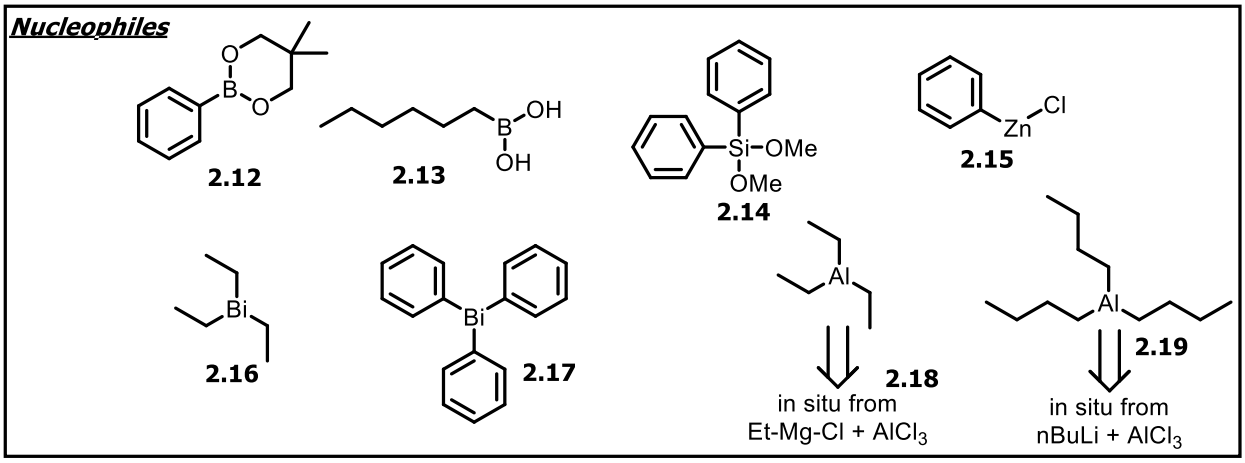
Other ligands that commonly frequent the ester cross-coupling literature are both mono and bi-dentate phosphine ligands. For this reason, dcype and PCy_3 were deemed valuable ligands to screen in our study. Our group has also published an extensive substrate dependant ligand study in the amidation of methyl esters.[118] This study identified a bidentate nitrogen ligand derived from 1,10-phenanthroline as the optimal ligand for a certain substrate pair. In light of this finding, the investigation of bidentate nitrogen ligands was deemed worthwhile for our project.

The primary objective of this project was to identify nucleophiles that have not previously been reported in methyl ester cross-coupling reactions. Towards our goal, we aimed to screen nucleophiles and conditions previously unexplored in our group and the existing literature.

The Chatani group have reported the use of aryl boronic esters to couple aryl methyl ethers in the presence of $Ni(cod)_2$ (**Scheme 67**).[33] Although not an ester, an aryl methyl ether is a similarly tough electrophile to activate towards cross-coupling reactions. The Gagnon group have invoked the use of aryl and alkyl organobismuth reagents in cross-coupling conditions with a variety of substrates.[137] We also attempted the in-situ

[137] (a) Gagnon, A.; Duplessis, M.; Albert, V. *Synlett* **2010**, *2010*, 2936. (b) Hébert, M.; Petiot, P.; Benoit, E.; Dansereau, J.; Ahmad, T.; Le Roch, A.; Ottenwaelder, X.; Gagnon, A. *J. Org. Chem.* **2016**, *81*, 5401. (c) Dansereau, J.; Gautreau, S.; Gagnon, A. *ChemistrySelect* **2017**, *2*, 2593. (d) Benoit, E.; Dansereau, J.; Gagnon, A. *Synlett* **2017**, *28*, 2833.

formation of organoaluminum species by combining $AlCl_3$ with Grignard or organolithium reagents. The inspiration of organoaluminum species was drawn from the existing Ni-catalyzed methyl ester cross-coupling published by Yamaguchi (see section 1.3.5.2); however, an in-situ method would be significantly more practical and would present a useful alternative to preparing and working with highly reactive organoaluminum species. [82] Our lab has also published work demonstrating that alkyl 9-BBN reagents are viable nucleophilic cross-coupling partners for methyl esters (see section 1.3.4.3). [123] At the time of this project, this worked was yet to be published, thus it was imperative we also investigated the use of alkyl boronic acids. Organozinc reagents are used extensively in the Negishi reaction and Ni-catalyzed methods are well established in the primary literature.[138] Organosilanes are another class of nucleophiles that our lab has not studied towards our goal. Organosilanes are a commonly used in the Hiyama reaction, which has also been well established in the literature.[139]



Scheme 67. Nucleophiles to be screened in plates 1 and 2

[138] (a) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177. (b) Melzig, L.; Gavryushin, A.; Knochel, P. *Org. Lett.* **2007**, *9*, 5529. (c) Iwasaki, T.; Kambe, N. *Ni- and Fe-based cross-coupling reactions*; springer, 2017.
[139] (a) Shi, S.; Zhang, Y. *J. Org. Chem.* **2007**, *72*, 5927. (b) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (c) Wu, Y.; Zhang, H.-R.; Cao, Y.-X.; Lan, Q.; Wang, X.-S. *Org. Lett.* **2016**, *18*, 5564. (d) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem.* **2007**, *119*, 3626.

The final variable parameter to be investigated was base/additive. Many of the nucleophiles listed above require bases when they are used in their conventional reactions. Commonly occurring bases across this assortment of reactions are fluoride, hydroxide or carbonate bases. However, it is important to note that the use of harsh hydroxide bases would lead to the hydrolysis of the esters, and would thus be incompatible for our reactions. For this reason, KF and Cs_2CO_3 were considered valuable bases to investigate for this project. Sporadically, organic bases are also used for several of these nucleophiles under their traditional reaction conditions. DIPEA was chosen as the organic base in order to explore more chemical space with the plates. Although the Yamaguchi cross-coupling of methyl esters with organoaluminums and other more conventional organoaluminum cross-couplings[140] do not require base, it has been reported that the presence of base in organoaluminum coupling can lead to the amelioration of the reaction and allow for milder reaction conditions.[141] Given the routinely harsh reaction conditions associated with most methyl ester cross-coupling reactions, the discovery of milder techniques would certainly be practical and thus in the context of this study organoaluminum reactants were screened in the presence of base. The sole nucleophile reacted in the absence of base was the organozinc reagent as Negishi cross-coupling do not require base. Instead, the organozinc reagent was screened in the presence of salt additives, as their presence has been known to often be favourable for Negishi couplings that employ arylzinc halides.[142]

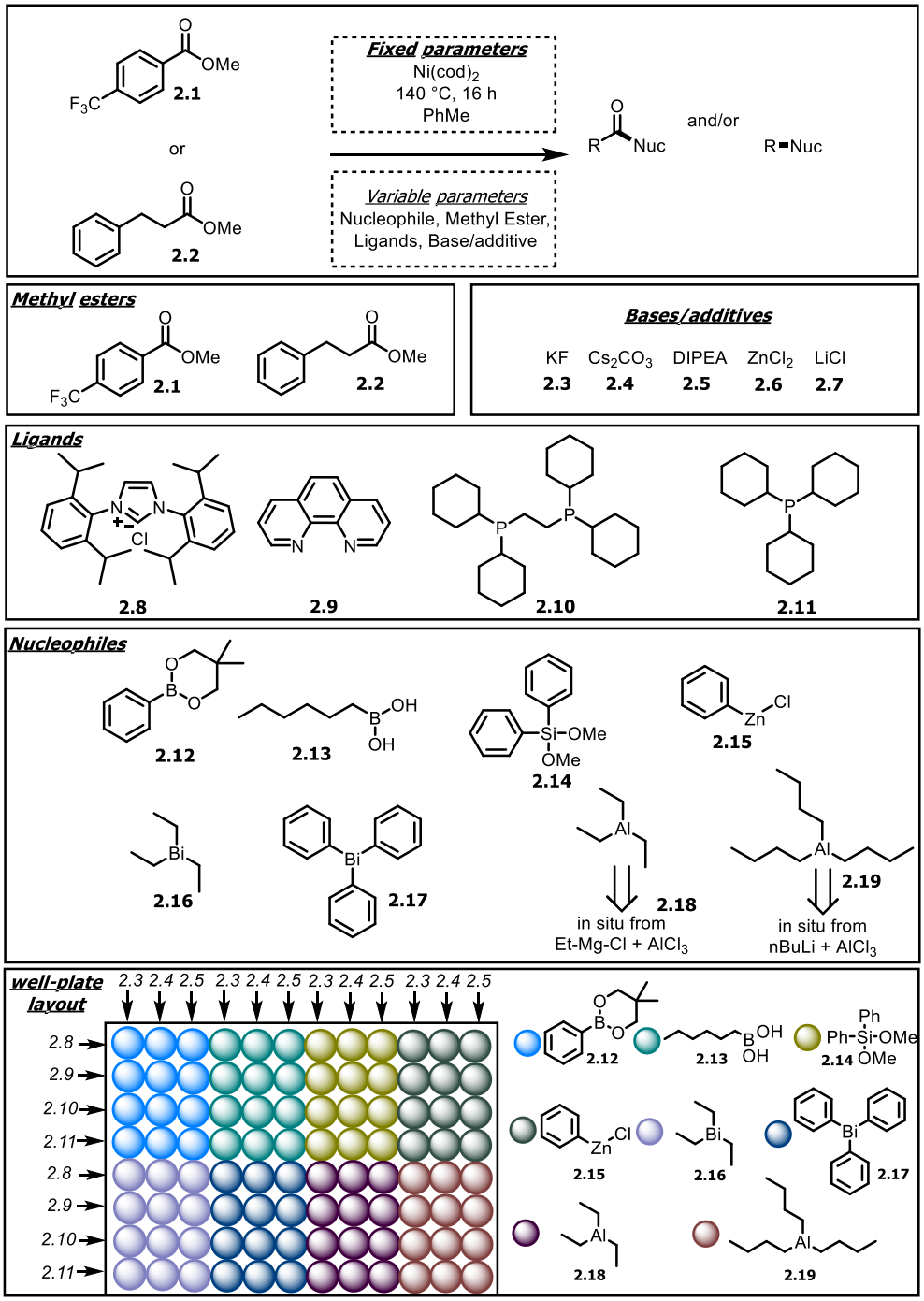
In Summary, there was a combination of 8 nucleophiles x 2 methyl esters x 4 ligands x 3 bases resulting in a total of 192 different reactions spread across two different 96 well

[140] (a) Naganawa, Y.; Guo, H.; Sakamoto, K.; Nakajima, Y. *ChemCatChem* **2019**, *11*, 3756. (b) He, F.; Wang, Z.-X. *Tetrahedron* **2017**, *73*, 4450. (c) Morioka, T.; Nishizawa, A.; Nakamura, K.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 1729.

[141] Gelman, D.; Schumann, H.; Blum, J. *Tett. Lett.* **2000**, *41*, 7555.

[142] (a) McCann, L. C.; Organ, M. G. *Angew. Chem. Int. Ed.* **2014**, *53*, 4386. (b) Eckert, P.; Sharif, S.; Organ, M. G. *Angew. Chem. Int. Ed.* **2021**, *60*, 12224.

plates (1 plate per methyl ester) (**Scheme 68**). The plates were organized into 8 separate quadrants that span 3x4 vials (one quadrant per nucleophile) as shown in **Scheme 68**. It is important to note that the wells screening organozinc nucleophile **2.15** did not feature KF, Cs_2CO_3 or DIPEA. KF was replaced by no additive (control well), Cs_2CO_3 was replaced by $ZnCl_2$, and DIPEA was replaced by LiCl.



Scheme 68. Screening parameters and well-plate layout for HTE plates 1 and 2

Immediately following the setup of the two plates mentioned above, a subsequent third plate was setup. The objective of this third plate remained the same; however, a greater emphasis was placed on investigating the formation of non-conventional ester cross-coupling nucleophiles in an in-situ manner. Although an organozinc compound was investigated in the previous HTE plates, their well established precedent in the literature[137] warranted further investigation in the context of in-situ organozinc nucleophile formation. Suzuki couplings were also investigated further by invoking the use of the "9-MeO-9-BBN" complementary variant where an organometallic reagent R-M is intercepted by 9-MeO-9-BBN to form the resulting nucleophilic borinate species in-situ (**Scheme 69**).[143] Organozirconium nucleophiles are relatively non-conventional for cross-coupling reactions; however, their use has been sparsely documented.[144] To our end, we combined Cp_2ZrCl_2 with Grignard and organolithium reagents to generate organozirconium nucleophiles in-situ.

Organoindium reagents are a class of nucleophiles that have begun to be investigated more commonly in the past two decades.[145]

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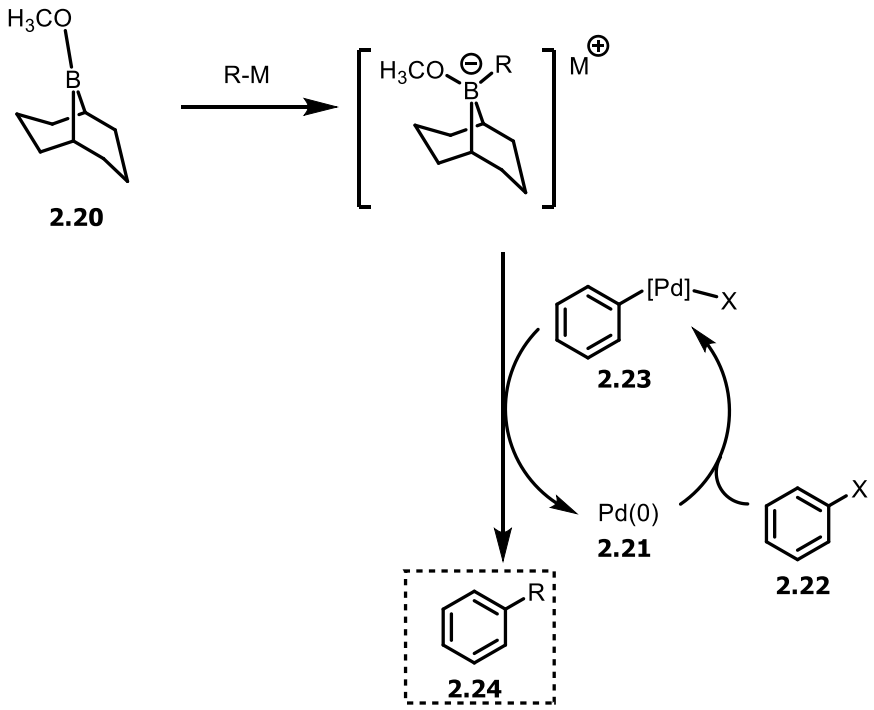
[143] Seidel, G.; Fürstner, A. *Chem. Commun.* **2012**, *48*, 2055.
[144] (a) Zhang, H.; Fu, X.; Chen, J.; Wang, E.; Liu, Y.; Li, Y. *J. Org. Chem.* **2009**, *74*, 9351. (b) Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tett. Lett.* **1998**, *39*, 6249. (c) Hanzawa, Y.; Narita, K.; Taguchi, T. *Tett. Lett.* **2000**, *41*, 109. (c) Thapa, S.; Basnet, P.; Gurung, S. K.; Giri, R. *Chem. Commun.* **2015**, *51*, 4009.
[145] Zhao, K.; Shen, L.; Shen, Z.-L.; Loh, T.-P. *Chem. Soc. Rev.* **2017**, *46*, 586.

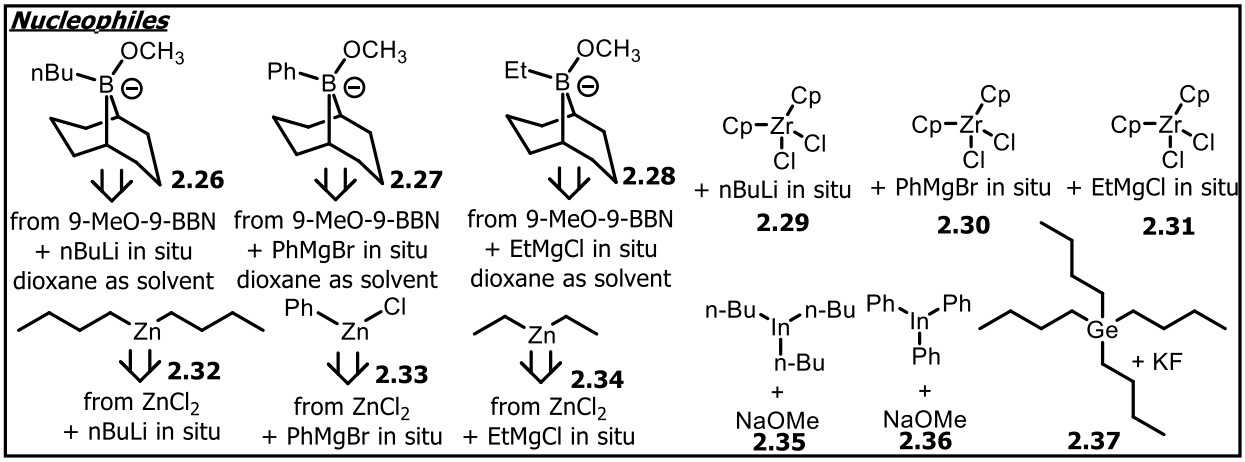


Scheme 69. General scheme of the 9-MeO-9-BBN variant of Suzuki-Miyaura cross-coupling reaction

Their mildness makes them an interesting nucleophile to investigate as there should not be background reactivity between the ester and the organoindium reagent. Lastly, we also decided to investigate the use of organogermanium nucleophiles. Organogermanium nucleophiles are highly unconventional cross-coupling partners but there have been a limited number of reports that invoke their use in cross-coupling reactions.[146] Although certainly an unorthodox nucleophile, we deemed it valuable to

[146] (a) Torres, N. M.; Lavis, J. M.; Maleczka, R. E. *Tett. Lett.* **2009**, *50*, 4407. (b) Xu, M.-Y.; Jiang, W.-T.; Li, Y.; Xu, Q.-H.; Zhou, Q.-L.; Yang, S.; Xiao, B. *J. Am. Chem. Soc.* **2019**, *141*, 7582. (c) Kosugi, M.; Tanji, T.; Tanaka, Y.; Yoshida, A.; Fugami, K.; Kameyama, M.; Migita, T. *Journal of Organometallic Chemistry* **1996**, *508*, 255. (d) Arkles, Barry, & Larson, Gerald L. (2016). Metal-Organics for Materials, Polymers and Synthesis (4th

explore as we had yet to find success with any nucleophiles apart from those already reported in the literature (see chapter 1). For reasons of simplicity, tetra-n-butylgermanium was chosen as it is commercially available. Simple tetraalkyl organogermanium nucleophiles are not used often for cross-coupling reactions and they are much less reactive than their non-commercially available counterparts[146c], however we deemed its use was satisfactory for this stage of the project. A summary of the nucleophiles screened is shown below in **Scheme 70**.



Scheme 70. Nucleophiles screened for HTE plate 3

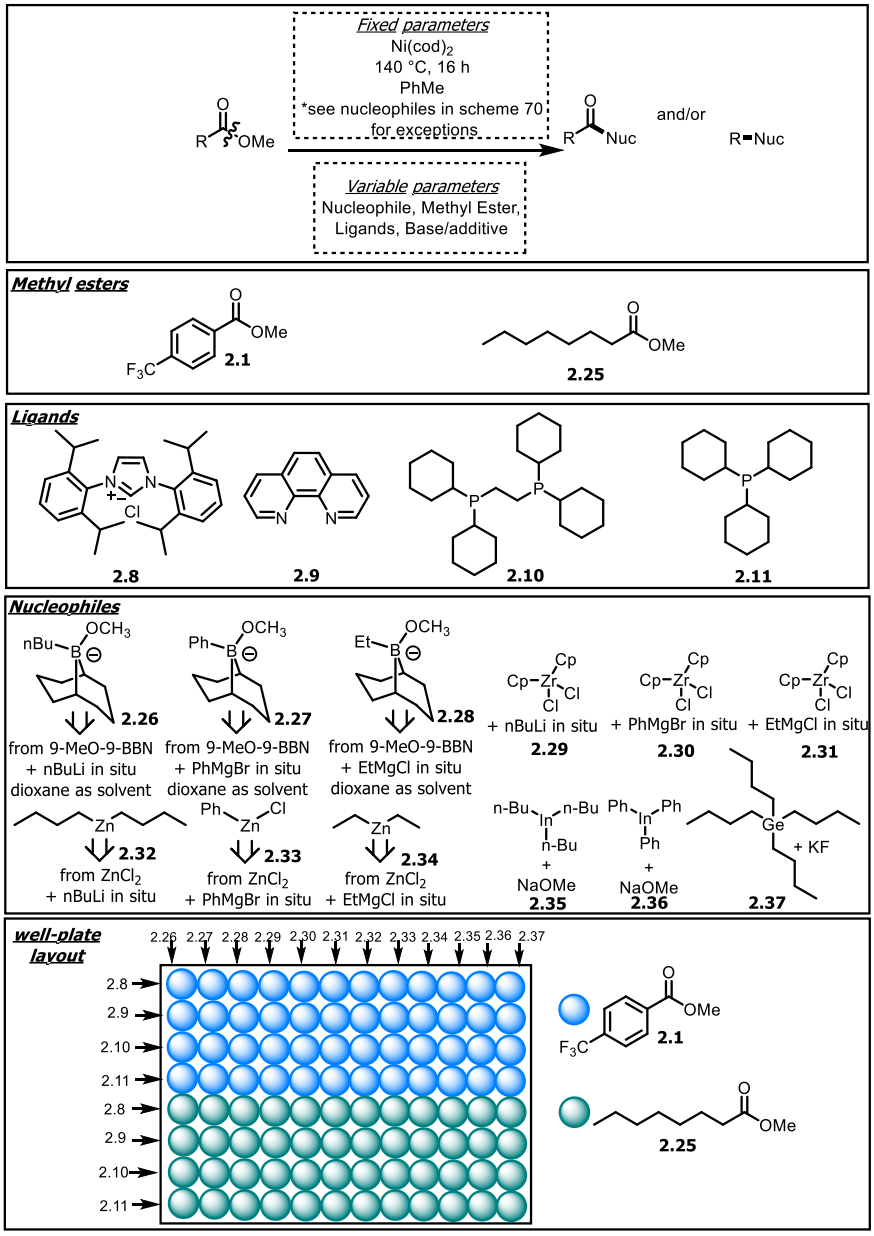
The fixed parameters for this third plate remained consistent with the previous two plates, with small exceptions needing to be made for certain nucleophiles

edition). In Metal-Organics for Materials, Polymers and Synthesis (4th edition) (pp. 1–400). Gelest Inc. https://doi.org/10.5281/zenodo.4694976

The 9-MeO-9-BBN variant of the Suzuki-Miyaura reaction is often run in polar solvents such as THF of DMF. [143] Throughout our research group's investigations into methyl ester cross-coupling, we have largely known these solvents to be problematic and incompatible, with toluene usually presenting itself as our solvent of choice. However, dioxane has often been a valuable alternative to toluene. We proposed that for the investigation of the 9-MeO-9-BBN variant of the Suzuki-Miyaura reaction, substituting THF with dioxane may be reasonable as they are both ethereal solvents. Furthermore, many reported cross-coupling reactions of organoindium reagents require polar solvents such as THF, DMF, or DMA to proceed efficiently.[145] When running organoindium cross-coupling reactions on the benchtop, we noticed that toluene would diminish or entirely shut down reactivity (see chapter 2, supporting information section 2.6.4). To overcome this issue, we added NaOMe as a promotor to improve the reactivity of the organoindium reagents in toluene. The final accommodation was required for the tetra-n-butylgermanium. Much like organosilane reagents, organogermaniums often require a promotor to improve the reactivity of the nucleophile. [146] All reactions investigating tetra-n-butylgermanium thus had KF added as a fluoride promotor.

With the exception of reactions exploring organoindium and organogermanium, this plate did not require base for the remaining nucleophiles. The ligands remained consistent with those used for the original two HTE plates. Ester **2.1** was used again to sample the reactivity of α-sp^2 methyl esters. Ester **2.2** was fully consumed in running the

second HTE plate, thus ester **2.25** was chosen to replace ester **2.2** in order to probe the reactivity of α-sp^3 methyl esters. Although the original two esters (**2.1 and 2.2**) were run on separate plates, this third plate ran both esters (**2.1** and **2.25**) concurrently. A summary of the third HTE plate can be found below in **Scheme 71**.

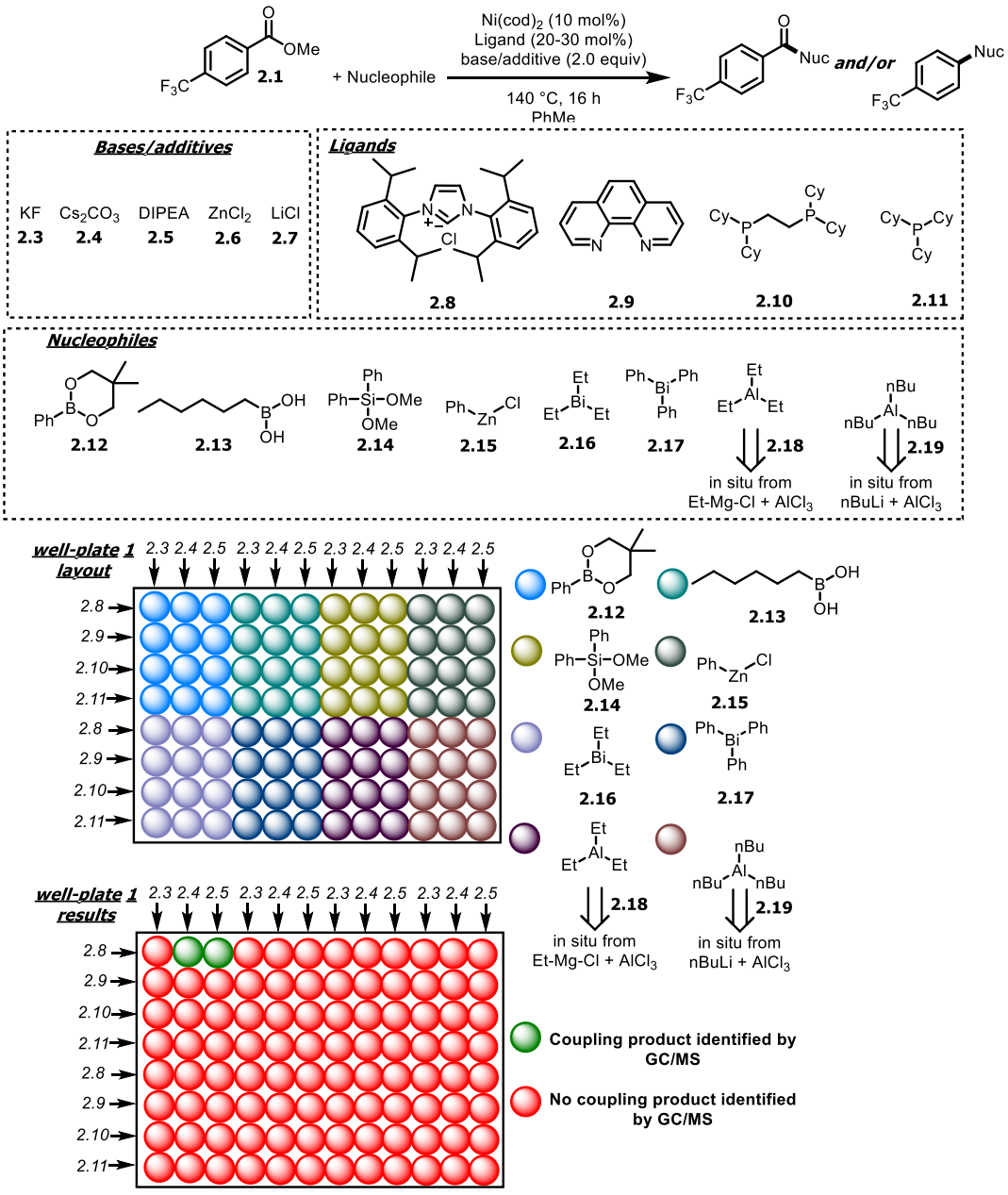


Scheme 71. Screening parameters and well-plate layout for HTE plate 3

2.2.4: Results of the three HTE plates screening for nucleophiles to engage in cross-coupling reactions with methyl esters

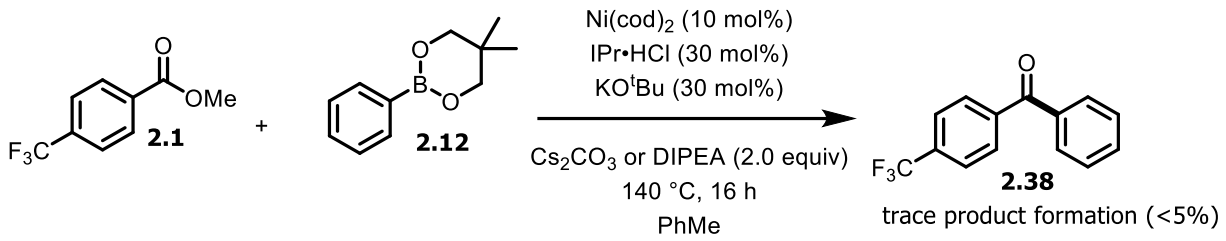
In summary of the previous section, towards our goal of discovering novel methyl ester cross-coupling reactivity, we performed 288 experiments across 3 separate 96 well-plates. The reactivity of α-sp^3 methyl esters and α-sp^2 methyl esters was probed in the presence of previously unexplored nucleophiles, in the hopes of discovering reaction conditions that result in the formation of carbonyl retentive and/or decarbonylative products.

The first 96 well-plate screened ester **2.1** in the presence of 8 different nucleophiles (**2.12-2,19**), 4 different ligands (**2.8-2.11**) and 3 different bases (**2.3-2.5**) (**Scheme 72**). When screening the organozinc nucleophile **2.15** salt additives were screened instead of bases (KF replaced by no additive, Cs_2CO_3 replaced by $ZnCl_2$, DIPEA replaced by LiCl).



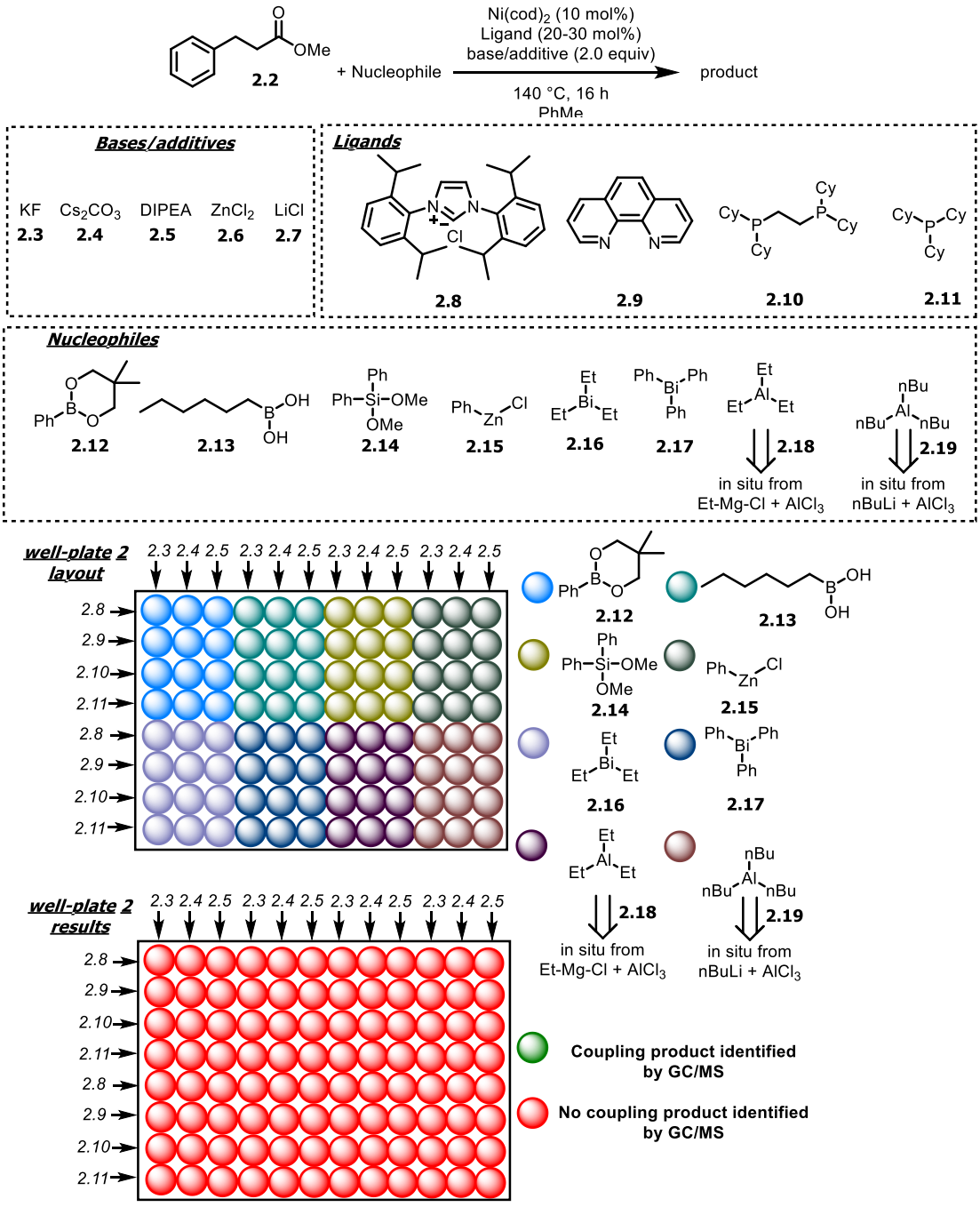
Scheme 72. First 96 well-plate layout and results

The sole hits were obtained with Phenyl-BPin as the nucleophile, IPr as the ligand, and either Cs_2CO_3 or DIPEA as the base (**Scheme 73**). These two conditions give rise to the formation of the carbonyl retentive product **2.38**, respectively, identified by a trace GC-MS peak. Both results were repeated on the bench top with identical results to ensure reproducibility.



Scheme 73 Reactions from plate 1 that resulted in product formation. Yield of product **2.38** estimated by GC analysis.

The second 96 well-plate screened ester **2.2** under identical conditions to the first 96-well plate (**Scheme 74**). Ultimately, this 96 well-plate resulted in no hits. GC-MS analysis determined that all reactions provided starting material recovery and/or degradation.

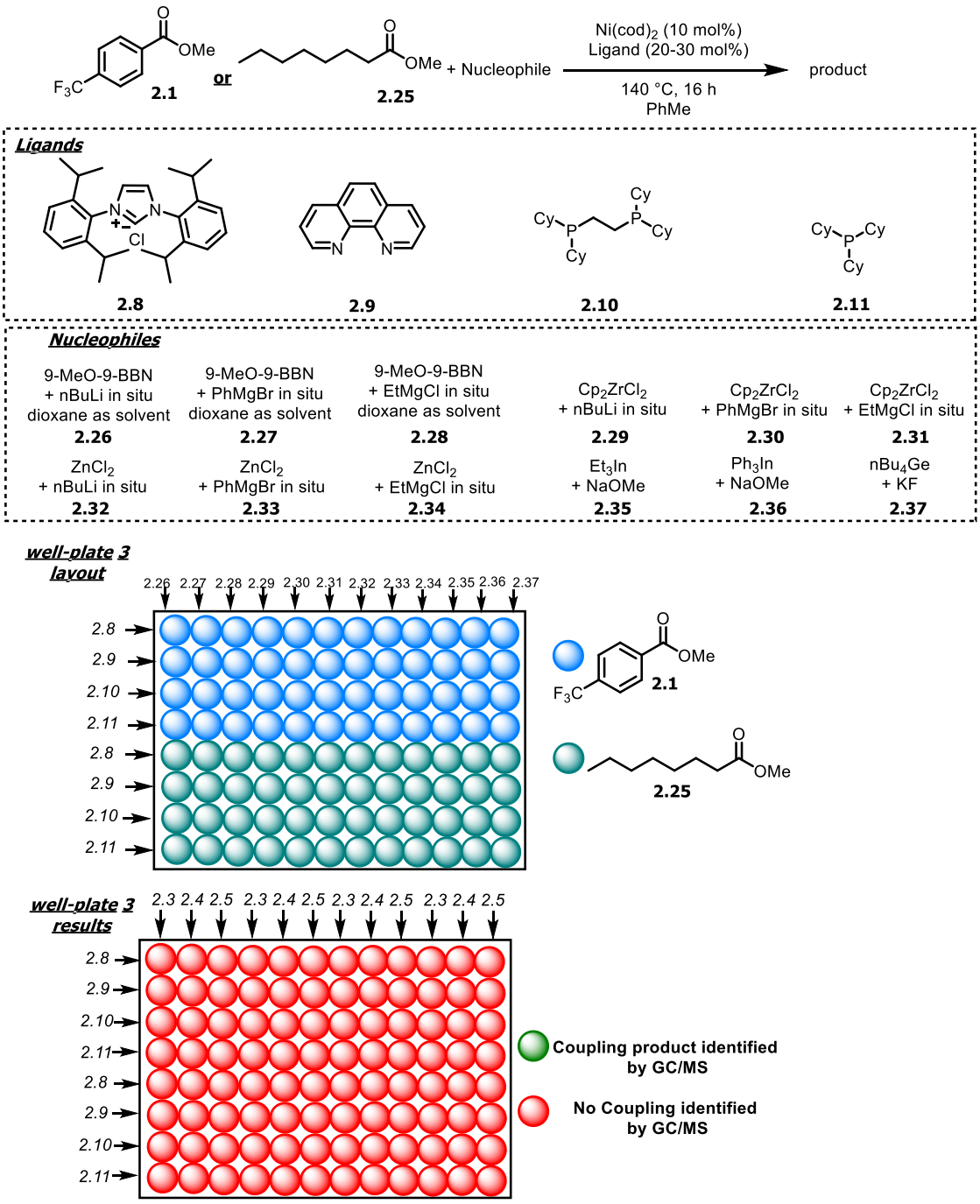


Scheme 74. Second 96 well-plate layout and results

It is difficult to make any concrete conclusions as to why all the reactions in this plate failed as there are many factors that could hinder productive chemistry. One reasonable explanation could simply be that α-sp^3 hybridized methyl esters are among the more difficult substrates to engage towards cross-coupling reactions. Of the existing reports of

intermolecular methyl ester cross-coupling, scope examples are largely limited to α-sp^2 hybridized methyl esters, with reports of amidation being the unique cases that can successfully couple some aliphatic methyl esters.[115, 119] The lack of α-sp^3 hybridized methyl esters among scope examples may be understood by DFT studies performed by Hong and co-workers on the amidation reaction of methyl esters.[117] Their work suggests that Ni(0) catalysts are capable of oxidatively adding into the C(acyl)-O bond of a methyl ester with reasonable activation energy. However, the formation of the acyl-Ni(II) complex is calculated to be thermodynamically uphill and reversible, meaning that the concentration of the reactive acyl-Ni(II) intermediate is likely very low at any given time in solution The DFT studies also demonstrated that the high energy rate determining step for α-sp^3 methyl esters is the proton transfer. Given that the concentration of reactive acyl-Ni(II) intermediate will be low, and proton transfer/transmetallation can be a problematic step in the catalytic cycle, it may be difficult to receive any appreciable yield of product as the Ni(II) intermediate and nucleophile must come together to react.

The third 96 well-plate also provided no evidence of product formation after GC-MS analysis (**Scheme 75**).



Scheme 75. Third well-plate layout and results

Much like the second plate, it is difficult to arrive to concrete conclusions as to why each individual reaction failed to provide product even in trace yields. These results do not suggest that nucleophiles such as organoindiums or the formation of organozincs in situ

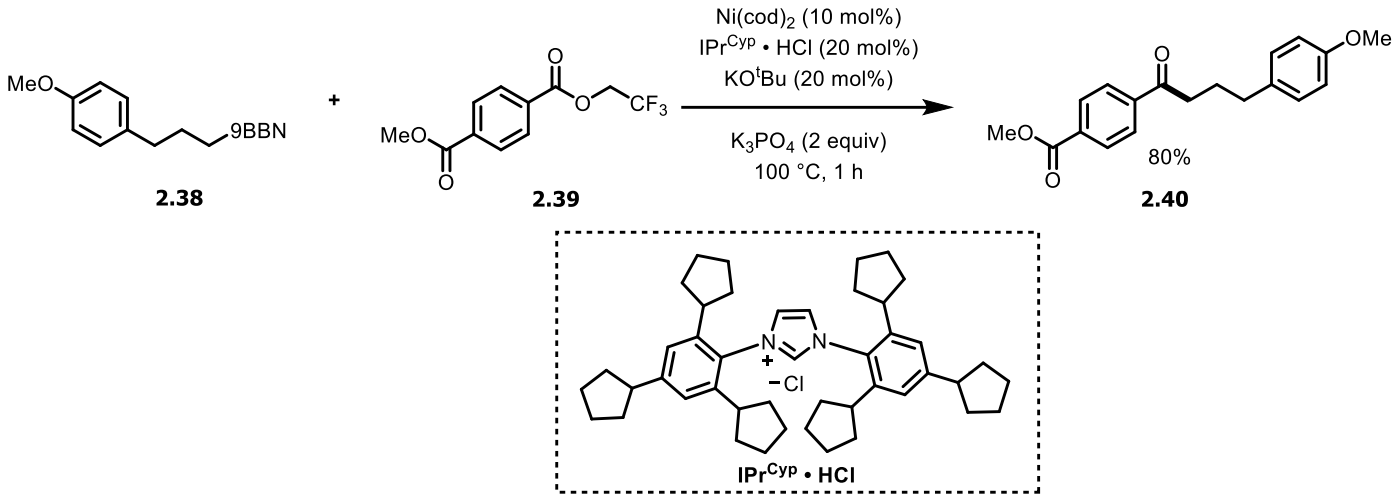
is entirely incompatible with Ni-catalyzed methyl ester cross-coupling. What we do learn however, is that the nucleophiles tested are incompatible with Ni-catalyzed methyl ester cross-coupling under these specific conditions. In exploring some of the chemical space, we have identified certain parameters that should be avoided when exploring novel methyl ester cross-coupling reactions in the future.

Of 288 reactions among 3 separate 96-well plates, only the reaction between Ester **2.1** and Bpin nucleophile **2.12** provided product under two slightly different conditions (**Scheme 72 and 73**). Although this project identified a new class of nucleophiles capable of cross-coupling with methyl esters, this result was ultimately not pursued. A former PhD student from the group, Taoufik Ben Halima, discovered that aryl boronic acids could be coupled to α-sp^2 hybridized methyl esters under very similar conditions. The initial conditions discovered by Dr. Ben Halima also resulted in the formation of the carbonyl retentive product in trace yields, and despite extensive optimization, the yields remained low (<20%). Given how similar aryl-Bpin nucleophiles and aryl boronic acids behave, we elected not to pursue this hit further. Nevertheless, we felt that screening aryl-Bpin nucleophiles was still worthwhile with other ester electrophiles.

2.3: Using HTE to explore coupling reactions between nucleophiles and privileged methyl esters

Our HTE investigation of nucleophiles previously unexplored in the context of methyl ester cross-coupling did not provide us with the hits of novel reactivity we were hoping to observe. Concurrent to the HTE investigations outlined in section 2.2, our group was also studying the Ni-catalyzed Suzuki-Miyaura reaction between methyl esters and alkyl-

9-BBN reagents to provide ketone products (see chapter 1, **Scheme 59**).[123] Interestingly, we observed that molecule **2.39** preferentially and selectively reacted at the trifluoroethanol-derived ester rather than the methyl ester to provide product **2.40** in an 80% yield. (**Scheme 76**).



Scheme 76. Interesting chemoselectivity observed in the study of Ni-catalyzed Suzuki-Miyaura reaction between methyl esters and alkyl-9-BBN reagents to provide ketone products

This result led us to hypothesize that privileged esters may be more successful as cross-coupling electrophiles. As they appear to be more reactive than methyl esters, perhaps they will be able couple with nucleophiles inaccessible to methyl esters. In order to test this hypothesis, we aimed to run a 96 well-plate where we screened privileged methyl esters with common cross-coupling nucleophiles. The nucleophiles screened for this plate differed from those screened in section **2.2** as they were nucleophiles our group has previously studied extensively towards methyl ester cross-coupling. Also, the nucleophiles screened for this plate are considerably more conventional and present

themselves more commonly among analogous reactions already established in the primary literature.

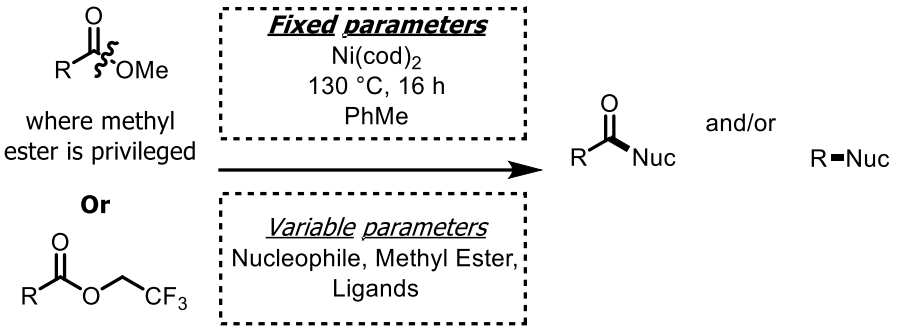
2.3.1: Choice of fixed parameters for the HTE screening of privileged methyl esters

We intended to keep our fixed parameters consistent with the previous 3 HTE plates ran in section **2.2**, as there were no apparent issues with the conditions. Given our knowledge of methyl ester cross-coupling, they seemed to be an exceedingly reasonable starting point (**Scheme 77**).

The limited reports of methyl ester activation all employ Ni catalysts (See chapter 1, section 1.3.4). For this reason, Ni-catalysis was deemed the most appropriate for this HTE study.

Although the choice of solvent can often be important, the majority of existing methyl ester cross-coupling conditions employ toluene and thus we deemed it a safe choice for this study.

Previous work in the field also led us to believe that time and temperature did not warrant screening at this early stage. The chemistry is known to function within the confines of 130 °C and 16 h. Although carbonyl retentive methyl ester cross-coupling has been demonstrated to work at temperatures much milder than 130 °C, decarbonylative reactions often require very aggressive temperatures.



Scheme 77. General overview of fixed and variable parameters for the HTE investigation of privileged methyl esters

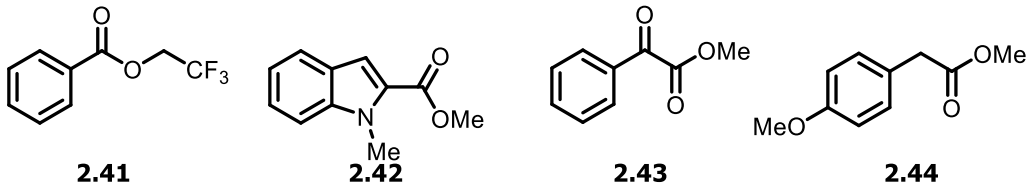
Choice of variables for the HTE screening of electronically activated methyl esters

Selection of substrates necessitated careful thought. The Gooßen group have developed several successful methods to cross-couple carboxylic acid derivatives.[147] However, they commonly exploit the leaving group abilities of anhydrides which cannot be considered methyl esters. Secondly, we wished to consider selecting substrates that were not highly contrived and were reasonably available.

This led us to select molecules **2.41, 2.42, 2.43** and **2.44** for this study (**Scheme 78**). Molecule **2.41** was chosen as we observed interesting reactivity from a trifluoroethanol-derived ester in a separate study conducted by our laboratory (See **Scheme 76** above). Molecule **2.42** was also chosen on the basis of findings from the same study involving the trifluoroethanol-derived ester. Molecule **2.42** generally reacted exceptionally well when cross-coupling with alkyl-9-BBN reagents to afford ketone products. For this reason, we deemed it worthwhile to investigate molecule **2.42** more closely for this study. Molecule **2.43** was chosen as the ester is alpha to a carbonyl which can draw electron density away from the ester, potentially resulting in a more facile oxidative addition and overall

[147] Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem. Int. Ed.* **2008**, *47* (17), 3100–3120.

reaction. Molecule **2.44** was chosen as the ester is located in the benzylic position and DFT studies have shown α-benzylic esters to be highly reactive (See section 1.3.4.1).



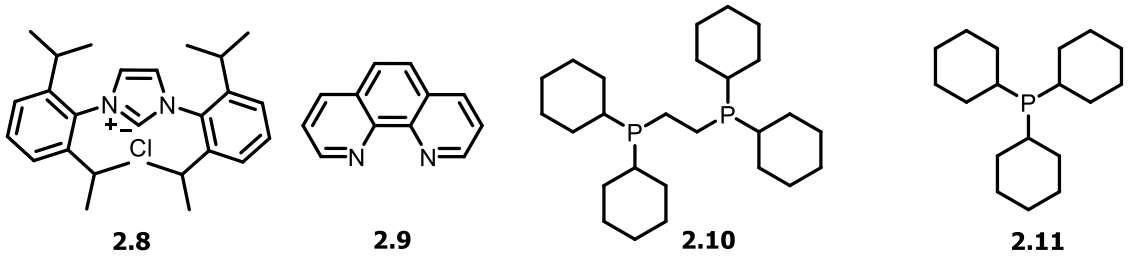
2.41 **2.42** **2.43** **2.44**

Scheme 78. Privileged esters chosen for THE

Given that the catalyst system can be so crucial to the success of methyl ester cross-coupling, we decided to screen 4 different ligands for this HTE study (**Scheme 79**). The ligands screened were identical to those in section **2.2**. IPr was chosen as NHCs are recurring ligands among successful ester cross-coupling reactions. Although a number of protocols call for the use of highly derivatized NHCs, we have failed to observe a scenario in which IPr fails to deliver a product when a derivate is successful. For reasons of availability and cost, IPr was chosen as the model NHC for this HTE screening. It is important to note that the IPr was in the HCl salt form, and thus require catalytic amounts of KO^{t}Bu to release the free ligand in situ.

Other ligands that commonly frequent the ester cross-coupling literature are both mono and bi-dentate phosphine ligands. For this reason, dcype and PCy_3 were deemed valuable ligands to screen in our study. Our group has also published an extensive substrate dependant ligand study in the amidation of methyl esters. [117] Although highly

uncommon among other ester coupling reactions, this study identified a bidentate nitrogen ligand derived from 1,10-phenanthroline as the optimal ligand for a certain substrate pair. In light of this finding, the investigation of bidentate nitrogen ligands was deemed worthwhile for this study.

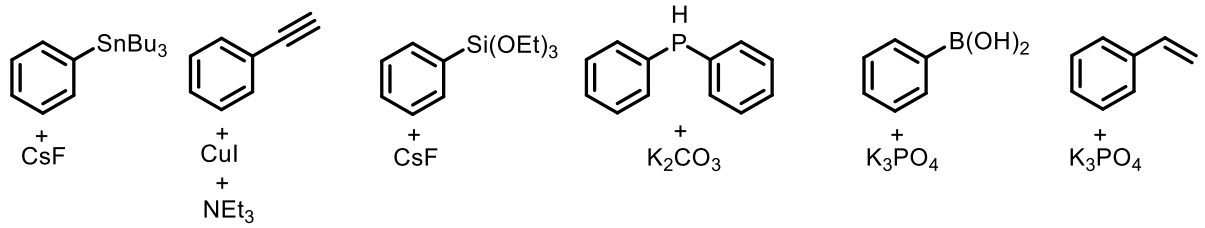


2.8 **2.9** **2.10** **2.11**

Scheme 79. Ligands screened for the HTE investigation of privileged activated methyl esters

The final variable parameter was the choice of nucleophile. The nucleophiles chosen for this HTE investigation of methyl esters were inspired by related literature (**Scheme 80**). This way, we were not basing success on discovering entirely new reactivity as in section **2.2**. Rather, we were seeking to test whether molecules **2.41-2.44** would be more reactive than simple, unactivated methyl esters which have thus far only provided trace yields of product or been entirely unreactive with some of the nucleophiles to be screened for this

study.



Scheme 80. Nucleophiles and their accompanying bases to be screened for cross-coupling with privileged methyl esters

Although a direct Stille cross-coupling of esters has yet to be reported, there has been precedent set on the use of organotin reagents for similar cross-coupling reactions. Stille and Hegedus have reported the use of Ph-$SnBu_3$ in the Pd-catalyzed coupling of allylic acetates[148] while more recently Yamaguchi has reported the Ni-catalyzed Stille coupling of tough C-N bonds.[149]

In 2017, the Itami and Yamaguchi group reported the Pd/Cu co-catalyzed Sonogashira-type coupling of phenyl esters (See chapter 1, **Scheme 34**). [71] Concurrently, the Rueping group reported an amide to alkyne interconversion via a Ni/Cu co-catalyzed deamidative cross-coupling. [150]

[148] Del Valle, L.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019.
[149] Wang, D.-Y.; Kawahata, M.; Yang, Z.-K.; Miyamoto, K.; Komagawa, S.; Yamaguchi, K.; Wang, C.; Uchiyama, M. *Nat. Commun.* **2016**, *7*, 12937.
[150] Srimontree, W.; Chatupheeraphat, A.; Liao, H.-H.; Rueping, M. *Org. Lett.* **2017**, *19*, 3091.

Very recently, the Lee group reported the Pd-catalyzed Hiyama cross-coupling of amides to generate ketones.[151]

The Han group have reported the Ni-catalyzed phosphinylation of C-S bonds forming C-P bonds. [152] Interestingly, prior to publishing this work, the Han group reported a Ni-catalyzed C-P bond formation reaction of 2-naphthyl pivalates. [153] In 2018, the Yamaguchi group were able to develop a Ni-catalyzed C-P bond forming reaction of phenyl esters (see chapter 1, section **1.3.2.7**). Thus far the scope of esters for C-P bond formation has been limited to phenyl esters and has not been extended to methyl esters.

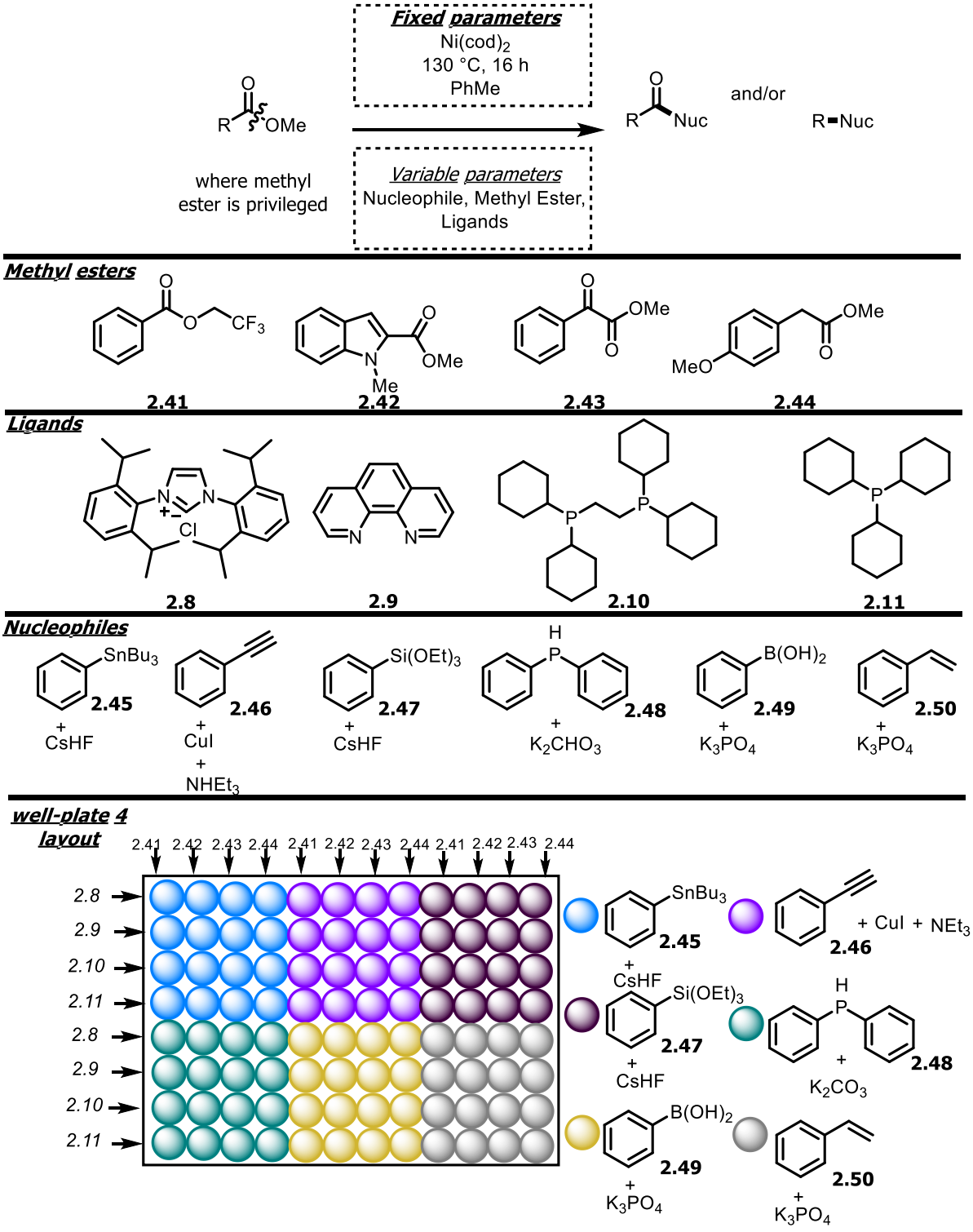
As for Suzuki-Miyaura cross-couplings, there have been numerous impactful reports published with phenyl esters as the electrophile. Decarbonylative methods as well as carbonyl retentive methods have been well established (see chapter 1, section **1.3.2.3** and **1.3.3.1**). Our group published the first Suzuki-Miyaura cross-coupling of methyl esters in 2021 using alkyl-9-BBN reagents to afford ketones (see chapter 1, section **1.3.4.3**). From our investigations, the Suzuki-Miyaura couplings of methyl esters have been limited to the alkyl-9-BNN reagents. Boronic acids have been largely unsuccessful and predominantly result in low yields of product formation (trace-20%). If molecules **2.41-2.44** were more reactive than their simple methyl ester counterparts, perhaps boronic

[151] Idris, M. A.; Lee, S. *Org. Lett.* **2020**, *22*, 9190.
[152] Yang, J.; Xiao, J.; Chen, T.; Yin, S.-F.; Han, L.-B. *Chem. Commun.* **2016**, *52*, 12233.
[153] Yang, J.; Chen, T.; Han, L.-B. *J. Am. Chem. Soc.* **2015**, *137*, 1782.

acids would no longer impede the success of methyl ester Suzuki-Miyaura cross-coupling reactions.

Lastly, we chose to screen styrene as a representative alkene for Mizoroki-Heck type reactivity. In the late 90s, de Vries and co-workers developed a Mizorki-Heck type coupling of carboxylic anhydrides (see chapter 1, section **1.3.1**). Several years later in 2017, In 2017, the groups of Garg[120] and Stanley[121] independently reported the trapping of N-boc amide derived acyl-Ni intermediates with tethered allyl fragments. Our group was able to expand the scope of this intramolecular coupling to include methyl esters (see chapter 1, section **1.3.4.2**). Although our efforts to develop an intermolecular Mizorki-Heck coupling of methyl esters have failed, we hypothesized that more activated esters would perhaps be the key to developing the novel Heck-type reactivity.

A summary of the screening conditions and well-plate layout can be found below in **Scheme 81**.



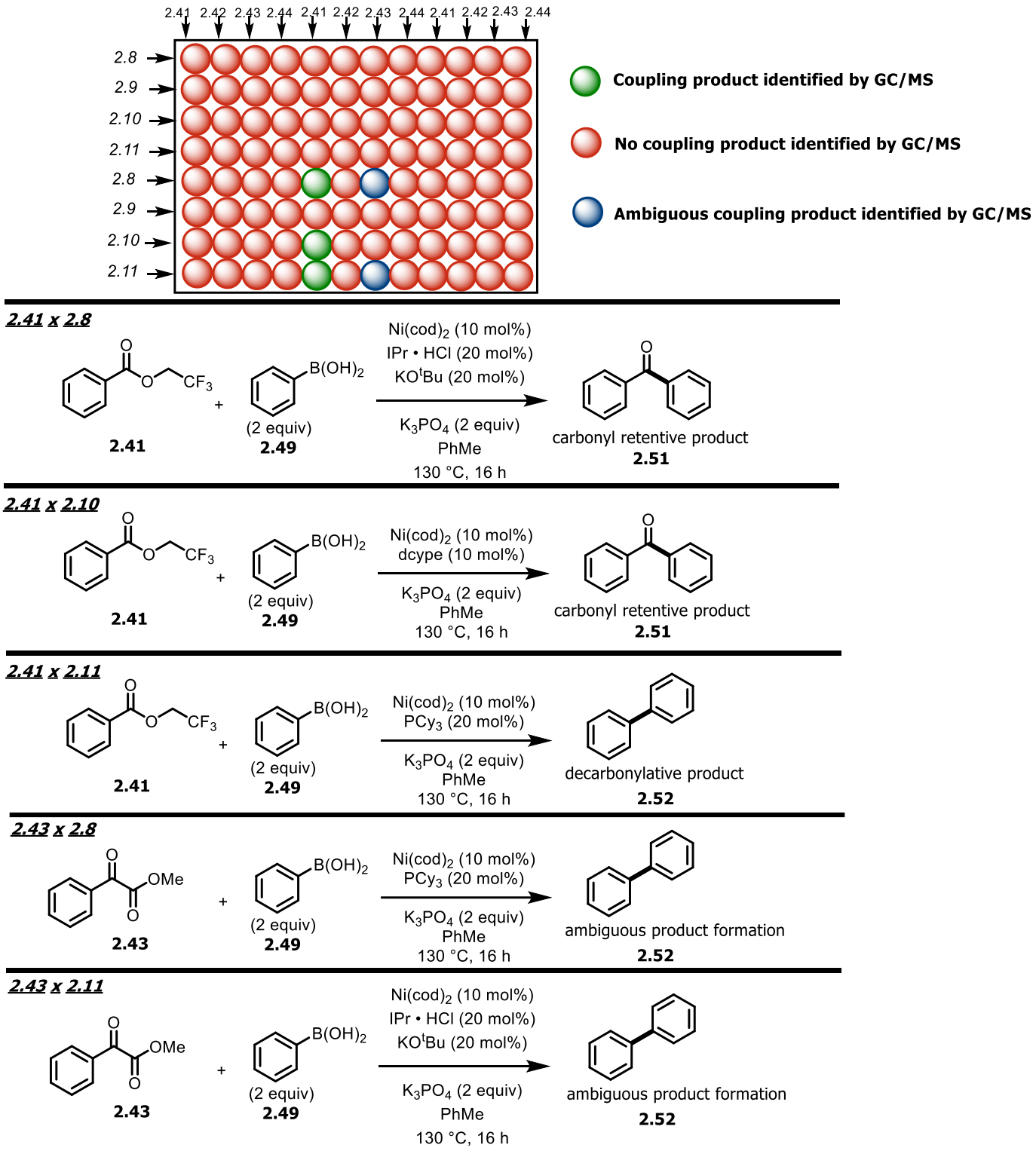
Scheme 81. Well-plate layout for screening privileged methyl esters

2.3.2: Results of HTE plate screening privileged methyl esters

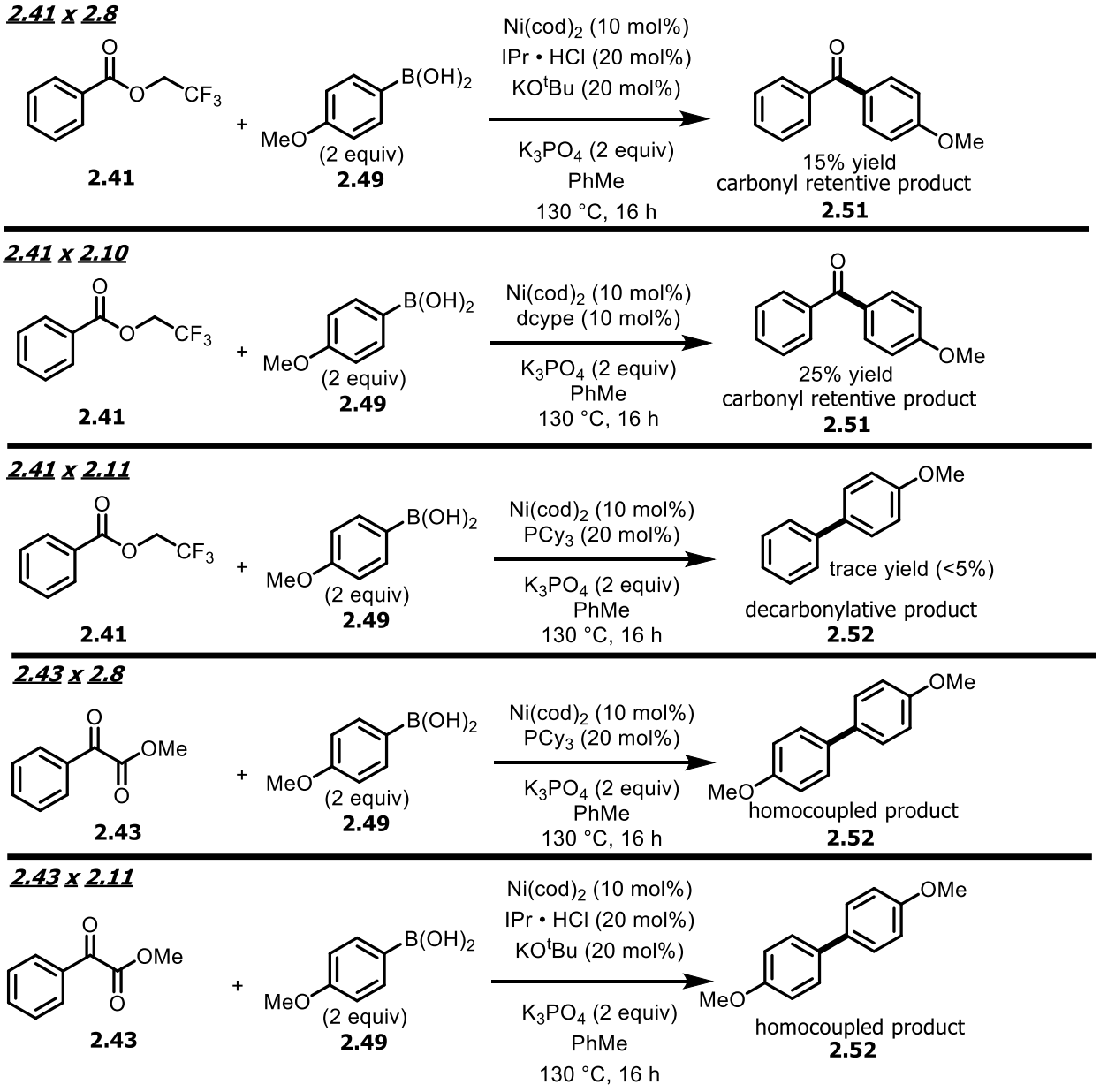
The results of the plate can be found below in **Scheme 82**. Ultimately, 5 hits were obtained. The trifluoroethanol derived ester **2.41** was able to provide either carbonyl retentive product **2.51** or decarbonylative product **2.52**. It appeared that both IPr and dcype would favour the formation of the carbonyl retentive product in a non-trace yield. When the monodentate phosphine PCy_3 was used, the decarbonylative product was formed selectively in a trace yield. Interestingly, methyl ester **2.43** provided what appeared to be a decarbonylative product from a Suzuki-Miyaura reaction with PCy_3 or IPr as the ligand. This was a surprising result as that would require methyl ester **2.43** to have lost two separate carbonyl groups. We believed the formation of biphenyl product **2.52** from ester **2.43** to be a false positive from the homocoupling of boronic acid.

We generally aim to reproduce HTE hits in a traditional reaction vial. In order to determine if the results from ester **2.43** were indeed a false positive, we used a slightly different boronic acid (**Scheme 83**). There was no reason to believe that the presence of the para-OMe group on the boronic acid would impede the productive chemistry and it would allow for the facile determination of homocoupling. The new boronic acid presented the added benefit of possessing a group that was easily identifiable via ^1H NMR, allowing us to determine the yield of the respective reactions.

The product arising from the Suzuki-Miyaura reaction involving ester **2.43** was ultimately determined to be the homocoupled boronic acid product. The results when conducting the Suzuki-Miyaura coupling of trifluoroethanol derived ester **2.41** were reproduced on the bench top. When using IPr, the carbonyl retentive product formed in a 15% yield. When using dcype, the carbonyl retentive product formed in a 25% yield. When using PCy_3, the decarbonylated product would form in a trace (<5%) yield.



Scheme 82. Results of HTE plate screening privileged methyl esters



Scheme 83. Benchtop reaction results when using conditions from HTE plate that provided hits. Yields for all products above were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

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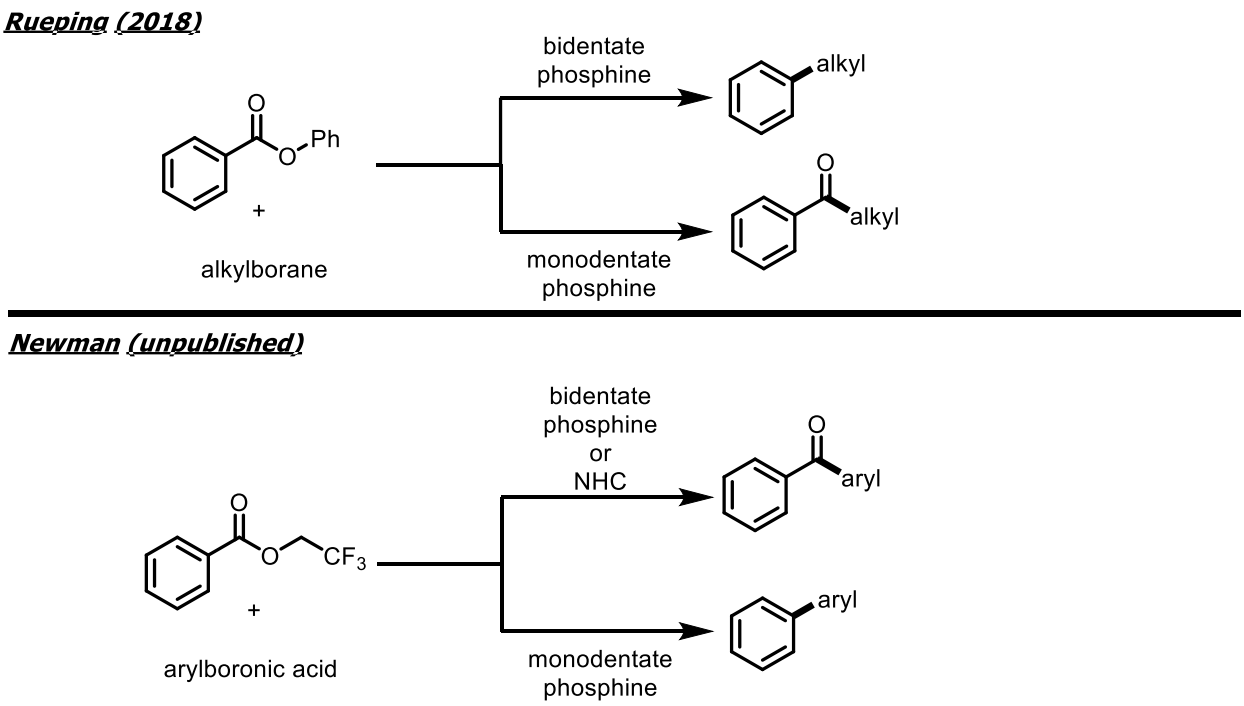
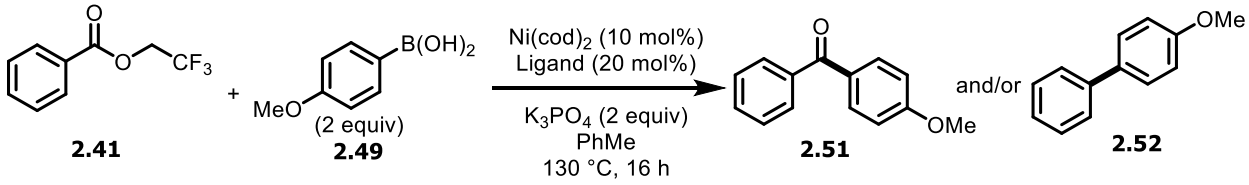
This manor of ligand-controlled selectivity is not novel in ester cross-coupling chemistry. In 2018, the Rueping group reported a ligand-controlled, site-selective nickel-catalyzed Suzuki-Miyaura coupling of phenyl esters with alkylborane reagents[59]. In Rueping's work the use of bidentate phosphines would lead to the formation of decarbonylated products. The use of monodentate phosphines would lead to the formation of the carbonyl retentive ketone products. Very interestingly, we observe the opposite selectivity when coupling trifluoroethanol derived ester **2.41** with arylboronic acids (**Scheme 84**).

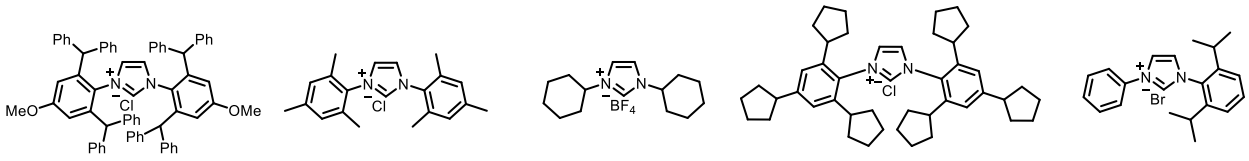


Scheme 84. Comparison of our ligand-controlled selectivity compared to analogous reactivity published by Rueping.

Given the nature of this interesting discovery, we found it appropriate to conduct a quick ligand screening to determine if this observation was unique to these specific ligands. Of the few ligands screened, the original ones from the plate were found to be the most successful as other ligands would simply provide trace amounts of product (Table 1 and 2). Interestingly, PCy_3 was the sole ligand that would favour the formation of the decarbonylative product.



Scheme 85. Ligand screen for Suzuki-Miyaura cross-coupling reaction of trifluoroethanol derived methyl ester



Entry	Ligand	Yield 2.51[a]	Yield 2.52[a]
1	IPr*OMe • HCl	0%	0%
2	IMes • HCl	Trace	0%
3	ICy • HBF_4	Trace	0%
4	IPr^{Cyp} • HCl	10%	0%
5	IPr • HCl	15%	0%
6	Pyridine NHC • Br	0%	0%

Table 1. NHC ligand screen for Ni-catalyzed Suzuki-Miyaura reaction of trifluoroethanol-derived ester. [a] Yields determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard

Entry	Ligand	Yield 2.51[a]	Yield 2.52[a]
1	PCy_3	0%	Trace (~5%)
2	Tris(4-methoxyphenyl) phosphine	Trace	0%
3	$(tBu)_3PHBF_4$	Trace	0%
4	dppf	0%	0%
5	dcype	25%	0%

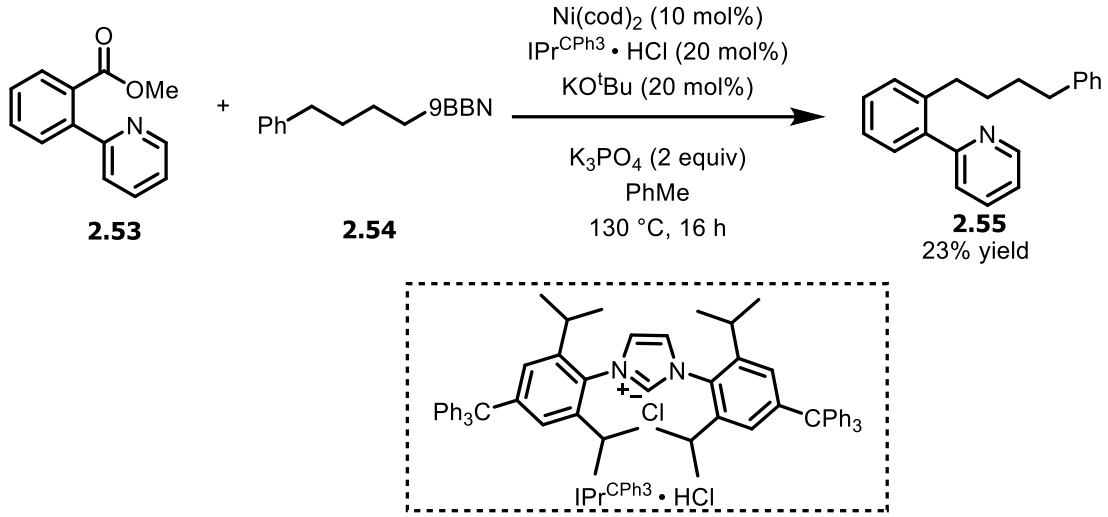
Table 2 Phosphine ligand screen for Ni-catalyzed Suzuki-Miyaura reaction of trifluoroethanol-derived ester. [a] Yields determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard

This discovery of unprecedented ligand-controlled selectivity was certainly very interesting and promising. However, given the results of the brief ligand screen, as well as our research group's extensive efforts in studying the Suzuki-Miyaura cross-coupling of methyl esters, we knew that these results required a significant amount of work. A high degree of time and resource commitment was necessary and due to time constraints, this avenue was abandoned for a project that had a much greater chance of success (see chapter 3).

2.4: Optimization of a decarbonylative alkyl-9-BBN Suzuki-Miyaura coupling

Concurrent to the HTE studies conducted throughout chapter 2, our group was developing a Ni-catalyzed carbonyl retentive alkyl-9-BBN Suzuki-Miyaura coupling of

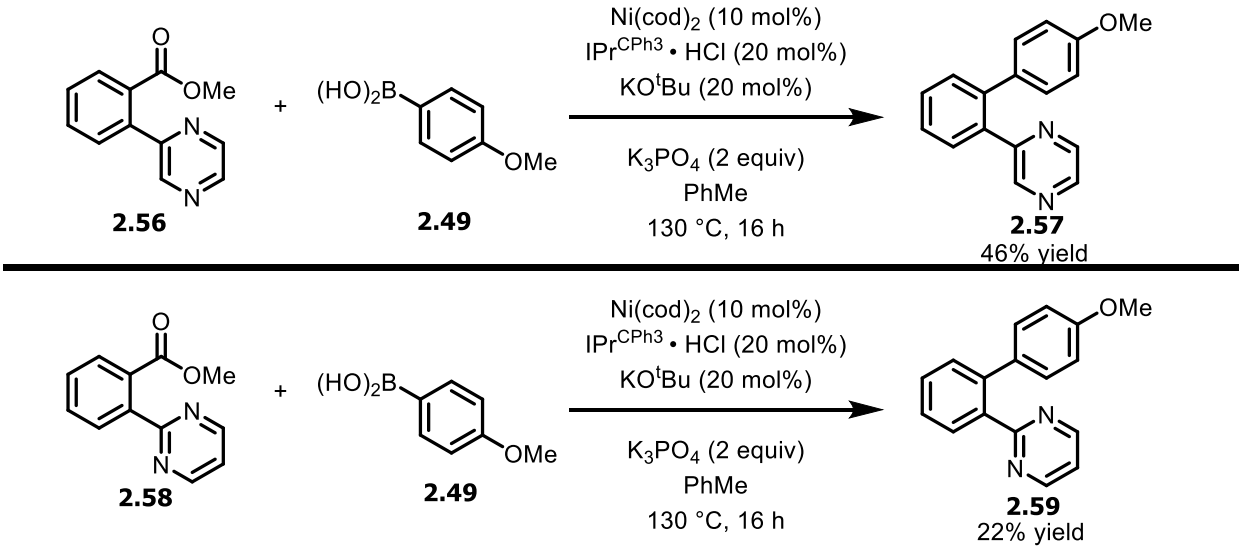
methyl esters (see chapter 1, section **1.3.4.3**). A previous lab member, Dr. Yanlong Zheng was primarily focussed on this project. While working on this project, Dr. Zheng discovered a decarbonylative product would form when the methyl esters contained an ortho-pyridine directing group (**Scheme 86**). My goal was to then attempt to optimize this reaction and isolate a few interesting scope examples.



Scheme 86. Ni-catalyzed decarbonylative Suzuki-Miyaura reaction of methyl esters discovered by Dr. Yanlong Zheng. Yield for product **2.55** was assessed by GC analysis via a 5-point calibration curve.

Many dozens of experiments were conducted while investigating the parameters of this reaction. Our observation during the optimization studies was that any changes to the conditions above in **Scheme 86** would be deleterious or would have no effect on the yield. What we concluded was that the traditional approach to optimization where small changes are made (changing identity of base, NHC ligand, solvent, increasing concentration, etc.) would not lead to the improvements in yield that we hoped to achieve. Instead, we hypothesized that more dramatic changes such as changing the identity of the directing group was necessary to greatly improve the yield. Several directing groups were synthesized and tested with both alkyl-9-BBN reagents and aryl

boronic acids. Of the few directing groups tested, 2 hits were obtained (**Scheme 87**). When using a pyrazine directing group as on molecule **2.56**, we observed a 46% yield of the corresponding product by ^{1}H NMR analysis. This was the largest observable increase in yield we had observed for the decarbonylative Suzuki-Miyaura reaction. Interestingly, when esters **2.56** and **2.58** were reacted with alkyl-9-BBN reagents there was no product formation and only starting material recovery. We concluded that our hypothesis was likely correct, that drastic changes such as different directing groups were necessary for this chemistry to be successful. There is likely some directing group that facilitates this reaction and leads to high yields of product. However, the ideal directing group is likely a highly contrived molecule. The significant amelioration of this reaction would likely be time consuming as well. For these reasons, this reaction was quickly abandoned.



Scheme 87. New directing groups identified for Ni-catalyzed decarbonylative Suzuki-Miyaura cross-coupling. Yields for products **2.57** and **2.59** were assessed by ^{1}H NMR analysis of the crude reaction mixture.

2.5: Conclusion and future work

In conclusion, HTE was applied to investigate the cross-coupling of methyl esters to identify novel reactivity. Two separate approaches were taken in these investigations.

The first was to study the application of nucleophiles previously unexplored in the context of methyl ester cross coupling. The second was the utilization of electronically activated methyl esters, which would perhaps facilitate an otherwise difficult transformation. Ligands were specifically chosen in this study that were known for their ability to oxidatively insert into the strong acyl(C)-O bond of methyl esters. The nucleophiles screened were influenced by conditions based on existing literature. In screening novel nucleophiles towards methyl ester cross-coupling, no promising hits were obtained. When screening electronically activated esters, an interesting ligand based selectivity was observed for a Ni-catalyzed Suzuki-Miyaura reaction of trifluoroethanol derived esters. Although not studied through the lens of HTE, a novel decarbonylative Suzuki-Miyaura reaction of methyl esters bearing directing groups was briefly studied and ultimately dropped as our preliminary results suggested that success was contingent on highly contrived molecules.

Due to time constraints, only very brief investigations were conducted on the Ni-catalyzed Suzuki-Miyaura coupling of trifluoroethanol derived esters. It is certainly worthwhile to spend some time conducting OVAT optimization and perhaps applying the knowledge learned to design more focussed HTE plates. Given that ligands seem to play an interesting role on this reaction by affecting selectivity, a thorough HTE screening of ligands may be very useful in ameliorating the reaction. IPr and dcype were most successful in providing access to the carbonyl retentive product, while PCy_3 was the sole ligand provided access to the decarbonylative product. HTE will generate a large data set which can perhaps shed light on some patterns associated with the observed selectivity in this reaction (e.g., the bulk of dcype/IPr being important).

Although no promising hits were obtained when screening nucleophiles unexplored in the context of methyl ester cross-coupling, valuable information was still obtained. We cannot conclude that any of the nucleophiles are entirely incompatible with methyl ester

cross-coupling. However, we can conclude that the nucleophiles are incompatible with the specific conditions screened. This data can help design further generations of HTE screenings to identify novel methyl ester reactivity. When screening nucleophiles via HTE in the future, it may be beneficial to dedicate entire plates to one nucleophile at a time. Nucleophiles for these future plates should also be chosen that have been well established in the literature to function with Ni-catalysts. As thoroughly described in chapter 1, the choice of catalyst system is of the utmost importance for the majority of ester cross-coupling reactions. By focussing on one nucleophile per plate, a greater variety of Ni catalysts and ligands can be screened.

In order to aide with future experimental design, collaboration with computational chemists and the use of machine-learning algorithms may be very useful. Many steps throughout the catalytic cycle of a given ester cross-coupling can be problematic. In running DFT studies on a specific reaction we are interested in, we can gain a further appreciation for the difficult steps and thus design our HTE studies with the difficult steps in mind. HTE generates large data sets, with some patterns often being unnoticed by the scientists. If all of the generated data is placed into machine-learning software, it can facilitate future studies by identifying patterns and suggesting experiments try.

2.6: Experimental section

2.6.1: General experimental details

Unless otherwise noted, reactions were conducted under an atmosphere of nitrogen. HTE reactions were conducted in 1.2 mL 8 x 40 mm glass vials enclosed within an aluminum 96-well plate. The 96-well plates were heated on a Heidolph magnetic stirrer/hotplate. Filtration was performed manually by passing 15 μL aliquots of each reaction mixture

through a short plug of Silicycle F60 40-63 μm silica gel, making use of a chemically-resistant 96-well filtration plate to filter samples into a second 96-well plate. Reactions ran on the benchtop to reproduce HTE results were set up inside of a glovebox using 8 mL vials. The vials were sealed and shipped out of the glovebox to be heated in a pre-heated silicone oil bath on a Heidolph magnetic stirrer/hotplate.

2.6.2: Instrumentation

GC data for HTE analysis was obtained using MS analysis on an Agilent Technologies 7890B GC with a 30 m x 0.25 mm HP-5 column which was equipped with an XYZ autosampler capable of accommodating multiwall plates. GC yields for optimization studies were obtained via a 5-point calibration curve using FID analysis (2,4,6-trimethoxybenzene as the internal standard) an Agilent Technologies 7890B GC with a 30 m x 0.25 mm HP-5 column. ^{1}H NMR were recorded on a Bruker AVANCE 400 spectrometer or a Bruker AVANCEII 300 MHz spectrometer. ^{1}H NMR spectra were internally referenced to the residual solvent signal (e.g., $CDCl_3$ = 7.26 ppm). Data for ^{1}H 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 were obtained by ^{1}H NMR analysis of the crude reaction mixture using dibromomethane or 2,4,6-trimethoxybenzene as an internal standard.

2.6.3: Materials

Organic solvents were purified by rigorous degassing with nitrogen before passing through a PureSolv solvent purification system. Low water content was confirmed by Karl Fischer titration (<20 ppm for all solvents). Unless otherwise noted, starting materials, ligands and bases were obtained commercially from Sigma Aldrich, Combi-Blocks or Strem chemicals and used as received. Non-commercially available NHC ligands were synthesized using established literature procedures.

2.6.4: Starting material and ligand synthesis

The following starting materials were synthesized according to literature procedures: Phenylzinc chloride (**2.15**),[154] triethyl bismuth (**2.16**),[155] triphenyl bismuth (**2.17**),[137b] tributyl indium (**2.35**),[156] triphenyl indium (**2.36**),[154] 2,2,2-trifluoroethyl benzoate (**2.41**),[157] methyl 1-methyl-1H-indole-2-carboxylate (**2.42**).[158]

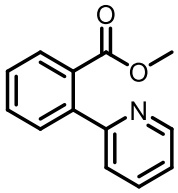
The following starting materials were synthesized with procedures from that literature that were slightly modified:

methyl 2-(2-pyridinyl)benzoate (**2.53**),[159] pyrazin-2-ylbenzoic acid methyl ester (**2.56**),[159] methyl 2-(pyrimidin-2-yl)benzoate (**2.58**).[159]

IPr^{CPh3}•HCl was synthesized according to a literature procedure [160] by Dr. Yanlong Zheng.

Organozinc and organomagnesium titrations were done via an established procedure.[161]

Organolithium titration was done using an established procedure.[162]



Methyl 2-(2-pyridinyl)benzoate (**2.53**)

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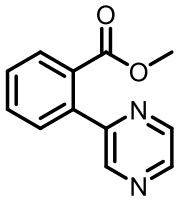
[154] Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137* (30), 9523.
[155] Gagnon, A.; Petiot, P. *heterocycles* **2014**, *88* (2), 1615.
[156] (a) Clark, H. C.; Pickard, A. L. Organoindium Chemistry. *J. Organomet. Chem.* **1967**, *8*, 427. (b) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155.
[157] Caldwell, N.; Jamieson, C.; Simpson, I.; Watson, A. J. *Chem. Commun.* **2015**, *51*, 9495.
[158] Song, X.; Xu, C.; Du, D.; Zhao, Z.; Zhu, D.; Wang, M. *Org. Lett.* **2017**, *19*, 6542.
[159] Iyori, Y.; Takahashi, K.; Yamazaki, K.; Ano, Y.; Chatani, N. *Chem. Commun.* **2019**, *55*, 13610.
[160] Dible, B. R.; Cowley, R. E.; Holland, P. L. *Organometallics* **2011**, 30, 5123.
[161] Knochel, P.; Krasovskiy, A. *Synthesis* **2006**, *2006*, 0890.
[162] W. G. Kofron, L. M. Baclawski, *J. Org. Chem*. **1976**, 41, 1879.

Molecule **2.53** was prepared via a modified procedure from the literature.[159] An oven dried (120 °C) high pressure flask was shipped inside a glovebox under an inert nitrogen atmosphere. The flask was charged with 1,4-dioxane (24 mL), 2-bromopyradine (1.58 g, 10 mmol), 2-(methoxycarbonyl)phenylboronic acid (1.5 g, 8.3 mmol), KF (1.55 g, 26.7 mmol) and $PdCl_2(PPh_3)_2$ (293 mg, 5 mol%). The vial was sealed and shipped outside of the glovebox. The mixture was stirred at 90 °C overnight. After cooling, the mixture was diluted with EtOAc (30 mL). The organic layer was washed with 5% K_2CO_3 (30 mL * 3) and was dried over Na_2SO_4. After the volatiles were removed under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent hexanes:EtOAc 10:1) to afford 712 mg (40% yield) of **2.53** as a brownish/yellow oil. NMR spectra matched the literature.[163]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 – 8.61 (m, 1H), 7.85 – 7.79 (m, 1H), 7.79 – 7.70 (m, 1H), 7.61 – 7.53 (m, 2H), 7.52 – 7.41 (m, 2H), 7.32 – 7.19 (m, 1H), 3.68 (s, 3H).



Pyrazin-2-ylbenzoic acid methyl ester (**2.56**)

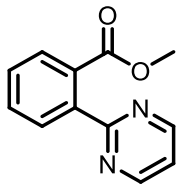
Molecule **2.56** was prepared via a slightly modified procedure from the literature.[159] An oven dried (120 °C) high pressure flask was shipped inside a glovebox under an inert

[163] Wang, Z.; Li, Y.; Zhu, F.; Wu, X.-F. *Adv. Synth. Catal.* **2016**, *358*, 2855.

nitrogen atmosphere. The flask was charged with 1,4-dioxane (8 mL), 2-chloropyrazine (390 mg, 3.4 mmol), 2-(methoxycarbonyl)phenylboronic acid (500 mg, 2.8 mmol), KF (523 mg, 9.0 mmol) and $PdCl_2(PPh_3)_2$ (98.3 mg, 5 mol%). The vial was sealed and shipped outside of the glovebox. The mixture was stirred at 90 °C overnight. After cooling, the mixture was diluted with EtOAc (10 mL). The organic layer was washed with 5% K_2CO_3 (10 mL * 3) and was dried over Na_2SO_4. After the volatiles were removed under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent hexanes:EtOAc 10:1) to afford 209 mg (35% yield) of **2.56** as a brownish/yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 1.6 Hz, 1H), 8.61 (dd, *J* = 2.6, 1.6 Hz, 1H), 8.54 (d, *J* = 2.6 Hz, 1H), 7.94 – 7.91 (m, 1H), 7.67 – 7.59 (m, 1H), 7.59 – 7.50 (m, 2H), 3.70 (s, 3H).

Regrettably, molecule **2.56** decomposed prior to the completion of full characterization.



Methyl 2-(pyrimidin-2-yl)benzoate (**2.58**)

Molecule **2.58** was prepared via a slightly modified procedure from the literature.[159] An oven dried (120 °C) high pressure flask was shipped inside a glovebox under an inert nitrogen atmosphere. The flask was charged with 1,4-dioxane (8 mL), 2-chloropyrimidine (390 mg, 3.4 mmol), 2-(methoxycarbonyl)phenylboronic acid (500 mg, 2.8 mmol), KF (523 mg, 9.0 mmol) and $PdCl_2(PPh_3)_2$ (98.3 mg, 5 mol%). The vial was sealed and shipped

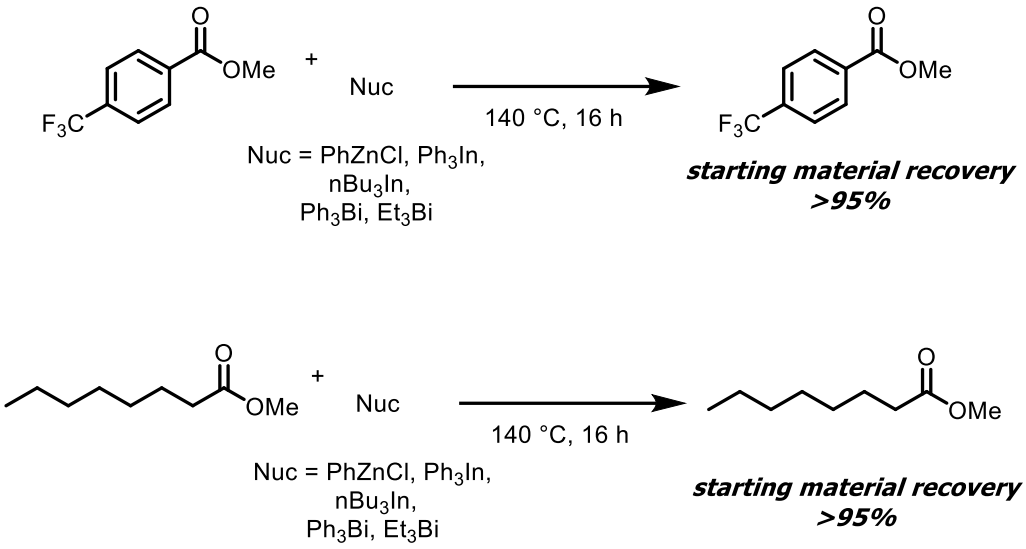
outside of the glovebox. The mixture was stirred at 90 °C overnight. After cooling, the mixture was diluted with EtOAc (10 mL). The organic layer was washed with 5% K_2CO_3 (10 mL * 3) and was dried over Na_2SO_4. After the volatiles were removed under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent hexanes:EtOAc 10:1) to afford 156.5 mg (26% yield) of **2.58** as a brownish/yellow oil. NMR spectra matched established literature.[164]

^{1}H NMR (400 MHz, CDCl3) δ 8.76 (d, *J* = 4.9 Hz, 2H), 8.00 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.69 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.55 (td, *J* = 7.6, 1.5 Hz, 1H), 7.48 (td, *J* = 7.5, 1.4 Hz, 1H), 7.18 (t, *J* = 4.9 Hz, 1H), 3.71 (s, 3H).

Background reactivity with organozincs, bismuth, indium:

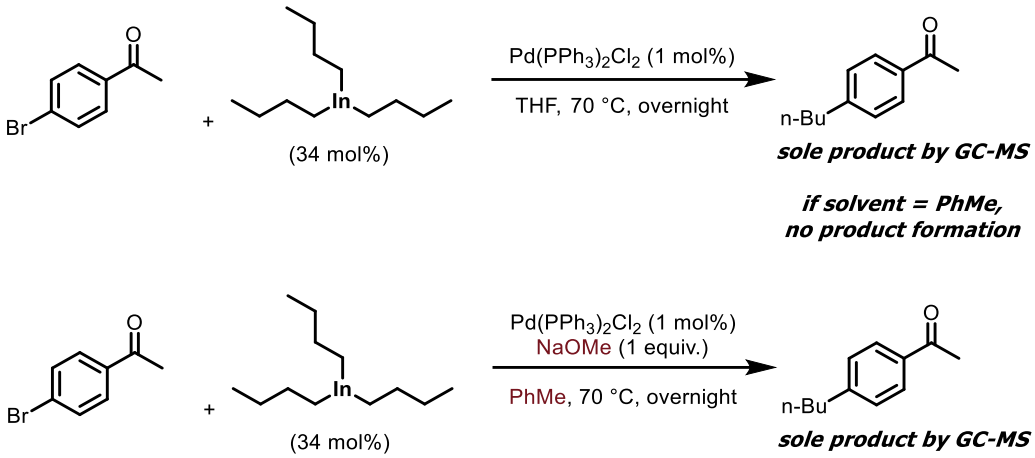
We were unfamiliar with the stability of our esters when reacted with organozinc, organobismuth, and organoindium reagents at high temperatures. Control reactions were run prior to the set up of the HTE plates in order to determine if background reactivity would be an issue (**Scheme 88**).

[164] Zhou, W.; Li, P.; Zhang, Y.; Wang, L. *Adv. Synth. Catal.* **2013**, *355*, 2343.



Scheme 88. Control reactions between methyl esters and organometallic reagents. Starting material recovery was assessed via ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard.

We reproduced existing literature reactions with the newly synthesized organometallic reagents to ensure that our syntheses were successful. When conducting benchtop reactions with the organoindium reagents, we noticed that reactivity would shut down when toluene was the solvent. This was problematic as toluene was the solvent of choice for the HTE plates. When using toluene, it was necessary to use NaOMe as a promotor to enhance the reactivity of the organoindium reagents (**Scheme 89**).



Scheme 89. Benchtop reactions with nBu_3In suggesting that the use of NaOMe is necessary.

2.6.5: Table of reagents for HTE plates

Entry	Compound	Molecular weight (g/mol)	Density (g/ml)	Amount (mg)	Mmol	Equiv.
1	Methyl 4-(trifluoromethyl)benzoate	204.15	1.268	10	0.0490	1
2	$Ni(cod)_2$	275.05	-	1.35	0.00490	10 mol%
3	IPr • HCl	425.06	-	6.25	0.147	30 mol%
4	KO^tBu	112.21	-	1.65	0.0147	30 mol%
5	Dcype	398.42	-	2.93	0.00735	15 mol%
6	PCy_3	280.43	-	2.75	0.00980	20 mol%
7	1,10-phenanthroline	180.21	-	1.77	0.00980	20 mol%
8	KF	58.10	-	5.70	0.0980	2
9	Cs_2CO_3	325.82	-	31.92	0.0980	2
10	DIPEA	129.25	0.742	12.7	0.0980	2
11	Ph-B(nep)	190.05	-	13.96	0.0735	1.5
12	Ph_3Bi	440.3	-	11	0.0250	0.51

13	Et_3Bi	296.16	-	14.5	0.490	1
14	PhZnCl	177.94	-	176.8 µL	0.490	1
15	EtMgCl	88.82	-	44.1 µL	0.490	1
16	nBuLi	64.06	-	30.24 µL	0.490	1
17	$Ph_2Si(OMe)_2$	244.365	-	17.95	0.0735	1.5
18	n-hex-$B(OH)_2$	129.99	-	9.55	0.0735	1.5
19	$AlCl_3$	133.34	-	9.80	0.0735	1.5
20	LiCl	42.394	-	4.15	0.0980	2
21	$ZnCl_2$	136.286	-	13.35	0.980	2

Table 3. Table of reagents for HTE plate 1. Note that volumes dispensed for PhZnCl, EtMgCl and nBuLi were based on the concentrations that were calculated after titration.

Entry	Compound	Molecular weight (g/mol)	Density (g/ml)	Amount (mg)	Mmol	Equiv.
1	Methyl 3-phenylpropionate	164.20	1.043	8.04	0.0490	1

Table 4. Table of reagents for HTE plate 2. Note that all reagents were identical to HTE plate 1 (**Table 3**) apart from the methyl ester.

Entry	Compound	Molecular weight (g/mol)	Density (g/ml)	Amount (mg)	Mmol	Equiv.
1	Methyl 4-(trifluoromethyl)benzoate	204.15	1.268	4.2	0.0205	1
2	Methyl octanoate	158.24	0.877	3.2	0.0205	1
3	$Ni(cod)_2$	275.06	-	0.563	0.00205	10 mol%
3	IPr • HCl	425.06	-	2.61	0.00614	30 mol%
4	KO^tBu	112.21	-	0.689	0.00614	30 mol%
5	Dcype	422.61	-	1.73	0.00409	20 mol%
6	PCy_3	280.43	-	1.15	0.00409	20 mol%
7	1,10-phenanthroline	180.21	-	0.738	0.00409	20 mol%
8	$ZnCl_2$	136.3	-	4.19	0.0307	1.5
9	Cp_2ZrCl_2	292.32	-	8.98	0.0307	1.5
10	9-BBN-OMe	152.04	-	20.5 µL	0.0205	1
11	nBuLi	64.06	-	12.6 µL	0.0205	1
12	PhMgBr	181.31	-	25.6 µL	0.0205	1
13	EtMgCl	88.82	-	18.4 µL	0.0205	1
14	nBu_4Ge	301.094	0.93	6.17	0.0205	1
15	KF	58.1	-	1.19	0.0205	1
16	nBu_3In	286.17	-	40.7	0.00696	34 mol%
17	Ph_3In	346.14	-	57.05	0.00696	34 mol%
18	NaOMe	54.03	-	1.1	0.0205	1

Table 5. Table of reagents for HTE plate 3 largely focussing on in-situ nucleophile formation. Note that volumes dispensed for PhZnCl, EtMgCl and nBuLi were based on the concentrations that were calculated after titration. Reactions with 9-BBN OMe were done in dioxane instead of toluene. Reactions with nBu_4Ge were done in dioxane with KF.

Entry	Compound	Molecular weight (g/mol)	Density (g/ml)	Amount (mg)	Mmol	Equiv
1	methyl 1-methyl-1H-indole-2-carboxylate	189.21	-	18.92	0.1	1
2	2,2,2-trifluoroethyl benzoate	204.15	-	20.42	0.1	1
3	Methyl benzoylformate	164.16	1.155	16.42	0.1	1
4	Methyl 4-methoxyphenylacetate	150.18	1.066	15.01	0.1	1
5	$Ni(cod)_2$	275.06	-	2.75	0.01	10 mol%
6	IPr • HCl	427.06	-	8.54	0.02	20 mol%
7	KO^tBu	112.21	-	2.24	0.02	20 mol%
8	PCy_3	280.43	-	5.61	0.02	20 mol%
9	Dcype	422.61	-	4.23	0.01	10 mol%
10	1,10-phenanthroline	180.21	-	1.80	0.01	10 mol%
11	$PhSnBu_3$	367.2	1.125	73.44	0.2	2
12	Phenylacetylene	102.13	0.93	20.43	0.2	2
13	$PhSi(OEt)_3$	240.37	0.996	48.07	0.2	2
14	$HPPh_2$	186.19	1.07	37.24	0.2	2
15	$Ph\text{-}B(OH)_2$	121.93	-	24.39	0.2	2
16	Styrene	104.15	0.906	20.83	0.2	2
17	CsF	151.9	-	30.38	0.2	2
18	CuI	190.45	-	1.90	0.01	10 mol%
19	NEt_3	101.19	0.726	20.24	0.2	2
20	K_2CO_3	138.21	-	27.64	0.2	2
21	K_3PO_4	212.27	-	42.45	0.2	2

Table 6. Table of reagents for HTE plate 4 focussing on privileged esters.

2.6.6: Experimental procedures

General procedure for HTE experimentation

HTE was performed using 96-well plates equipped with 1.2 mL 8 x 40 mm glass vials. Mini magnetic stir bars were placed inside the glass vials. Non-soluble, air-stable solids were weighed out on the benchtop and added to their appropriate glass vials. The plate, now equipped with several air-stable solids was shipped into a glovebox under an inert nitrogen atmosphere. Inside the glovebox, stock solutions in the reaction solvent were prepared for non air-stable solids such $Ni(cod)_2$, dcype, PCy_3, etc. All other reagents that were soluble in the reaction solvent (esters, nucleophiles, bases) were similarly prepared as stock solutions and dispensed accordingly. All reactions were subsequently diluted up to 500 μL. The 96-well plate was subsequently sealed using 2 rubber gaskets, a PTFE sheet and screws. Once sealed, the plate was removed from the glovebox and heated at the appropriate temperature with stirring for 16 hours on a Heidolph magnetic stirrer/hotplate. After cooling down, the plate was opened and the internal standard 1,3,5-trimethoxybenzene as a stock solution in toluene was added. 15 μL aliquots were taken of each reaction mixture and passed through a short plug of silica gel with EtOAc as an eluent, making use of a chemically-resistant 96-well filtration plate to filter samples into a second 96-well plate. The filtrates were diluted to an appropriate concentration and underwent subsequent analysis by GC-MS. For any hits, crude yields were calculated by integration of the product peak relative to the internal standard. The reactions that provided hits were subsequently repeated on the bench top to ensure that they were reproducible.

Important note regarding HTE plate 3 which was primarily using nucleophiles formed in-situ: The reagents which would be attacked ($ZnCl_2$, 9-BBN-OMe, etc.) were added in excess relative to the nucleophile (PhMgBr, nBuLi, etc.). This was done to avoid background reactivity with the harsh organometallics and the esters. The nucleophile

precursors were allowed to stir together for 10 minutes, prior to the addition of other reagents to ensure that no harsh organometallic remained.

Scale-up reactions to confirm reproducibility on the bench top

A specific procedure will be given to provide adequate context. For other reactions, the appropriate amounts according to the table of reagents above were added. For set up of the plates, see **chapter 2**.

To an oven dried (120 °C) 8-mL Teflon screw cap vial was added a magnetic stir bar. The vial was then shipped inside a glovebox under an inert, nitrogen filled atmosphere. The vial was charged with $Ni(cod)_2$ (10 mol %, 2.75 mg), IPr • HCl (20 mol%, 8.54 mg), KO^tBu (20 mol%, 2.24 mg) and 250 μL of toluene. The metal and ligands were allowed to stir together for 10 min to promote ligation. Next, 2,2,2-trifluoroethyl benzoate (0.1 mmol, 20.42 mg), 4-methoxyphenylboronic acid (0.2 mmol, 30.39 mg) and K_3PO_4 were added. The reaction mixture was then diluted up to 500 μL of toluene. The vial was sealed, shipped outside of the glovebox and placed into a pre-heated silicone oil bath at 130 °C for 16 h. The reaction was then allowed to cool to room temperature and was subsequently quenched with the addition of 5 mL of ethyl acetate. The internal standard 1,3,5-trimethoxybenzene as a stock solution (0.05 M) in toluene was added. The crude reaction mixture was then filtered through a plug of silica gel with ethyl acetate. The filtrate was then concentrated using a rotary evaporator. The crude residue was subsequently analyzed by ^1H NMR in order to determine a yield.

General procedure for decarbonylative alkyl 9-BBN Suzuki-Miyaura coupling

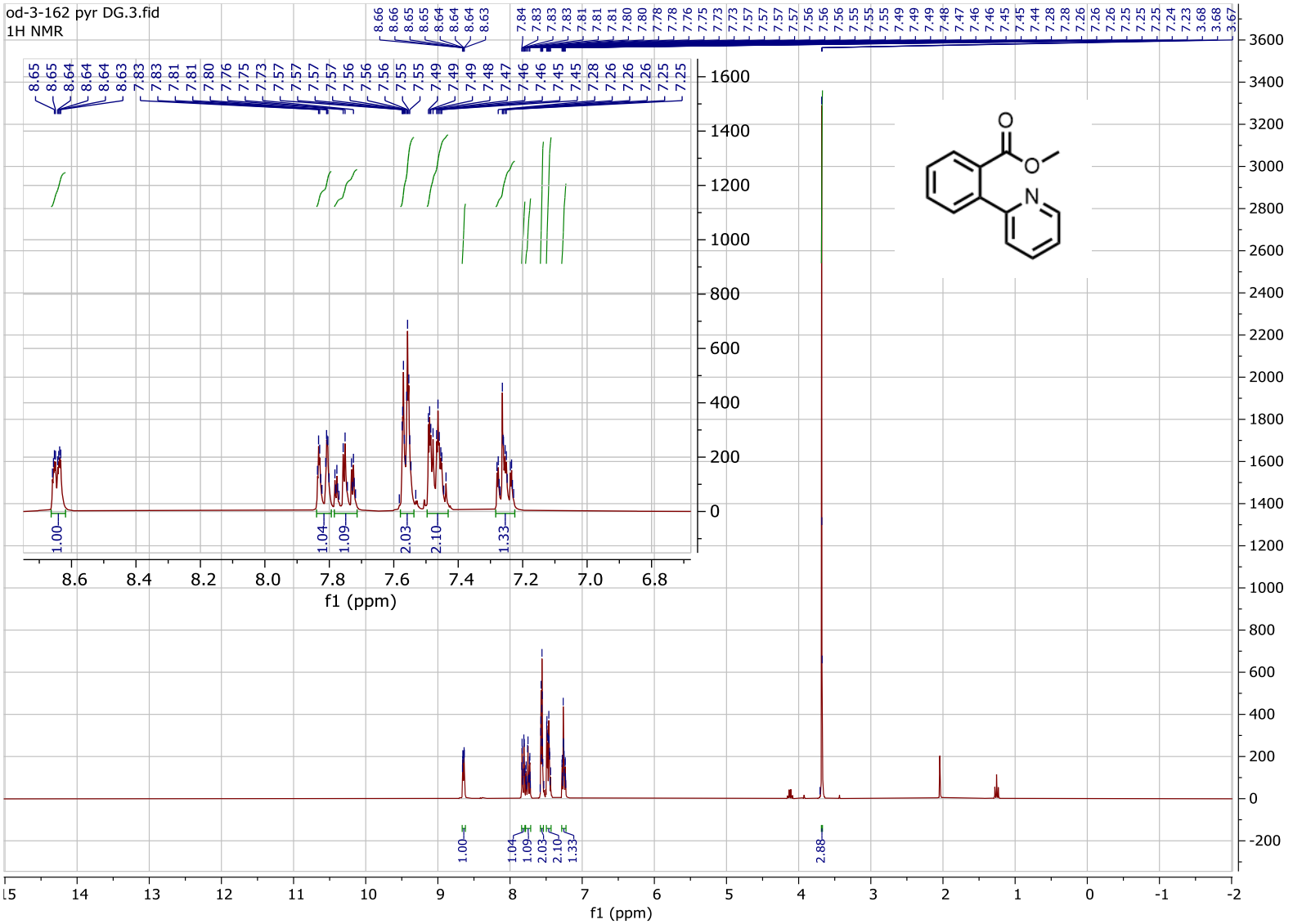
Alkyl-9-BBN reagents were prepared as reported in our ketone synthesis from methyl esters.[123] In a glovebox, an oven dried (120 °C) screw-capped 8 mL vial was charged with a magnetic stir bar, $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 10 mol%), IPr^{CPh3} • HCl (36.4 mg, 0.04

mmol, 20 mol%) and KO^{t}Bu (4.5 mg, 0.04 mmol, 20 mol%). Degassed toluene (1.6 mL) was then added and the catalyst mixture was stirred at rt for 20 min, after which a black solution is formed. Methyl ester (0.2 mmol), K_3PO_4 (85 mg, 0.4 mmol) and B-alkyl-9BBN reagent (0.4 mL, 0.4 mmol, 1.0 M) were then added successively. The vial was sealed with a Teflon-lined screw cap, shipped outside of the glovebox, and added to a pre-heated silicone oil bath at 130 °C for 16 h. The reaction was then allowed to cool to room temperature and quenched with 2 mL of water. A stock solution of 1,3,5-trimethoxybenzene in toluene (0.05 M) was added. Then, the reaction mixture was extracted with ethyl acetate (5 x 3 mL). An aliquot was taken of the crude reaction mixture and was passed through a plug of silica, and magnesium sulfate. The resulting filtrate was analyzed via GC. A 5-point calibration curve was used to determine the yield of the reaction.

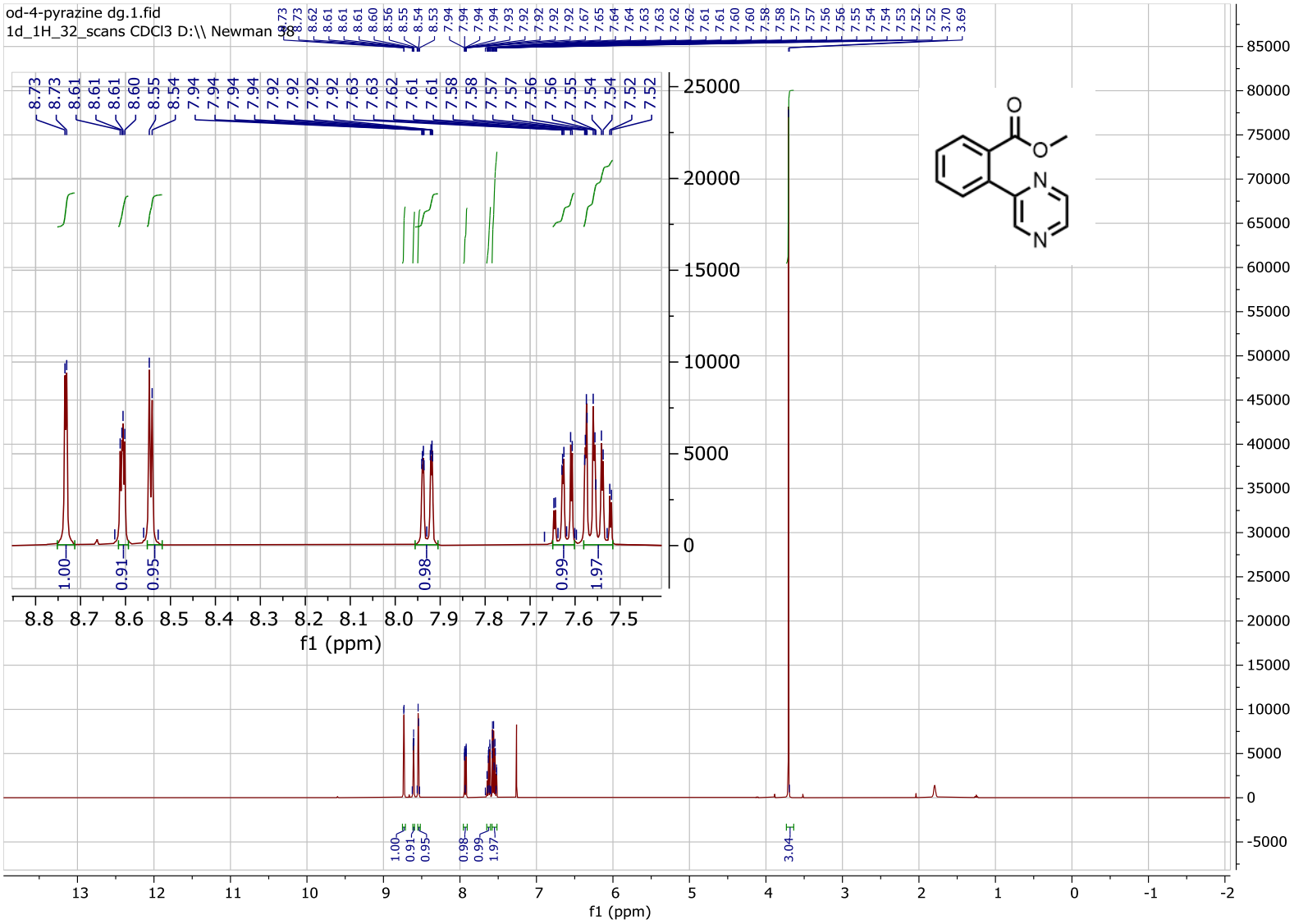
For some decarbonylative reactions in chapter 2, boronic acid (2 equiv.) was used in place of alkyl-9-BBN nucleophiles. The general procedure remained the same apart from the fact that these reactions were not analyzed via GC. Following quenching and work-up, the crude reaction mixture underwent ^{1}H NMR analysis to determine the yield of the reaction.

2.6.7: Copies of NMR spectra

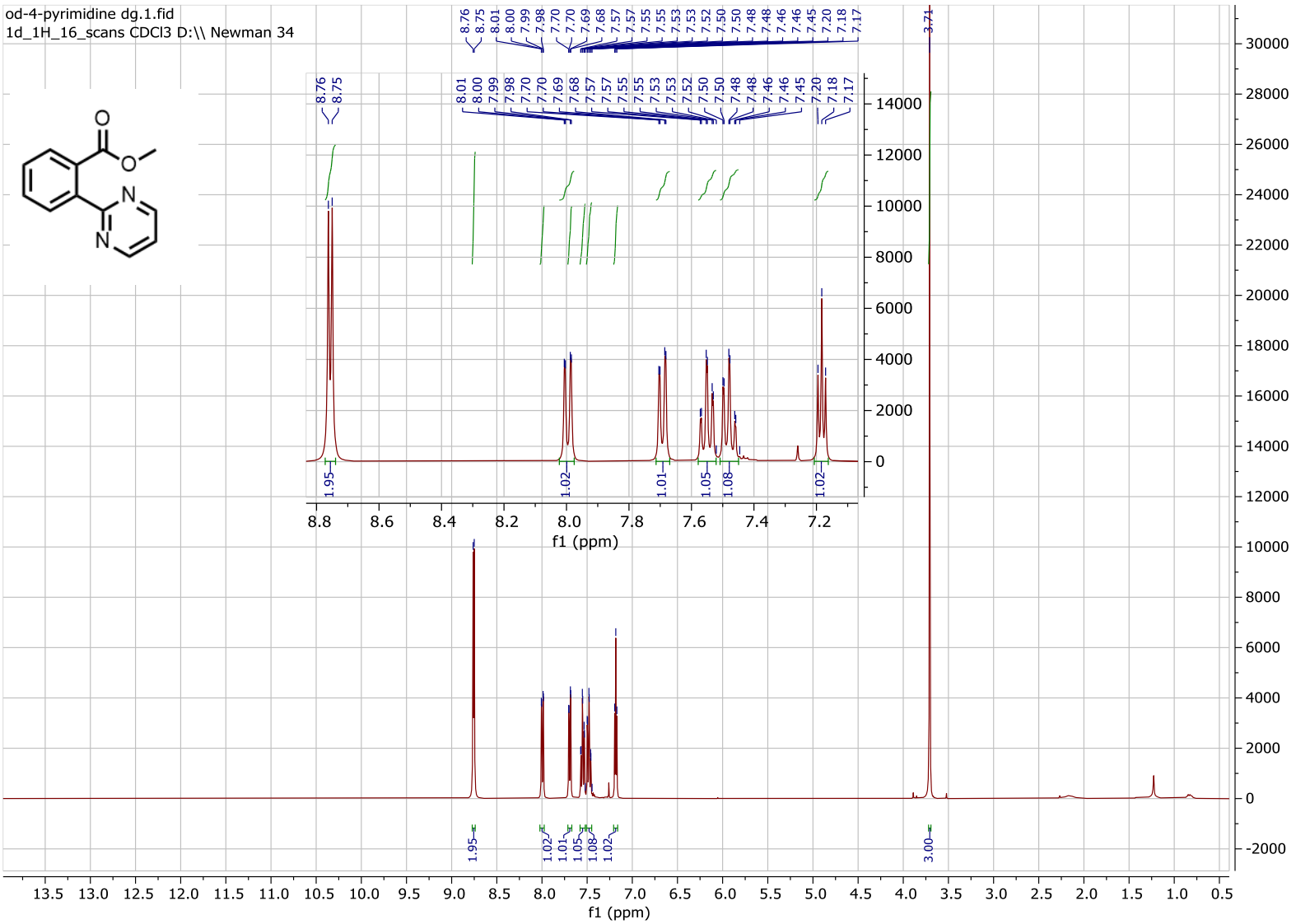
Methyl 2-(2-pyridinyl)benzoate (**2.53**) ($CDCl_3$, 300 MHz)



Pyrazin-2-ylbenzoic acid methyl ester (**2.56**) ($CDCl_3$, 400 MHz)



methyl 2-(pyrimidin-2-yl)benzoate (**2.58**) ($CDCl_3$, 400 MHz)



Chapter 3: Ni-catalyzed transesterification reaction

Note: The initial discovery of a Ni-catalyzed transesterification reaction was made by Taoufik Ben Halima and Jeanne Masson-Makdissi. This discovery is highlighted in ***scheme 92****. Initial optimization of the reaction was carried out by Honours student Émile Pinault-Masson. Second generation optimization was carried out by Jeanne Masson-Makdissi. The outcome from both rounds of optimization are summarized in* ***scheme 93****. The yields of product in* ***table 7*** *with Phos1 and NHC1 were obtained by Jeanne Masson-Makdissi and Dr. Yanlong Zheng via* ^{1}H *NMR analysis using 1,3,5-trimethoxybenzene as the internal standard.Starting material methyl (E)-4-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (molecule* ***3.40****) was synthesized by a previous lab member and was found among our lab's library of non-commercial methyl esters. Starting material Methyl 4-(N,N-dipropylsulfamoyl) benzoate (molecule* ***3.52****) was synthesized by a previous lab member and was found among our lab's library of non-commercial methyl esters. Dr. Yanlong Zheng's* ^{13}C *NMR data was used for (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl nicotinate (****molecule 3.5****) and (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl thiophene-3-carboxylate (****molecule 3.8****). Unless otherwise stated, all other results discussed in chapter 3 were obtained by me.*

3.1: Background on transesterification reactions

Fisher esterification is the acid-catalyzed reaction between a carboxylic acid and alcohol, which yields an ester and an equivalent of water. Carboxylic acids can occasionally present properties that may be unfavourable and can lead to the failure of the desired esterification reaction. The carboxylic acid may be insoluble in the desired organic media, it may not be readily available and moreover it is possible that the desired esterification reaction be contingent on anhydrous conditions.[165] To bypass these potential shortcomings, a transesterification reaction via the exchange of the alcohol components can be a viable alternative.

[165] Otera, J.; Nishikido, J. *Esterification methods, reactions, and applications*; Wiley-VCH: Weinheim, 2010.

Transesterification reactions can be facilitated by invoking the use of Brønsted acid/base or Lewis acid catalysis, which aid in lowering the transition state barrier of the reaction toward the products (**Scheme 90**). Although these methods have been well established in the primary literature, they suffer from several drawbacks.

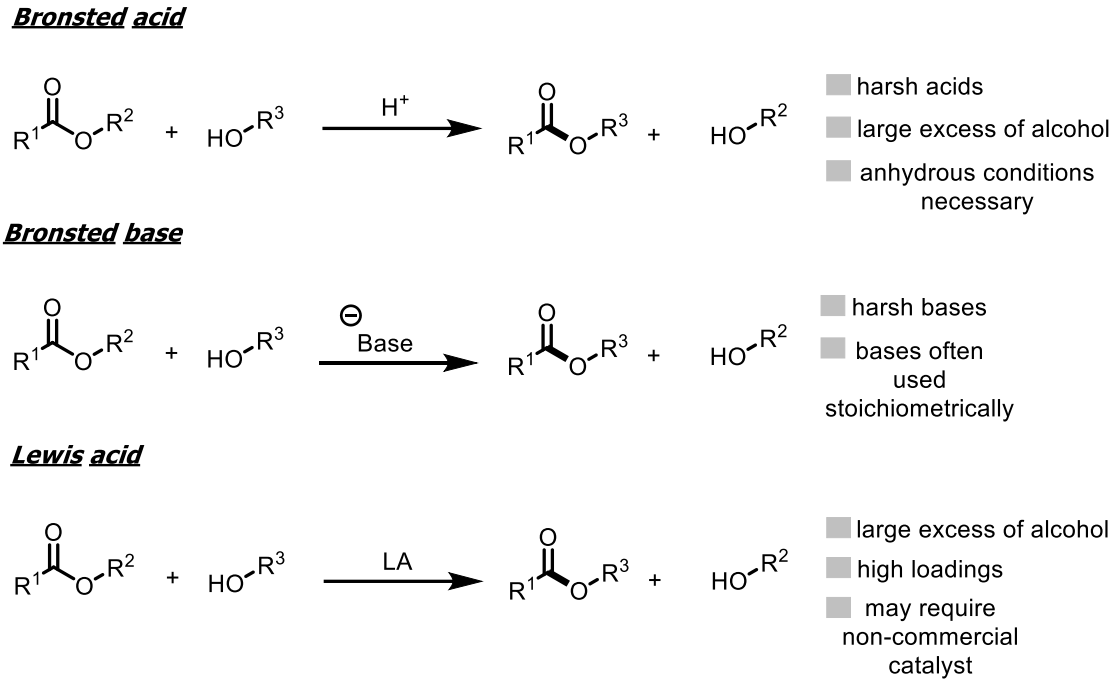
The Brønsted acids commonly applied towards transesterification are relatively harsh. This limits the scope of esters that can be successfully exposed to these conditions as those with acid-sensitive functionalities and racemizable protons will likely not be tolerated. These reactions are often run under anhydrous conditions as the presence of water can lead to the hydrolysis of the esters. For this reason, acids such as HCl cannot be easily used directly. Rather, they are often generated in situ by combining TMSCl with an alcohol.[166] Brønsted acid transesterification methods commonly call for the use of a large excess of alcohol, which can be particularly problematic if the alcohol is not readily available.

The Brønsted bases commonly used towards transesterification can be equally harsh. Much like with Brønsted acids, this limits the scope of compatible esters as those with base sensitive functionalities and racemizable protons will likely not be tolerated. Although a Brønsted base can catalyze a transesterification reaction, they are frequently used stoichiometrically in order to greatly accelerate the rate of reaction. Unlike acid-catalyzed methods, Brønsted base mediated transesterifications often do not require large excesses of alcohol.

Lewis acid catalysis can be a viable alternative to Brønsted acid/base chemistry for transesterification reactions. Although the conditions are often milder than those employed in Brønsted acid/base chemistry, they still often require a large excess of alcohol. Large loadings of Lewis acid are also relatively common. For highly specific

[166] Eras, J.; Llovera, M.; Ferran, X.; Canela, R. *Synth. Commun.* **1999**, *29*, 1129.

reactions such as enol ester acylation, powerful and efficient yttrium catalysts have been developed.[167] Occasionally, such as in the special circumstances of enol ester acylation, the Lewis acids required are not readily available and must be synthesized prior to use.



Scheme 90. Traditional approaches to transesterification

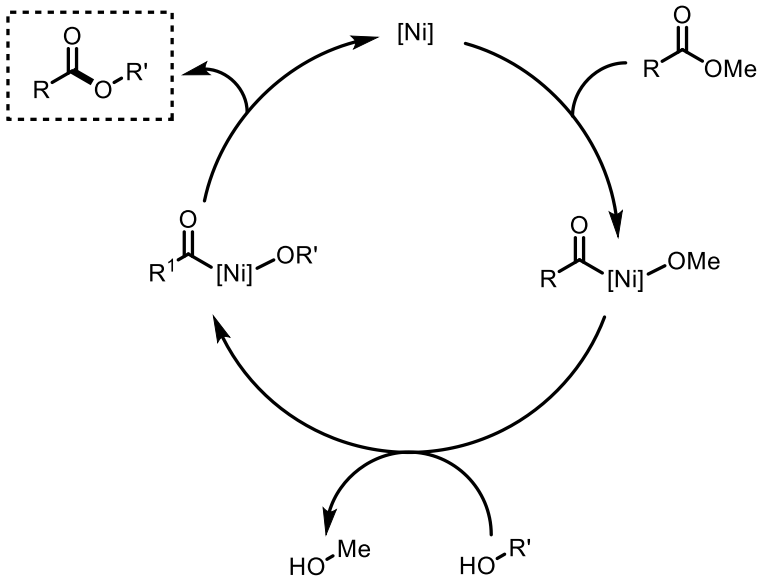
The aforementioned transesterification methods have been used routinely and studied extensively for several decades. The past two decades have seen the development of novel methods to perform transesterification reactions. In 2002, the Nolan group reported the NHC-catalyzed transesterification reaction of esters under mild conditions.[168] More recently, the power of enzymes (transesterases) has been expanded to be capable of catalyzing a diverse range of transesterification reactions.[169] The development of enzymes

[167] Lin, M.-H.; RajanBabu, T. V. *Org. Lett.* **2002**, *4*, 1607.
[168] Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583
[169] Winkler, C. K.; Schrittwieser, J. H.; Kroutil, W. *ACS Cent. Sci.* **2021**, *7*, 55

for these transformations can be highly beneficial as the enzyme can be engineered to be highly selective for specific ester and/or alcohol partners.

We envisioned that a transition metal-catalyzed transesterification of methyl esters could circumvent many of the issues plaguing the existing protocols **(scheme 91**). Relatively low quantities of alcohol could be used, high loadings of base/Lewis acid would be avoided, and acid/base sensitive functionalities could be tolerated, most notably alpha-epimerizable stereocentres. Most importantly, our method will be operating via a mechanistically distinct pathway from the existing protocols. A transition metal-catalyzed approach will not operate via traditional nucleophile and electrophile chemistry, and thus could have its own associated benefits and drawbacks.

The field of ester cross-coupling has seen many significant advances through the use of phenyl esters and related directing group containing esters (See **Chapter 1**).



Scheme 91. A Ni-catalyzed approach to transesterification

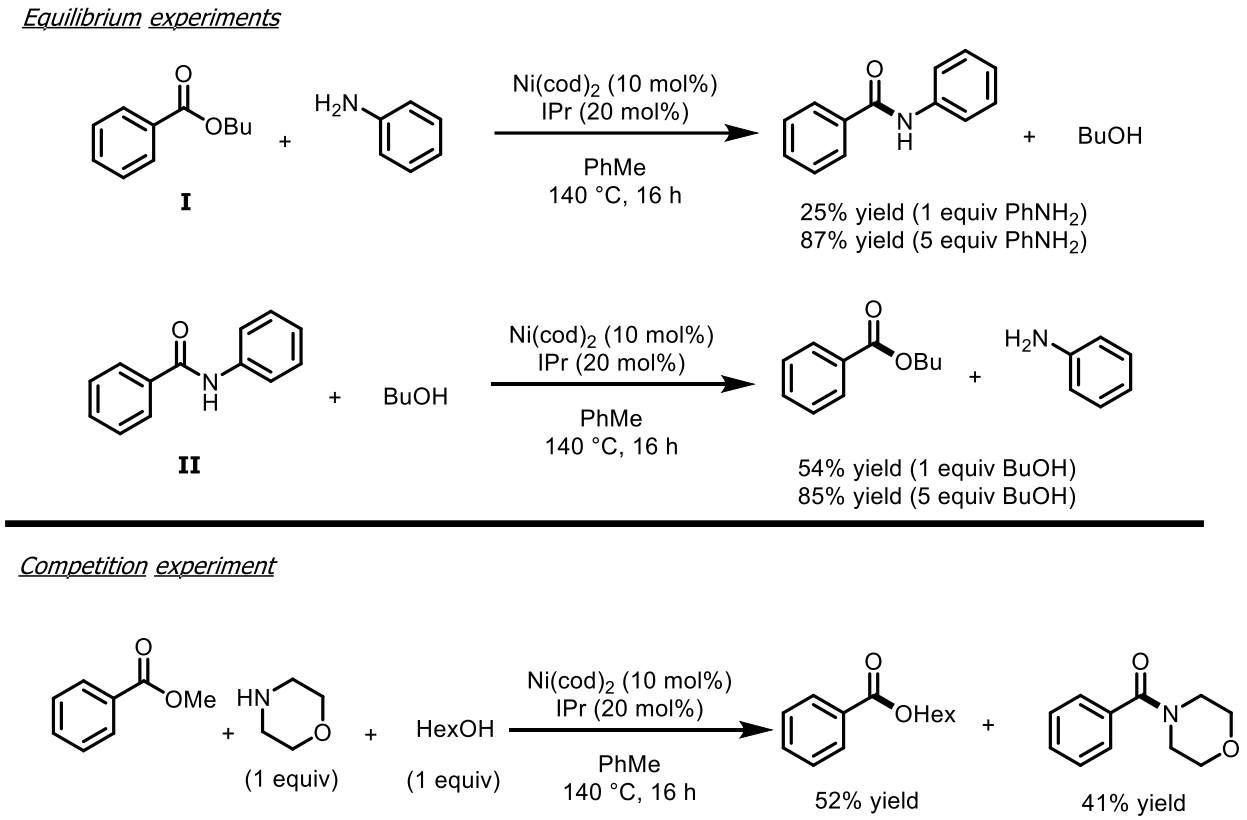
Simple methyl esters have a strong C(acyl)-bond relative to their phenyl ester counterparts and they lack any significant coordinating ability, thus the engagement of

methyl esters as cross-coupling electrophiles remains a noteworthy challenge. The first methyl ester cross coupling was reported by Garg and Houk in 2016 (see chapter 1, **section 1.3.4.1**), which successfully coupled 1-naphthyl esters with amines in the presence of a Ni-catalyst and $Al(O^tBu)_3$ to furnish amide products. Since then, modest advancements have been made in methyl esters cross-coupling, with nucleophiles being largely limited to amines. In developing a Ni-catalyzed transesterification reaction, we broaden the scope of available nucleophiles that can participate in coupling reactions with methyl esters. In developing this method, we would contribute valuable knowledge to the field in our efforts of reporting one of the sole additive free, intermolecular couplings of methyl esters.

3.2: Initial investigations of a Ni-catalyzed transesterification reaction

The possibility of Ni-catalyzed transesterification was realized by our group when Taoufik Ben Halima and Jeanne Masson-Makdissi conducted studies on Ni-catalyzed methyl ester amidation reactions (see chapter 1, **Scheme 56**). Equilibrium experiments were conducted with butyl benzoate **I** and benzanilide **II** (**Scheme 92**). When using butyl benzoate **I**, the desired amidation product is only provided in 25% yield. Running the reverse reaction by treating Benzanilide **II** with 1 equiv. of butanol (BuOH) under the reaction conditions is more efficient, providing butyl benzoate **I** in 54% yield. Both the forward and reverse reactions can be driven nearly to completion when using an excess of the nucleophilic coupling component, suggesting that the amine and alcohol compete in the coupling. Competition experiments were also conducted between methyl benzoate, morpholine and hexanol, which gave a mixture of the ester and amide products in 52%

and 41% yield, respectively. Overall, these results suggested that the reaction is reversible and that the reverse reaction, esterification, is more facile.

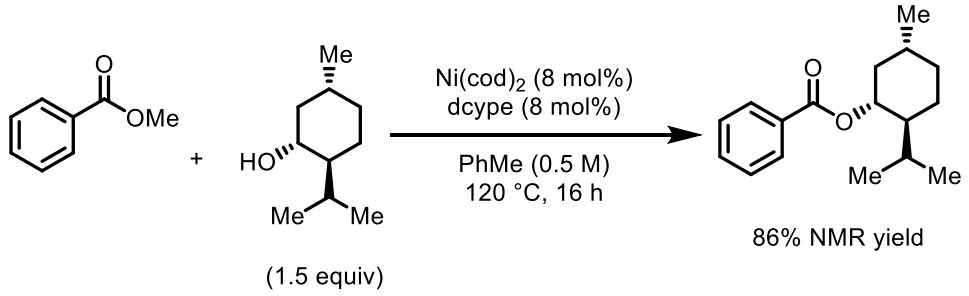


Scheme 92. Equilibrium and competition experiments suggesting esterification is feasible

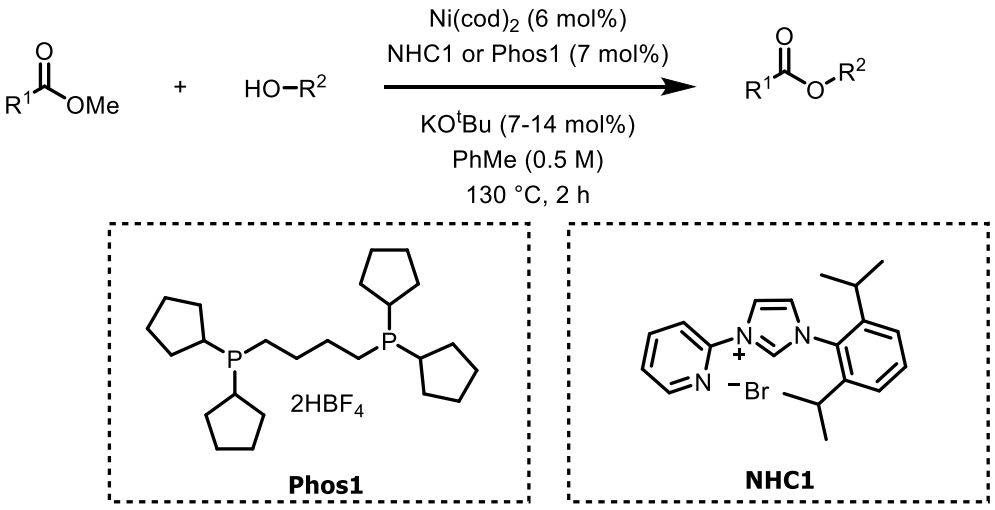
The initial efforts of optimizing this reaction were carried out by Honours student Émile Pinault-Masson. Dcype was identified as an effective ligand for this transformation. The optimized reaction conditions identified by Émile are shown below (**Scheme 93**). In order to overcome some scope limitations, Jeanne Masson-Makdissi conducted further optimization experiments by conducting thorough HTE studies. These studies also aimed to examine the performance of 16 different ligands in order to identify other high performing ligands apart from dcype. The HTE experiments demonstrated that dcype

was a consistent high performer; however, phosphine ligand **1** and NHC ligand **1** were identified as the ligands that performed the best, on average.

Generation 1 optimization



Generation 2 optimization



Scheme 93. Initial efforts of optimization of the transesterification reaction

With generation 2 optimized conditions in hand, our group aimed to explore the scope of this reaction. While conducting control experiments, it was discovered that the ligand and the KO^{t}Bu would lead to the formation of transesterification product. The KO^{t}Bu was required to release the free ligand in situ, however it was leading to background reactivity.

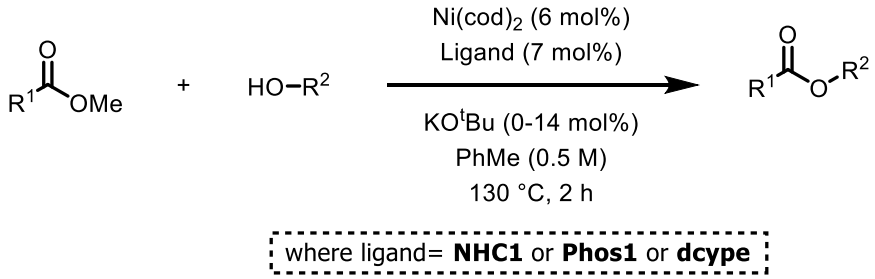
This issue of background reactivity had clear solutions. A simple and non-strenuous protocol of deprotonating **Phos1** and **NHC1** was required prior to engaging them for the transesterification. However, the use of NHCs could be problematic for this transformation as they have been known to catalyze transesterification reactions.[168] Another viable path to explore was the use of entirely base free conditions, where free ligands are used.

Of the two options, it seemed most reasonable for us to explore dcype as our model ligand yet again. When using dcype the need for base is obviated. Our group's previous data has consistently suggested that dcype was a relatively useful ligand for this transformation. Dcype is commercially available, whereas **NHC1** is not. In addition, the deprotonation of **Phos1** and **NHC1** may not have been straightforward.

This led us to repeat several successful couplings, but using dcype in place of **Phos1** or **NHC1**. When comparing several of the yields we obtained with dcype, we noticed that the yields were generally comparable to those obtained with **Phos1** or **NHC1** (**Table 7**) except in the case of entry 4 which provided only 35% yield of product. However, it is important to note that in the reactions where **Phos1** or **NHC1** were used there was some KO^tBu present. KO^tBu was not innocent in the reaction and would lead to some background base-catalyzed reactivity. **Phos1** and **NHC1** provided the product in entry 4 in excellent yields, whereas dcype simply provided trace product formation. This result was not entirely discouraging as perhaps a portion of the difference in reactivity can be attributed to the background base-catalyzed reaction.

Given the successful results obtained from Entries **1-3** in **Table 7,** we felt it was appropriate to be diligent and stress the parameters of the reaction. In doing so, we could determine if there was further optimization necessary. The model reaction for these studies was the reaction presented in entry **3**. Entries **1-2** were already providing near

quantitative yields of their respective products, making it difficult to observe any improvement in yields by deviating from the standard conditions.



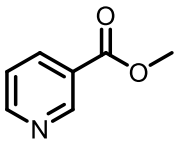
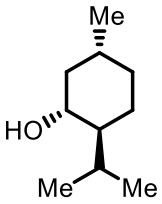
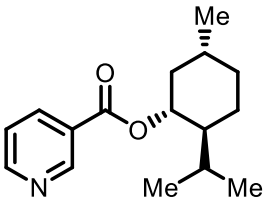
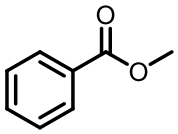
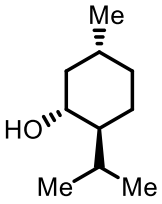
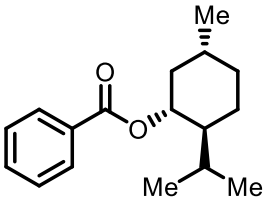
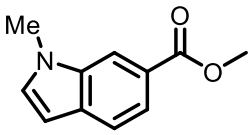
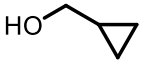
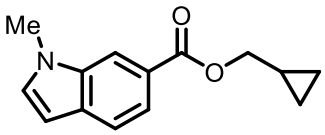
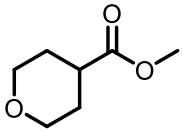
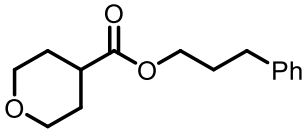
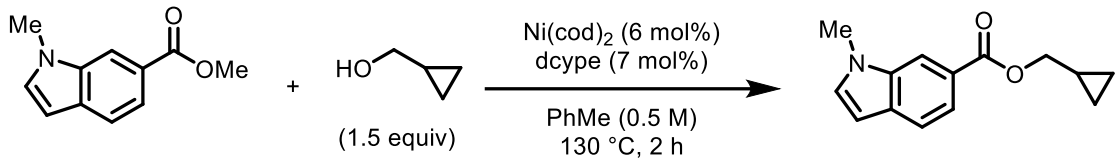
Entry	Starting ester	Starting alcohol	Product	Yield dcype[a] (%)	Yield Phos1 (%)	Yield NHC1 (%)
1				95%	75%	99%
2				95%	96%	91%
3				65%	61%	99%
4				35%	94%	90%

Table 7. Comparing the reactivity of dcype to Phos1 and NHC2 for established esterification reactions developed by our lab. General conditions [a]: as per the general procedure in section **3.6.5** [b]: Ester (0.2 mmol), alcohol (0.3 mmol), $Ni(cod)_2$ (3.3 mg, 6 mol%), **Phos1** (8.0 mg, 7 mol%) or **NHC1** (5.4 mg, 7 mol%), KO^tBu (7-14 mol%), PhMe

(0.4 mL) at 130 °C for 2 h, under inert atmosphere. [a]Yields were calculated by ^{1}H NMR using dibromomethane as the internal standard.

No deviation of the standard conditions affords the product in a 65% yield (**Table 8,** entry 1). Running the reaction with near equimolar quantity of alcohol results in a diminished yield (entry 2). Decreasing the concentration (entry 3) and changing the solvent to dioxane (entry 4) is less efficient. Lowering the temperature beneath the boiling point of toluene results in reduced yields of product (entry 5). We believe an efficient purge of methanol from the solution is necessary as a driving force to push the reaction forward, perhaps explaining why a high temperature of 130 °C is necessary. Lower catalyst loadings (entry 6) and an increased metal-to-ligand ratio (entry 7) result in diminished yields of product. Control reactions (entries 8 and 9) demonstrated that the catalyst system of Ni/dcype was necessary for a productive reaction to take place.



Entry	Deviation from standard conditions	Yield of product (%)
1	none	65
2	1.1 equiv alcohol	28
3	0.2 M concentration	37
4	dioxane (0.5 M)	25
5	100 °C	30
6	3 mol% $Ni(cod)_2$, 3.5 mol% dcype	Trace
7	12 mol% dcype	15
8	$Ni(cod)_2$ without dcype	0
9	dcype without $Ni(cod)_2$	0

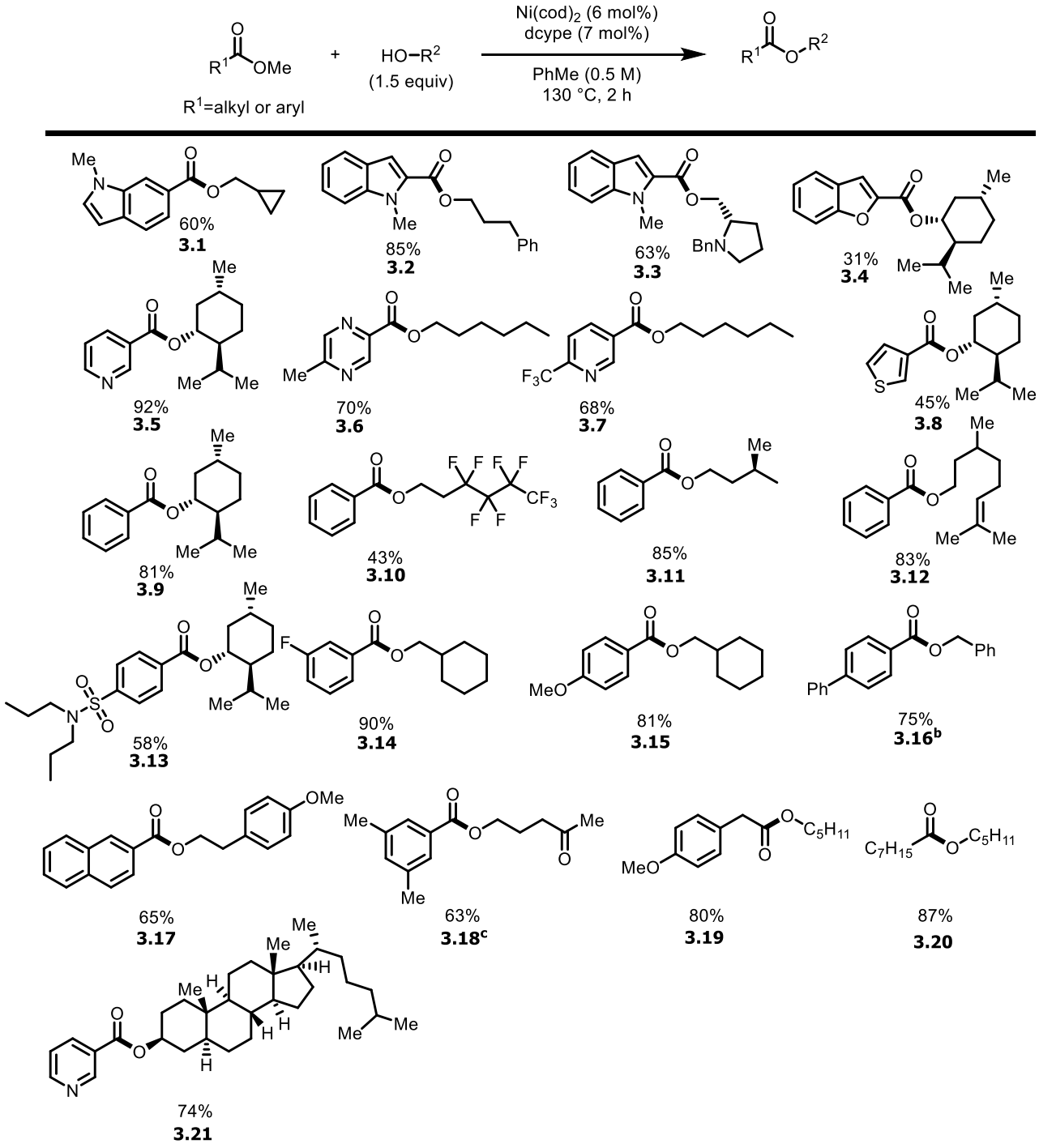
Table 8. Stressing the standard conditions of the esterification reaction. Reactions run on 0.2 mmol scale. Yields were calculated by ^1H NMR using dibromomethane as the internal standard. The remainder of the mass balance was largely starting material recovery.

The results from **Table 8.** suggested that the standard conditions were the optimized conditions. With optimized conditions in hand, we turned our attention to the reaction scope.

3.3: Scope of the Ni-catalyzed transesterification reaction

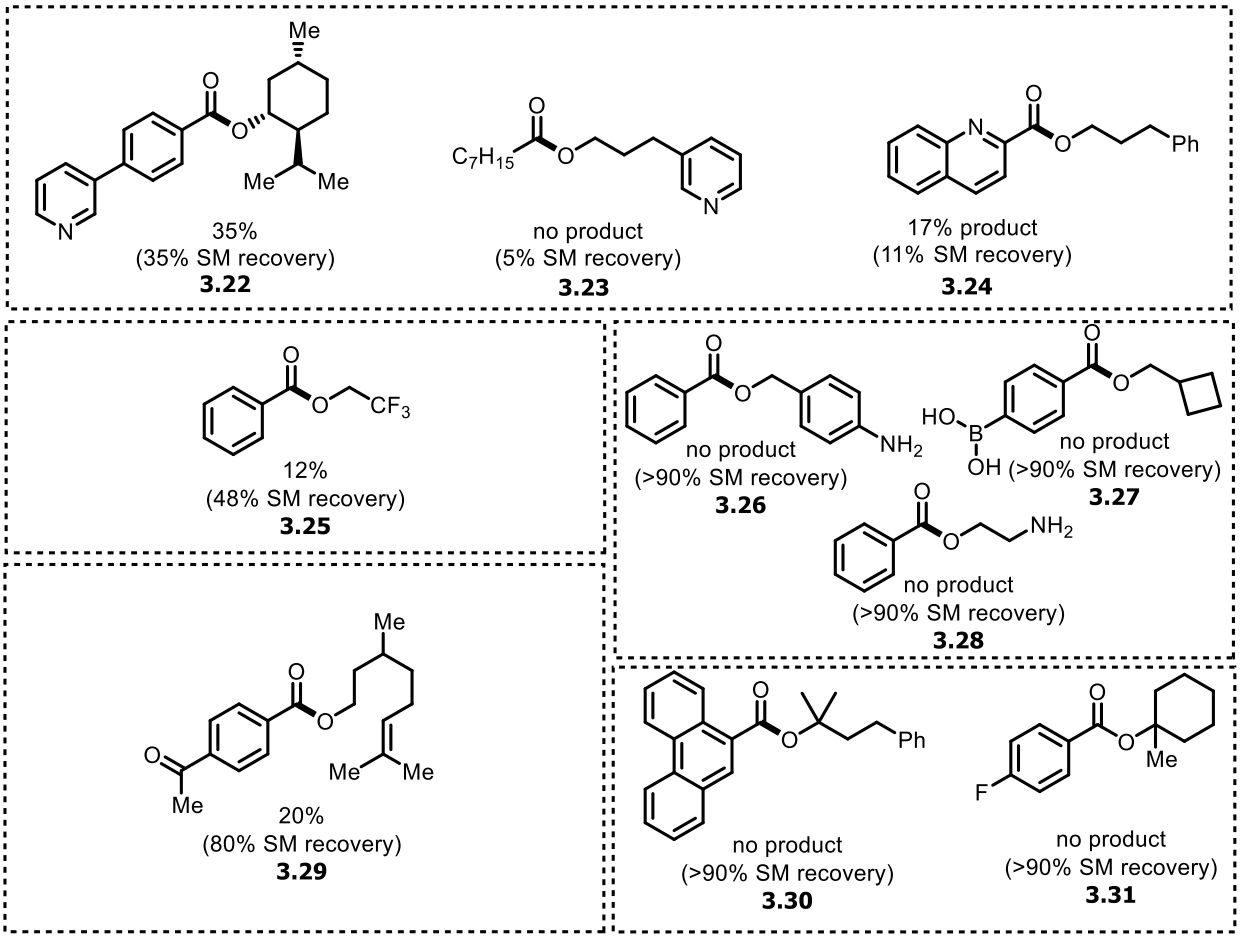
A scope table for this reaction is presented below in **Scheme 94.** A number of heteroaromatic esters seem to be well tolerated in this reaction (molecules **3.1-3.8**). The alcohol fragment was not limited to simple alkyl scaffolds as poly-fluorinated (**3.10**), alkenes (**3.12**) and ketones (**3.18**) could be tolerated. A variety of primary and secondary

alcohols were shown to be well tolerated under the reaction conditions. Electron-withdrawing and electron-donating (**3.13-3.15**) groups were also well tolerated on the esters. Interestingly, molecule **3.16** was synthesized using benzyl alcohol. This was a surprising result as the product of coupling between a benzylic alcohol and a methyl ester, is likely a more reactive ester relative to the methyl ester (See also **Scheme 95** for some failed scope examples). Although the majority of examples were α-sp^2 hybridized methyl esters, molecules **3.19** and **3.20** were α-sp^3 hybridized. Lastly, molecule **3.21** was coupled using a cholesterol derivate, demonstrating that this method could be useful for bioactive molecule synthesis.



Scheme 94. Scope table for a Ni-catalyzed transesterification reaction of methyl esters.[a] [a]General reaction conditions 0.2 mmol of ester, 0.3 mmol of alcohol, 6 mol% $Ni(cod)_2$, 7 mol% dcype, in anhydrous toluene (0.5 M). Reactions set up in glovebox under nitrogen. Reported yields are isolated. [b]Product contained inseparable benzyl alcohol contaminants. [c]Reported yield was obtained by ^1H NMR analysis with dibromomethane as the internal standard; product was not isolated.

While conducting studies to investigate the scope of this reaction, we noticed several trends among some of the failed scope examples (**Scheme 95**). These trends aided in identifying some scaffolds that likely could not be tolerated in this reaction. Heterocyclic esters **3.5-3.7** were well tolerated under the reaction conditions. The couplings of molecules **3.22-3.24** failed to provide product in a meaningful yield. The nitrogen atoms on molecules **3.5-3.7** are less Lewis basic than those found in molecules **3.22-3.24**. Strongly Lewis basic moieties are likely not well tolerated in this reaction. Molecule **3.10** was successfully synthesized in a modest yield by using a poly-fluorinated alcohol. A much simpler fluorinated alcohol provided just a 12% yield of product (**3.25**). This difference in reactivity can likely be attributed to the difference in boiling points of the two alcohols. 2,2,2-trifluoroethanol has a boiling point of 78 °C whereas 3,3,4,4,5,5,6,6,6-Nonafluoro-1-hexanol has a boiling point of 140-143 °C, which highlights the importance of the alcohol coupling partner being able to remain in solution. Molecules **3.26-3.28** were not observed under the reaction conditions. The presence of protic functional groups apart from an alcohol may have been the reason for unsuccessful couplings. Molecule **3.12** was synthesized in a relatively high yield, whereas molecule **3.29** was obtained in a low 20% yield. The presence of the para-ketone group greatly diminished the reactivity and led to a low yield of **3.29**. However, molecule **3.18** (see scope **Scheme 94**) tolerated a ketone on the alcohol fragment relatively well. These results suggested that on occasion, the specific combination of ester and alcohol can be critical to the success of the reaction. We have also failed to achieve successful coupling with tertiary alcohols, suggesting that they may be incompatible coupling partners (**3.30, 3.31**).



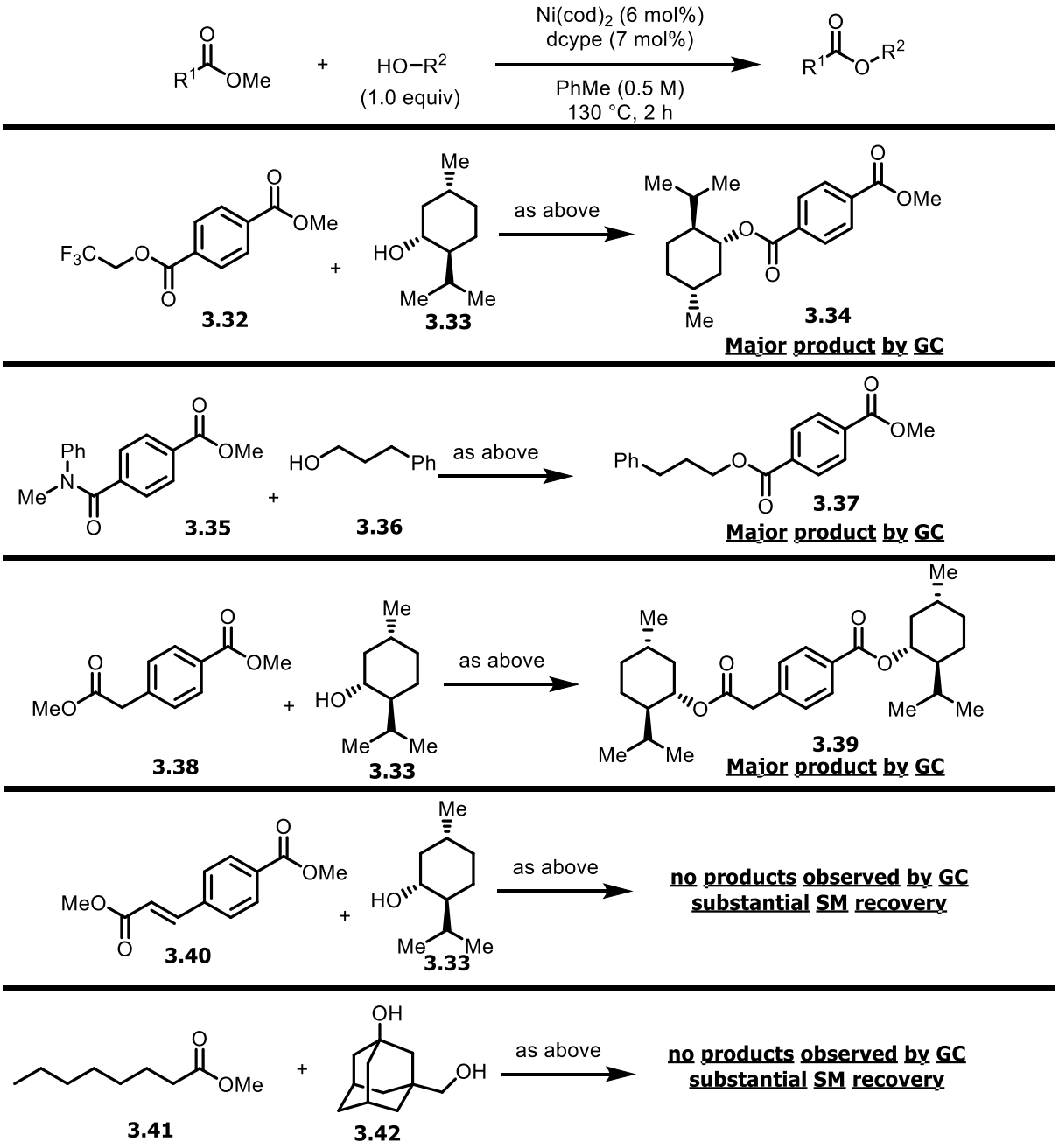
Scheme 95. Learning from some failed scope examples.[a] [a]General reaction conditions 0.2 mmol of ester, 0.3 mmol of alcohol, 6 mol% $Ni(cod)_2$, 7 mol% dcype, in anhydrous toluene (0.5 M). Reactions set up in glovebox under nitrogen. Reported yields and starting material recovery were calculated by ^1H NMR analysis using dibromomethane as the internal standard.

We also felt it was important to conduct chemoselectivity studies (**Scheme 96**) as we may observe interesting reactivity and further our understanding of this reaction. When molecule **3.32** was subjected to the reaction conditions, it led primarily to the formation of molecule **3.34**. The trifluoroethanol-derived ester seemed to react preferentially over the methyl ester. The product that arose from the selective reaction between the methyl ester and menthol **3.33** was only observed in trace yield. The product arising from the

functionalization of both esters (methyl ester and trifluoroethanol-derived ester) was also observed in a trace yield. When molecule **3.35** was subjected to the reaction conditions, it lead to the formation of molecule **3.37**, selectively reacting at the amide. No other products were observed. Molecule **3.38** contains two methyl esters. One being α-sp^2 hybridized, the other being α-sp^3 hybridized. This molecule has demonstrated interesting reactivity in some of our previous work, where selective coupling of each respective ester can be obtained based on the catalyst system and reaction conditions.[118, 123] Under the reaction conditions for Ni-catalyzed transesterification, the bis-functionalized molecule **3.39** is the sole product, suggesting that there is no selectivity between the α-sp^2 hybridized and α-sp^3 hybridized methyl esters. These results likely suggest that the catalyst system used in this transformation is generic for acyl type electrophiles and is not specific to methyl esters. Ni/dcype is a common catalyst system for phenyl ester activation (see chapter 1) as it is known to activate tough acyl electrophiles.

Molecule **3.40** bears two α-sp^2 hybridized methyl esters, one being aryl and the other alkenyl. We thought it would be interesting to probe whether our reaction conditions could preferentially react at one ester over the other, however the molecule was entirely unreactive under the reaction conditions. In our failed scope examples, we noticed that the use of tertiary alcohols did not lead to any product formation (**Scheme 95**). Alcohol **3.42** was used to investigate whether we could achieve selective coupling of primary alcohols in the presence of tertiary alcohols however there was no product formation.

Thus far, out data suggests the reaction is not selective between methyl esters and other similar acyl electrophiles. We have also failed to observe any selectivity between primary and tertiary alcohols.



Scheme 96. Reactions to investigate the chemoselectivity of the Ni-catalyzed transesterification reaction. General reaction conditions 0.2 mmol of ester, 0.2 mmol of alcohol, 6 mol% $Ni(cod)_2$, 7 mol% dcype, in anhydrous toluene (0.5 M). Reactions set up in glovebox under nitrogen. Reactions were quenched, filtered through a plug containing silica and celite and analyzed by GC-MS.

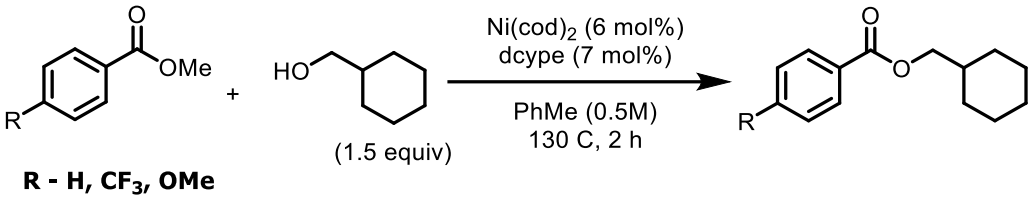
3.4: Preliminary reaction kinetics of the Ni-catalyzed transesterification reaction

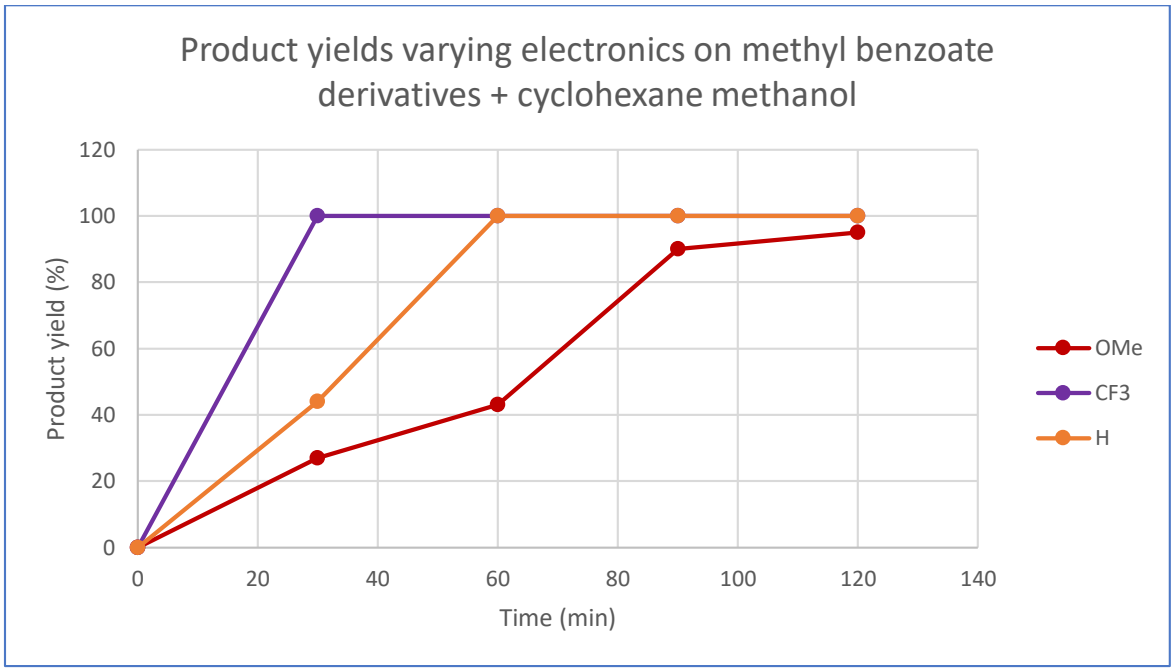
Methyl ester cross-coupling is a difficult transformation with few reports in the primary literature. There have been DFT studies (see Chapter 1) to support the proposed mechanisms of ester cross coupling however experimental evidence has remained elusive. The sole reports of experimental evidence can be attributed to the Shi group (See **Scheme 32**) and Sanford groups (see **Scheme 41**), who isolated acyl Ni(II) species. [67, 88] Although, it is important to note that the acyl Ni(II) species were derived from phenyl esters. The current methyl ester literature lacks experimental evidence to support the mechanisms that are believed to be in play.

In order to expand our understanding of the Ni-catalyzed transesterification, we deemed the study of the reaction kinetics to be a worthwhile goal. In the existing methyl ester literature, there is a lack of experimental kinetic data. If kinetic studies were successful, they would be a valuable addition of knowledge to the field of ester cross-coupling.

We explored the possibility of conducting Hammett studies to elucidate details on the rate-determining step of the mechanism. Our model reaction to attempt Hammett studies was the reaction with methyl 4-methoxybenzoate and cyclohexane methanol to yield product **3.15** (see **Scheme 94**) as it was high yielding and used readily available esters. Reactions were set up where R=H, CF_3 and OMe, with aliquots taken at times 30 min, 60 min, 90 min and 120 min (**Scheme 97**). What was observed was that the reactions where R=CF_3 or H went to completion rapidly, while the reaction where R=OMe lagged behind and seemed to take around 2 hours to approach completion. This was problematic as it suggested that much of the chemistry in the cases of R=CF_3 or H was occurring prior to the 60 min mark. Given that CF_3 was the faster of the two, we decided to take a closer look into this reaction, at time points of 5-15 min (**Table 9**) to determine if this reaction was amenable to Hammett parameter studies. The temperature was also dropped down

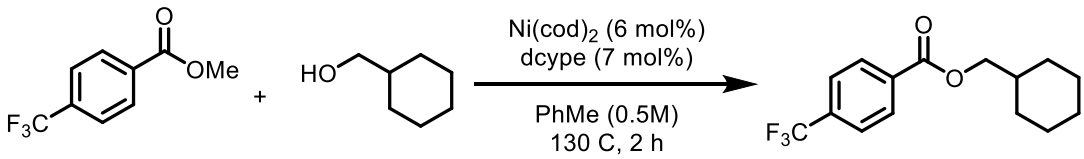
slightly to 115 °C to attempt to slow the reaction down, making it more facile for Hammett studies.





Scheme 97. Initial exploration of reaction kinetics with varying R groups on methyl benzoate. [a] [a]General reaction conditions 0.2 mmol of ester, 0.3 mmol of alcohol, 6 mol% Ni(cod)2, 7 mol% dcype, in anhydrous toluene (0.5 M). Reactions for each time point were set up in duplicate inside a glovebox under nitrogen. Reaction yields were determined by [1]NMR analysis with dibromomethane as the internal standard. The data for each time point is the average yield calculated from the duplicate reactions.

Dropping the temperature down to 115 °C seemed to have no effect on the overall yield of product (Entry 1). Nevertheless, within 10 min the yield of product was 64% meaning that this reaction was considerably fast and likely unable to provide high quality data for Hammett studies. We were successful in slowing down the reaction such that meaningful Hammett studies could be conducted by dropping the temperature down to 110 °C and halving the catalyst and ligand loadings (Entries 5-7). However, once the conditions in entries 5-7 were employed for methyl benzoate and Methyl 4-methoxybenzoate there was only trace product formation up to 15 min. The reaction was sufficiently slowed in the case of R= CF_3, but it was too slow in the case of R= H or OMe.



Entry	Change in conditions	Time point (min)	Yield of product
1	115 °C	120 (control)	98
2	115 °C	5	13
3	115 °C	10	64
4	115 °C	15	87
5	110 °C, 3 mol% Ni, 3.5 mol% dcype	5	2
6	110 °C, 3 mol% Ni, 3.5 mol% dcype	10	4
7	110 °C, 3 mol% Ni, 3.5 mol% dcype	15	12

Table 9. Examining the reaction R=CF_3 within the window of 15 min. [a] [a]General reaction conditions 0.2 mmol of ester, 0.3 mmol of alcohol, 6 mol% $Ni(cod)_2$, 7 mol% dcype, in anhydrous toluene (0.5 M). Reactions were set up inside a glovebox under nitrogen. Reported yields were calculated via ^1H NMR analysis using dibromomethane as the internal standard.

Thus far, the data suggested that CF_3 was too extreme of an electron withdrawing group. Other EWGs weaker than CF_3 could be placed on the aryl ring however the options were limited. Thus far, ketones have been problematic (See **Scheme 95,** molecule **3.29**), esters

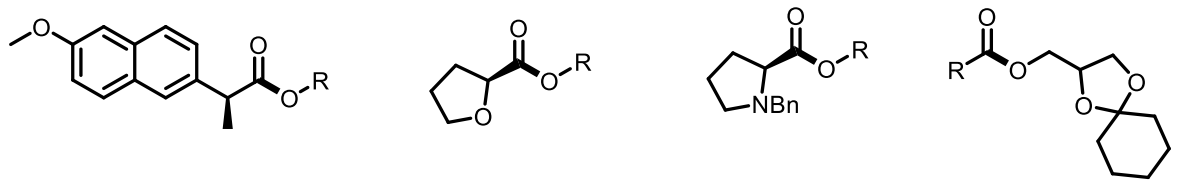
and amides are incompatible as they would react with the alcohol under the reaction conditions, and halogens apart from fluorine are also incompatible. There are several parameters yet to be investigated, which may also be helpful in slowing the reaction down such as changing the alcohol to a secondary alcohol. Due to time constraints, this endeavor remains incomplete.

3.5: Conclusions and future work

In conclusion, a novel base free Ni-catalyzed transesterification of methyl esters was developed based on precedence set by existing results from our group. This method is one of the sole additive free reports of intermolecular methyl ester cross-coupling, and the only report that uses alcohols as nucleophiles. A scope of 21 molecules was obtained with modest to excellent yields. During scope studies, we observed patterns and identified scaffolds that are likely incompatible with our reaction conditions such as tertiary alcohols and strong Lewis basic molecules. Chemoselectivity studies were conducted to gauge if the catalyst system of Ni/dcype was selective for methyl esters. Ultimately, it was observed that the catalyst system was promiscuous and struggled to selectively functionalize methyl esters in the presence of similar electrophiles such as amides and trifluoroethanol derived esters. Reaction kinetics were briefly explored in the context of Hammett studies. Under our current reaction conditions, the reaction may be too fast and not suitable for Hammett studies. A more exhaustive exploration of modified reaction conditions and various coupling partners is required to thoroughly determine if Hammett studies would be suitable for this reaction.

By the time we reached 20 isolated molecules for the scope, we were satisfied with the results for the time being and moved onto other areas. Due to time constraints, we were unable to revisit the scope and finish it. We aspired to have the last few scope examples highlight the benefit of a Ni-catalyzed transesterification reaction compared to more traditional acid/base catalyzed techniques (**Scheme 98**). The cross-coupling of

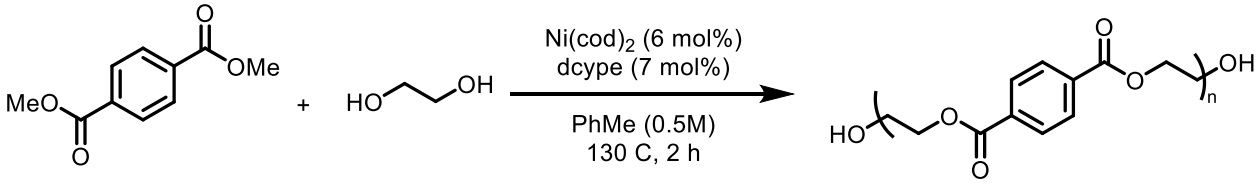
enantiopure esters would have been excellent in highlighting the advantage that our method has. The coupling of acid sensitive alcohol moieties would have also been highly interesting.



Scheme 98. Esters and alcohols to try

In 2020, the Sanford group reported an aryl amine synthesis via the decarbonylative cross-coupling between phenyl esters and silylated amines (See **Scheme 41**). [88] Notably, the catalyst system was identical to our transesterification reaction. Although we have never observed any hints of decarbonylated product, it would be certainly interesting to pursue if it was possible to form decarbonylated products as it could open up an entirely new class of molecules that can be synthesized. Using the precedence set by the Sanford group, it may be worthwhile to explore the coupling of silylated alcohols with methyl esters.

Lastly, it may be interesting to attempt couplings with poly-alcohols to observe if polymer formation could occur (**Scheme 99**).



Scheme 99. Polymer formation with poly-alcohol

3.6: Experimental section

3.6.1: General experimental details

Unless otherwise indicated, reactions were conducted under an inert atmosphere of nitrogen in 8 mL screw-capped vials that were oven dried (120 °C) prior to use. Column chromatography was performed manually using Silicycle F60 40-63 μm silica gel. Analytical thin layer chromatography (TLC) was conducted with aluminum-backed EMD Millipore Silica Gel 60 F254 pre-coated plates. Visualization of developed plates was performed under UV light (254 nm) and using $KMnO_4$.

3.6.2: Instrumentation

^{1}H, ^{13}C and ^{19}F NMR were recorded on a Bruker AVANCE 400 MHz spectrometer. ^{1}H NMR spectra were internally referenced to the residual solvent signal (e.g., $CDCl_3$ = 7.26 ppm). ^{13}C NMR spectra were internally referenced to the residual solvent signal (e.g., $CDCl_3$ = 77.16 ppm). Data for ^{1}H 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 ^{1}H NMR analysis of the crude reaction mixture using dibromomethane as an internal standard. Accurate mass data (EI) was obtained from an Agilent 5977A GC/MSD using MassWorks 4.0 from CERNO Bioscience. HRMS data was obtained from a MIcromass Q-TOF 2 quadrupole time-of-flight mass spectrometer with ESI source.

3.6.3: Materials

Organic solvents were purified by rigorous degassing with nitrogen before passing through a PureSolv solvent purification system. Low water content was confirmed by Karl Fischer titration (< 20 ppm for all solvents). Unless otherwise noted, starting materials and ligands were obtained commercially from Sigma Aldrich, Combi-Blocks or Strem chemicals and used as received.

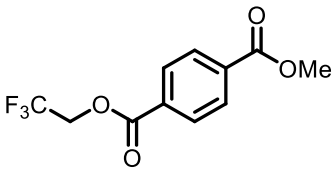
3.6.4: Starting material synthesis

The following starting material was synthesized according to a modified literature procedure:

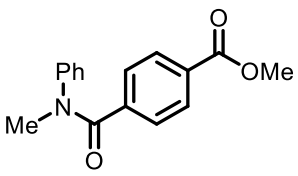
Methyl(2,2,2-trifluoroethyl)terephthalate(molecule **3.32**).[170]

The following starting materials were synthesized according to literature procedures:

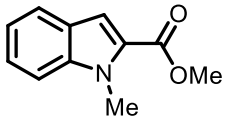
Methyl4-(methyl(phenyl)carbamoyl)benzoate(molecule **3.35**), [171] methyl 1-methyl-1H-indole-2-carboxylate(molecule **3.50**).[157]



3.32

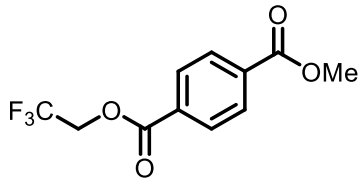


3.35



3.50

[170] Chen, J.; Namila, E.; Bai, C.; Baiyin, M.; Agula, B.; Bao, Y.-S. *RSC Adv.* **2018**, *8*, 25168.
[171] Huang, P.-Q.; Chen, H. *Chem. Commun.* **2017**, *53*, 12584.



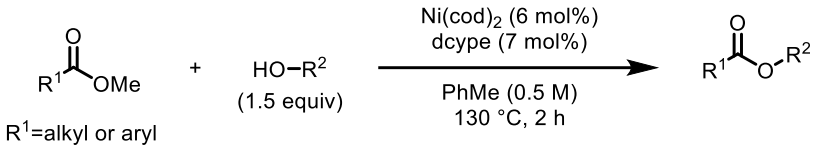
Methyl (2,2,2-trifluoroethyl) terephthalate (molecule **3.32**)

An oven dried (120 °C) round bottom flask was equipped with a magnetic stir bar, Monomethyl terephthalate (1 g, 5.6 mmol), 2,2,2-trilfluoroethanol (2.8 g, 28 mmol), DMAP (684 mg, 5.6 mmol) 1-ethyl-3-(3-dimethylaminopropyl)carbodiamide hydrochloride (5.4 g, 28 mmol) and NEt_3 (2.83 g, 28 mmol) in DCM (18.5 mL). The reaction mixture was stirred at room temperature overnight. The resulting mixture was quenched with H_2O and extracted with DCM (3 x 30 mL). The organic layers were combined and the volatiles were evaporated under reduced pressure. The crude mixture was purified by flash column chromatography (eluent system hexanes:EtOAc 5:1) to afford 476 mg of molecule **3.32** as a white solid (32% yield). NMR data is in accordance with established literature.[172]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 4H), 4.73 (q, *J* = 8.4 Hz, 2H), 3.96 (s, 3H).

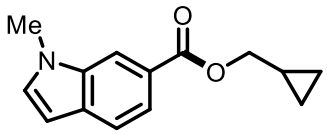
[172] Current Patent Assignee: JIANGXI NORMAL UNIVERSITY - CN108503549, 2018, A

3.6.5: General procedure and characterization for the Ni-catalyzed transesterification



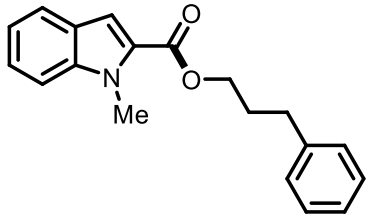
In a glovebox, an oven dried (120 °C) screw-capped vial was charged with a magnetic stir bar, $Ni(cod)_2$ (3.3 mg, 6 mol%), and dcype (5.9 mg, 7 mol%). Thoroughly degassed toluene (0.4 mL, 0.5 M) obtained from a solvent purification system was then added. Then, ester (0.2 mml) and alcohol (0.3 mmol, 1.5 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 (650 rpm) in a silicone oil bath at 130 °C for 2 hours. After cooling to room temperature, the reaction mixture was quenched with ethyl acetate and filtered through a plug containing silica gel and celite (10 mL of ethyl acetate eluent). The crude mixture was then concentrated under reduced pressure, analyzed by ^1H NMR, followed by purification via column chromatography.

3.6.6: Characterization for the Ni-catalyzed transesterification products



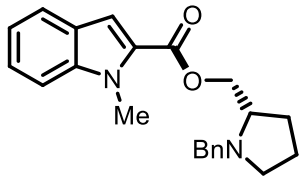
Cyclopropylmethyl 1-methyl-1H-indole-6-carboxylate (**molecule 3.1**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 8:1 hexanes:EtOAc to afford **3.1** as a brown solid (27.5 mg, 60% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.82 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.62 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.19 (d, *J* = 3.0 Hz, 1H), 6.51 (dd, *J* = 3.0, 0.9 Hz, 1H), 4.17 (d, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 1.36 – 1.21 (m, 1H), 0.67 – 0.55 (m, 2H), 0.42 – 0.34 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.9, 136.1, 132.1, 132.0, 123.5, 120.4, 120.3, 111.7, 101.3, 69.5, 33.1, 10.1, 3.3. **Accurate mass (EI)**: m/z calcd for $C_{14}H_{15}NO_2$: 229.1097; found 229.1062, spectral accuracy = 98.2 %



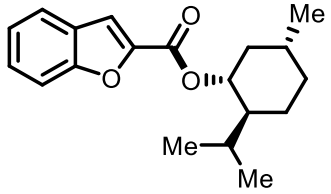
3-phenylpropyl 1-methyl-1H-indole-2-carboxylate (**molecule 3.2)** was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 10:1 hexanes:EtOAc to afford **3.2** as a red oil (49.9 mg, 85% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 1H), 7.41 – 7.36 (m, 2H), 7.34 – 7.29 (m, 3H), 7.26 – 7.21 (m, 3H), 7.17 (m, 1H), 4.35 (t, *J* = 6.5 Hz, 2H), 4.09 (s, 3H), 2.82 (t, *J* = 8.5, 2H), 2.19 – 2.03 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 162.3, 141.2, 139.7, 128.55, 128.52, 127.9, 126.1, 125.9, 125.03, 122.6, 120.6, 110.3, 110.2, 63.8, 32.3, 31.7, 30.4. **Accurate mass (EI)**: m/z calcd for $C_{19}H_{19}NO_2$: 293.1410; found 293.1451, spectral accuracy 98.9%.



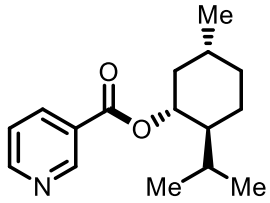
(S)-(1-benzylpyrrolidin-2-yl)methyl 1-methyl-1-H-indole-2-carboxylate (**molecule 3.3**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.3** as a light yellow oil (43.9 mg, 63% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dq, *J* = 8.0, 0.9 Hz, 1H), 7.44 – 7.20 (m, 8H), 7.13 (ddt, *J* = 8.2, 6.4, 1.6 Hz, 1H), 4.38 – 4.26 (m, 2H), 4.18 (d, *J* = 13.0 Hz, 1H), 4.08 (s, 3H), 3.47 (d, *J* = 13.0 Hz, 1H), 2.96 (qd, *J* = 8.0, 3.5 Hz, 2H), 2.42 – 2.21 (m, 1H), 2.10 – 1.95 (m, 1H), 1.88 – 1.61 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 162.2, 139.7, 128.9, 128.3, 127.8, 126.9, 125.9, 125.0, 122.6, 120.6, 110.27, 110.23, 62.2, 59.5, 54.5, 31.7, 28.6, 23.0. Note: Due to the frequency of the ^{13}C NMR, there are two missing peaks which are likely overlapping with other peaks. **HRMS** (ESI-TOF): m/z calcd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$: 349.1921, found 349.1912.



(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl benzofuran-2-carboxylate (**molecule 3.4**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.4** as a clear oil (18.6 mg, 31% yield)

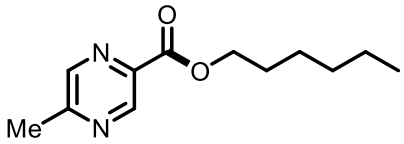
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.65 (m, 1H), 7.61 - 7.58 (m, 1H), 7.51 (d, *J* = 1.0 Hz, 1H), 7.44 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.32 – 7.27 (m, 1H), 5.00 (td, *J* = 10.9, 4.4 Hz, 1H), 2.18 – 2.11 (m, 1H), 2.01 – 1.91 (m, 1H), 1.79 – 1.70 (m, 2H), 1.64 – 1.51 (m, 2H), 1.28 – 1.07 (m, 2H), 0.96 – 0.90 (m, 7H), 0.82 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.4, 155.9, 146.1, 127.6, 127.2, 123.8, 122.9, 113.7, 112.5, 75.7, 47.3, 41.0, 34.4, 31.6, 26.6, 23.8, 22.2, 20.8, 16.6. **HRMS** (ESI-TOF): m/z calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$: 323.1628, found 323.1623.



(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl nicotinate (**molecule 3.5**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.5** as a colourless oil (48.1 mg, 92% yield). NMR data is in accordance with established literature.[173]

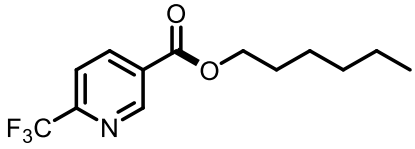
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.76 (s, 1H), 8.31 (s, 1H), 7.39 (s, 1H), 4.96 (td, *J* = 10.9, 4.4 Hz, 1H), 2.19 – 2.07 (m, 1H), 1.99 – 1.85 (m, 1H), 1.79 – 1.67 (m, 2H), 1.55 (m, 2H), 1.21 – 1.05 (m, 2H), 0.92 (t, *J* = 6.6 Hz, 8H), 0.79 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.8, 153.1, 150.8, 137.0, 75.5, 47.2, 40.9, 34.2, 31.4, 26.5, 23.6, 22.0, 20.7, 16.5.

[173] Dev, D.; Palakurthy, N. B.; Thalluri, K.; Chandra, J.; Mandal, B. *J. Org. Chem.* **2014**, *79*, 5420.



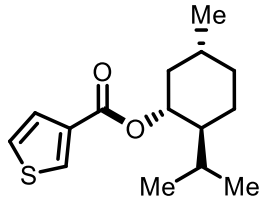
Hexyl 5-methylpyrazine-2-carboxylate (**Molecule 3.6**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 10:1 PhMe:EtOAc to afford **3.6** as a colourless oil (31.1 mg, 70% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 1.4 Hz, 1H), 8.58 (d, *J* = 1.4 Hz, 1H), 4.42 (t, *J* = 6.9 Hz, 2H), 2.66 (s, 3H), 1.85 – 1.76 (m, 2H), 1.49 – 1.25 (m, 7H), 0.93 – 0.83 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.3, 157.6, 145.3, 144.3, 140.8, 66.3, 31.4, 28.6, 25.5, 22.5, 21.9, 14.0. Note: Only the corresponding carboxylic acid was observed by mass spec, suggesting McLafferty rearrangement prevents observation of the molecular ion.



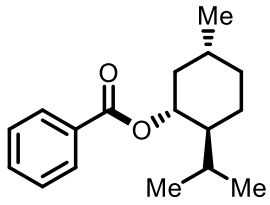
Hexyl 6-(trifluoromethyl)nicotinate (**molecule 3.7**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 10:1 hexanes:EtOAc to afford **3.7** as a colourless oil (37.4 mg, 68% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J*= 2.0 Hz, 1H), 8.47 (ddd, *J* = 8.1, 2.0, 0.8 Hz, 1H), 7.77 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.38 (t, *J* = 6.7 Hz, 2H), 1.78 (m, 2H), 1.44 (m, 2H), 1.33 (m, 4H), 0.95 – 0.84 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 163.5, 144.7 (q, *J* = 1300.2 Hz), 138.1, 128.3, 120.7 (q, *J* = 275.2 Hz), 119.6 (q, *J* = 2.8 Hz), 119.2, 65.6, 30.8, 28.0, 25.0, 22.0, 13.4. **^{19}F NMR (377 MHz, $CDCl_3$)** δ -68.27. Note: HRMS analysis within the John L. Holmes Mass Spectrometry Facility was unsuccessful.



(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl thiophene-3-carboxylate (**molecule 3.8**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 60:1 hexanes:EtOAc to afford **3.8** as colourless oil (24.0 mg, 45% yield). Spectral data was in accordance with established literature.[174]

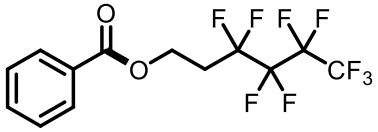
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.53 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.29 (dd, *J* = 5.1, 3.1 Hz, 1H), 4.87 (td, *J* = 10.9, 4.4 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.99 – 1.89 (m, 1H), 1.77 – 1.66 (m, 2H), 1.60 – 1.45 (m, 2H), 1.20 – 1.01 (m, 2H), 0.92 (m, 7H), 0.79 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** *δ* 162.3, 134.4, 132.3, 128.0, 125.8, 74.5, 47.2, 41.0, 34.3, 31.4, 26.5, 23.7, 22.0, 20.7, 16.6.



(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl benzoate (**molecule 3.9**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 10:1 hexanes:EtOAc to afford **3.9** as a colourless oil (42.2 mg, 81% yield). Spectral data is in accordance with established literature.[175]

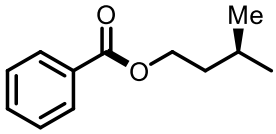
[174] Chen, H.; Farizyan, M.; Ghiringhelli, F.; van Gemmeren, M. *Angew. Chem. Int. Ed.* **2020**, *59*, 12213.
[175] Farizyan, M.; Mondal, A.; Mal, S.; Deufel, F.; van Gemmeren, M. *J. Am. Chem. Soc.* **2021**, *143*, 16370.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.01 (m, 2H), 7.59 – 7.50 (m, 1H), 7.46 – 7.41 (m, 2H), 4.94 (td, *J* = 10.9, 4.4 Hz, 1H), 2.19 – 2.09 (m, 1H), 2.01 – 1.92 (m, 1H), 1.79 – 1.68 (m, 2H), 1.66 – 1.49 (m, 2H), 1.18 – 1.05 (m, 2H), 1.01 – 0.86 (m, 7H), 0.80 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.1, 132.7, 130.9, 129.6, 128.3, 74.8, 47.3, 41.0, 34.3, 31.5, 26.5, 23.6, 22.1, 20.8, 16.5.



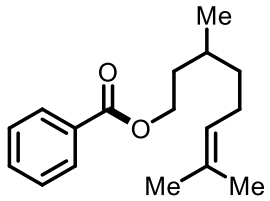
3,3,4,4,5,5,6,6,6-nonafluorohexyl benzoate (**molecule 3.10**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.10** as a colourless oil (31.7 mg, 43% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.01 (m, 1H), 7.63 – 7.54 (m, 1H), 7.50 – 7.41 (m, 1H), 4.63 (t, *J* = 6.4 Hz, 1H), 2.70 – 2.53 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.1, 133.3, 129.7, 129.5, 128.5, 56.8 (t, *J* = 4.5 Hz), 30.5 (t, *J* = 21.7 Hz). Note: The low signal:noise and multiplicity of fluorine-bearing carbons prevented identification of these atoms. **^{19}F NMR (377 MHz, $CDCl_3$)** δ -81.04 (tt, *J* = 9.1, 3.3 Hz), -113.75 – -133.87 (m), -124.4 – -124.57 (m), -125.91 – -126.12 (m). **Accurate mass (EI)**: m/z calcd for $C_{13}H_9F_9O_2$: 368.0453; found 368.0486, spectral accuracy 99.1%.



Isopentyl benzoate (**molecule 3.11**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.11** as a colourless oil (32.7 mg, 85% yield).

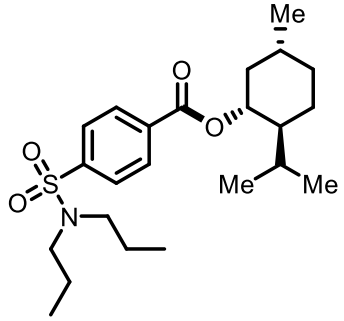
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.02 (m, 1H), 7.60 – 7.51 (m, 1H), 7.44 (m, 1H), 4.21 (dd, *J* = 10.7, 6.0 Hz, 1H), 4.13 (dd, *J* = 10.7, 6.6 Hz, 1H), 1.95 – 1.79 (m, 1H), 1.54 (m, 1H), 1.29 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 1H), 0.96 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.8, 132.9, 130.7, 129.7, 128.5, 69.7, 34.4, 26.3, 16.7, 11.44. **HRMS** (ESI-TOF): m/z calcd for $C_{12}H_{16}O_2Na$ $[M+Na]^+$: 215.1053, found 215.1048.



3,7-dimethyloct-6-en-1-yl benzoate (**molecule 3.12**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.12** as a colourless oil (43.2 mg, 83% yield). Spectral data is in accordance with established literature.[176]

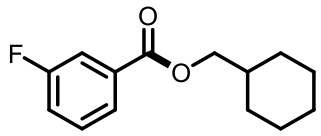
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 2H), 7.58 – 7.49 (m, 1H), 7.42 (m, 2H), 5.08 (m, 1H), 4.42 – 4.27 (m, 2H), 2.09 – 1.89 (m, 2H), 1.85 – 1.75 (m, 1H), 1.70 – 1.50 (m, 8H), 1.44 – 1.33 (m, 1H), 1.27 – 1.16 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.2, 132.3 132.2, 130.8, 129.0, 127.8, 124.0, 62.9, 36.4, 34.9, 29.0, 25.1, 24.8, 18.9, 17.1.

[176] Nikitas, N. F.; Apostolopoulou, M. K.; Skolia, E.; Tsoukaki, A.; Kokotos, C. G. *Chem. Eur. J.* **2021**, *27*, 7915.



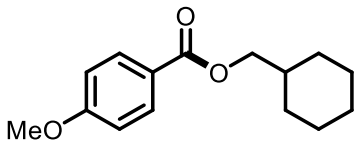
(1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl 4-(N,N-dipropylsulfamoyl)benzoate (**molecule 3.13**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.13** as a colourless oil (49.1 mg, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.13 (m, 2H), 7.92 – 7.85 (m, 2H), 4.95 (td, *J* = 10.9, 4.4 Hz, 1H), 3.32 – 3.18 (m, 4H), 2.18 – 2.06 (m, 1H), 1.93 (m, 1H), 1.81 – 1.67 (m, 6H), 1.57 (m, 2H), 1.18 – 1.03 (m, 2H), 1.00 – 0.85 (m, 7H), 0.79 (dd, *J* = 7.0, 3.5 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.9, 144.1, 134.2, 130.3, 127.1, 75.8, 50.1, 47.3, 41.0, 34.3, 31.6, 26.64, 23.7, 22.1, 20.9, 16.6, 11.3. **HRMS** (ESI-TOF): m/z calcd for $C_{23}H_{37}NO_4SNa$ $[M+Na]^+$: 446.2346, found 446.2341.



Cyclohexylmethyl 3-fluorobenzoate (**molecule 3.14**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.14** as a colourless oil (42.5 mg, 90% yield)

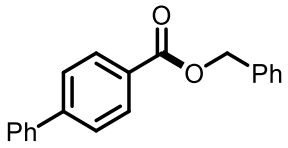
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.72 (ddd, *J* = 9.4, 2.7, 1.5 Hz, 1H), 7.41 (td, *J* = 8.0, 5.5 Hz, 1H), 7.30 – 7.20 (m, 1H), 4.14 (d, *J* = 6.3 Hz, 2H), 1.87 – 1.65 (m, 6H), 1.40 – 1.17 (m, 3H), 1.15 – 0.88 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 165.5 (d, *J* = 3.2 Hz), 163.8, 132.7 (d, *J* = 7.4 Hz), 128.0 (d, *J* = 7.8 Hz), 125.3 (d, *J* = 3.0 Hz), 119.9 (d, *J* = 21.3 Hz), 116.4 (d, *J* = 22.9 Hz), 70.4, 37.2, 29.7, 26.4, 25.7. **^{19}F NMR (377 MHz, $CDCl_3$)** δ -112.49. **HRMS** (ESI-TOF): m/z calcd for $C_{14}H_{17}FO_2Na$ $[M+Na]^+$: 259.1116, found 259.1110



Cyclohexylmethyl 4-methoxybenzoate (**molecule 3.15**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.15** as a colourless oil (40.2 mg, 81% yield). Spectral data is in accordance with established literature.[177]

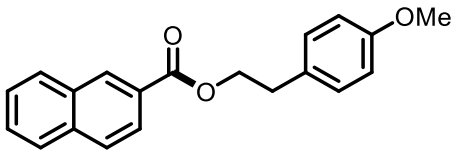
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.95 (m, 2H), 6.95 – 6.87 (m, 2H), 4.10 (d, *J* = 6.4 Hz, 1H), 3.85 (s, 3H), 1.88 – 1.64 (m, 6H), 1.36 – 1.13 (m, 3H), 1.12 – 1.00 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.5, 163.2, 131.5, 123.0, 113.6, 69.8, 55.4, 37.3, 29.8, 26.4, 25.7.

[177] Leng, L.; Ready, J. M. *ACS Catal.* **2021**, *11*, 13714.



Benzyl [1,1′-biphenyl]-4-carboxylate (**molecule 3.16**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 20:1 hexanes:EtOAc to afford **3.16** as a white solid (43.3 mg, 75% yield), which included inseparable benzyl alcohol contaminants. Spectral data is in accordance with established literature.[178]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.09 (m, 2H), 7.64 – 7.58 (m, 4H), 7.50 – 7.31 (m, 8H), 5.39 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.3, 145.8, 140.0, 136.1, 130.2, 130.1, 128.9, 128.6, 128.3, 128.19, 128.17, 127.3, 127.1, 66.7.

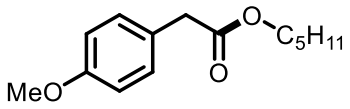


4-methoxyphenethyl 2-naphthoate (**molecule 3.17**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.17** as a white solid (39.8 mg, 65% yield). Spectral data is in accordance with established literature.[179]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.55 (s, 1H), 8.04 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.94 (d, *J* = 8.0, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.62 – 7.49 (m, 2H), 7.27 – 7.19 (m, 2H), 6.91 – 6.83 (m, 2H), 4.55 (t, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.07 (t, *J* = 7.0 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**

[178] Rout, S. K.; Guin, S.; Ghara, K. K.; Banerjee, A.; Patel, B. K. *Org. Lett.* **2012**, *14*, 3982.
[179] Yamane, M.; Ren, W.; Emi, A. *Synthesis* **2011**, *2011*, 2303.

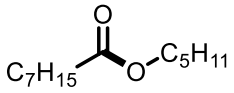
δ 166.1, 157.8, 135.0, 131.9, 130.5, 129.41, 129.38, 128.8, 127.65, 127.57, 127.2, 127.1, 126.0, 124.7, 113.4, 65.3, 54.7, 33.9.



Pentyl 2-(4-methoxyphenyl)acetate (**molecule 3.19**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 30:1 hexanes:EtOAc to afford **3.19** as a colourless oil (37.8 mg, 80% yield). Spectral data is in accordance with established literature.[180]

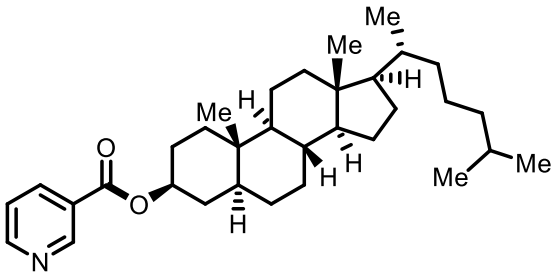
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.18 (m, 2H), 6.90 – 6.83 (m, 2H), 4.07 (t, *J* = 6.7 Hz, 2H), 3.79 (s, 3H), 3.55 (s, 2H), 1.68 – 1.56 (m, 2H), 1.38 – 1.22 (m, 4H), 0.93 – 0.84 (m, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 158.7, 130.4, 126.4, 114.0, 65.1, 55.3, 40.7, 28.4, 28.1, 22.4, 14.1.

[180] Sadeghian, H.; Attaran, N.; Jafari, Z.; Saberi, M. R.; Pordel, M.; Riazi, M. M. *Bioorg. Med. Chem.* **2009**, *17*, 2327.



Pentyl octanoate (**molecule 3.20**) was prepared according to the general procedure. The product was isolated via column chromatography using a solvent system of 50:1 hexanes:EtOAc to afford **3.20** as a colourless oil (37.3 mg, 87% yield). Spectral data is in accordance with established literature.[181]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (t, *J* = 6.7 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.68 – 1.55 (m, 4H), 1.37 – 1.22 (m, 12H), 0.94 – 0.83 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 174.1, 64.5, 34.5, 31.8, 29.2, 29.1, 28.5, 28.2, 25.1, 22.7, 22.4, 14.2, 14.1.



(3*S*,5*S*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl nicotinate (**molecule 3.21**) was prepared according to the general procedure. The product was isolated via column chromatography using a gradient of 30:1 to 20:1 hexanes:EtOAc to afford **3.21** as a light yellow solid (73.1 mg, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.74 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.27 (dt, *J* = 8.1, 1.9 Hz, 1H), 7.36 (dd, *J* = 7.9, 4.8 Hz, 1H), 5.00 – 4.89 (m, 1H), 2.05 – 1.88 (m, 2H), 1.87 – 1.58 (m, 5H), 1.58 – 1.42 (m, 4H), 1.35 – 1.20 (m, 10H), 1.12 – 0.95 (m, 9H), 0.89 – 0.83 (m, 14H), 0.65 – 0.60 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.8, 153.2, 150.9, 137.1, 126.8, 123.3,

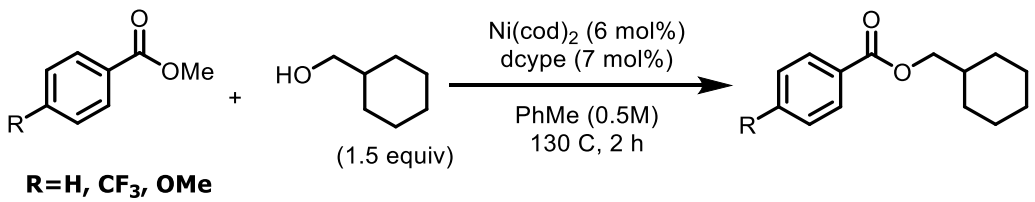
[181] Liu, J.; Shao, C.; Zhang, Y.; Shi, G.; Pan, S. *Org. Biomol. Chem.* **2014**, *12*, 2637.

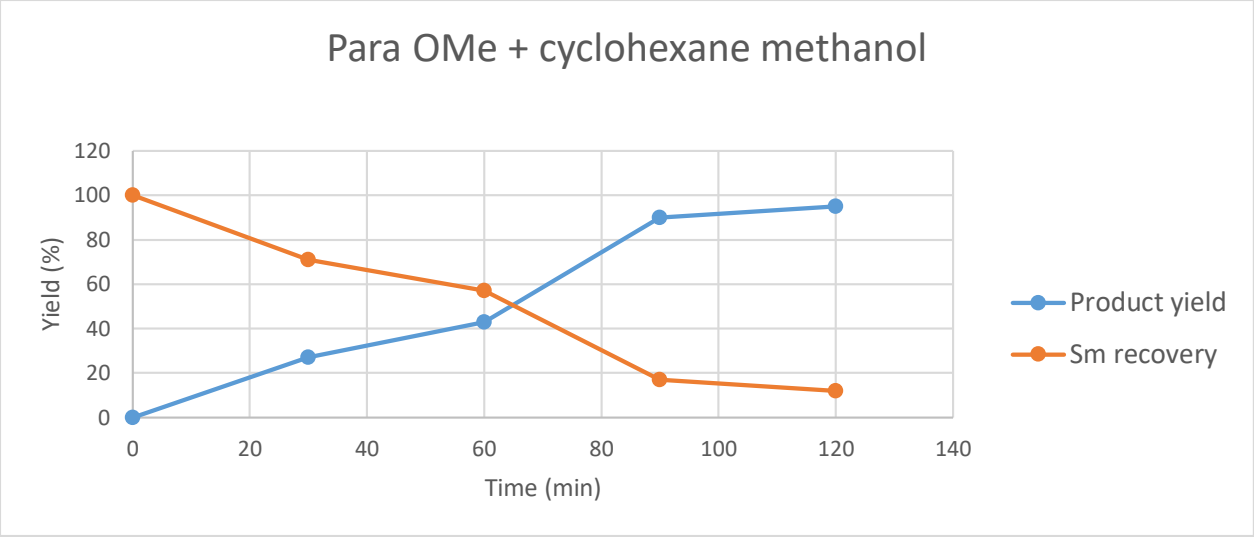
75.1, 56.5, 56.4, 54.3, 44.8, 42.7, 40.1, 39.6, 36.8, 36.3, 35.9, 35.59, 35.57, 34.1, 32.1, 28.7, 28.3, 28.1, 27.6, 24.3, 23.9, 22.9, 22.7, 21.3, 18.8, 12.4, 12.2. **HRMS** (ESI-TOF): Note: HRMS analysis within the John L. Holmes Mass Spectrometry Facility was unsuccessful.

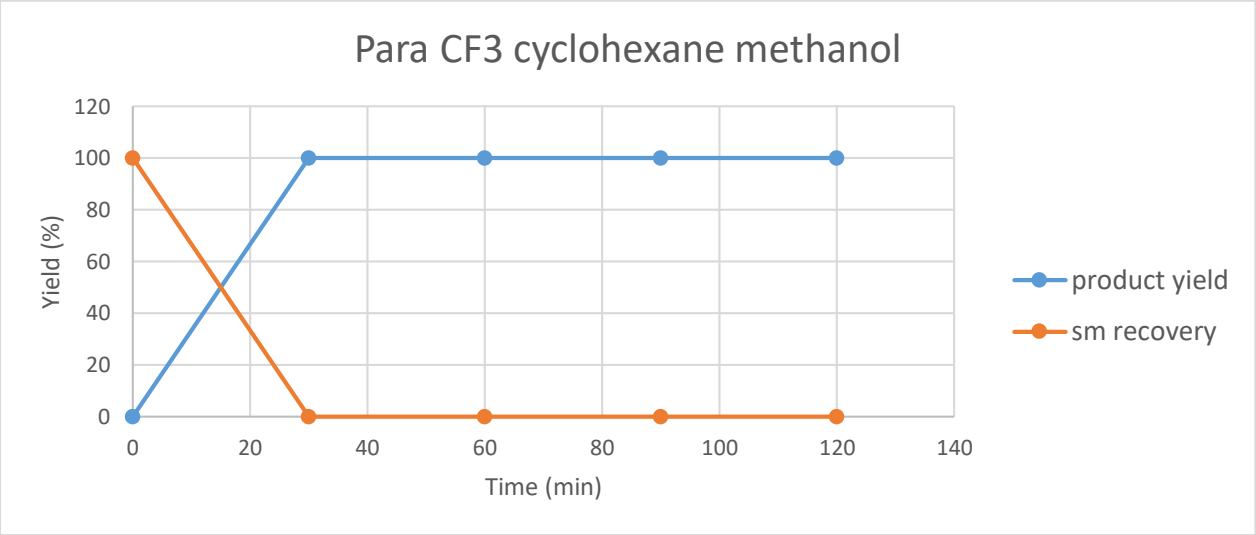
3.6.7: General procedure and data points for investigating the kinetics of the Ni-catalyzed transesterification reaction

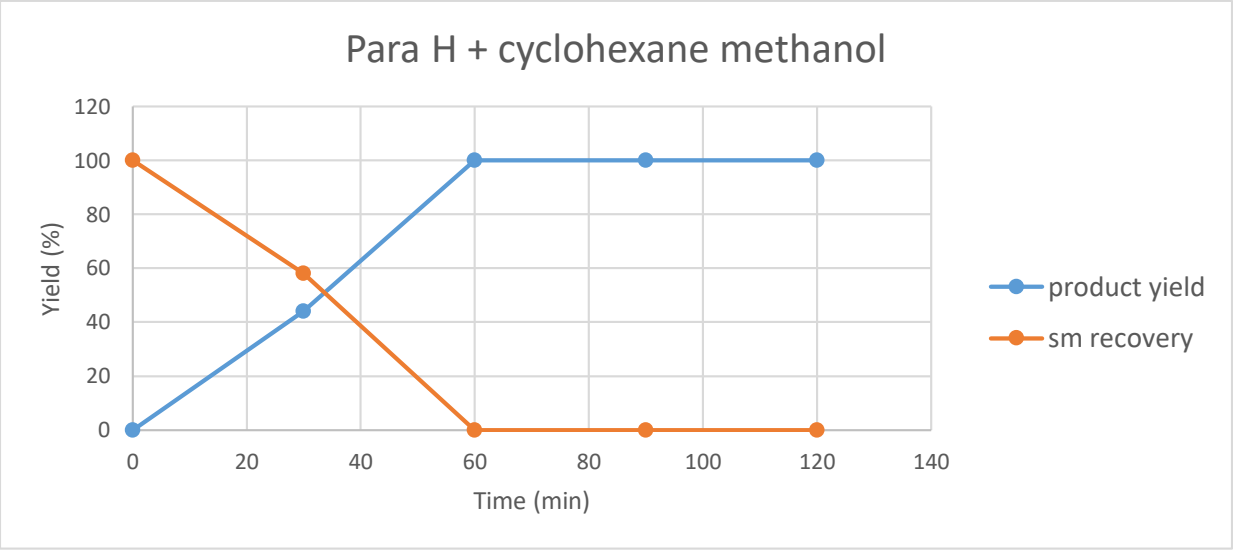
A traditional approach to kinetic sampling was avoided for the Ni-catalyzed transesterification reaction. The catalyst is highly sensitive to the atmosphere and only a few aliquots taken via needle through the Teflon line screw-cap would introduce enough oxygen to poison the catalyst. The kinetic monitoring reactions were also not run inside the glovebox due to the difficulty surrounding the logistics of heating the reaction at 130 °C reliably without fluctuation. Instead, the reaction was set up in duplicate as per the general procedure. To gather data from a time point, both reactions were quenched as per the general procedure and analyzed via ^{1}H NMR with dibromomethane as the internal standard. The average of the two time points was taken to generate the data.

The data used to generate **Scheme 97** can be found below.



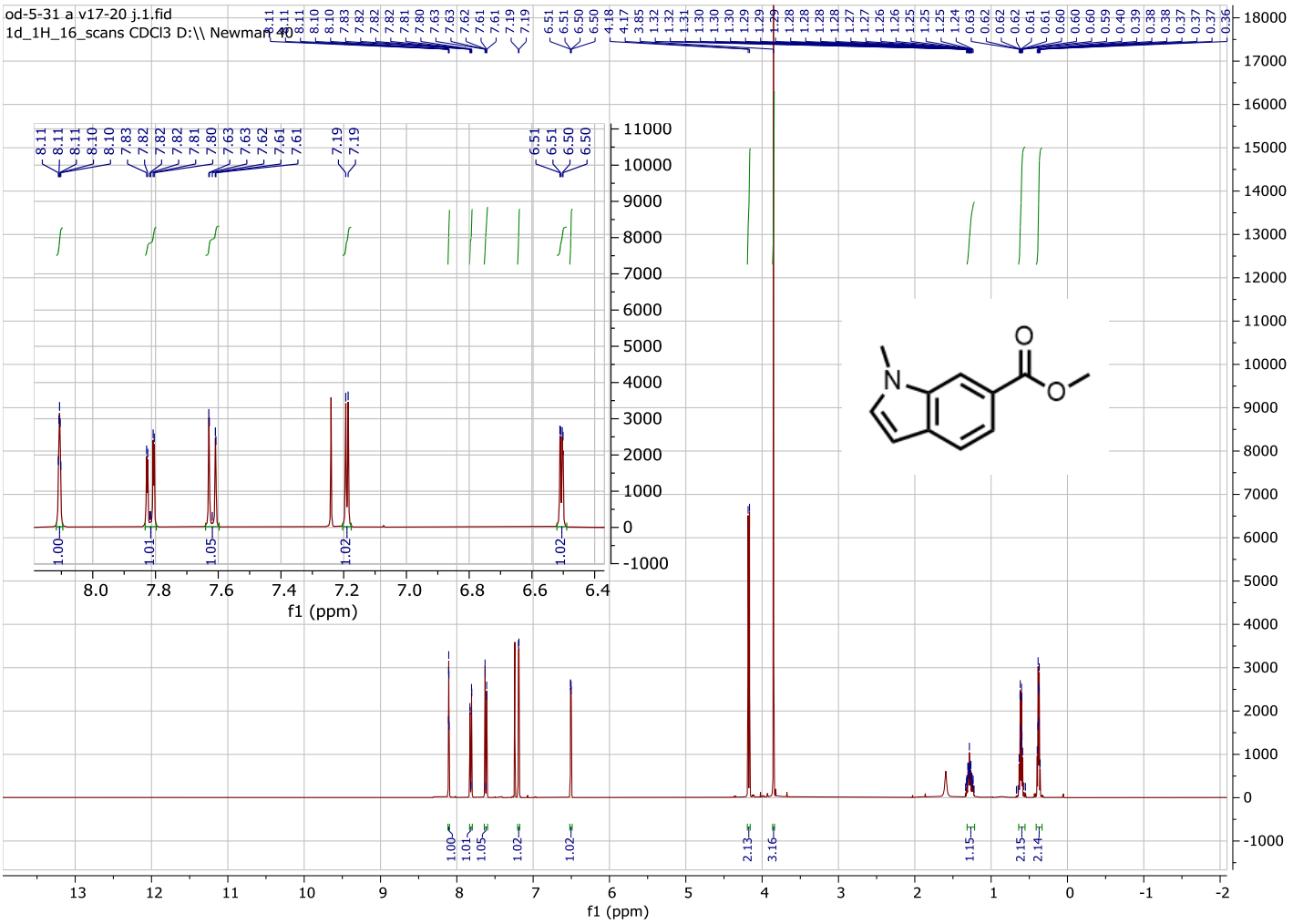

Para OMe + cyclohexane methanol
Yield (%)
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Time (min)
Product yield
Sm recovery

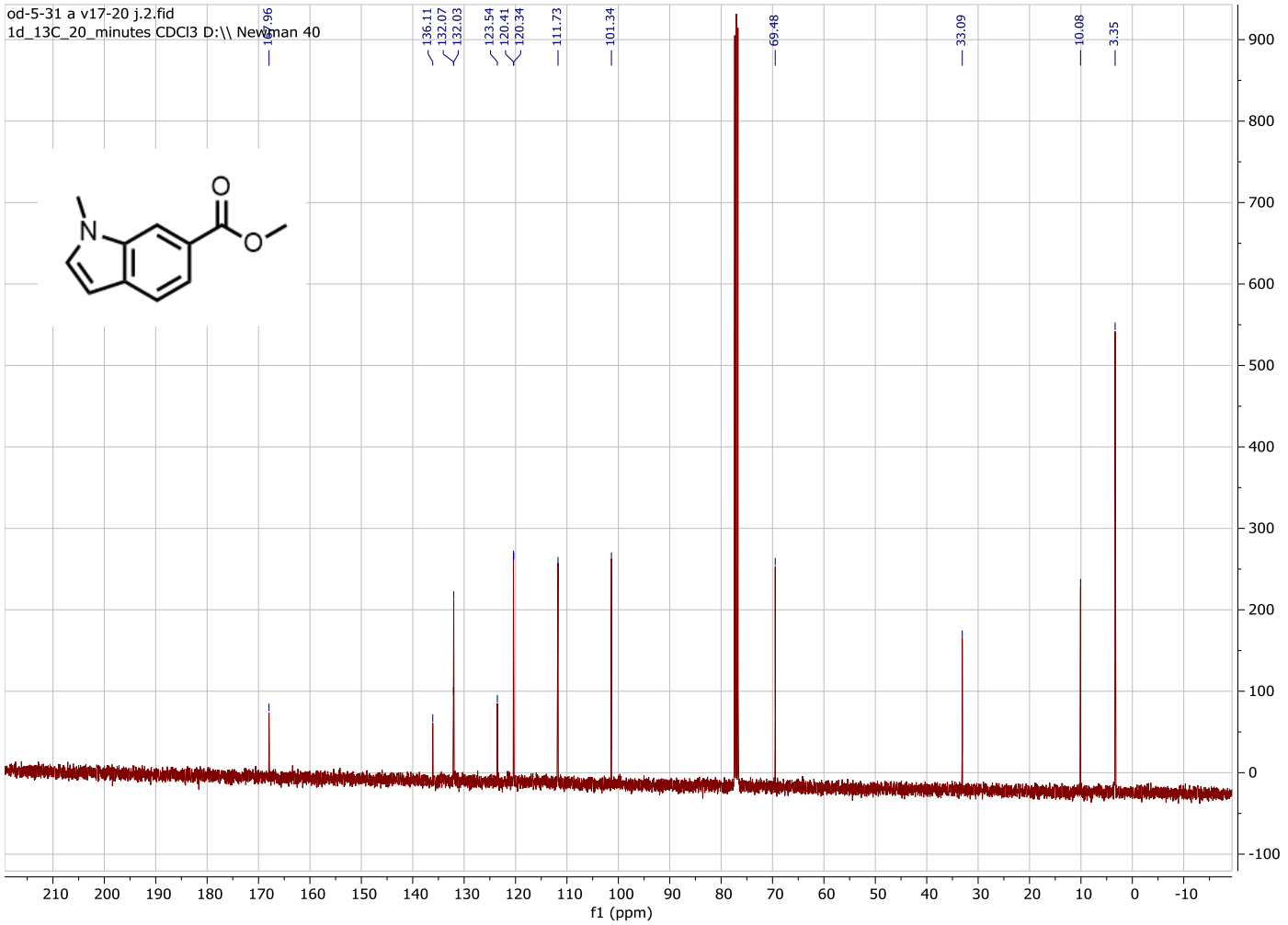

Para CF3 cyclohexane methanol
Yield (%)
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Time (min)
product yield
sm recovery


Para H + cyclohexane methanol
Yield (%)
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Time (min)
product yield
sm recovery

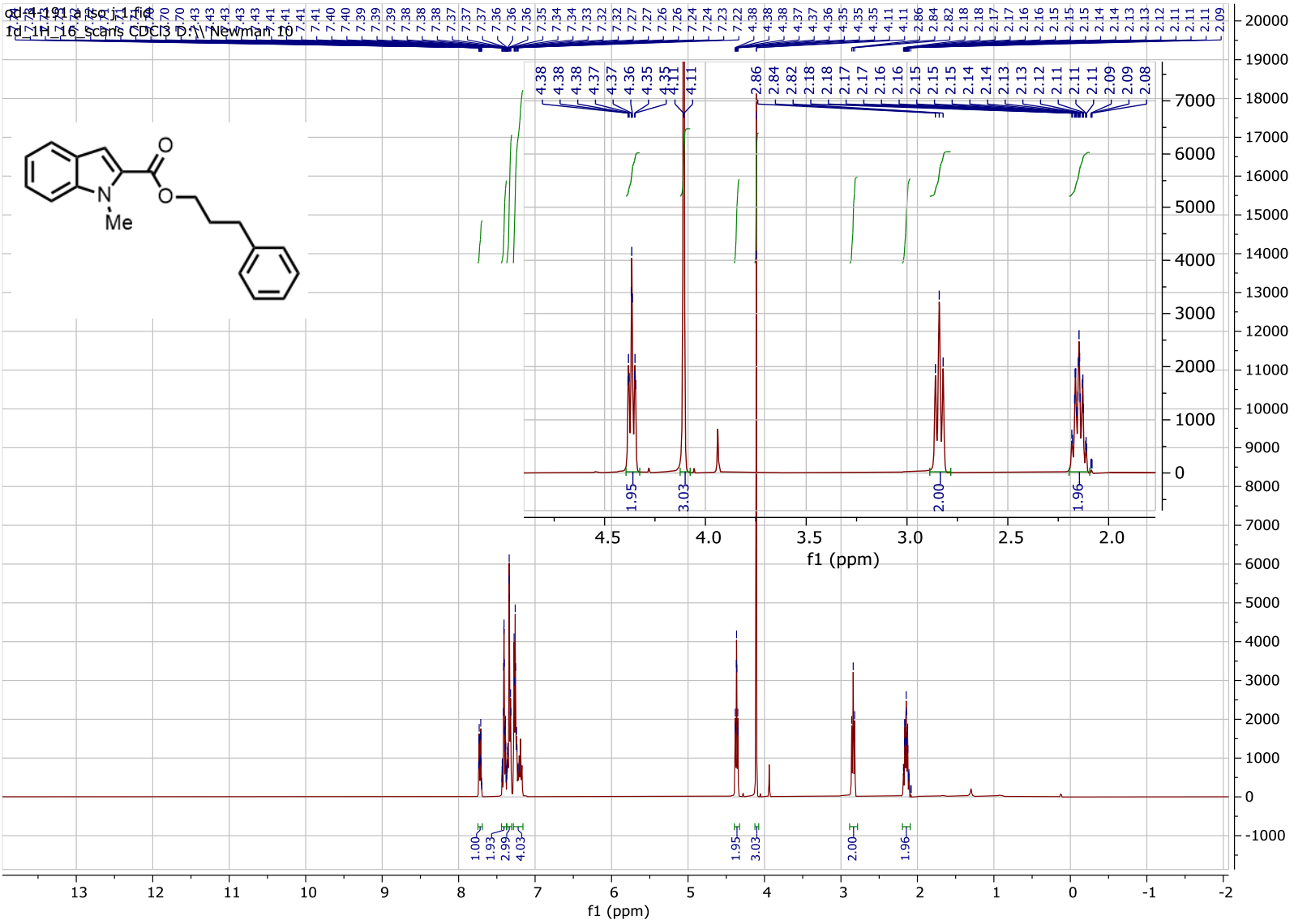
3.6.8: Copies of NMR spectra

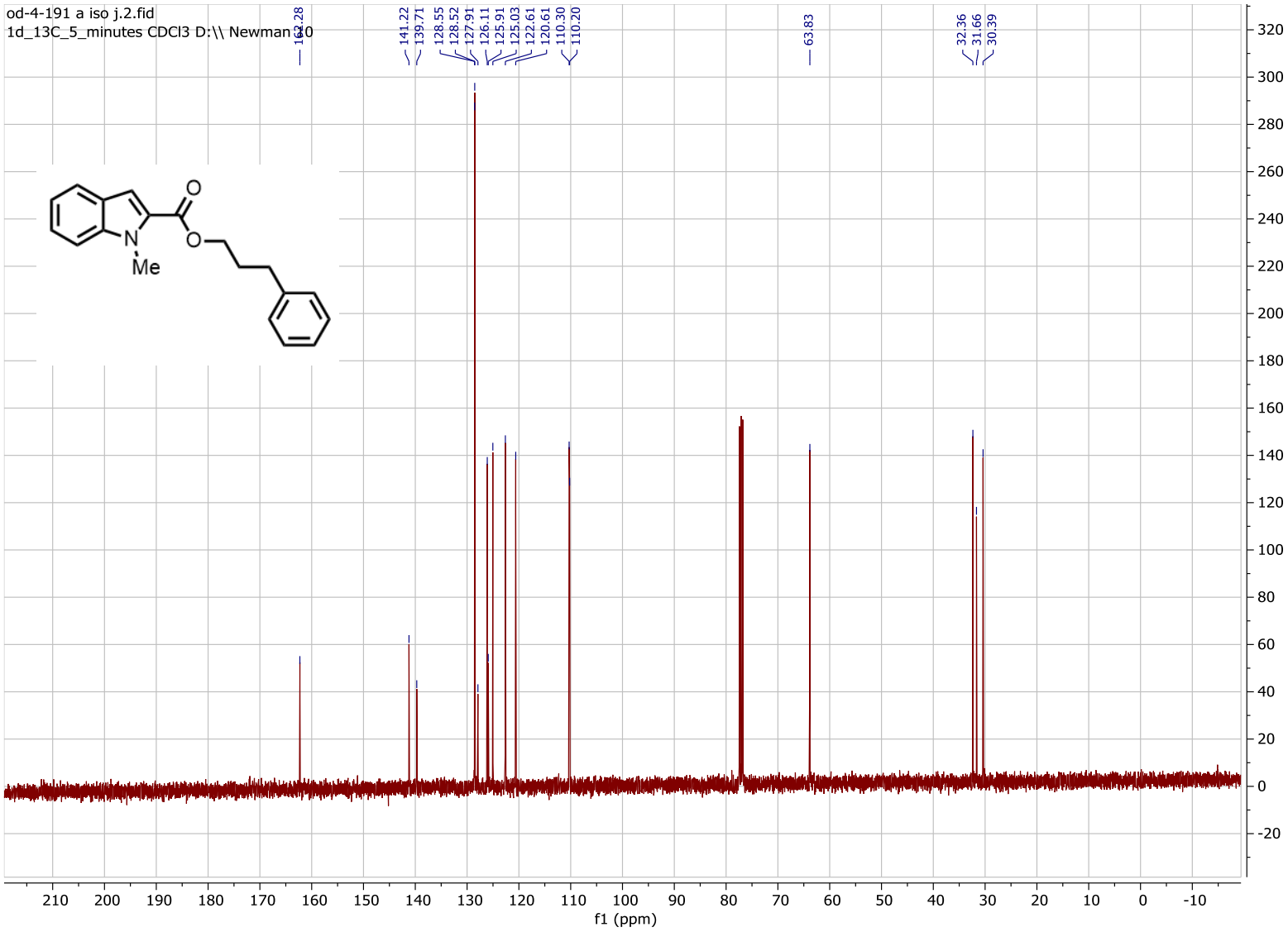
Cyclopropylmethyl 1-methyl-1H-indole-6-carboxylate (**molecule 3.1**) ($CDCl_3$, 400 MHz)



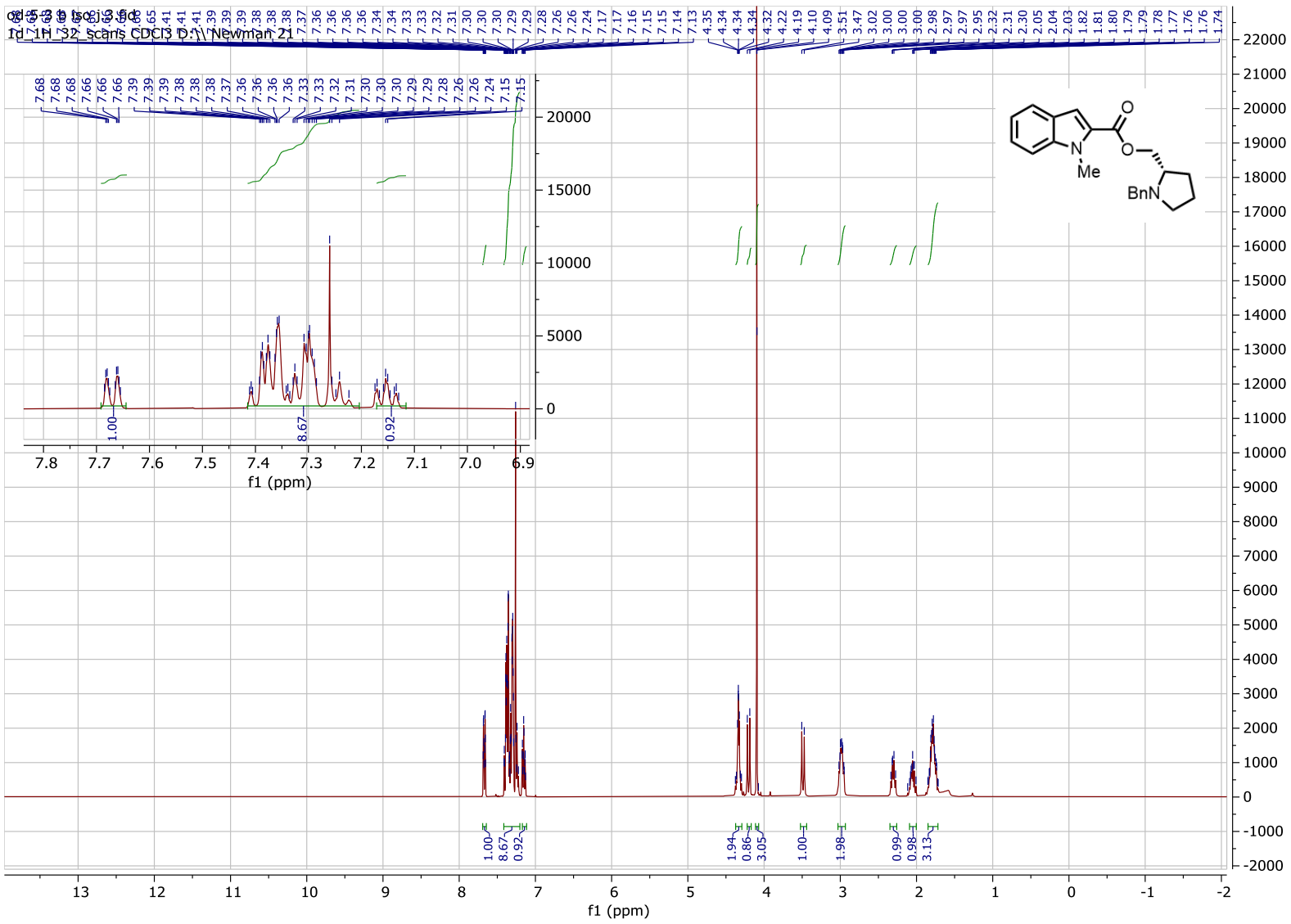

od-5-31 a v17-20 j.2.fid
1d_13C_20_minutes CDCl3 D:\\ Newman 40
171.96
136.11
132.07
132.03
123.54
120.41
120.34
111.73
101.34
69.48
33.09
10.08
3.35
N
O
O
900
800
700
600
500
400
300
200
100
0
-100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

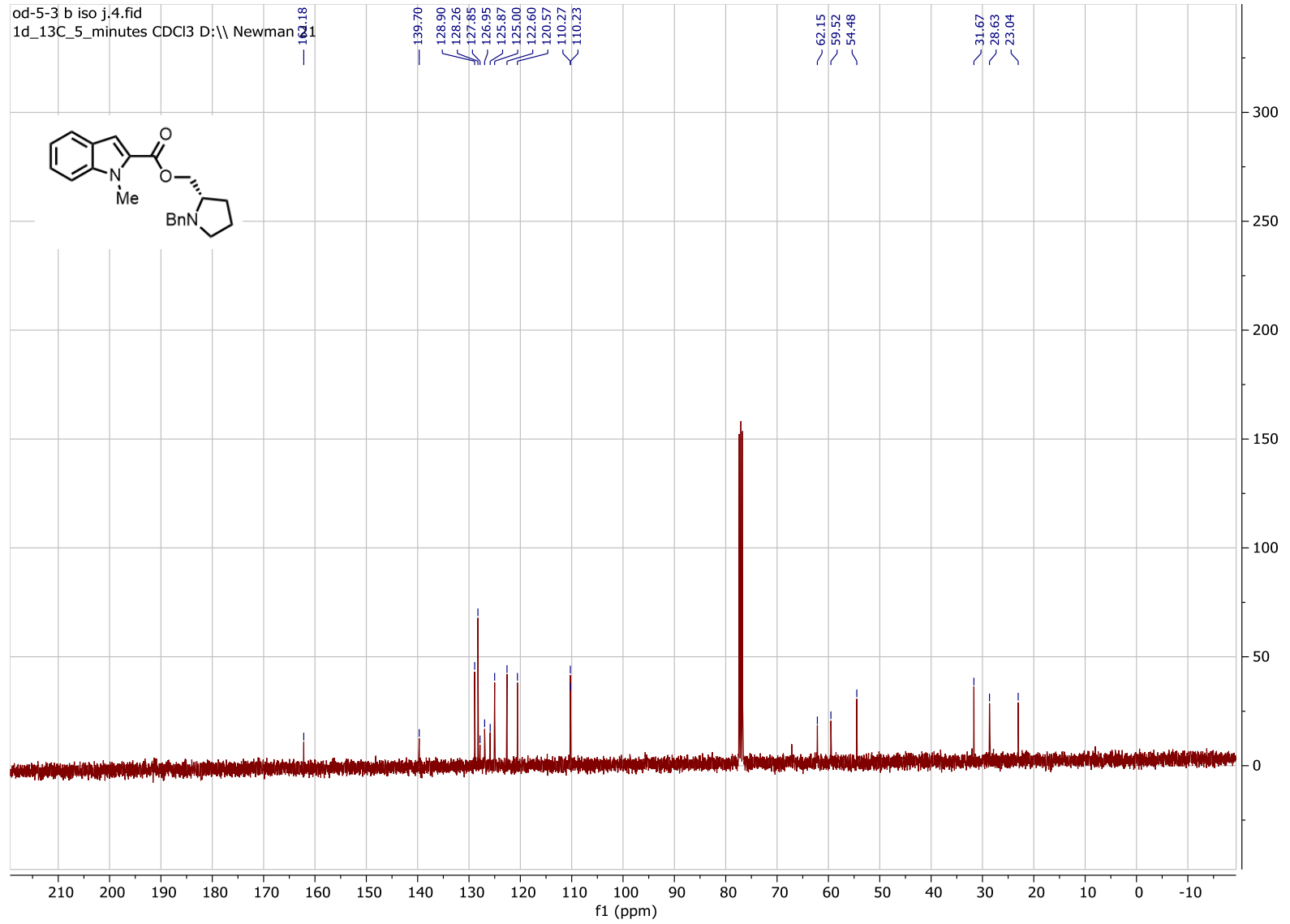
3-phenylpropyl 1-methyl-1H-indole-2-carboxylate (**molecule 3.2)** ($CDCl_3$, 400 MHz)



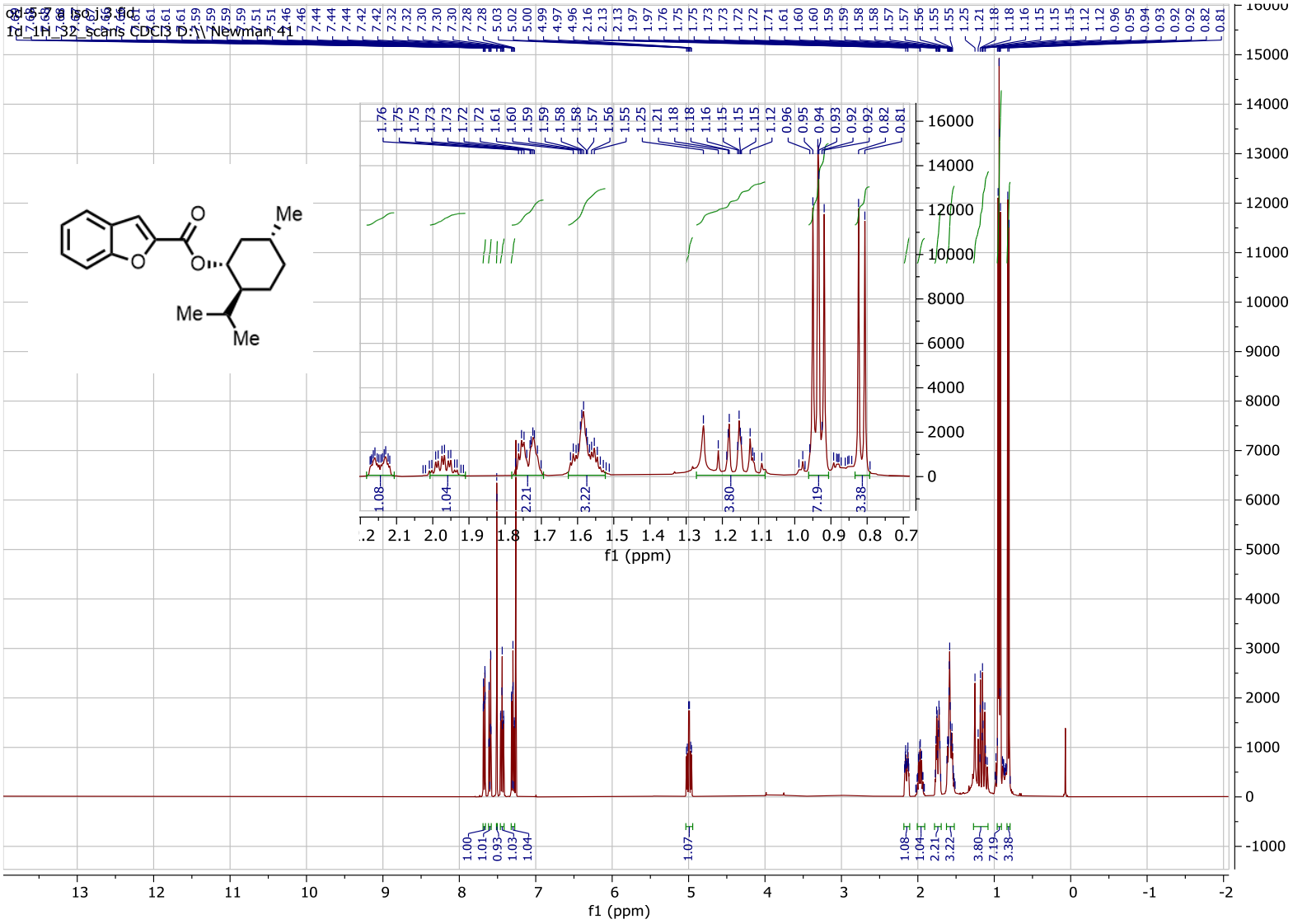

od-4-191 a iso j.2.fid
1d_13C_5_minutes CDCl3 D:\\ Newman 10
158.28
141.22
139.71
128.55
128.52
127.91
126.11
125.91
125.03
122.61
120.61
110.30
110.20
63.83
32.36
31.66
30.39
N
Me
O
O
f1 (ppm)

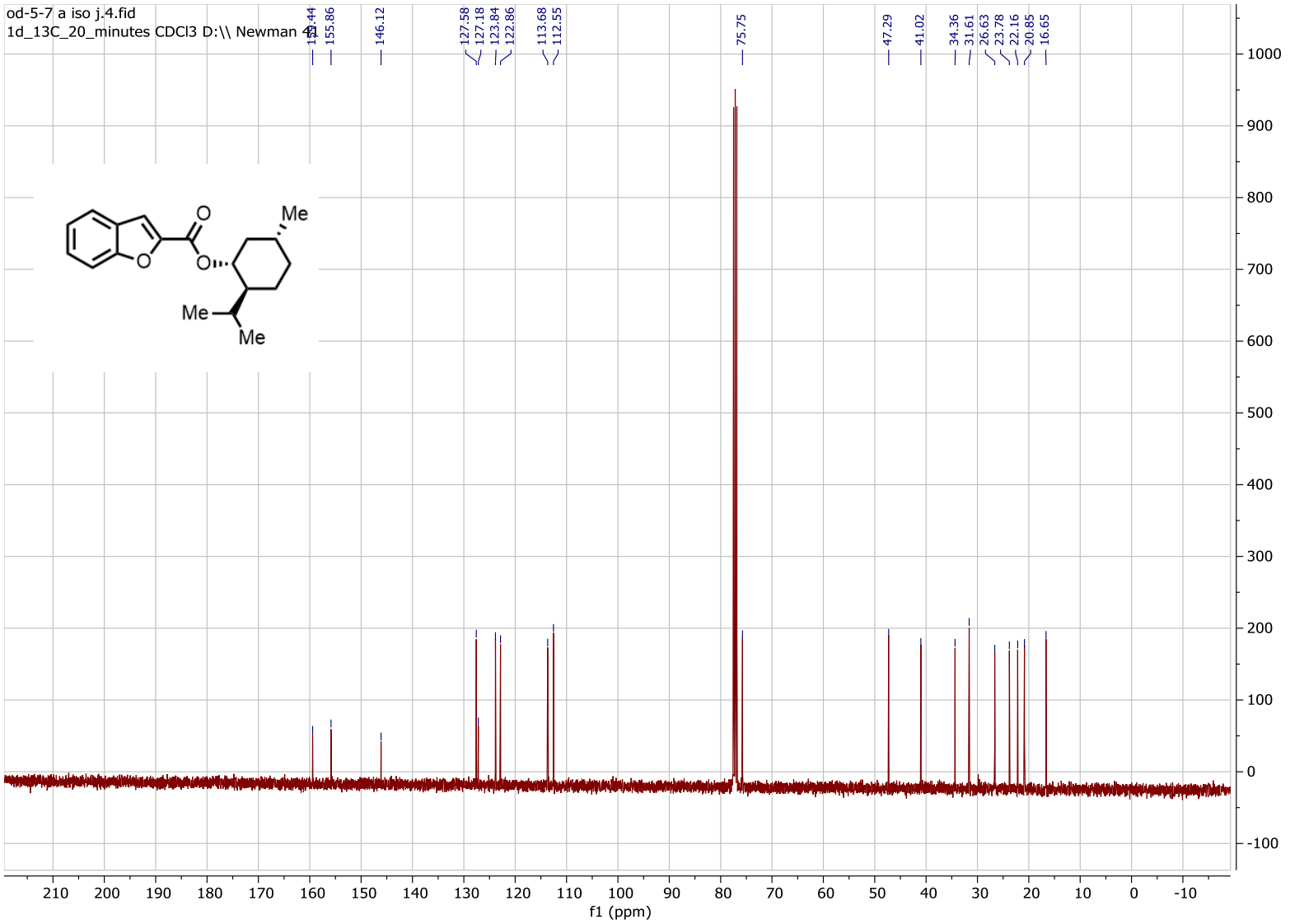
(S)-(1-benzylpyrrolidin-2-yl)methyl 1-methyl-1-H-indole-2-carboxylate (**molecule 3.3**) ($CDCl_3$, 400 MHz)



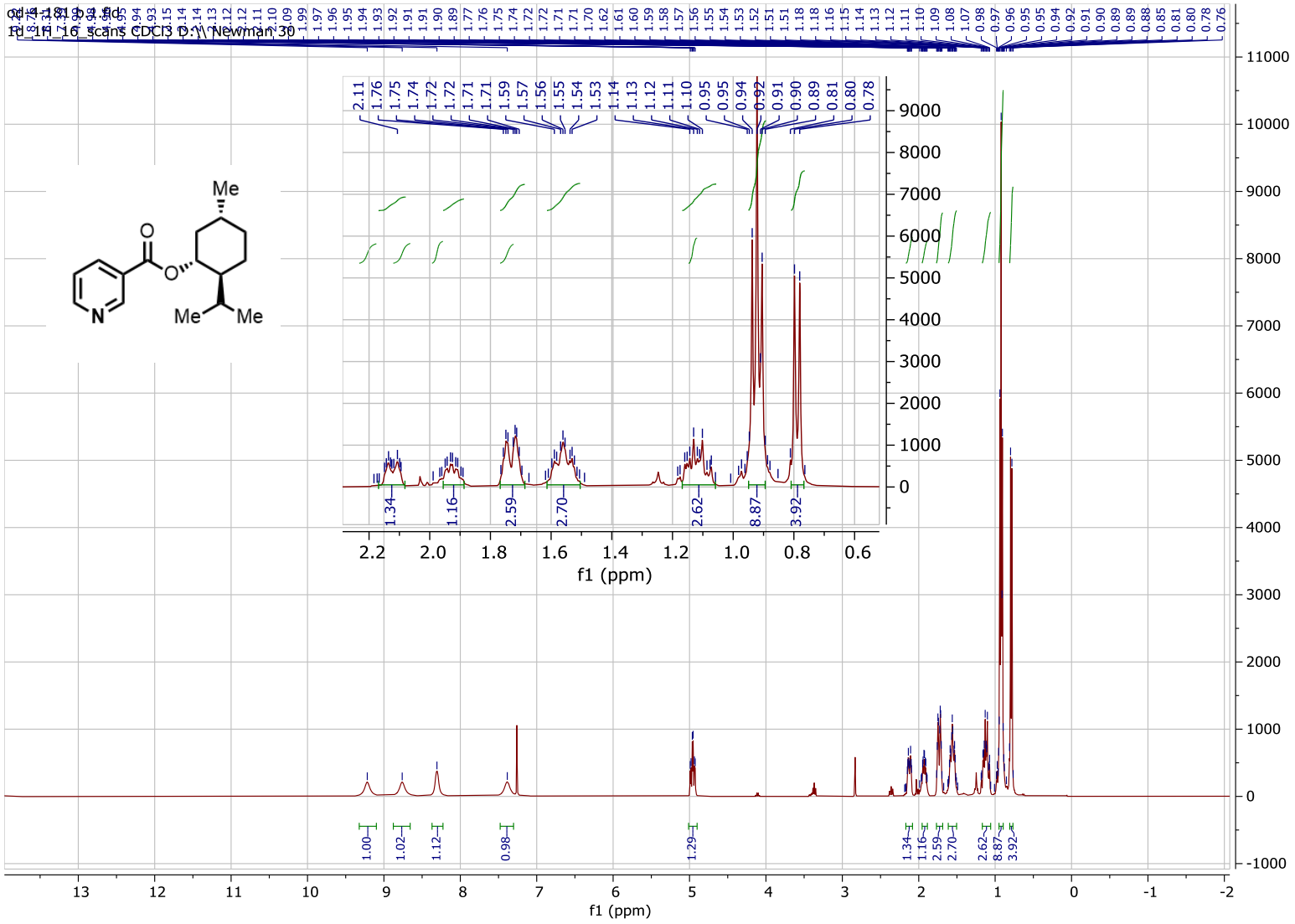

od-5-3 b iso j.4.fid
1d_13C_5_minutes CDCl3 D:\\ Newman 21
162.18
139.70
128.90
128.26
127.85
126.95
125.87
125.00
122.60
120.57
110.27
110.23
62.15
59.52
54.48
31.67
28.63
23.04
N
Me
O
O
BnN
300
250
200
150
100
50
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

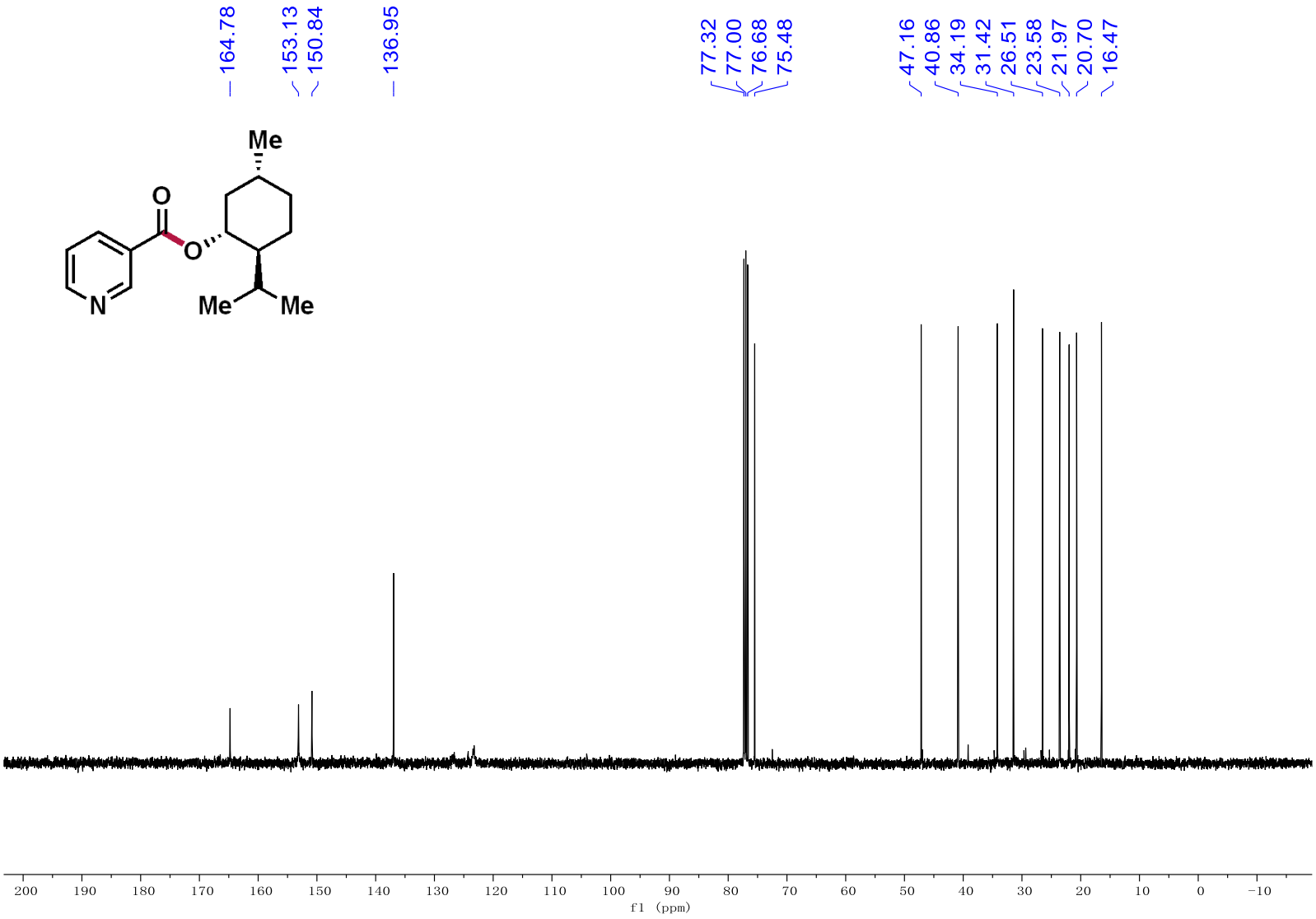
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl benzofuran-2-carboxylate (**molecule 3.4**) ($CDCl_3$, 400 MHz)



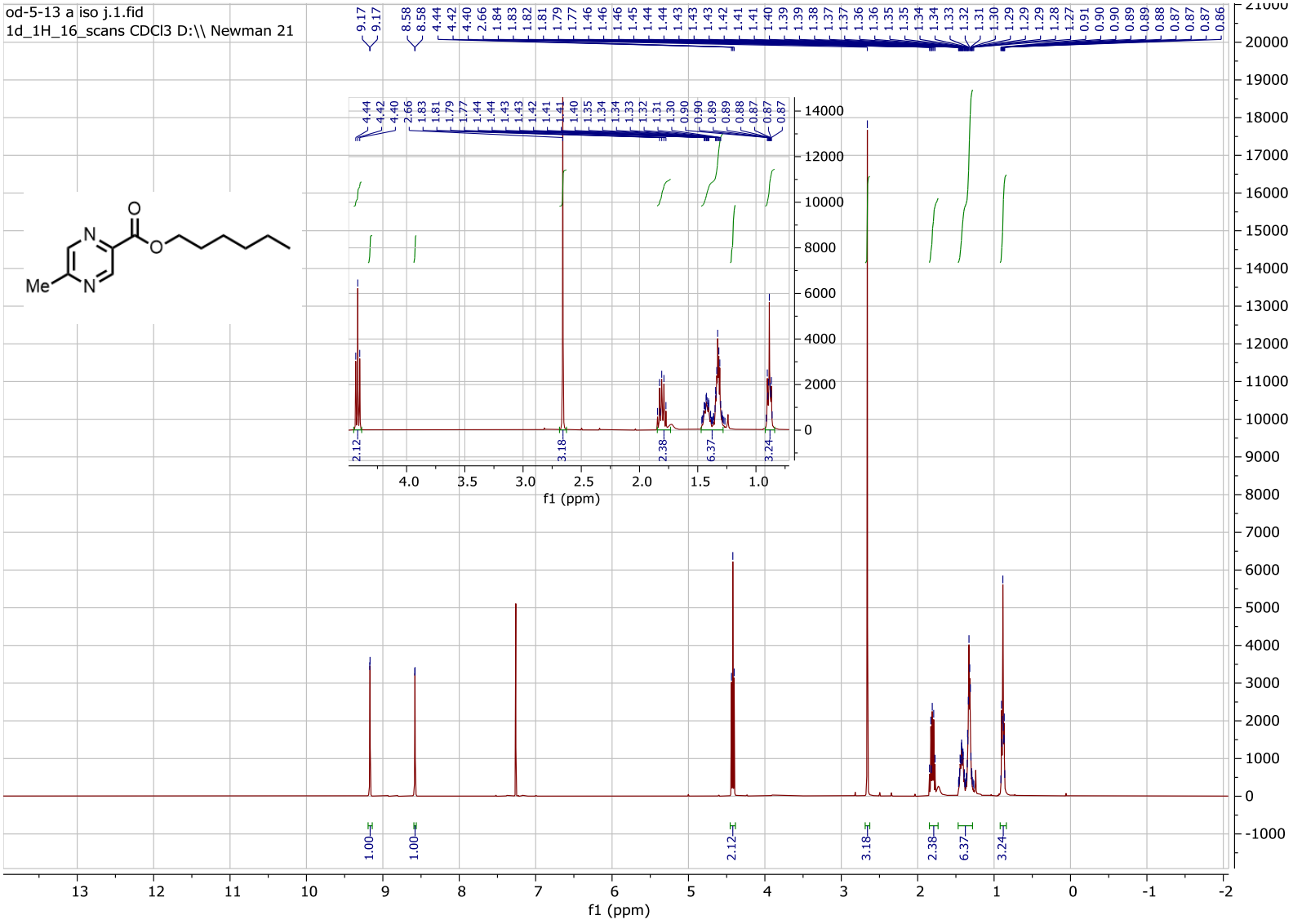

od-5-7 a iso j.4.fid
1d_13C_20_minutes CDCl3 D:\\ Newman 4
155.86
146.12
127.58
127.18
123.84
122.86
113.68
112.55
75.75
47.29
41.02
34.36
31.61
26.63
23.78
22.16
20.85
16.65
O
O
O
Me
Me
Me
f1 (ppm)

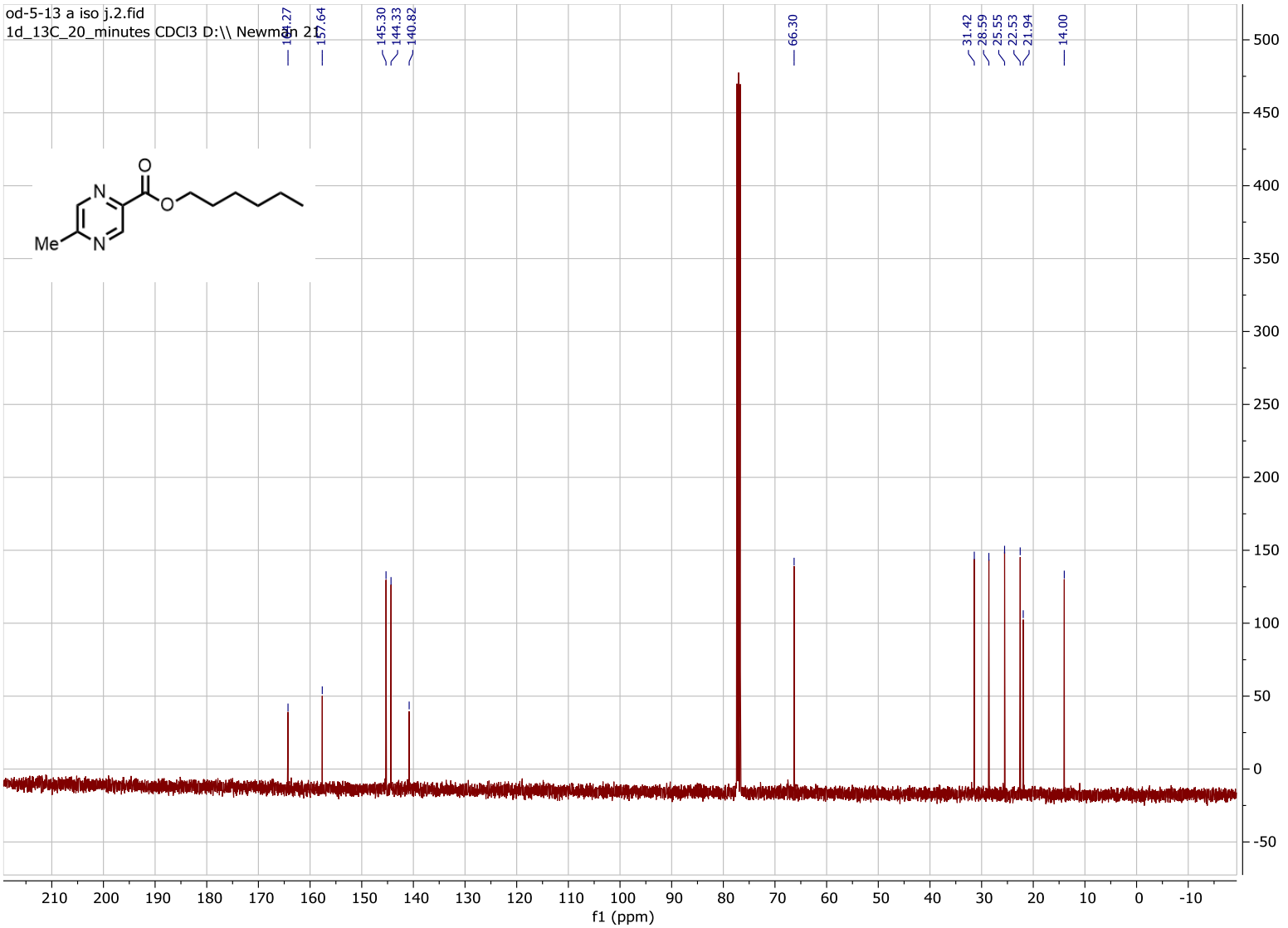
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl nicotinate (**molecule 3.5**) ($CDCl_3$, 400 MHz)



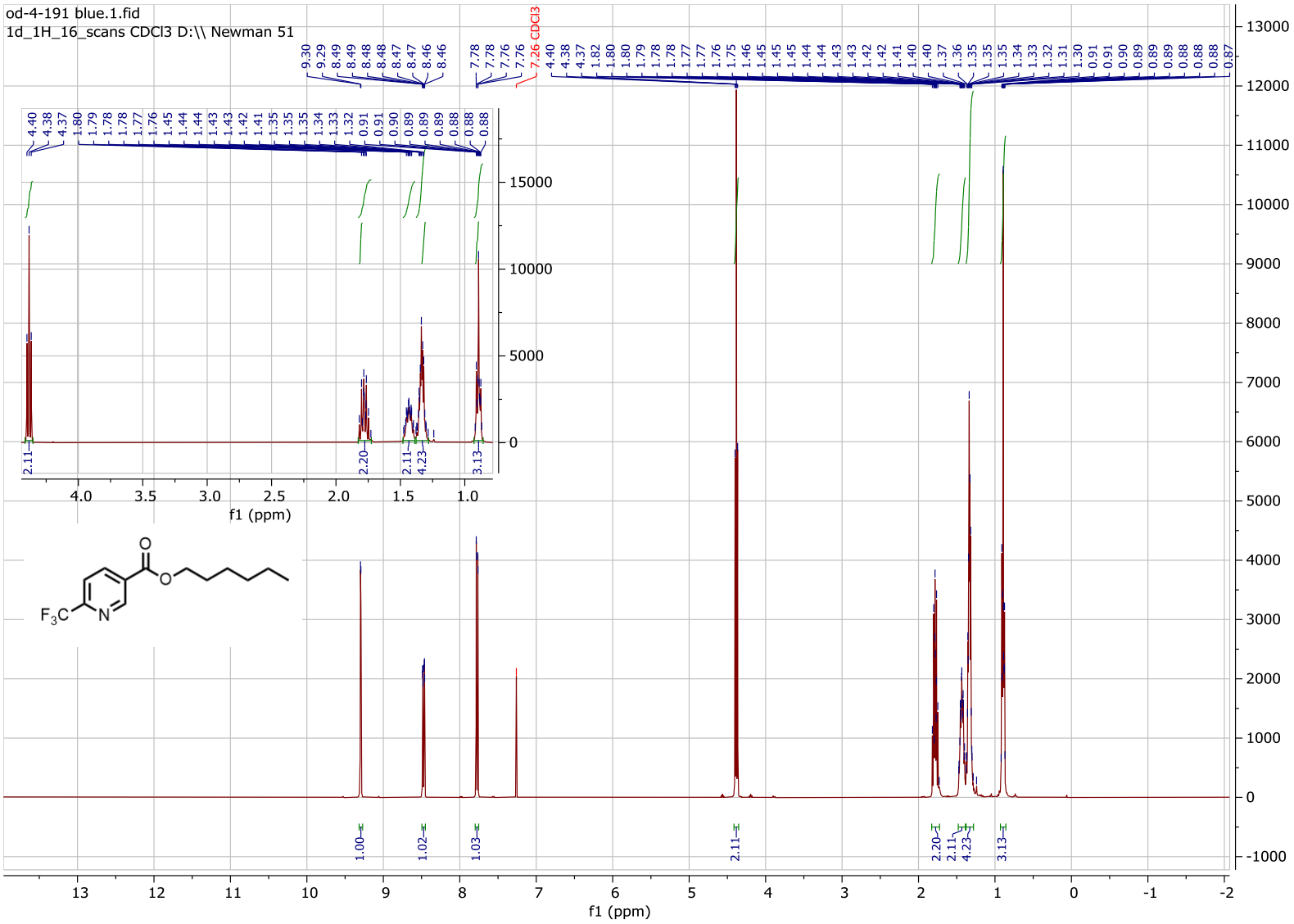

164.78
153.13
150.84
136.95
77.32
77.00
76.68
75.48
47.16
40.86
34.19
31.42
26.51
23.58
21.97
20.70
16.47
Me
O
O
N
Me
Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

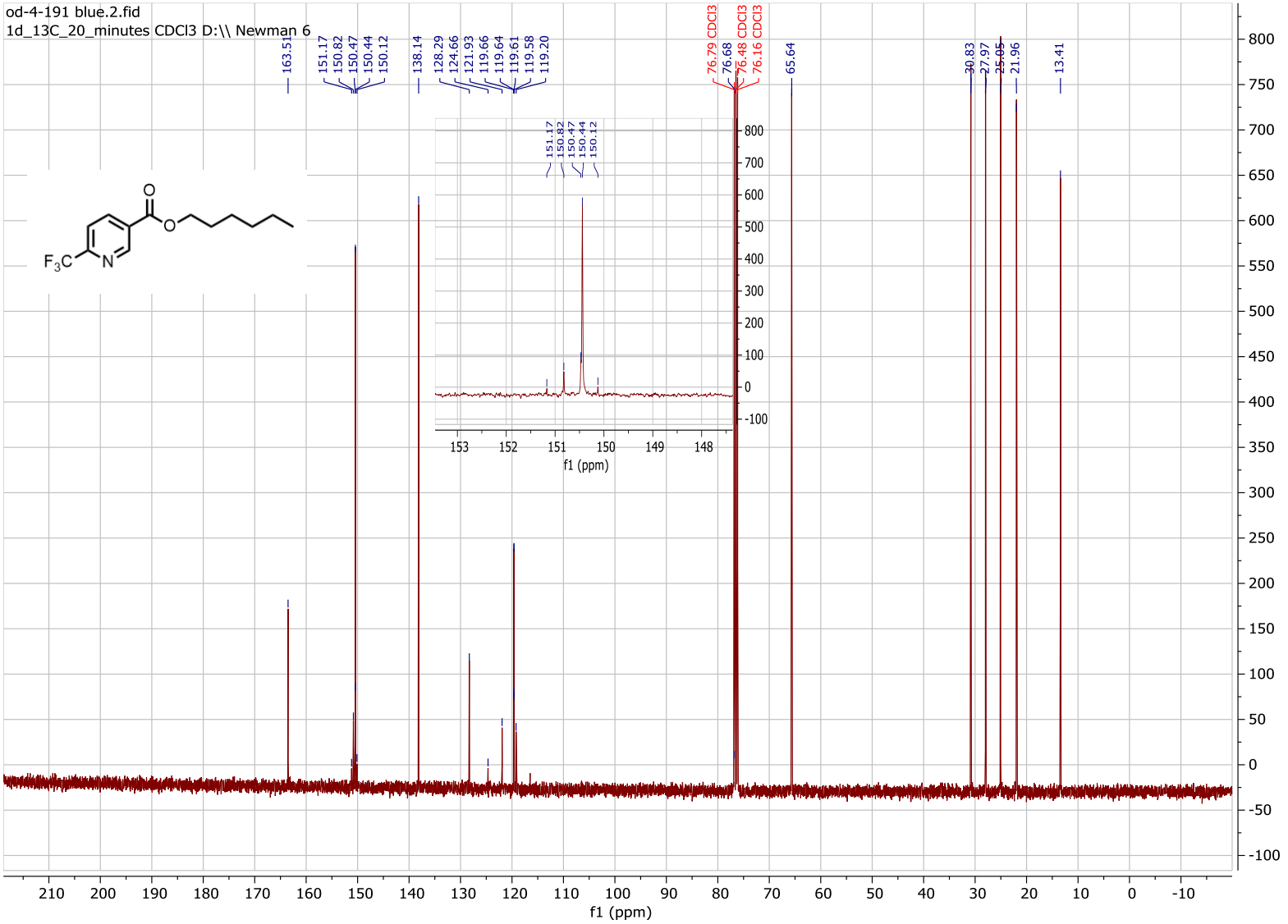
Hexyl 5-methylpyrazine-2-carboxylate (**Molecule 3.6**) ($CDCl_3$, 400 MHz)

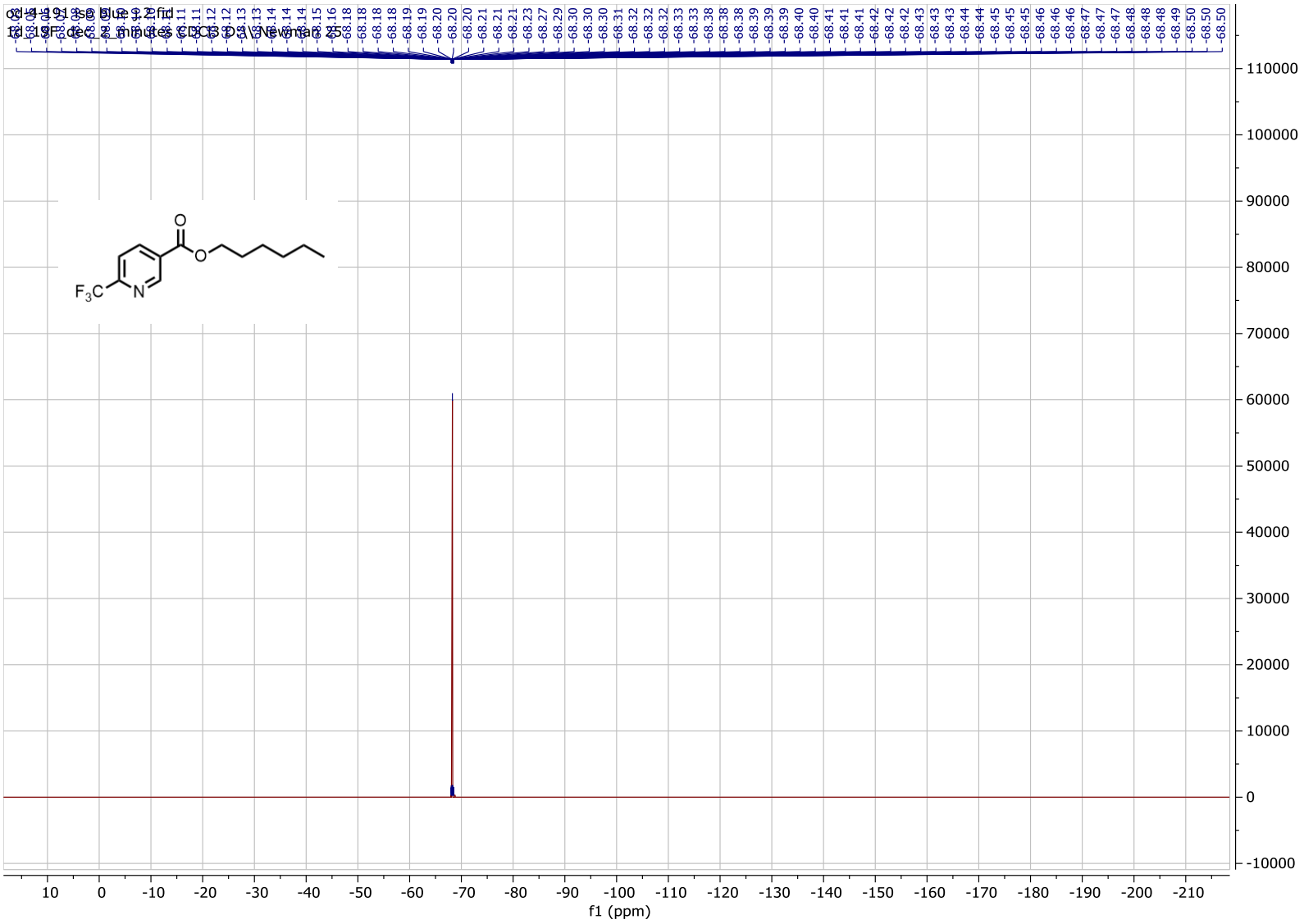



od-5-13 a iso j.2.fid
1d_13C_20_minutes CDCl3 D:\\ Newman 21
164.27
157.64
145.30
144.33
140.82
66.30
31.42
28.59
25.55
22.53
21.94
14.00
Me
N
N
O
O
f1 (ppm)

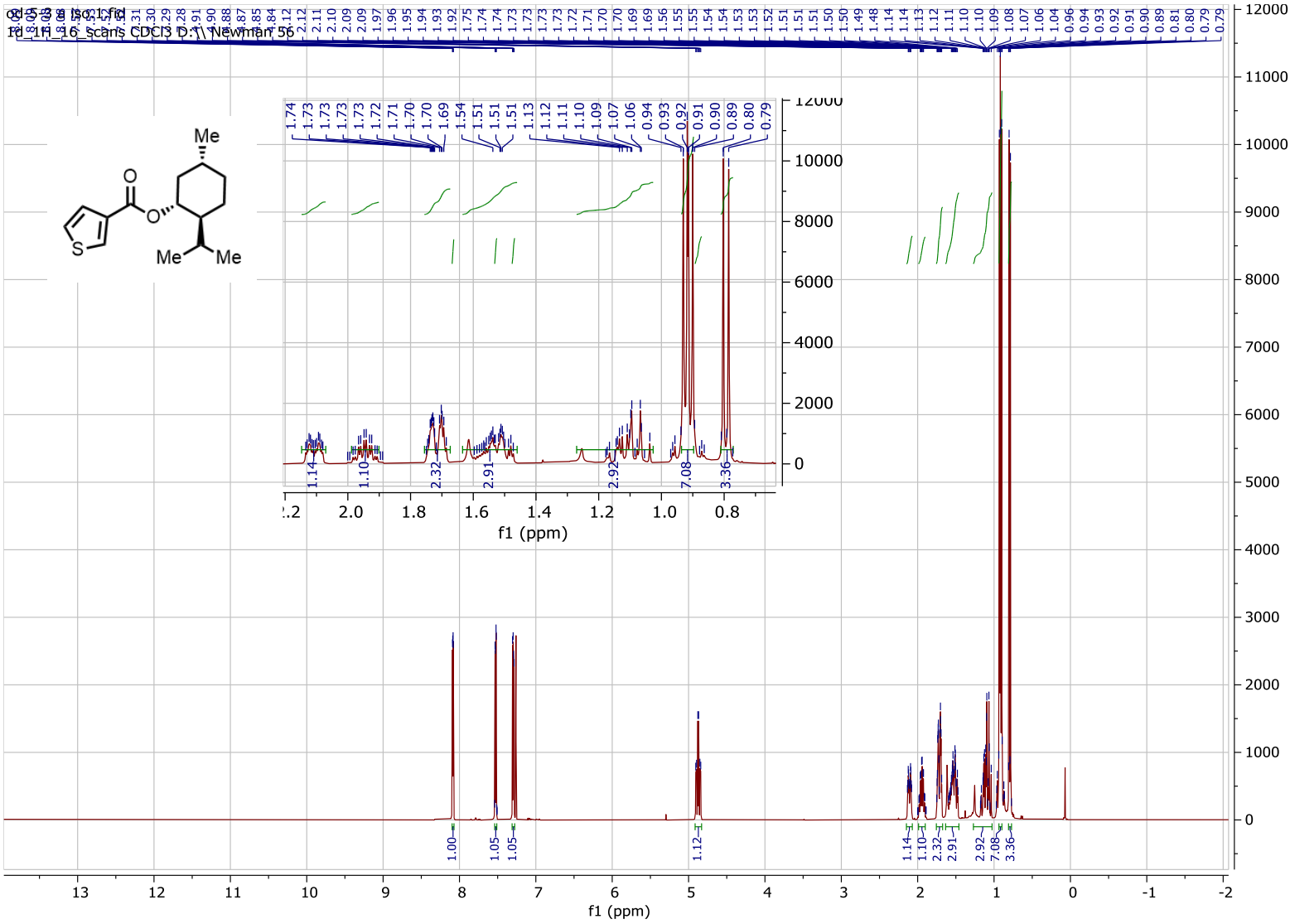
Hexyl 6-(trifluoromethyl)nicotinate (**molecule 3.7**) ($CDCl_3$, 400 MHz)

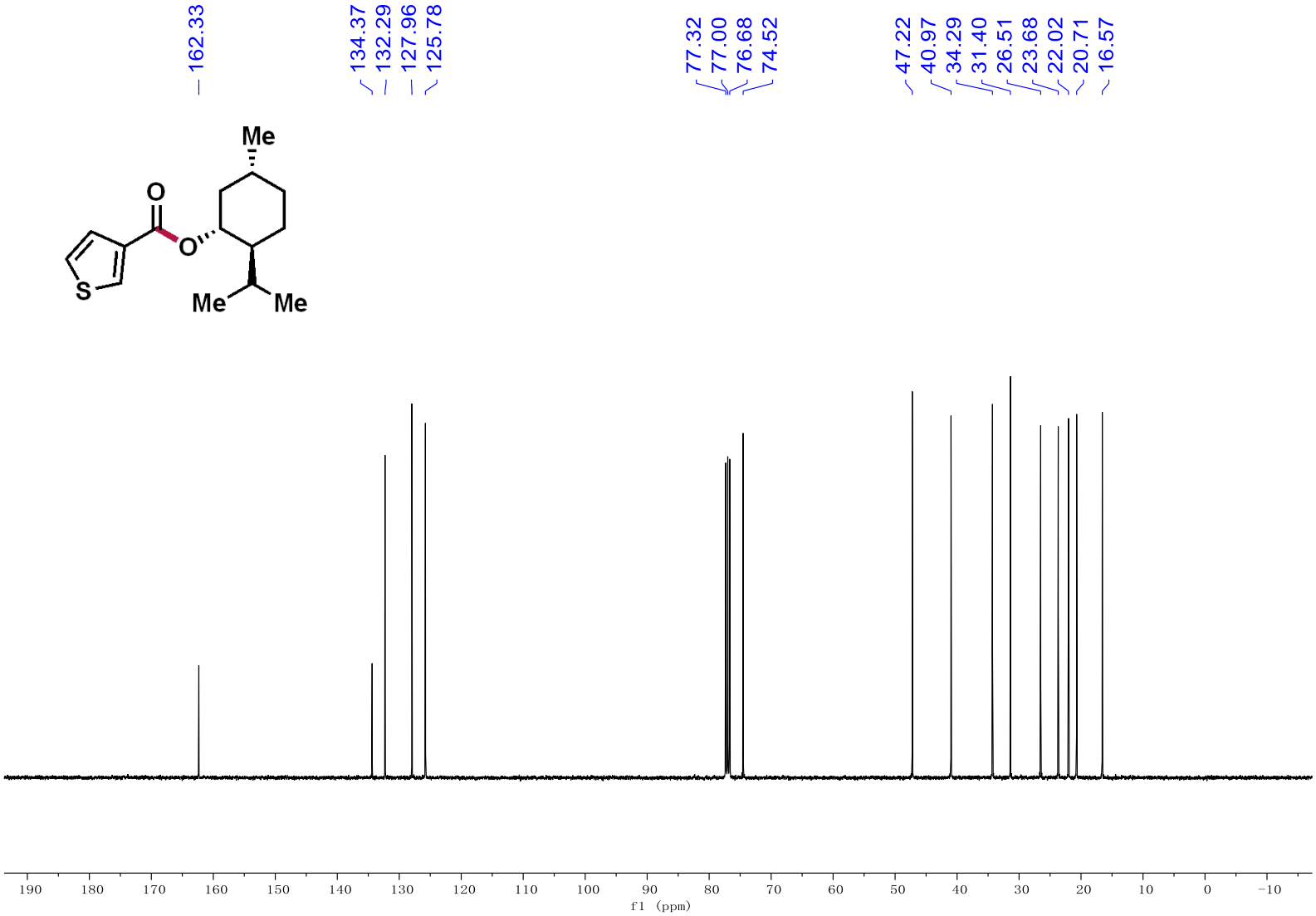



od-4-191 blue.2.fid
1d_13C_20_minutes CDCl3 D:\\ Newman 6
163.51
151.17
150.82
150.47
150.44
150.12
138.14
128.29
124.66
121.93
119.66
119.64
119.61
119.58
119.20
76.79 CDCl3
76.68
76.48 CDCl3
76.16 CDCl3
65.64
30.83
27.97
25.05
21.96
13.41
F3C
N
O
f1 (ppm)

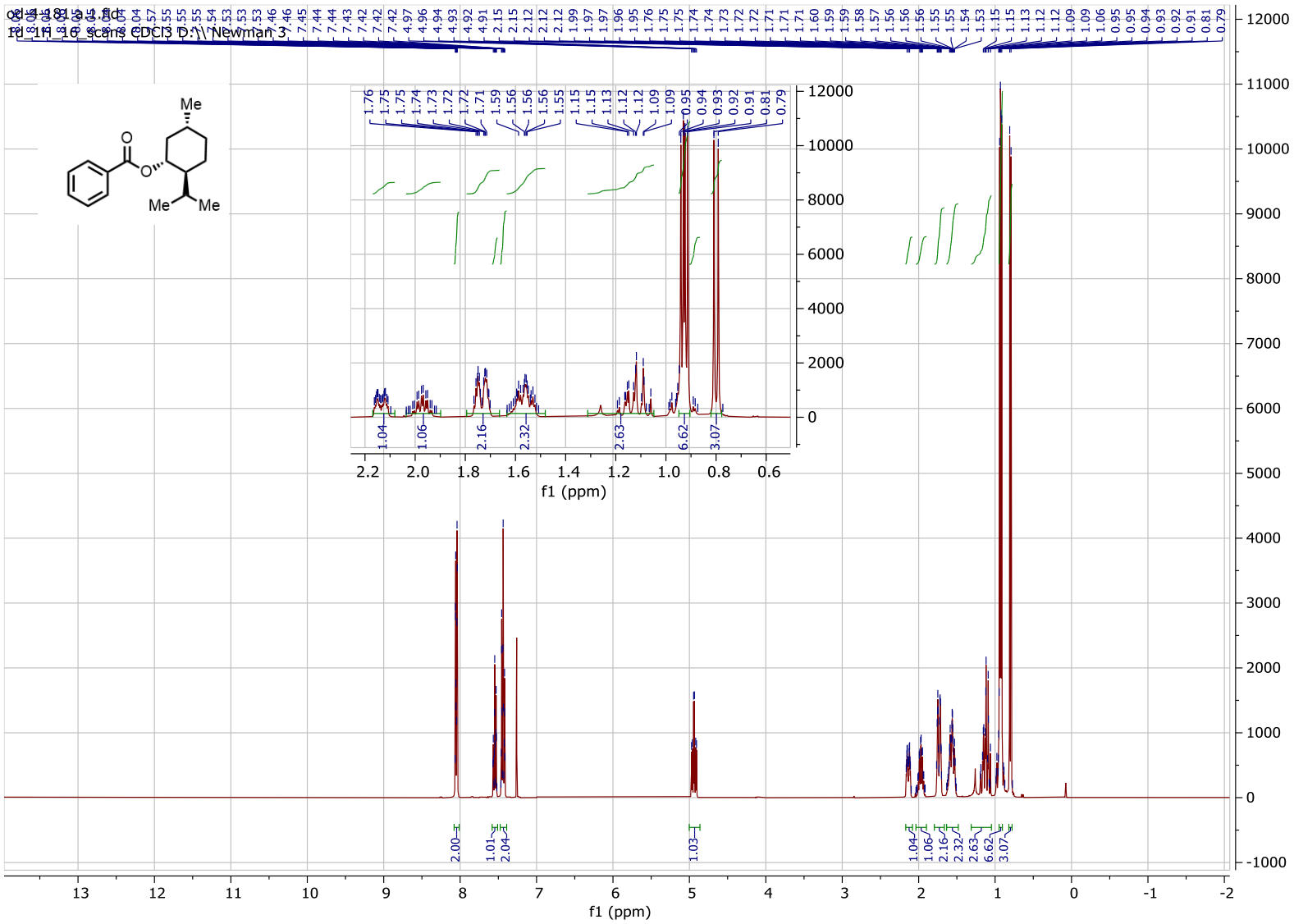

O
O
F3C
N
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

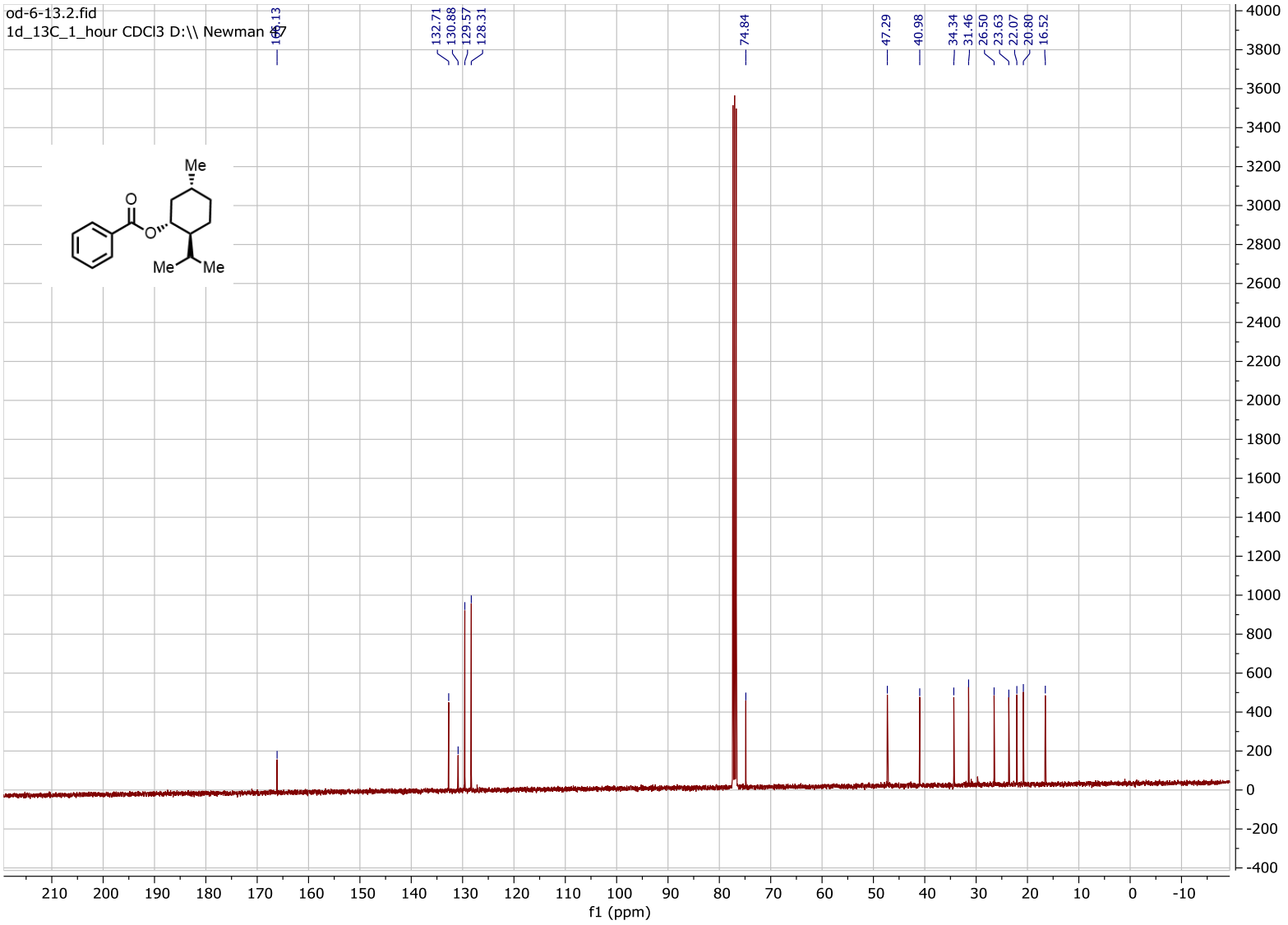
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl thiophene-3-carboxylate (**molecule 3.8**) ($CDCl_3$, 400 MHz)



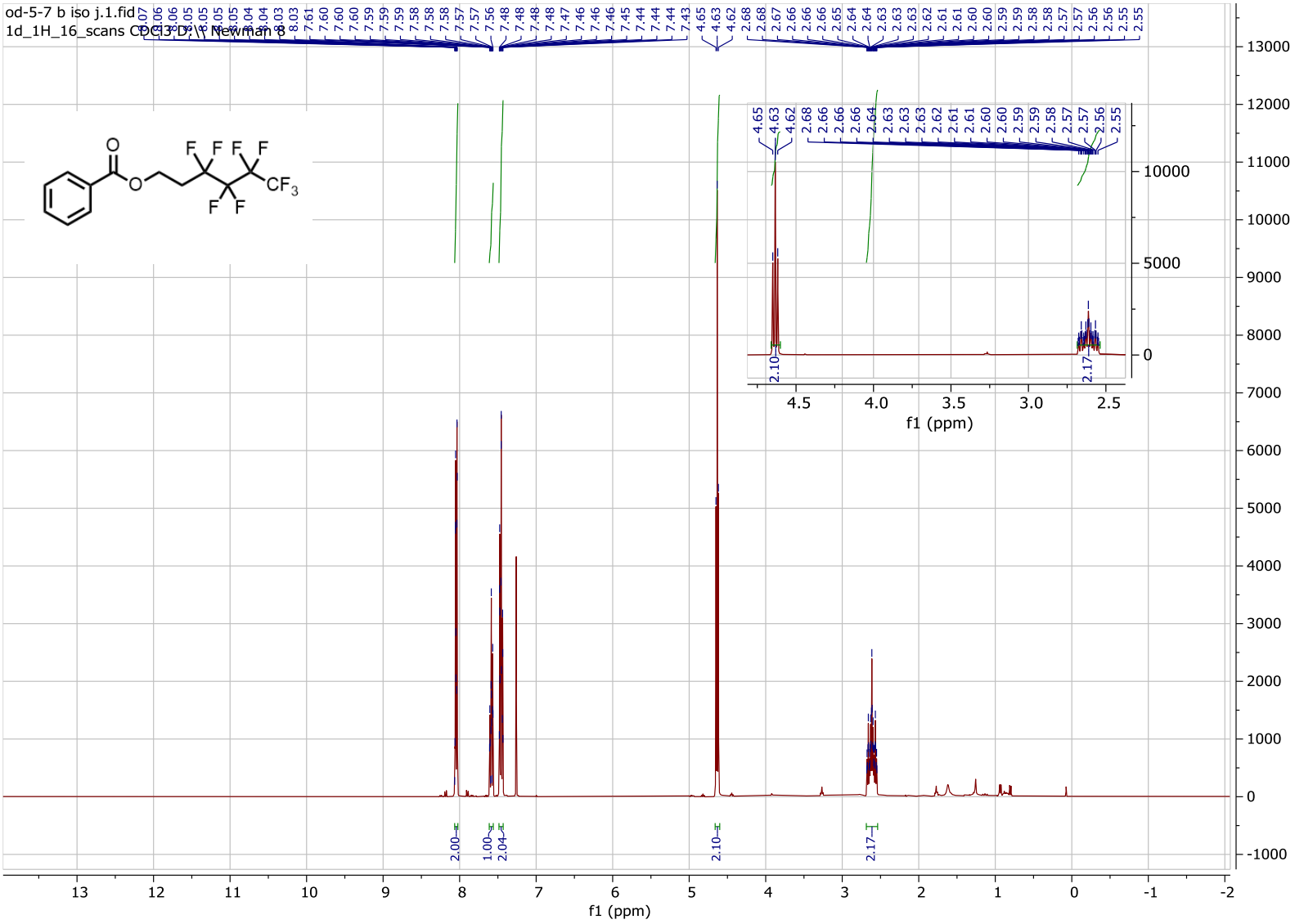

162.33
134.37
132.29
127.96
125.78
77.32
77.00
76.68
74.52
47.22
40.97
34.29
31.40
26.51
23.68
22.02
20.71
16.57
Me
O
O
S
Me
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

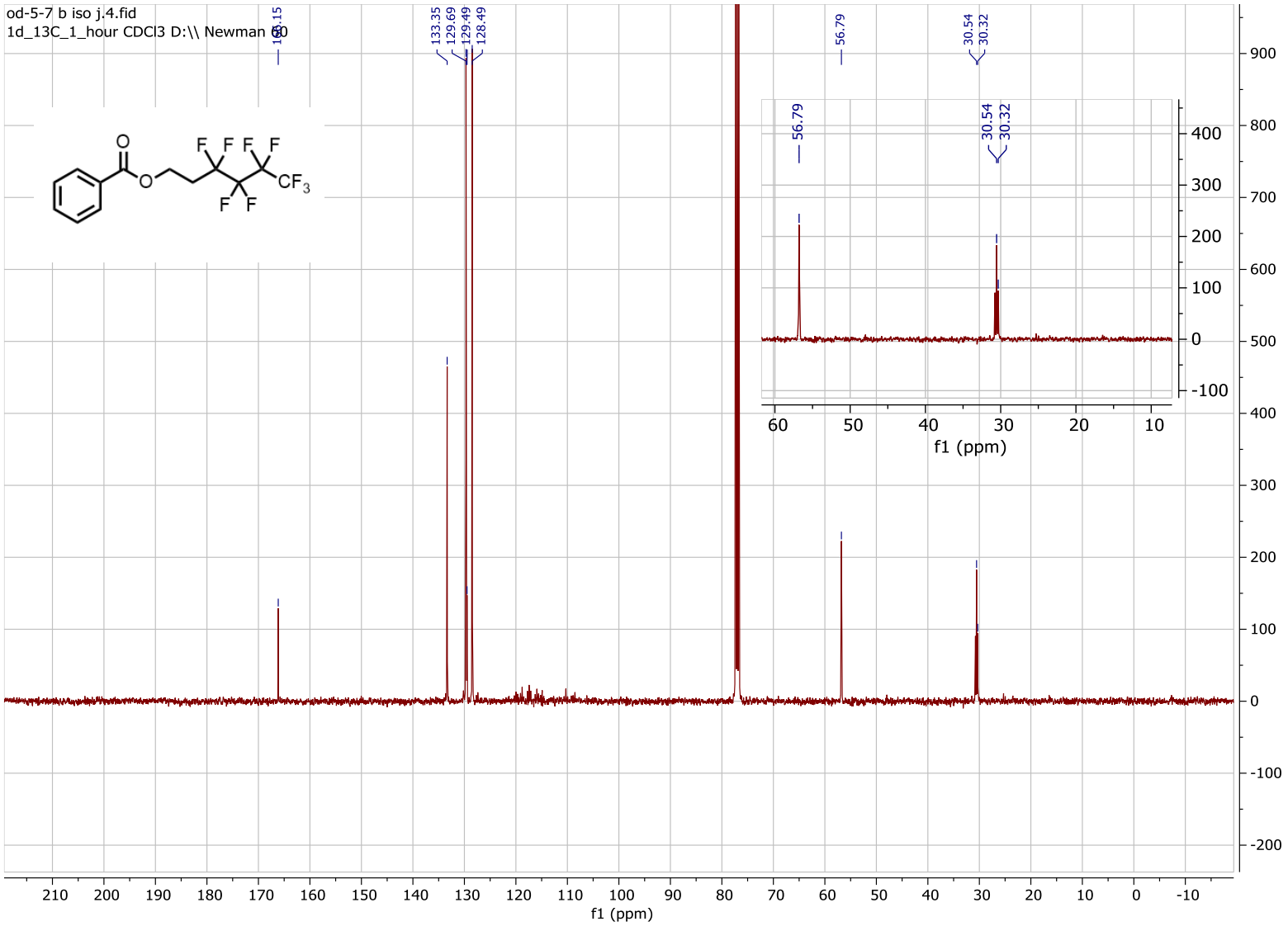
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl benzoate (**molecule 3.9**) ($CDCl_3$, 400 MHz)

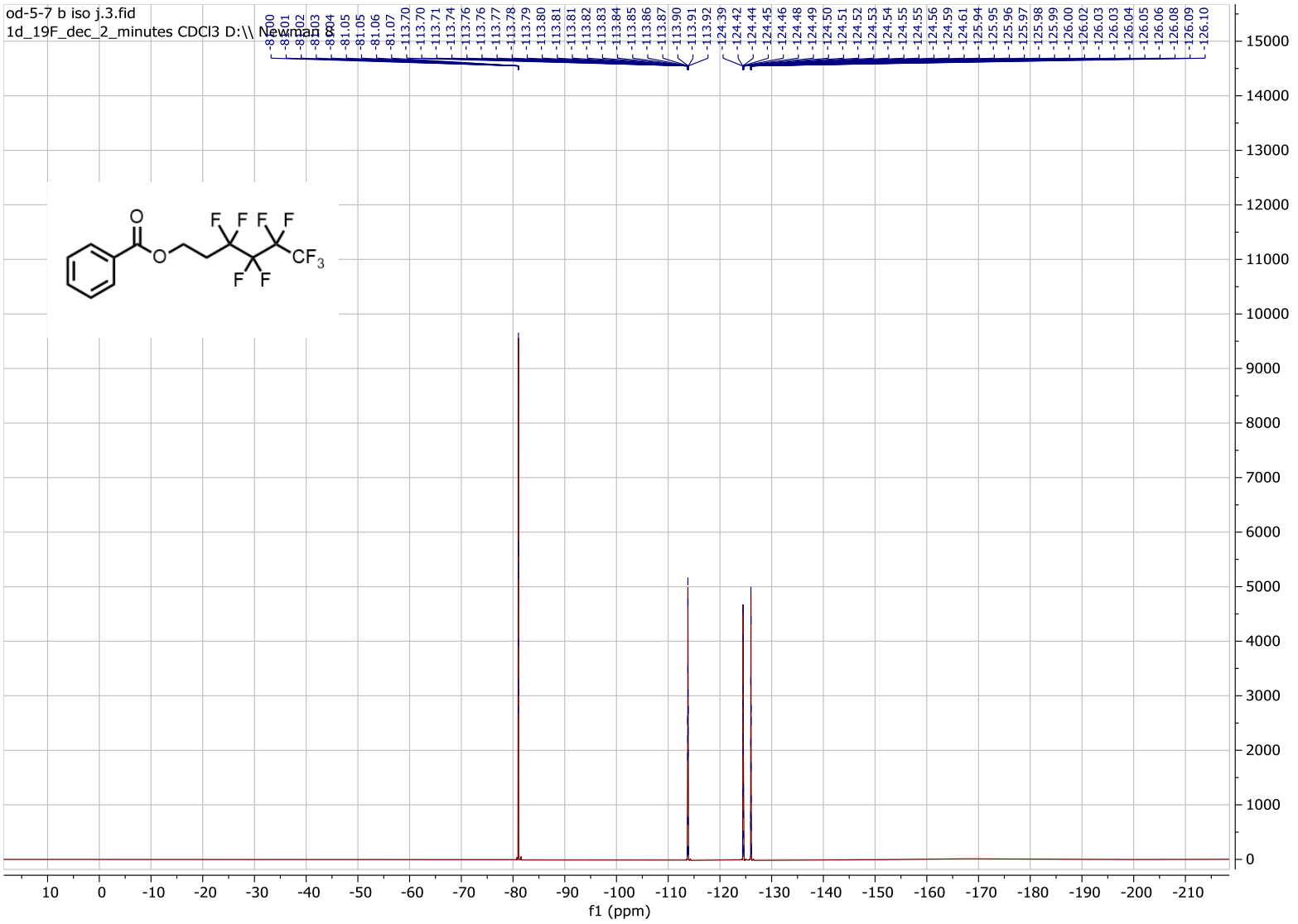



od-6-13.2.fid
1d_13C_1_hour CDCl3 D:\\ Newman 67
173.13
132.71
130.88
129.57
128.31
74.84
47.29
40.98
34.34
31.46
26.50
23.63
22.07
20.80
16.52
Me
O
O
Me
Me
f1 (ppm)

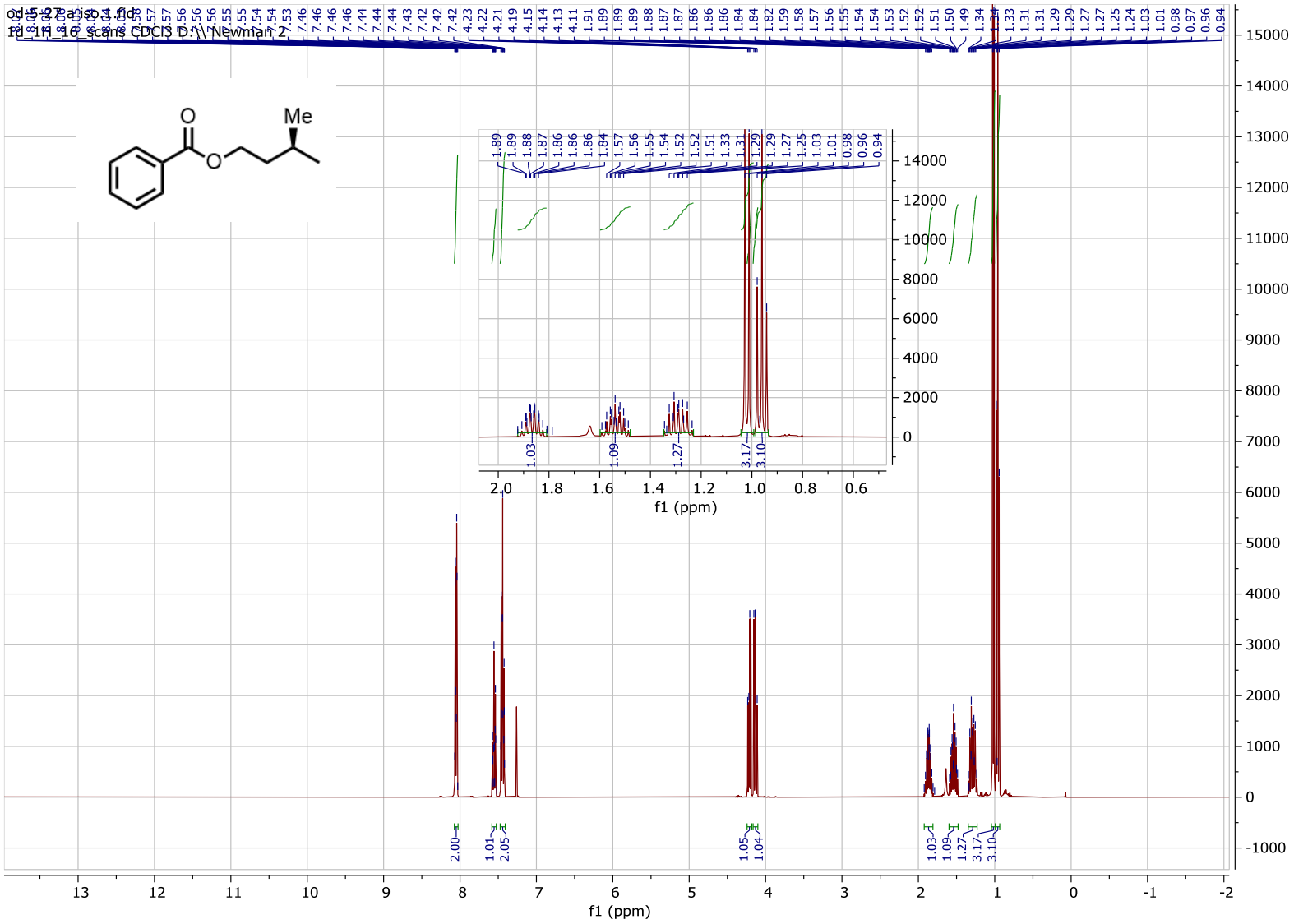
3,3,4,4,5,5,6,6,6-nonafluorohexyl benzoate (**molecule 3.10**) ($CDCl_3$, 400 MHz)

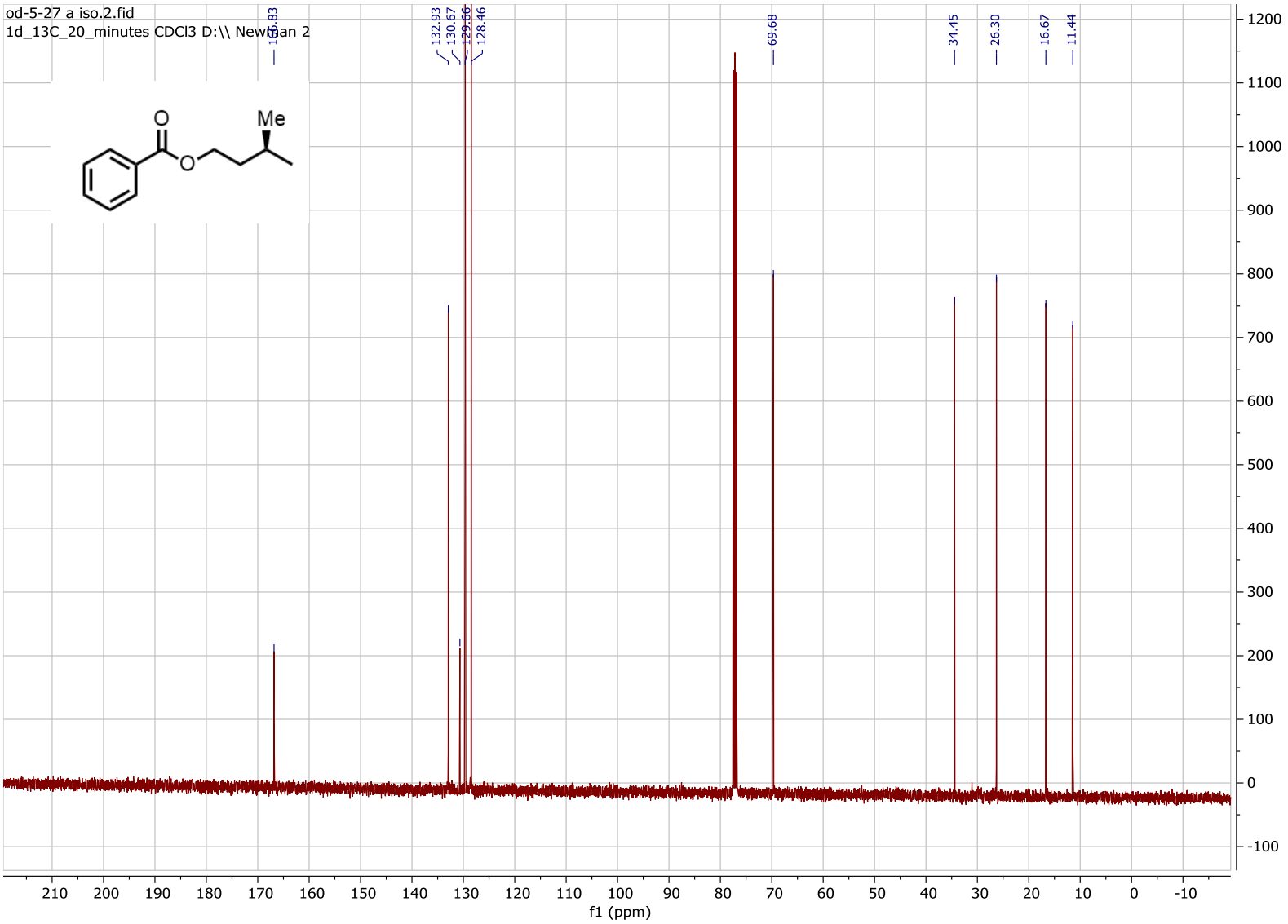



od-5-7 b iso j.4.fid
1d_13C_1_hour CDCl3 D:\\ Newman 60
166.15
133.35
129.69
129.49
128.49
56.79
30.54
30.32
f1 (ppm)

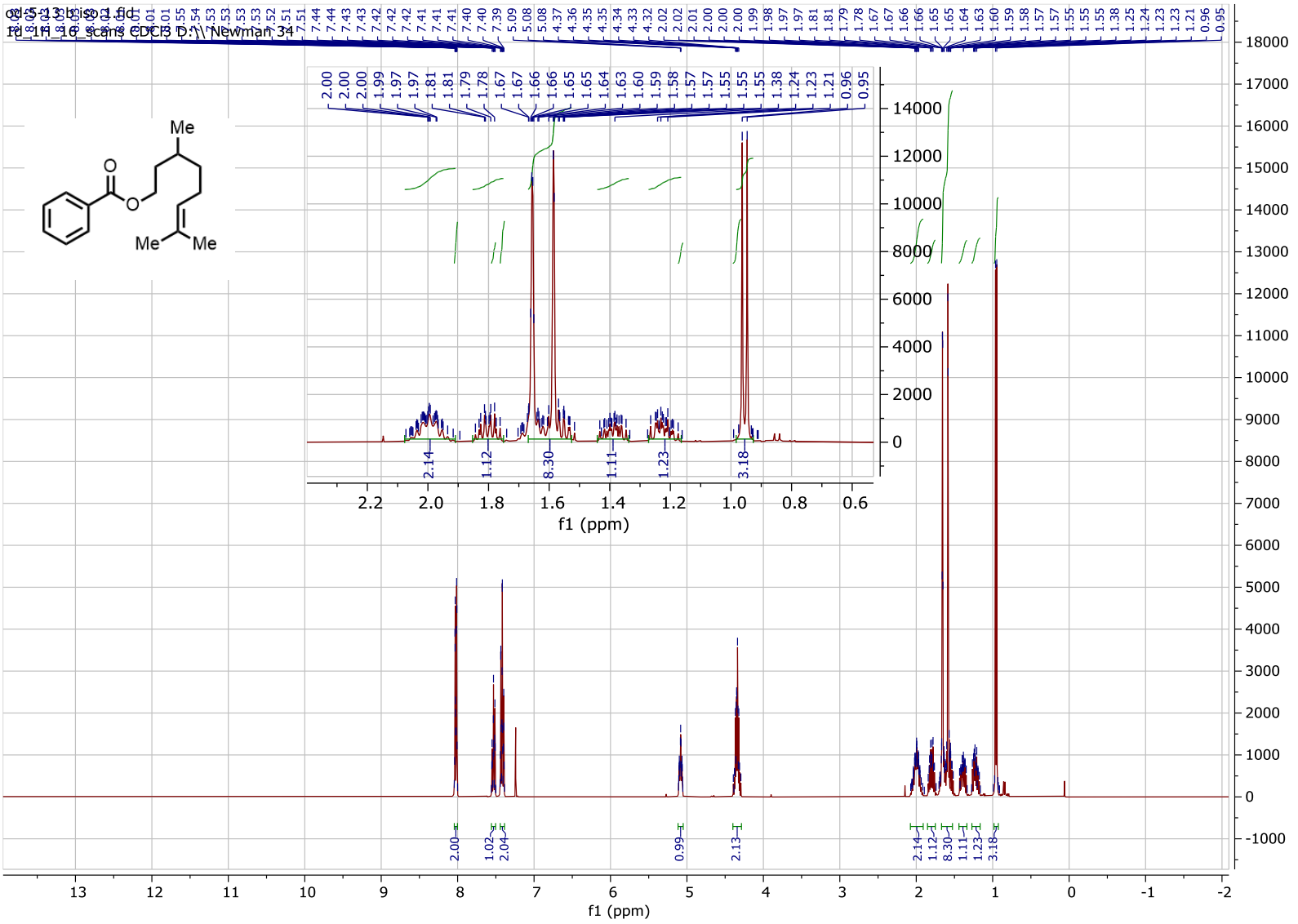

od-5-7 b iso j.3.fid
1d_19F_dec_2_minutes CDCl3 D:\\ Newman
O
O
F F F F
F F
CF3
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

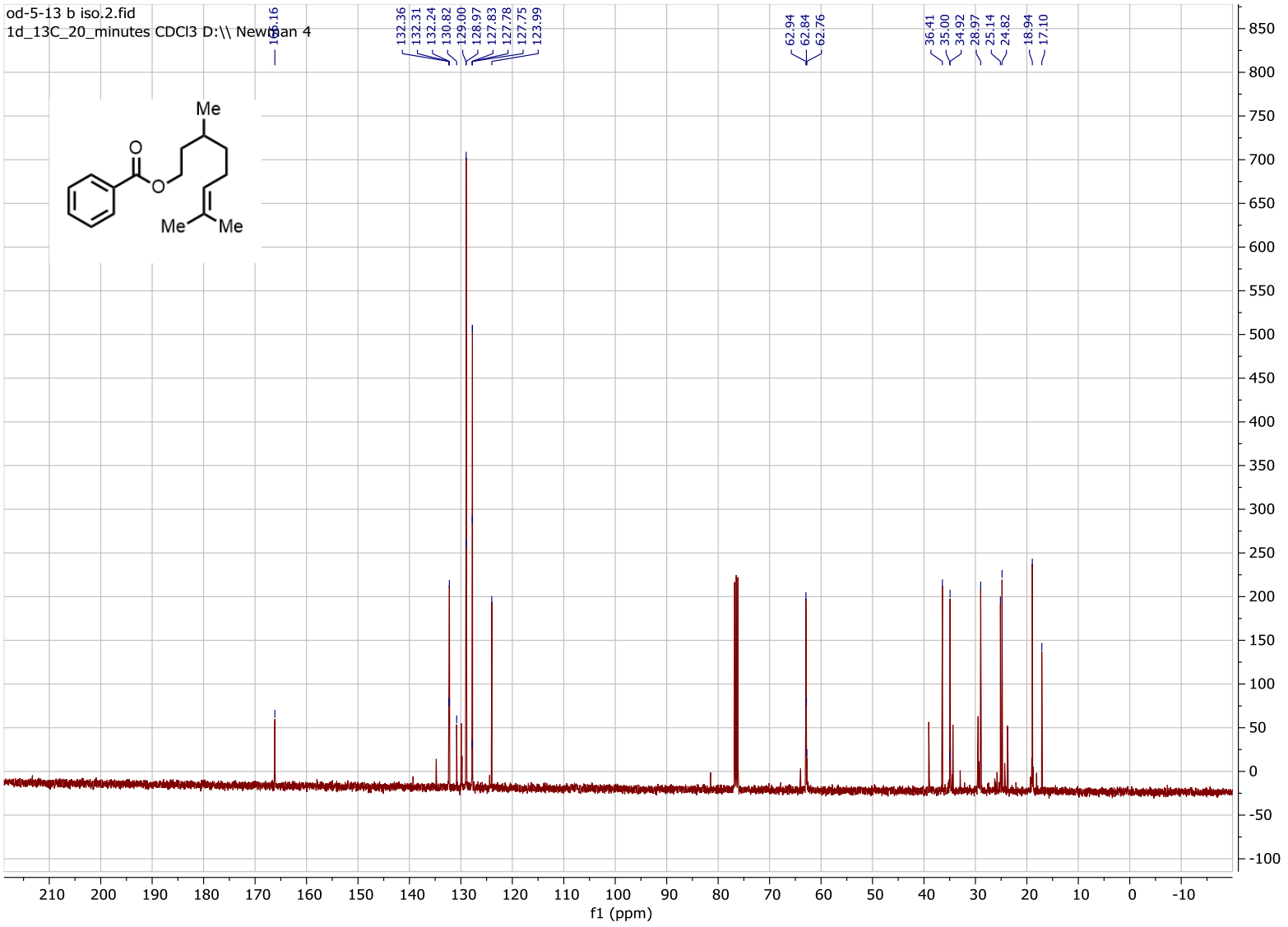
Isopentyl benzoate (**molecule 3.11**) ($CDCl_3$, 400 MHz)



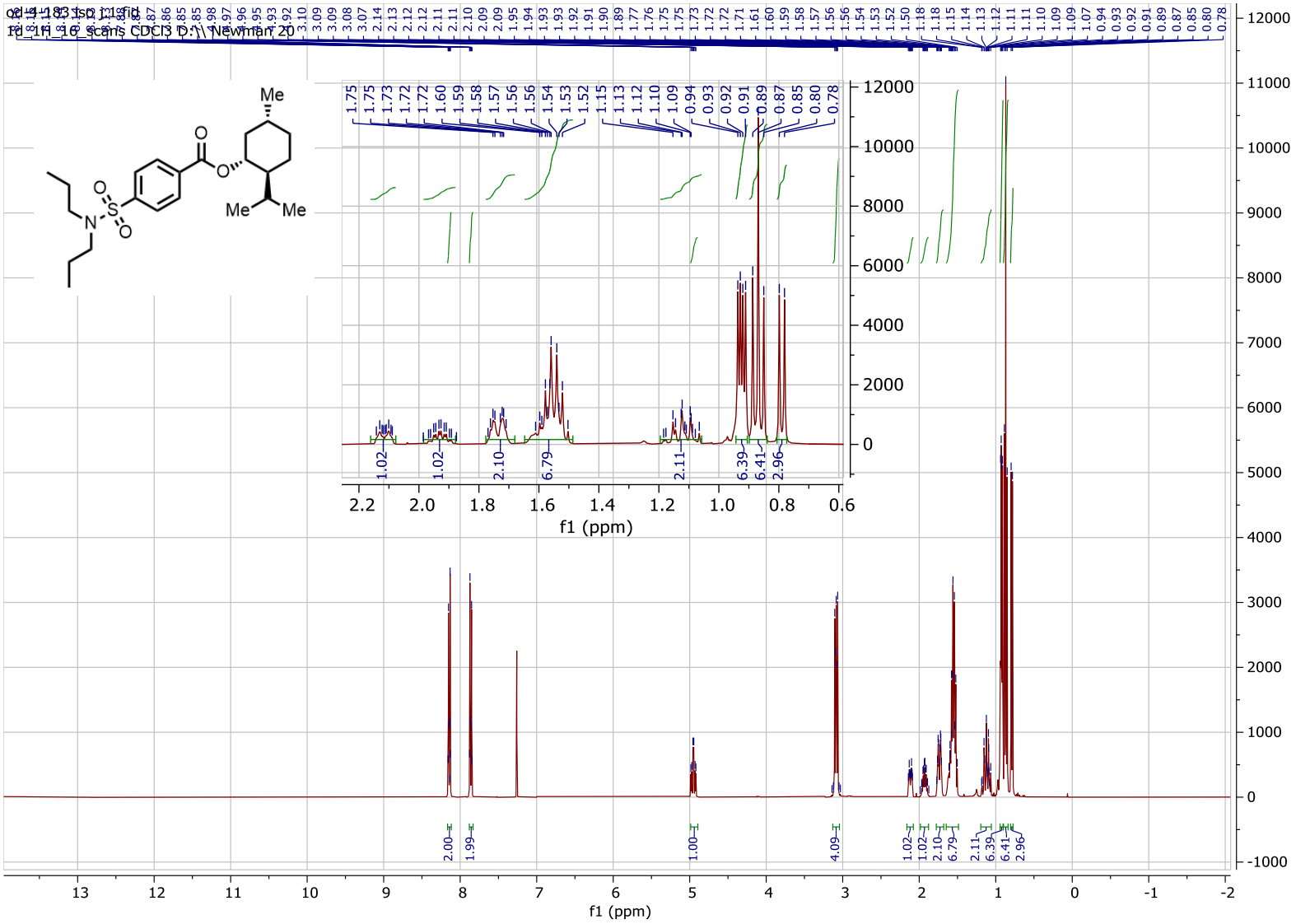

od-5-27 a iso.2.fid
1d_13C_20_minutes CDCl3 D:\\ Newman 2
166.83
132.93
130.67
129.66
128.46
69.68
34.45
26.30
16.67
11.44
O
O
Me
f1 (ppm)

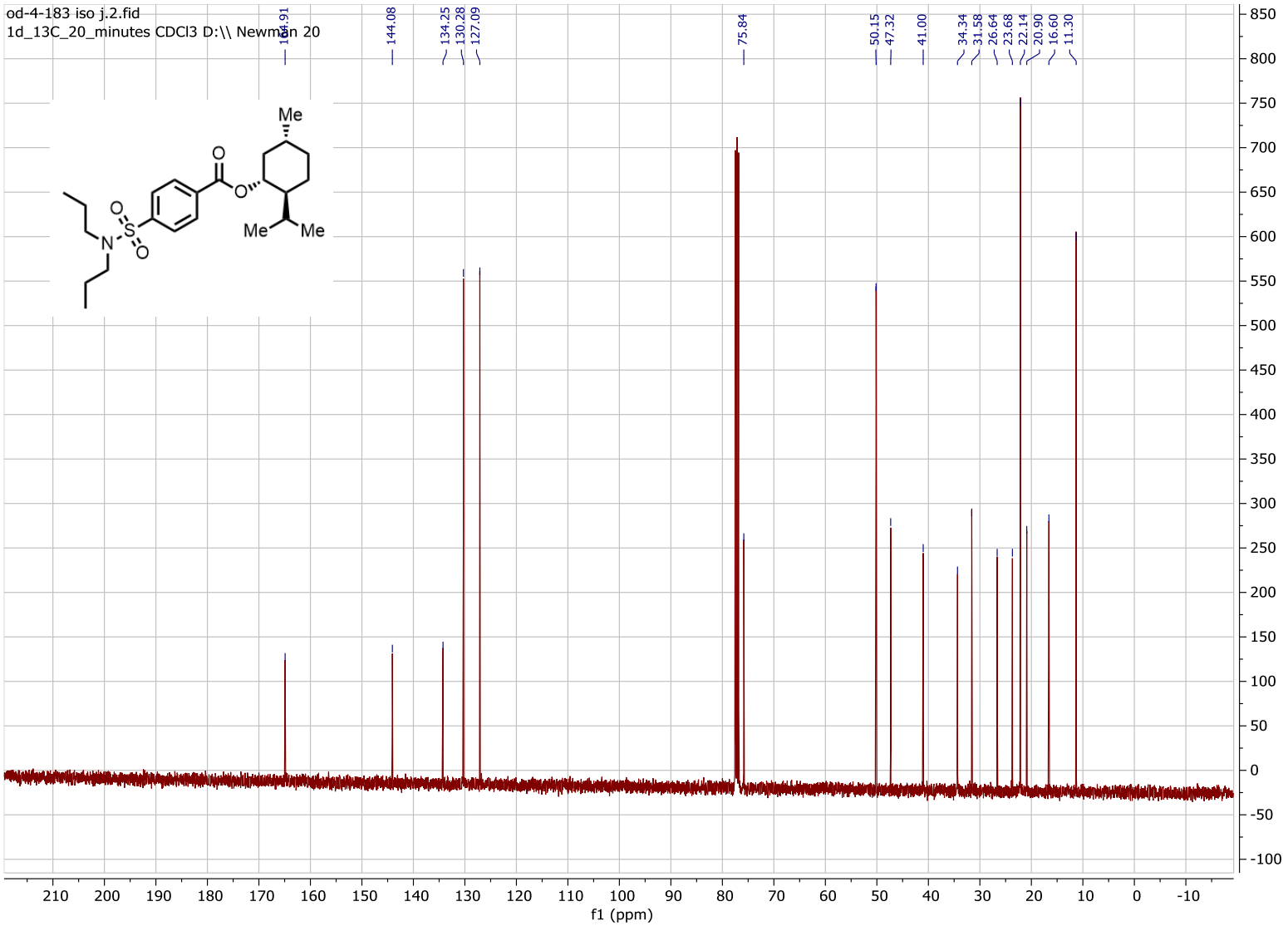
3,7-dimethyloct-6-en-1-yl benzoate (**molecule 3.12**)



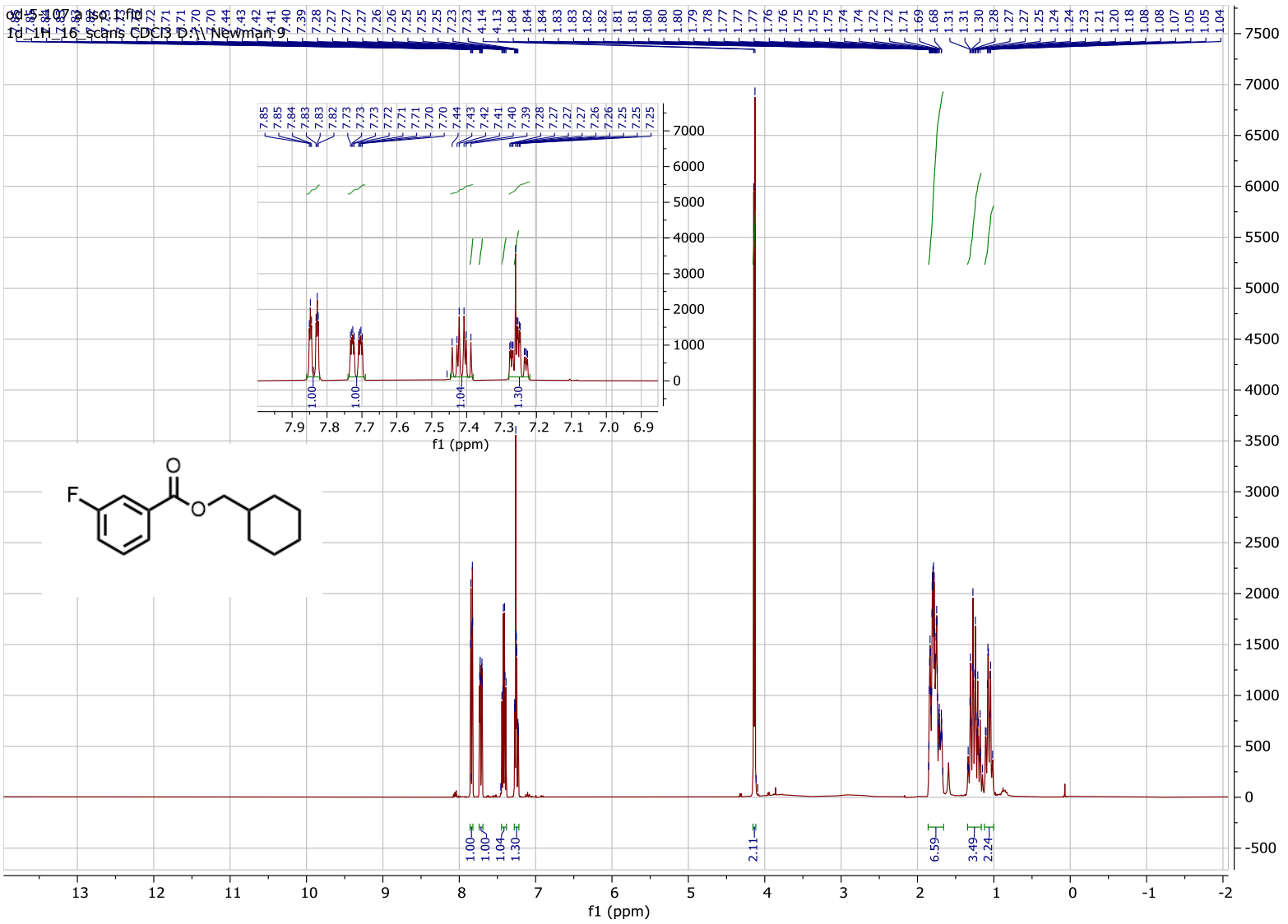

od-5-13 b iso.2.fid
1d_13C_20_minutes CDCl3 D:\\ Newman 4
166.16
132.36
132.31
132.24
130.82
129.00
128.97
127.83
127.78
127.75
123.99
62.94
62.84
62.76
36.41
35.00
34.92
28.97
25.14
24.82
18.94
17.10
Me
O
O
Me
Me
f1 (ppm)

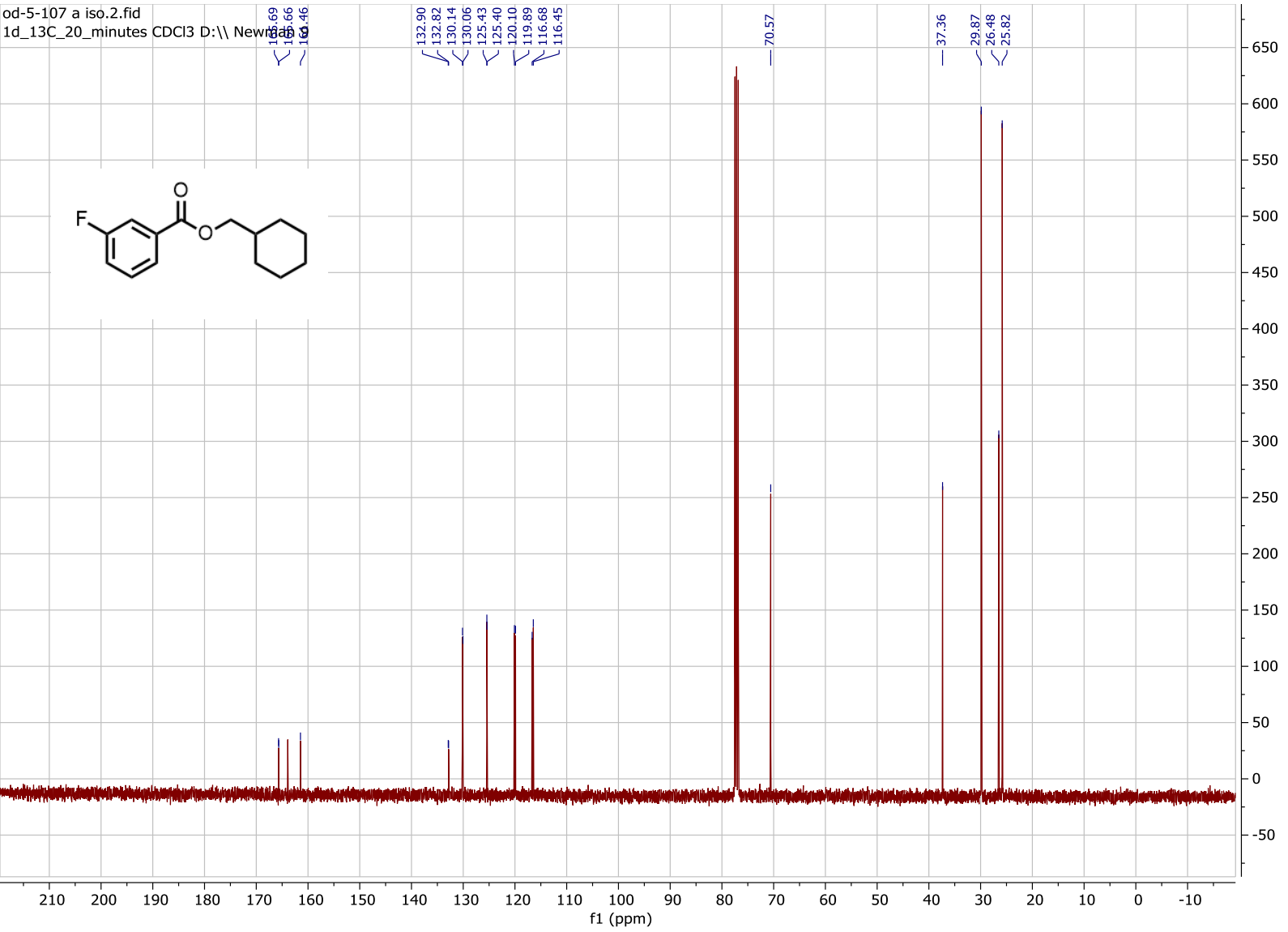
(1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl 4-(N,N-dipropylsulfamoyl)benzoate (**molecule 3.13**) ($CDCl_3$, 400 MHz)

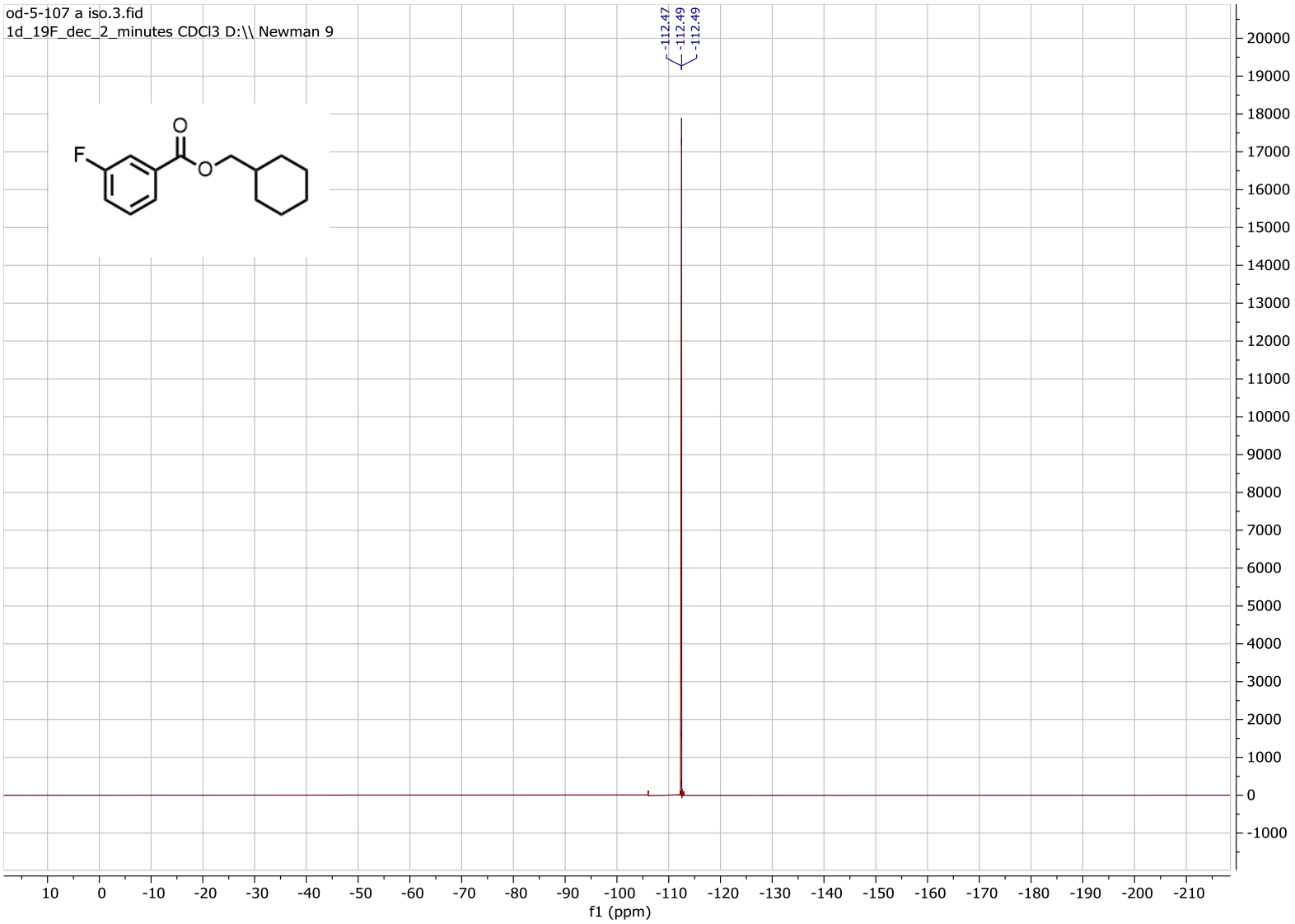



od-4-183 iso j.2.fid
1d_13C_20_minutes CDCl3 D:\\ Newman 20
164.91
144.08
134.25
130.28
127.09
75.84
50.15
47.32
41.00
34.34
31.58
26.64
23.68
22.14
20.90
16.60
11.30
Me
O
O
O
O
N
S
Me
Me
f1 (ppm)

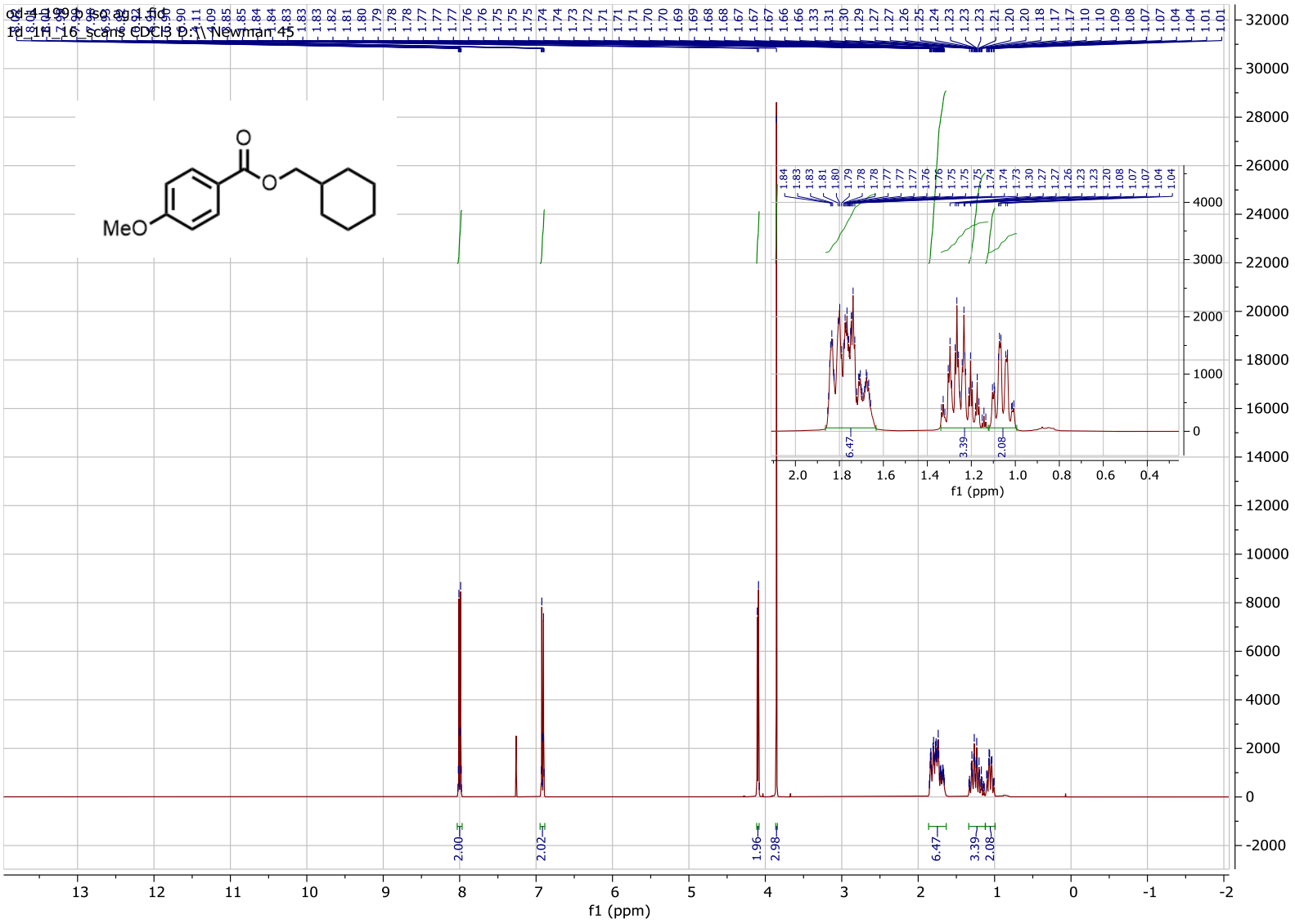
Cyclohexylmethyl 3-fluorobenzoate (**molecule 3.14**) ($CDCl_3$, 400 MHz)

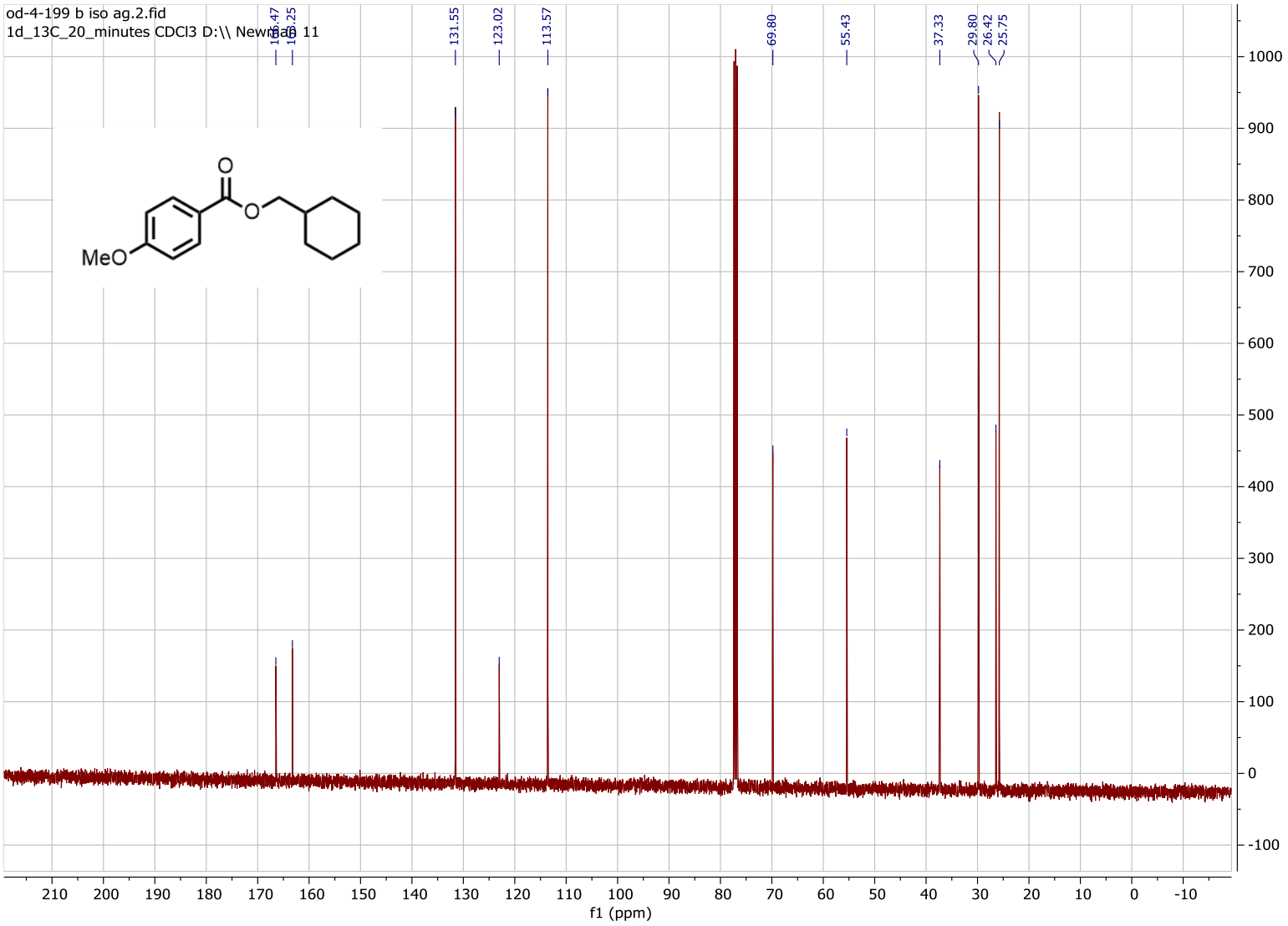



od-5-107 a iso.2.fid
1d_13C_20_minutes CDCl3 D:\\ Newmdata
165.69
165.66
163.46
132.90
132.82
130.14
130.06
125.43
125.40
120.10
119.89
116.68
116.45
70.57
37.36
29.87
26.48
25.82
F
O
O
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

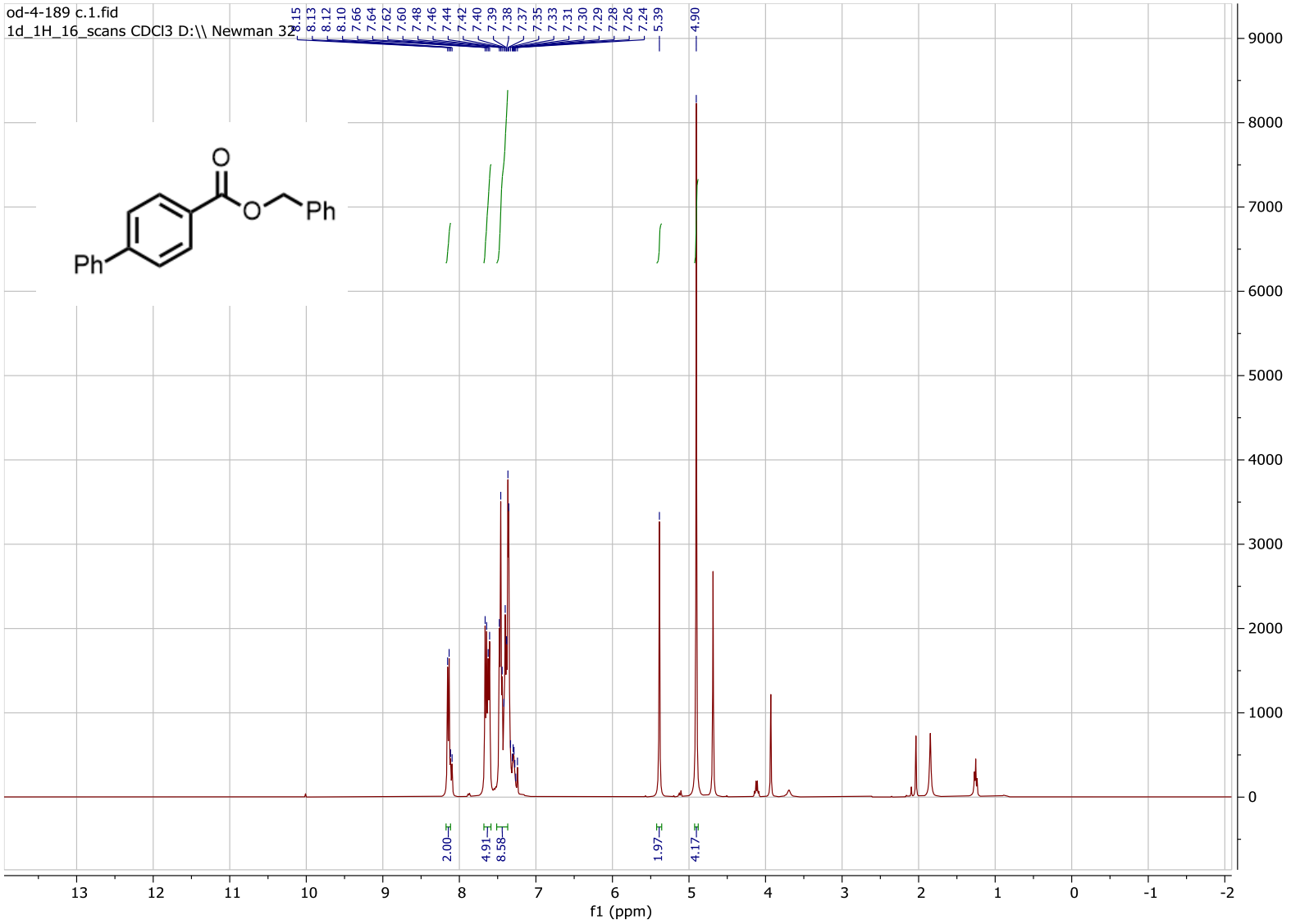

od-5-107 a iso.3.fid
1d_19F_dec_2_minutes CDCl3 D:\\ Newman 9
-112.47
-112.49
-112.49
F
O
O
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

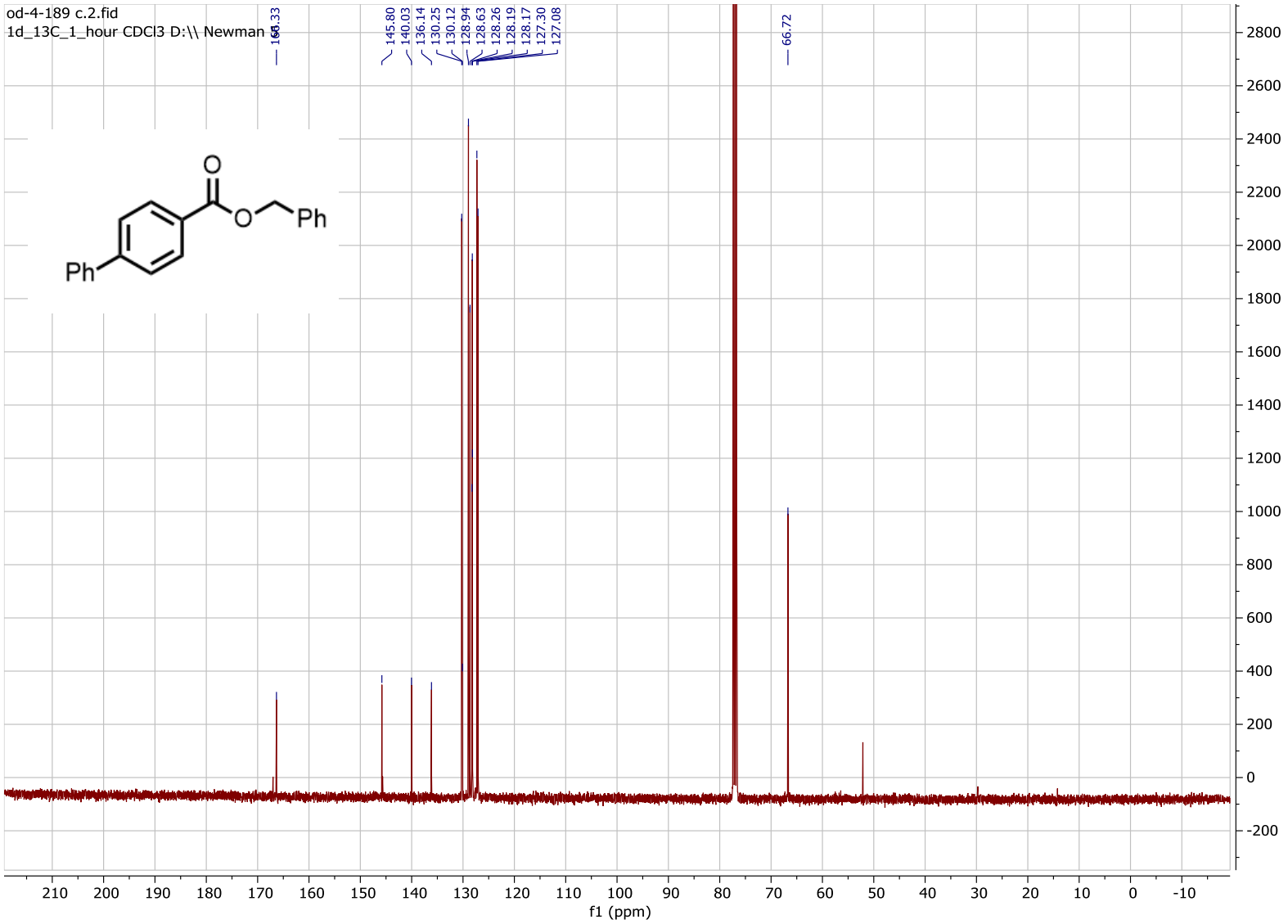
Cyclohexylmethyl 4-methoxybenzoate (**molecule 3.15**) ($CDCl_3$, 400 MHz)



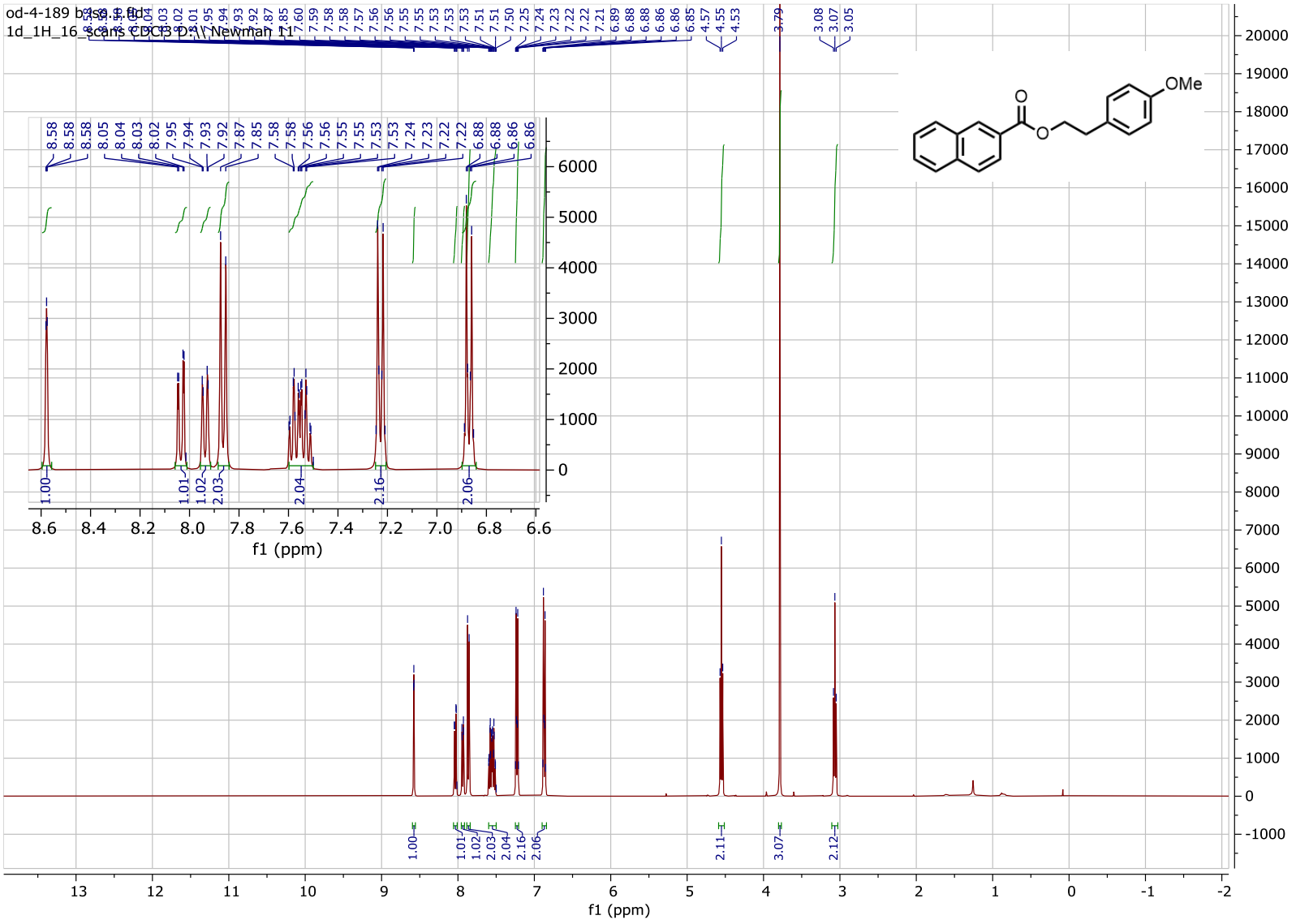

od-4-199 b iso ag.2.fid
1d_13C_20_minutes CDCl3 D:\\ Newdata 11
166.47
166.25
131.55
123.02
113.57
69.80
55.43
37.33
29.80
26.42
25.75
MeO
O
O
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

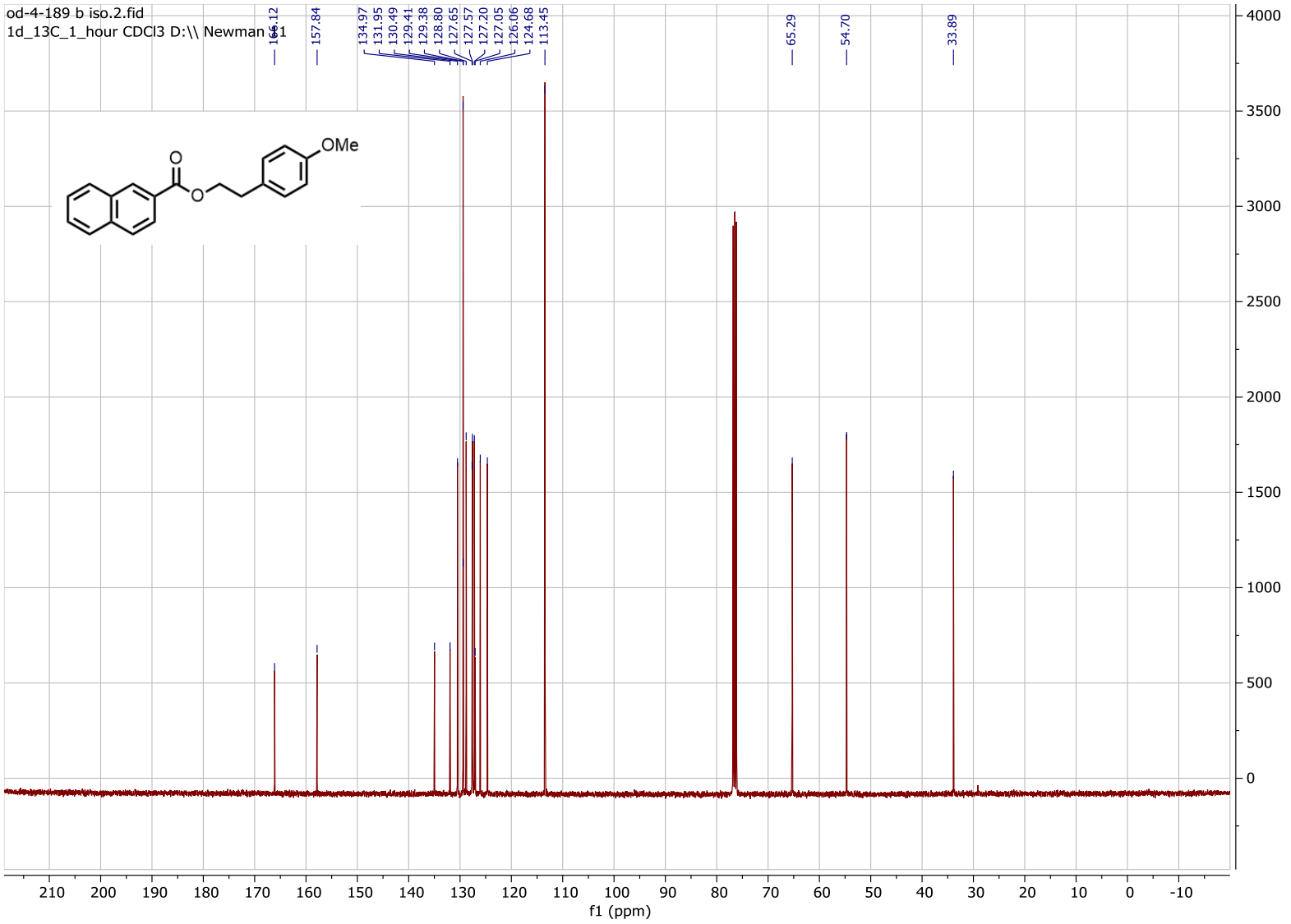
Benzyl [1,1′-biphenyl]-4-carboxylate (**molecule 3.16**) ($CDCl_3$, 400 MHz)



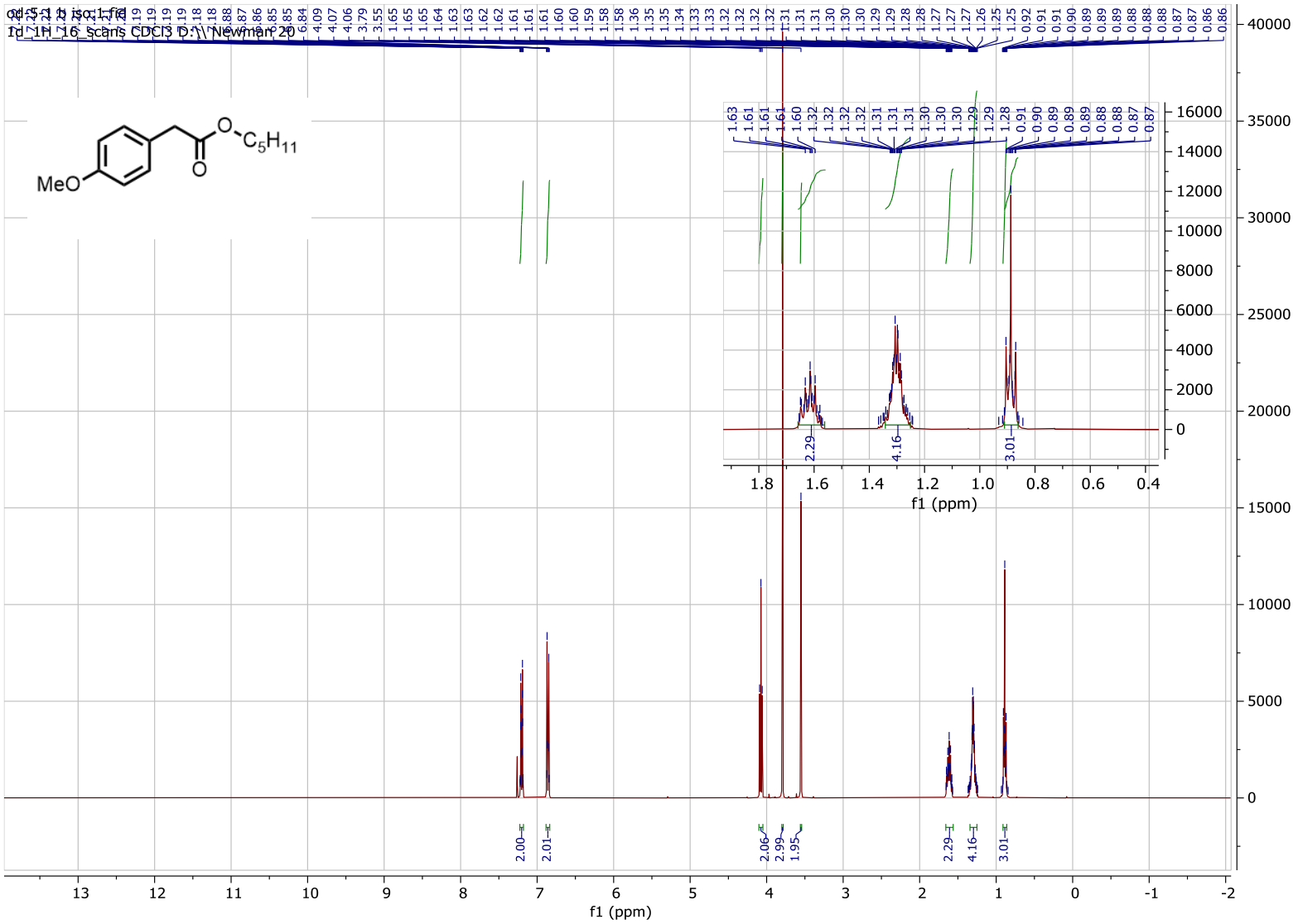

od-4-189 c.2.fid
1d_13C_1_hour CDCl3 D:\\ Newman
166.33
145.80
140.03
136.14
130.25
130.12
128.94
128.63
128.26
128.19
128.17
127.30
127.08
66.72
O
O
Ph
Ph
f1 (ppm)

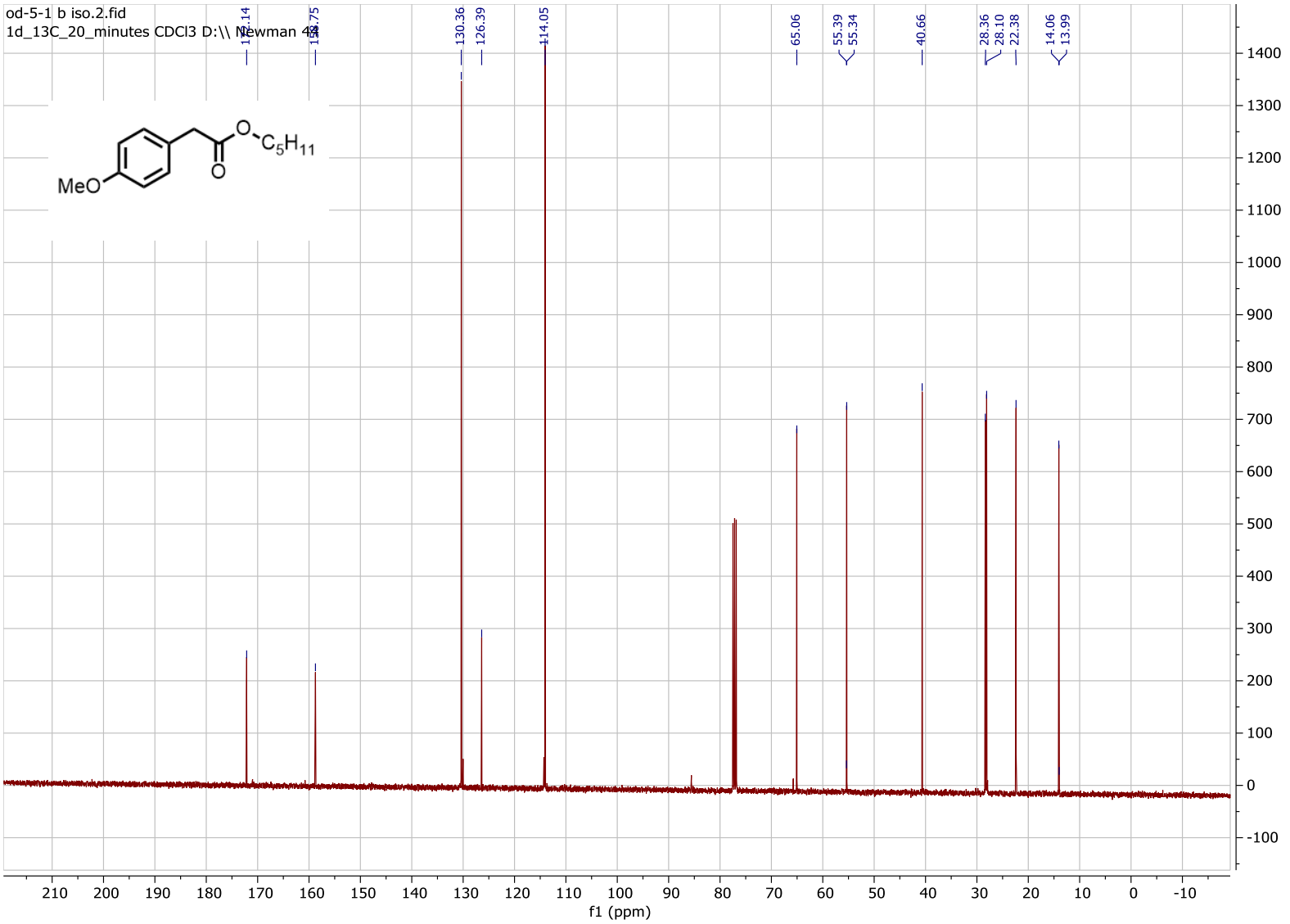
4-methoxyphenethyl 2-naphthoate (**molecule 3.17**) ($CDCl_3$, 400 MHz)



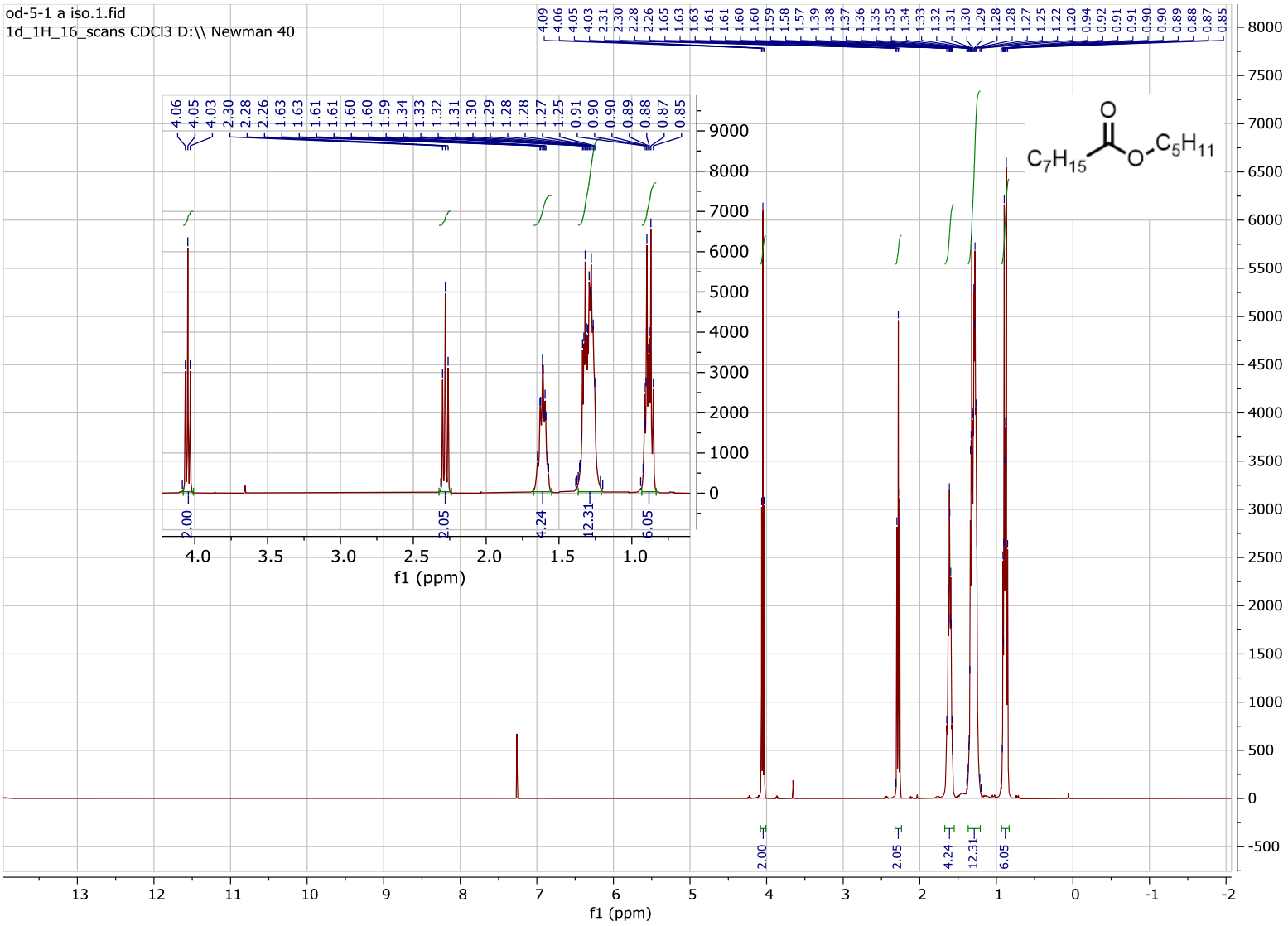

od-4-189 b iso.2.fid
1d_13C_1_hour CDCl3 D:\\ Newman 1
166.12
157.84
134.97
131.95
130.49
129.41
129.38
128.80
127.65
127.57
127.20
127.05
126.06
124.68
113.45
65.29
54.70
33.89
OMe
O
O
4000
3500
3000
2500
2000
1500
1000
500
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

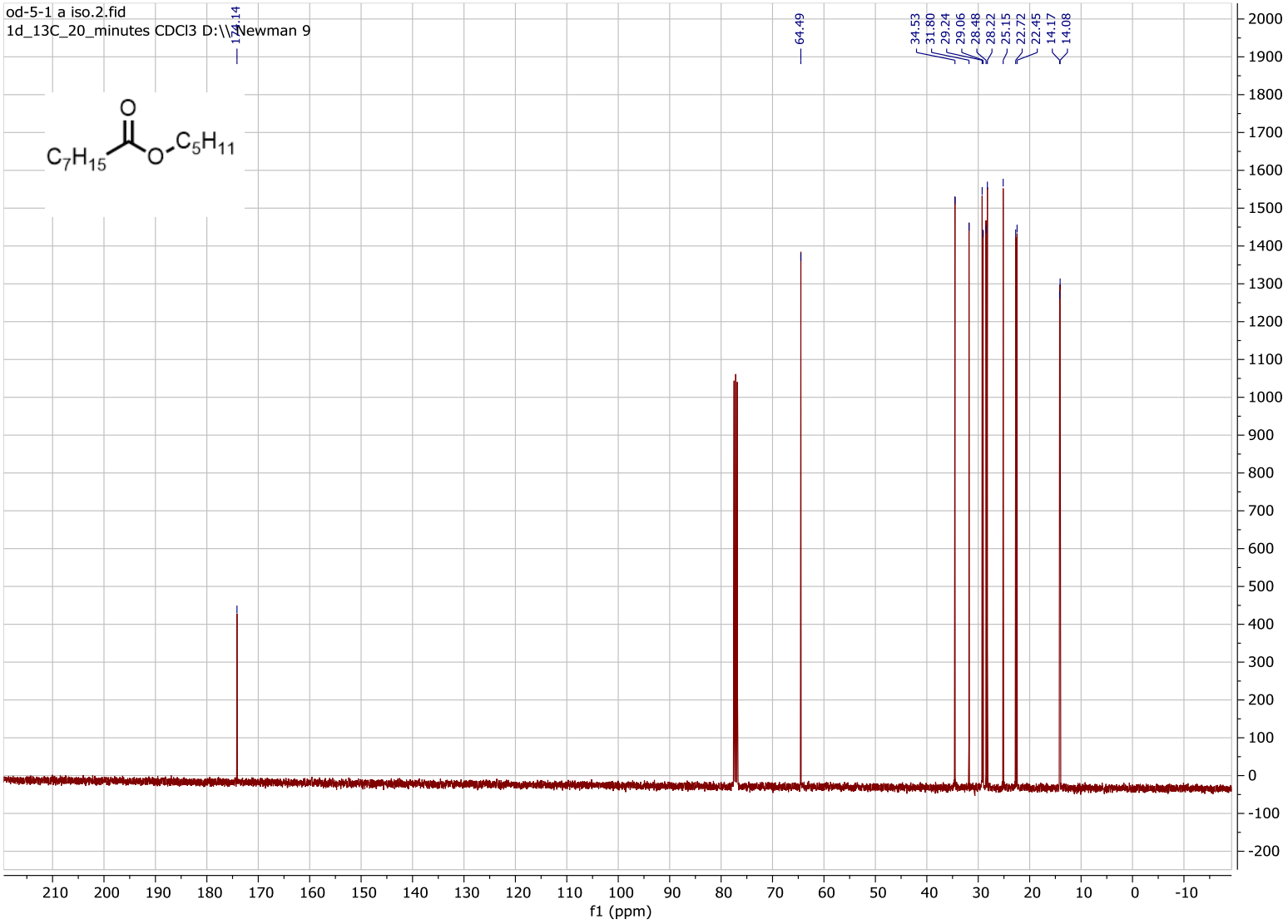
Pentyl 2-(4-methoxyphenyl)acetate (**molecule 3.19**) ($CDCl_3$, 400 MHz)



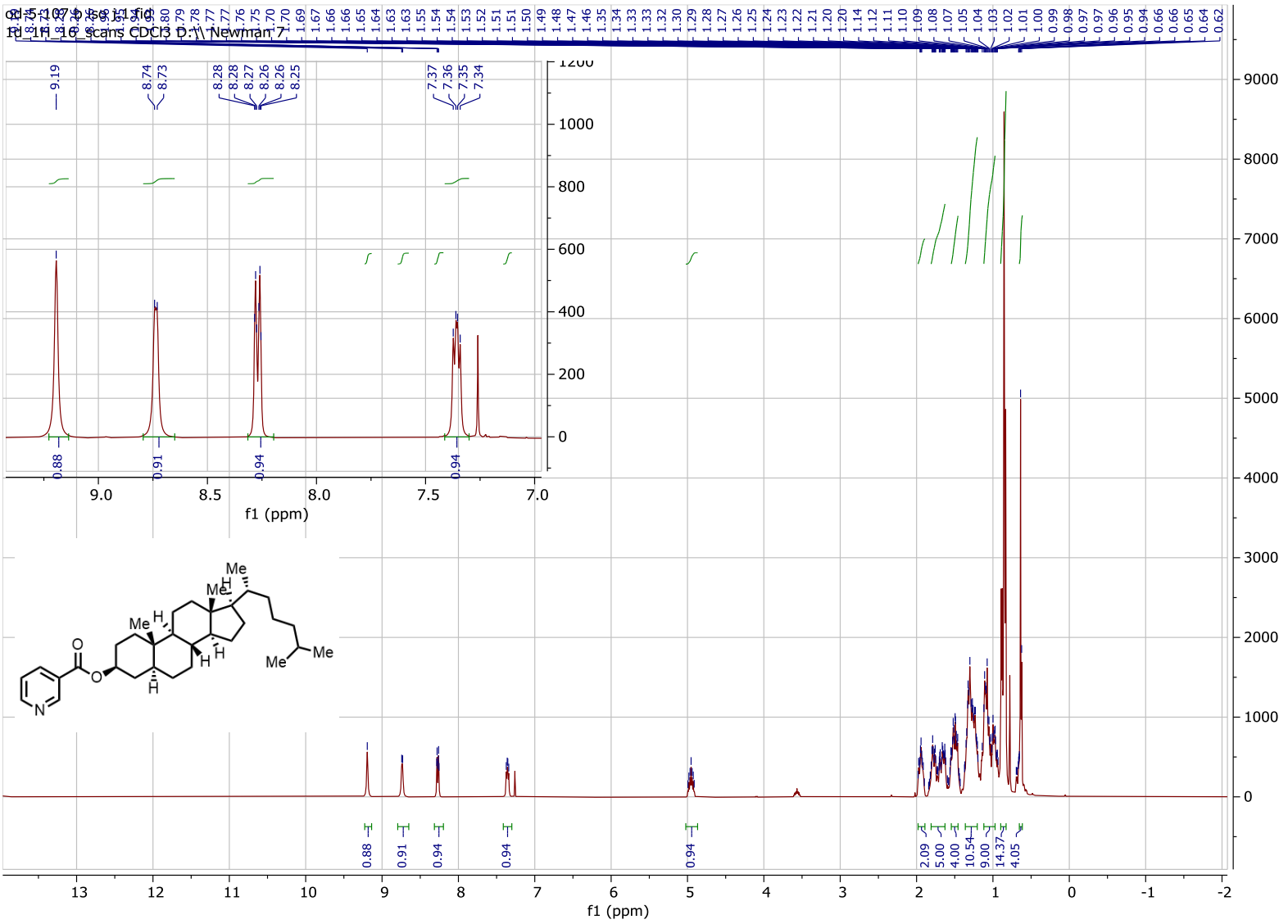

od-5-1 b iso.2.fid
1d_13C_20_minutes CDCl3 D:\\ Newman 48
167.14
158.75
130.36
126.39
114.05
65.06
55.39
55.34
40.66
28.36
28.10
22.38
14.06
13.99
MeO
O
O
C5H11
f1 (ppm)

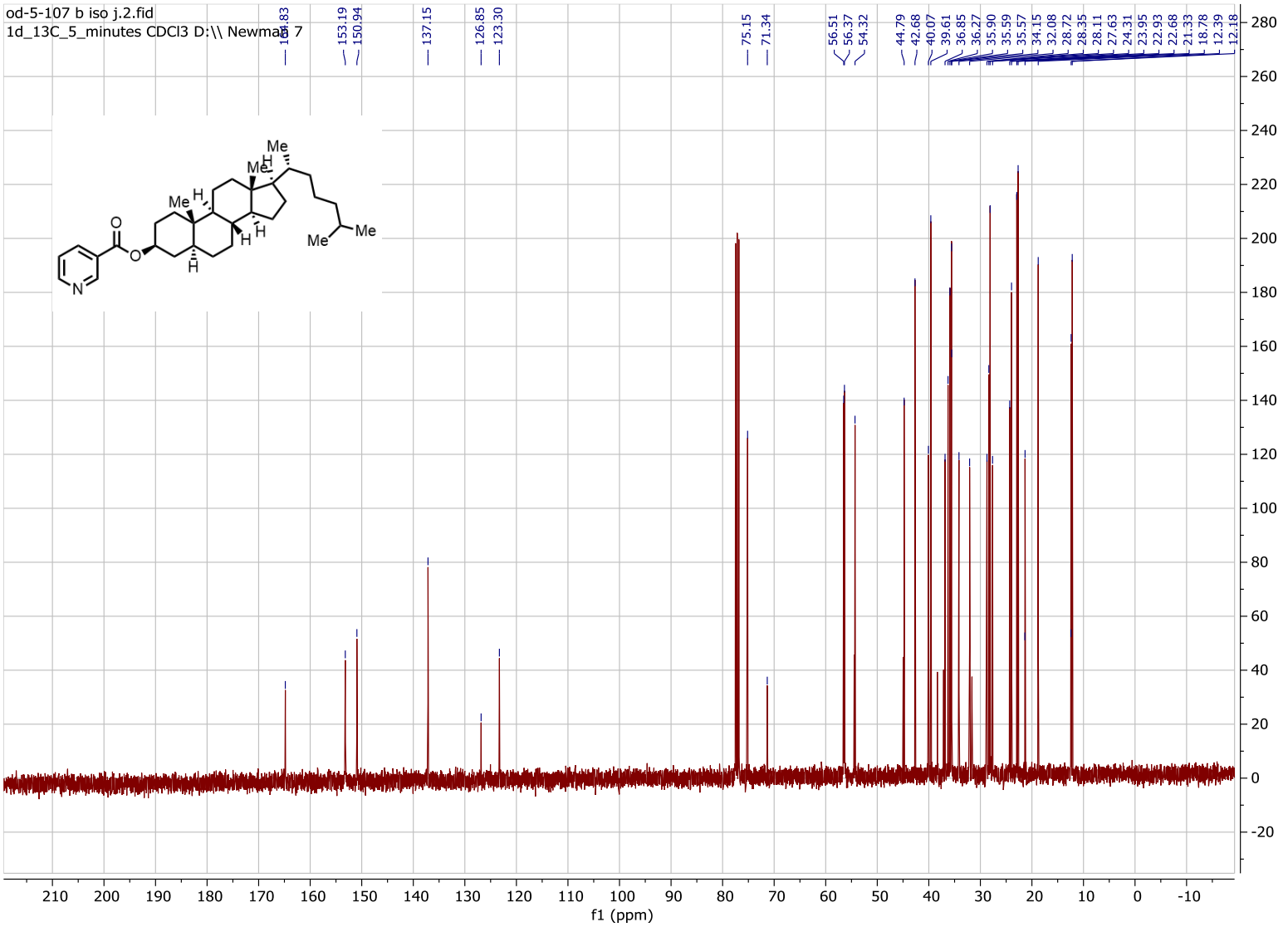
Pentyl octanoate (**molecule 3.20**) ($CDCl_3$, 400 MHz)




od-5-1 a iso.2.fid
1d_13C_20_minutes CDCl3 D:\\Newman 9
174.14
64.49
34.53
31.80
29.24
29.06
28.48
28.22
25.15
22.72
22.45
14.17
14.08
C7H15
O
O
C5H11
f1 (ppm)

(3*S*,5*S*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl nicotinate (**molecule 3.21**) ($CDCl_3$,400 MHz)




od-5-107 b iso j.2.fid
1d_13C_5_minutes CDCl3 D:\\ Newman 7
165.83
153.19
150.94
137.15
126.85
123.30
75.15
71.34
56.51
56.37
54.32
44.79
42.68
40.07
39.61
36.85
36.27
35.90
35.59
35.57
34.15
32.08
28.72
28.35
28.11
27.63
24.31
23.95
22.93
22.68
21.33
18.78
12.39
12.18
Me
H
Me
Me
H
H
H
Me
Me
O
O
N
f1 (ppm)

Methyl (2,2,2-trifluoroethyl) terephthalate (molecule **3.32**) ($CDCl_3$, 400 MHz)