

**ACYL AND DECARBOXYLATIVE CROSS-COUPING OF AMIDES AND
CARBOXYLIC ACIDS**

By

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ABSTRACT OF THE DISSERTATION

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Professor Michal Szostak

The amide bond represents one of the most important functional motifs in chemistry and biology. However, despite the central role of amides as ubiquitous pharmacophores in medicinal chemistry and common intermediates in organic synthesis, transition-metal-catalyzed transformations of amides by N–C bond activation have remained largely unexplored. The major reason is that high activation energy is required for the N–C(O) bond scission due to $n_N \rightarrow \pi^*_{C=O}$ conjugation (amide bond resonance of 15–20 kcal/mol in planar amides, ca. 40% double bond character). Our group has introduced a new generic mode of activation of amide bonds by geometric distortion, whereby metal insertion into an inert amide bond can proceed effectively if the classic Pauling's amide bond resonance has been disrupted. During my Ph.D. research, we

have successfully developed new classes of reactive amides as well as established previously unknown transition-metal-catalyzed transformations of amides and related electrophiles using ground-state-destabilization concept.

The focus of this thesis is on three major areas: (1) the use of amides as acyl electrophiles in palladium-catalyzed Suzuki-Miyaura acyl cross-coupling reactions; (2) the use of amides as aryl electrophiles in transition-metal-catalyzed aryl cross-coupling reactions; (3) the development of carboxylic acids as aryl electrophiles in transition-metal-catalyzed decarbonylative cross-coupling reactions by a redox-neutral manifold. Overall, these studies have demonstrated the potential of amides as acyl and aryl electrophiles and carboxylic acids as aryl electrophiles in catalytic cross-coupling reactions of broad synthetic interest.

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List of Abbreviations

Ac	acetyl
Ac ₂ O	acetic anhydride
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
B ₂ nep ₂	bis(neopentyl glycolato)diboron
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
B ₂ pin ₂	bis(pinacolato)diboron
DavePhos	2-Dicyclohexylphosphino-2'-(<i>N,N</i> -dimethylamino)biphenyl
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DPEPhos	Bis(2-diphenylphosphinophenyl)ether
DPPB	1,4-Bis(diphenylphosphino)butane
DPPE	1,2-Bis(diphenylphosphino)ethane
DPPF	1,1'-Ferrocenediyi-bis(diphenylphosphine)
DPPHex	1,6-Bis(diphenylphosphino)hexane
DPPM	Bis(diphenylphosphino)methane
DPPII	1,3-Bis(diphenylphosphino)propane
DPPPent	1,5-Bis(diphenylphosphino)pentane
Mes	mesityl
Ms	mesyl / methanesulfonyl
Ni(acac) ₂	Nickel(II) acetylacetone
Ni(dppe)Cl ₂	[1,2-Bis(diphenylphosphino)ethane]dichloronickel(II)
Ni(dppf)Cl ₂	[1,1'-Bis(diphenylphosphino)ferrocene]dichloronickel(II)
Ni(dppp)Cl ₂	[1,3-Bis(diphenylphosphino)propane]dichloronickel(II)
Ni(OAc) ₂	Nickel(II) acetate
Ni(PCy ₃) ₂ Cl ₂	Bis(tricyclohexylphosphine)nickel(II) dichloride
Ni(PPh ₃) ₂ Cl ₂	Bis(triphenylphosphine)nickel(II) dichloride
NMP	1-methyl-2-pyrrolidone
PCy ₃ HB ₄	Tricyclohexylphosphonium tetrafluoroborate
PCy ₂ Ph	Dicyclohexylphenylphosphine
PCyPh ₂	Cyclohexyldiphenylphosphine
PdCl ₂	Palladium(II) chloride
Pd(dba) ₂	Bis(dibenzylideneacetone)palladium(0)
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
Pd(OAc) ₂	Palladium(II) acetate
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
PEt ₃ HB ₄	Triethylphosphonium tetrafluoroborate
PivCl	pivaloyl chloride / trimethylacetyl chloride
Piv ₂ O	pivalic anhydride / trimethylacetic anhydride
PivOH	pivalic acid

PMe_3HBF_4	Trimethylphosphonium tetrafluoroborate
$\text{PMet-Bu}_2\text{HBF}_4$	Di- <i>tert</i> -butyl(methyl)phosphonium tetrafluoroborate
$\text{P(4-MeO-C}_6\text{H}_4)_3$	Tris(4-methoxyphenyl)phosphine
$\text{P(n-Bu)}_3\text{HBF}_4$	Tri- <i>n</i> -butylphosphonium tetrafluoroborate
P(o-tol)_3	Tri(<i>o</i> -tolyl)phosphine
PPh_3	Triphenylphosphine
$\text{P(t-Bu)}_3\text{HBF}_4$	Tri- <i>tert</i> -butylphosphonium tetrafluoroborate
RE	resonance energy
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
THF	tetrahydrofuran
Ts	tosyl / 4-toluenesulfonyl
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Chapter 1

Introduction

Parts of this section were adapted with permission from the article “Twisted Amides: From Obscurity to Broadly Useful Transition-Metal-Catalyzed Reactions by N–C Amide Bond Activation” (*Chem. Eur. J.* **2017**, *23*, 7157). Copyright ©2017, Thieme Gruppe.

1.1 Amide bond and their versatile applications

The amide bond resonance represents a classic effect in organic chemistry.^{1–4} As predicted by Pauling in 1931, typical amides contain planar bonds of approximately 40% partial double bond character.^{5,6} The n_N to $\pi^*_{C=O}$ conjugation (resonance energy (RE) of 21.84 kcal mol⁻¹) renders the amide bond one of the most robust and least reactive functional groups in organic synthesis (Figure 1.1).¹ These features are critical to the role of amides as robust building blocks of life.^{2–4} However, the remarkable stability of amides also means that selective organic reactions by amide bond cleavage remain extremely difficult.⁵

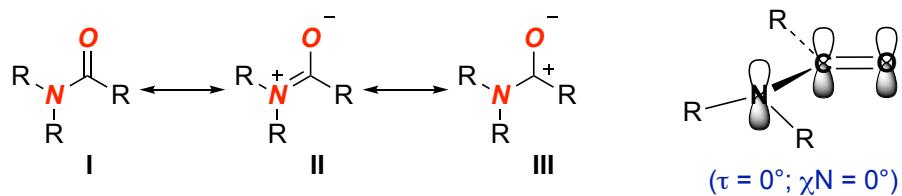


Figure 1.1 Planar amides: amide bond resonance.

Historically, the prospect of disrupting amidic resonance by placing the amide bond in a rigid bicyclic ring system with nitrogen at the ring fusion was considered as early as in the 1930s and 1940s, undoubtedly sparked by the instability of the strained amide bond in

beta-lactam antibiotics.^{5,6} Over the years, several research groups addressed the problem of ring strain in twisted amides with some notable contributions by Pracejus, Yakhontov, Brown, Blackburn, Shea, Greenberg, and Williams, among others.^{7,8} However, it was not until 1998 when Kirby and co-workers disclosed the synthesis and full structural characterization of 1-aza-2-adamnatanone containing a perfectly perpendicular amide bond (Winkler–Dunitz distortion parameters,⁹ $\tau = 85.88$; $\chi_N = 61.78$).¹⁰ As expected, the amide showed some remarkable properties, in essence, behaving as a highly reactive amino-ketone. Shortly thereafter, in 2006, Stoltz and Tani succeeded in the synthesis of the archetypal twisted amide, 2-quinuclidonium tetrafluoroborate ($\tau = 89.18$; $\chi_N = 59.58$).¹¹ The structure was unambiguously solved by X-ray crystallography, quantitatively illustrating the effect of amide bond twist on the geometry (Figure 1.2). These two amides tested the limits of disrupting the amide bond resonance and are now considered classics in organic chemistry textbooks.

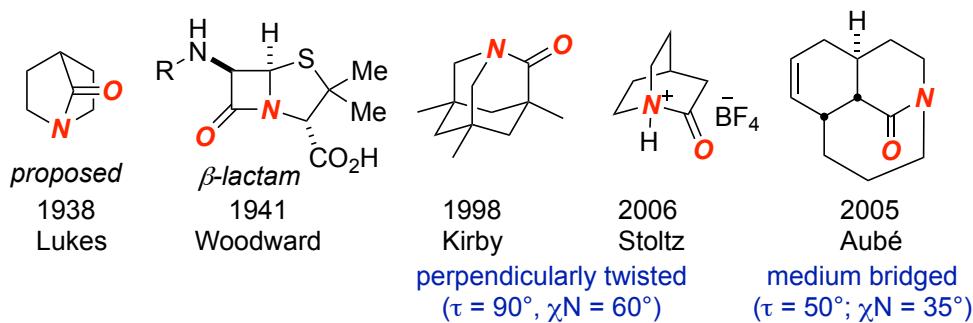


Figure 1.2 Selected examples of bridged lactams.

In the last five years, the use of amide bond twist (distortion) in simple acyclic amides has advanced to the general organic chemistry applications enabling new highly attractive N–C amide bond cross-coupling reactions of great synthetic relevance.¹² In contrast to

conformationally locked bridged lactams, these new acyclic twisted amides feature unlocked non-planar amide bonds that can be systematically engaged in powerful cross-coupling manifolds by metal insertion into the N–C(O) bond (Figure 1.3).¹³

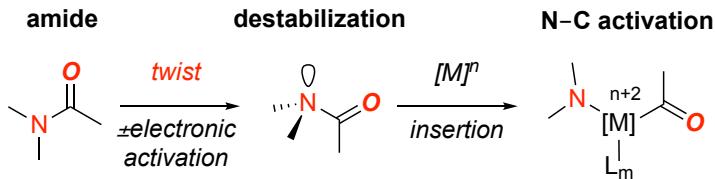


Figure 1.3 New strategy for activation of amide N–C(O) bonds via ground-state destabilization.

It is fair to say that transition-metal-catalyzed cross-coupling has revolutionized the way organic molecules are built today.¹⁴ In general, transition-metal-catalyzed cross-coupling of amides can be classified as acyl and aryl cross-coupling (Figure 1.4). High stability, abundance, ease of synthesis, low price, and lack of toxicity have made the amide linkage a privileged functional group in organic synthesis. Amides represent some of the most widely utilized motifs in pharmaceuticals, agro-chemicals, and functional materials.¹⁻⁴ Considering the prevalence of the amide bond in all fields of chemistry (Figure 1.5), rationally designed, transition-metal-catalyzed, chemoselective cross-coupling of ubiquitous amides by the strain-driven N–C bond cleavage is likely to take a central place in the chemical toolbox.

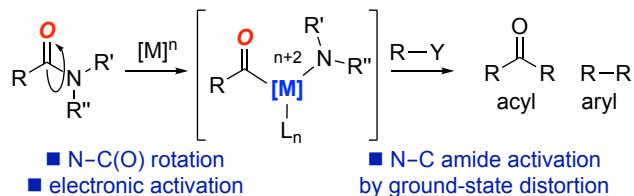


Figure 1.4 Metal-catalyzed acyl and aryl cross-coupling of amides.

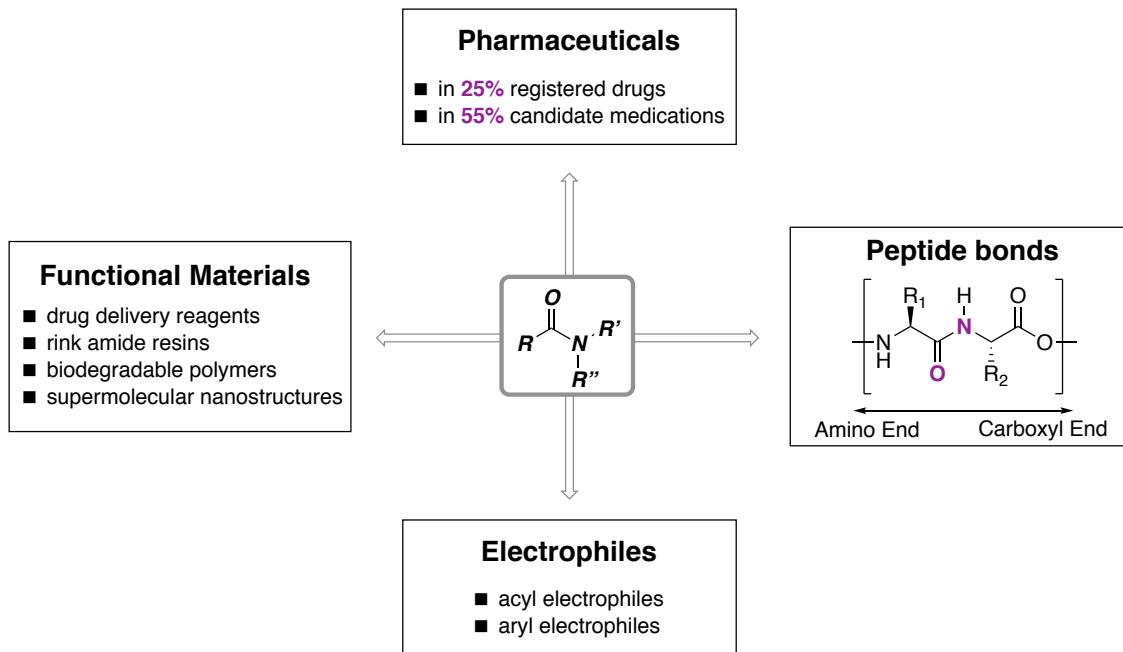


Figure 1.5 The broad utility of amide bonds.

1.2 Amides in transition-metal-catalyzed acyl cross-coupling reactions

Transition-metal-catalyzed cross-coupling reactions are widely used in the field of organic synthesis.^{13,14} Recent impressive progress has been achieved in the activation of inert C–H, C–O, C–F, and C–C bonds.¹⁵ However, the cross-coupling by amide bond activation was absent from the transition-metal-catalyzed cross-coupling toolbox until 2015 (Figure 1.6).¹⁶ Unsurprisingly, the classic amidic resonance renders selective low-valent metal insertion into the amide bond unfavorable. Therefore, to achieve synthetically useful oxidative addition of an N–C amide bond, the amide bond resonance (RE in planar amides of 15–20 kcal mol⁻¹) must be disfavored by steric and/or electronic methods.

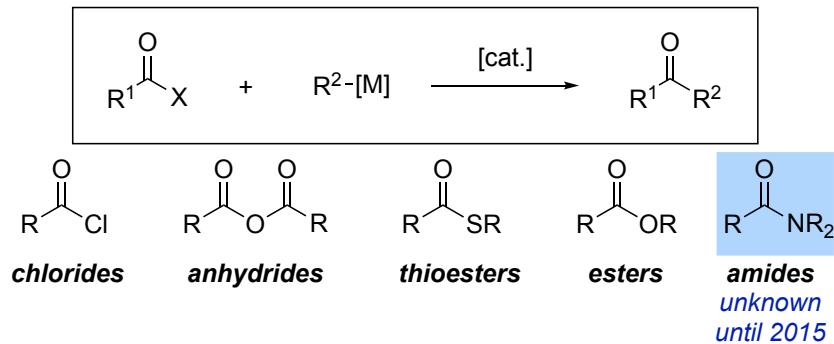


Figure 1.6 General classes of acyl electrophiles.

The benefits of using amides as cross-coupling partners are significant, and include: (1) the abundance of amide bonds, also in biological contexts;¹⁻⁴ (2) the ability to selectively functionalize the amide group by orthogonal/iterative cross-couplings. In the last five years this mode of amide cross-coupling has resulted in more than 10 new reaction types (Figure 1.7).¹⁶⁻²²

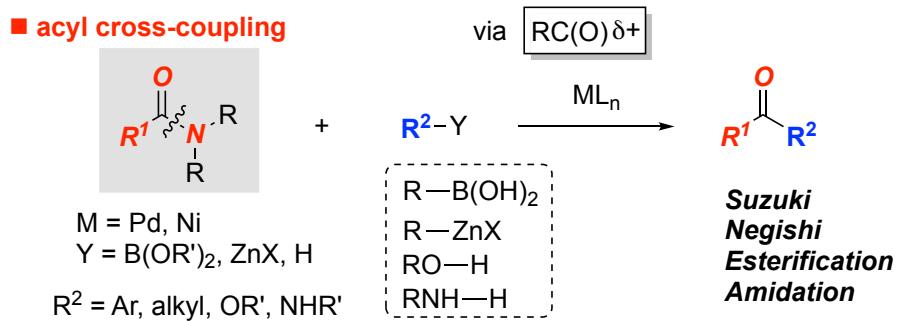


Figure 1.7 Metal-catalyzed cross-coupling of amides via acyl intermediates.

All examples of the amide bond cross-coupling reported to date engage non-planar destabilized amides. The concept of distorting the amide bond has evolved from elegant but less synthetically useful bridged lactams to valuable cross-coupling reactions by N–C bond cleavage to deliver versatile motifs of broad synthetic importance. A generalized

mechanism of cross-coupling reactions involving acyl amide bond N–C(O) activation is presented in Figure 1.8.

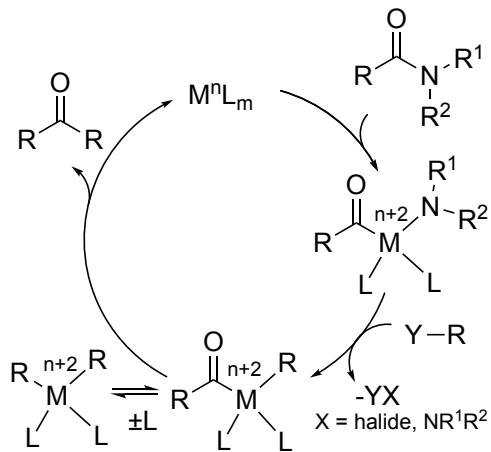


Figure 1.8 Mechanism of metal-catalyzed acyl cross-coupling of amides.

1.3 Amides in transition-metal-catalyzed aryl cross-coupling reactions

In addition to acyl cross-couplings, amides could also be engaged in decarbonylative cross-couplings by a tandem acyl N–C(O)/C–C bond activation. In 2015, our group reported a new generic mode of activation of amide bonds by geometric distortion, whereby metal insertion into an inert amide bond (amide bond resonance of 15-20 kcal/mol in planar amides, ca. 40% double bond character) can proceed selectively if the classic amide bond resonance has been disrupted.^{5,6} The structural studies demonstrated that modulation of amidic resonance is in fact, in contrast to the textbook knowledge, quite easy,⁷ which opened the door for utilization of the amide bond as aryl electrophiles in cross-coupling reactions of broad synthetic interest (Figure 1.9).⁸ In this context, this new manifold of cross-coupling of amide bonds is synthetically unique because it enables (1) late-stage functionalization of amide-containing synthetic intermediates, (2) site-selective functionalization of biomolecules, and (3) the development of new orthogonal

cross-coupling amide-based precursors with selectivity unattainable to other aryl electrophiles.

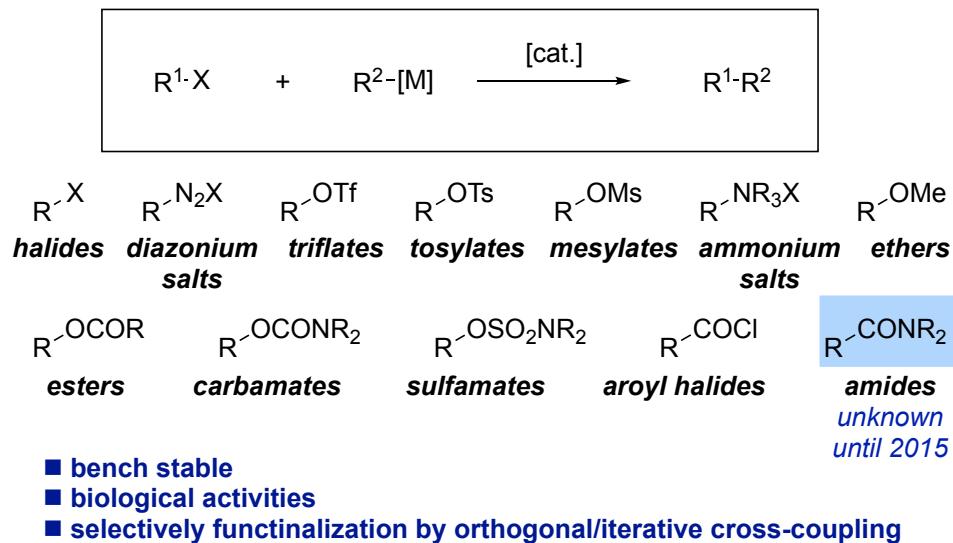


Figure 1.9 General classes of aryl electrophiles.

Mechanistically, decarbonylative activation of the amide bond proceeds via selective metal insertion into the N–C(O) acyl amide bond to generate acyl metal intermediate (Figure 1.10).⁹ The resulting acyl–metal intermediate can undergo direct transmetallation (ligand exchange), followed by reductive elimination to afford acyl cross-coupling product.^{10,11} Alternatively, the acyl-intermediate resulting from the selective oxidative addition of a low-valent metal into the N–C(O) amide bond can be subject to a decarbonylative pathway, prior to or after the transmetallation step. This process, which ultimately depends on the ability of acyl–metal to undergo carbon monoxide deinsertion¹² and can be regarded as a formal double N–C(O)/C–C bond activation, generates a versatile aryl–metal intermediate as an attractive unconventional strategy to traditional cross-coupling reactions of aryl halides and pseudohalides.

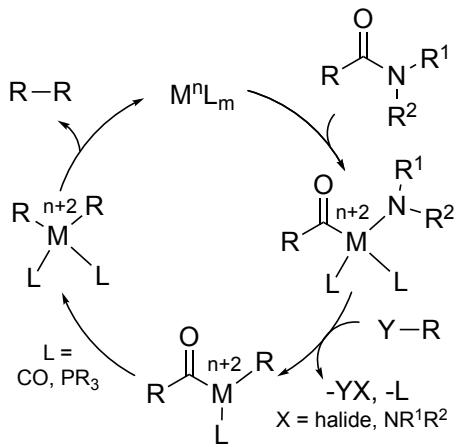


Figure 1.10 Mechanism of metal-catalyzed aryl cross-coupling of amides.

The field of decarbonylative cross-coupling of amides has started with Pd-catalyzed decarbonylative Heck cross-coupling of amides reported by our group in 2015.²³ This was quickly followed by the first examples of Rh-catalyzed and Ni-catalyzed decarbonylative cross-couplings of amides also reported by our group.²⁴⁻²⁶ In the last five years, this decarbonylative cross-coupling technology of amides has experienced a rapid growth. At present, decarbonylative cross-couplings of amides represent an attractive method for the construction of a wide variety of carbon–carbon and carbon–heteroatom bonds, allowing for synthetically-valuable functional group inter-conversion of amides to other functional groups (Figure 1.11). Again, all examples of amides undergoing the decarbonylative N–C(O) bond cross-coupling feature non-planar destabilized amide bonds. More generally, the ability to promote previously elusive transformations of amides via generic transition-metal-catalyzed reactions represents a new powerful disconnection in organic synthesis with great relevance to biology, medicinal chemistry, polymers and materials science.

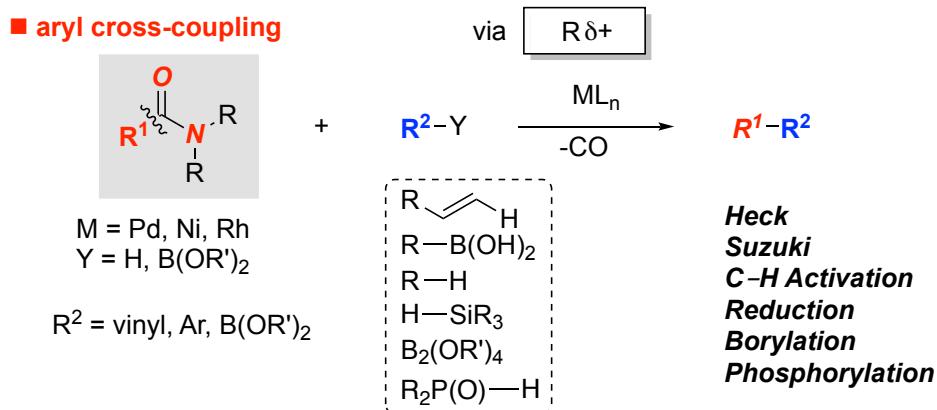


Figure 1.11 Metal-catalyzed cross-coupling of amides via aryl intermediates.

1.4 Carboxylic acids as electrophiles in decarbonylative cross-coupling

In the context of decarbonylative reactions of amides, while decarboxylative cross-coupling reactions (loss of CO₂) of carboxylic acids have been utilized to great extent to generate aryl nucleophiles, the development of decarbonylative reactions (loss of CO) of carboxylic acids and derivatives to provide aryl electrophiles has met with limited success. In contrast to decarboxylative cross-couplings of carboxylic acids which typically generate aryl nucleophiles or are performed under oxidative conditions, decarbonylative manifold proceeds under redox-neutral conditions and employs readily accessible activated carboxylic acid derivatives that allow for a selective oxidative addition to a low valent metal center under mild and functional group tolerant conditions.²⁷

A general mechanism for the cross-coupling of carboxylic acid derivatives by decarbonylation is shown in Figure 1.12. The key step involves metal insertion into the acyl bond. In this mechanism, bench-stable, readily accessible derivatives of carboxylic acids serve as precursors to aryl electrophiles. The advantages of using carboxylic acids

as cross-coupling partners include (1) low-price; (2) stability; (3) low toxicity; (4) orthogonal cross-coupling conditions; (5) the potential to functionalize biologically-active molecules.

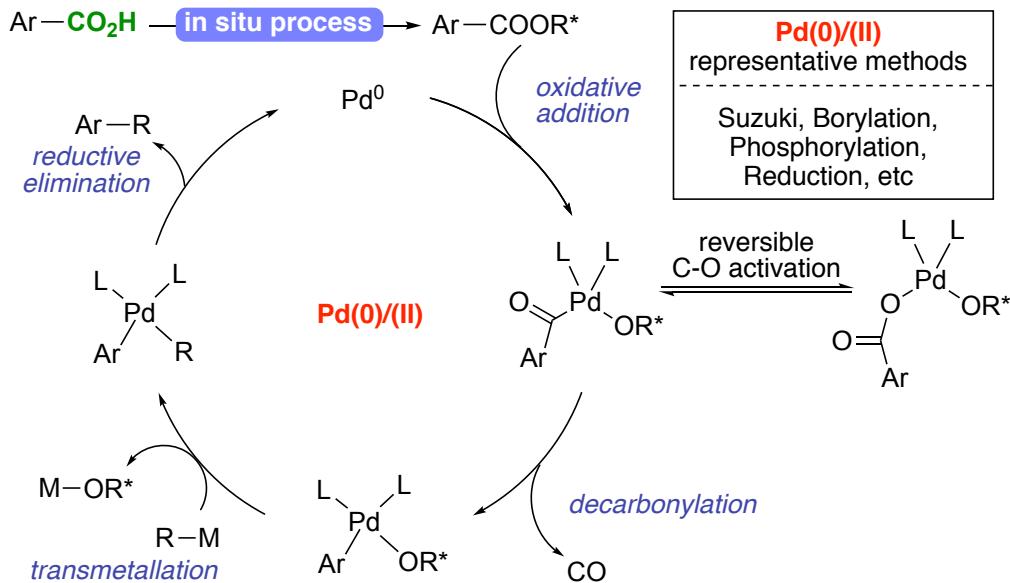


Figure 1.12 Mechanism of decarbonylative cross-coupling of carboxylic acids.

One of the goals of our group is to develop new broadly useful decarbonylative cross-couplings of carboxylic acids and derivatives. In this methodology, aryl electrophiles are generated directly after reagent-enabled decarbonylation of the in situ accessible acyl derivatives of carboxylic acids under catalyst-controlled conditions (Figure 1.13). The scope and the potential impact of this method have been demonstrated in highly selective decarbonylative (1) borylation,²⁷ (2) reduction,²⁸ (3) Suzuki-Miyaura cross-coupling,²⁹ and (4) phosphorylation (Hirao cross-coupling).³⁰ By circumventing the challenging decarboxylation (loss of CO₂), this strategy provides a general platform to access arylpalladium species for a wide array of cross-coupling reactions from abundant carboxylic acids.

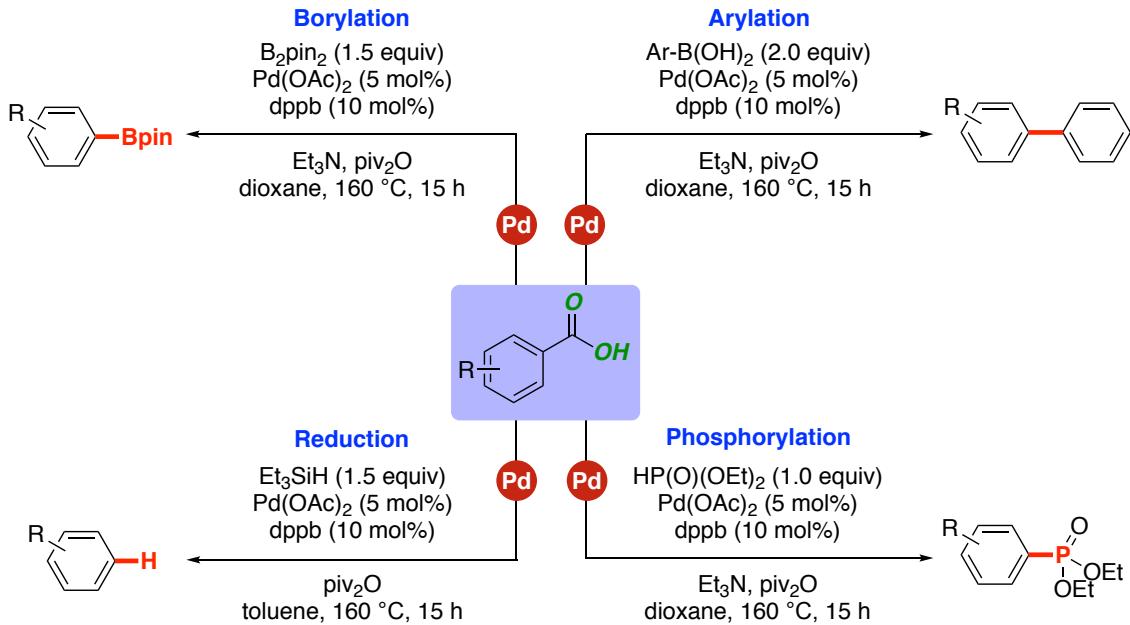


Figure 1.13 Metal-catalyzed cross-coupling of carboxylic acids via aryl intermediates.

1.5 Brief summary of the work in this thesis

Building upon our new concept for activation of amide bonds, we have made several key contributions to the cross-coupling reactions of amide bonds. We have discovered a series of new twisted amides, applied them in acyl and aryl cross-coupling reactions via N–C(O) bond activation, and performed full structural characterization. In this context, we have developed the first transition-metal-catalyzed decarbonylative cross-coupling of amides, namely the Heck reaction for the synthesis of olefins. This method represented the first example of a decarbonylative cross-coupling of amides of any type, including Suzuki-Miyaura coupling, phosphorylation, cyanation, C–H/C–N bond activation. These decarbonylative reactions further demonstrated the utility of amides as aryl electrophilic cross-coupling partners.

On the other hand, carboxylic acids are considered as perfect substrates for organic synthesis. We have discovered the first transition-metal-catalyzed decarbonylative borylation, reduction, Suzuki-Miyaura and phosphorylation of carboxylic acids under redox-neutral conditions. These carboxylic acid cross-coupling reactions demonstrate new potential of ubiquitous and versatile carboxylic acids as electrophiles for catalytic organic synthesis.

The research outlined in this thesis aims to employ amides as electrophiles in metal-catalyzed acyl and decarbonylative cross-coupling reactions, and carboxylic acids as electrophiles in metal-catalyzed decarbonylative cross-coupling reactions. Furthermore, this research also aims to demonstrate novel synthetic methods for the transformation of generic amides and carboxylic acids that would provide alternative toolbox reactions for synthetic chemists to construct complex molecules by manipulation of ubiquitous bonds. After introductory Chapter I, Chapter II will discuss the development of new acyl cross-coupling reactions of amides by acyl-metal intermediates. This chapter will include a detailed study of four distinct projects: (1) the discovery of moderately twisted, electronically-activated *N*-acylsaccharine amides and their application in palladium-catalyzed acyl Suzuki-Miyaura cross-coupling; (2) the discovery of atom-economic *N*-Ms amides (Ms = mesyl) and their application in palladium-catalyzed acyl Suzuki-Miyaura cross-coupling; (3) the discovery of mono-twisted *N*-Ac amides and their application in palladium-catalyzed acyl Suzuki-Miyaura cross-coupling; (4) the development of palladium-catalyzed acyl Suzuki-Miyaura cross-coupling for the synthesis of sterically-hindered ketones.⁴⁹⁻⁵⁰ Chapter III will discuss metal-catalyzed decarbonylative cross-coupling reactions of amides and thioesters. This chapter will focus on three separate

projects: (1) palladium-catalyzed decarbonylative Heck cross-coupling of *N*-acylsaccharine amides; (2) palladium- and nickel-catalyzed decarbonylative phosphorylation of amides (Hirao cross-coupling); (3) nickel-catalyzed decarbonylation of thioesters to yield thioethers. Chapter IV will discuss palladium-catalyzed decarbonylative cross-coupling of carboxylic acids under redox-neutral conditions. This chapter will focus on four separate projects: (1) palladium-catalyzed decarbonylative borylation of carboxylic acids; (2) palladium-catalyzed decarbonylative reduction of carboxylic acids; (3) palladium-catalyzed decarbonylative Suzuki-Miyaura cross-coupling of carboxylic acids; (4) palladium-catalyzed decarbonylative phosphorylation of carboxylic acids.

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Chapter 2

Cross-Coupling of Amides by Acyl-Metal Intermediates

2.1 *N*-Acylsaccharine amides and their reactivity in acyl Suzuki-Miyaura cross-coupling

Parts of this section were adapted with permission from the article: “*N*-Acylsaccharins: Stable Electrophilic Amide-Based Acyl Transfer Reagents in Pd-Catalyzed Suzuki-Miyaura Coupling via N–C Cleavage” (*Org. Lett.* **2016**, *18*, 4194). Copyright ©2016, American Chemical Society.

2.1.1 Introduction

The incorporation of the acyl group into organic molecules is a fundamental transformation in biology and synthetic chemistry.^{1,2} In this context, the transition-metal-catalyzed acylation of organometallic reagents represents a powerful strategy to produce functionalized ketones with a range of applications in pharmaceutical, dye, and agrochemical industries.^{3,4} A number of methods and reagents have been developed, including palladium- and nickel-catalyzed cross-coupling reactions of acyl chlorides, thioesters, and anhydrides.⁵ By contrast, the transition-metal-catalyzed acylation by N–C cleavage⁶ in amides is a significant challenge due to $n \rightarrow \pi^*$ conjugation and the resulting partial double bond character of the amide bond.⁷ In general, the amide bond resonance prohibits direct metal insertion into the N–C(O) bond in planar amides. As a consequence, at the start of this project, there have been very few reports of the cross-coupling of amides with organometallic reagents^{8–10} despite the potential versatility of amides as

acylating reagents and the fundamental role of amides in biology and medicinal chemistry.^{7b} In 2015, in consideration of amidic resonance, our laboratory introduced the concept of amide bond ground-state destabilization to enable a range of metal-catalyzed transformation of amides by N–C cleavage in C–C bond-forming reactions of general importance (Figure 2.1.1A).⁸ Independently, at the start of this project, palladium- and nickel-catalyzed cross-coupling of amides with boronic acids⁸ and nickel-catalyzed borylation by N–C cleavage have been developed.¹⁰ Unsurprisingly, all amides utilized contained destabilized (twisted) amide bonds,¹¹ while *N*-glutarimide amides introduced by our laboratory showed the highest reactivity in a range of cross-coupling reactions employing Pd, Rh, and Ni catalysis.⁸

Continuing this theme, we became interested in using *N*-acylsaccharins as selective amide-based acyl transfer reagents in transition-metal catalysis.¹² The use of halo-saccharins as electrophilic reagents has been widely studied in organic synthesis.¹³ Recently, some important examples have advanced the scope of saccharins as efficient functional group transfer reagents, including trifluoromethyl-thiolation,^{14a} formylation,^{14b} and alkoxy carbonylation^{14c} reactions (Figure 2.1.1B). In this study, we developed the first example of palladium-catalyzed Suzuki-Miyaura cross-coupling of *N*-acylsaccharins with boronic acids by N–C bond cleavage.¹⁵ We have further demonstrated that *N*-acylsaccharins serve as new, highly reactive, bench-stable, economical, amide-based, electrophilic acyl transfer reagents for C–C bond forming reactions via acyl-metal intermediates by selective N–C bond cleavage. This finding opened the door for using *N*-acylsaccharins in transition-metal-catalyzed reaction manifolds.³⁻⁵

N-Acylsaccharins offer several major advantages over other amides and derivatives: (1) saccharin is a cheap, widely accessible commodity chemical produced on >50,000 ton scale annually with a bulk price of <\$0.10/gram;¹⁶ (2) the presence of an electron-withdrawing sulfonyl moiety results in an enhanced electrophilicity of the acyl–carbonyl group; (3) saccharin is commonly used as an artificial sweetener and is virtually nontoxic; (4) *N*-acylsaccharins are bench-stable and easy to handle crystalline solids, with no decomposition observed over a period of 3 months at ambient conditions; (5) the geometric properties of *N*-acylsaccharins allow fine-tuning of the reactivity of the amide N–C bond by distortion, resulting in a distinct class of highly chemoselective acyl transfer reagents with orthogonal functional group tolerance to other carbonyl groups, while avoiding the handling of moisture sensitive and corrosive halides in transition-metal-catalysis.¹⁷

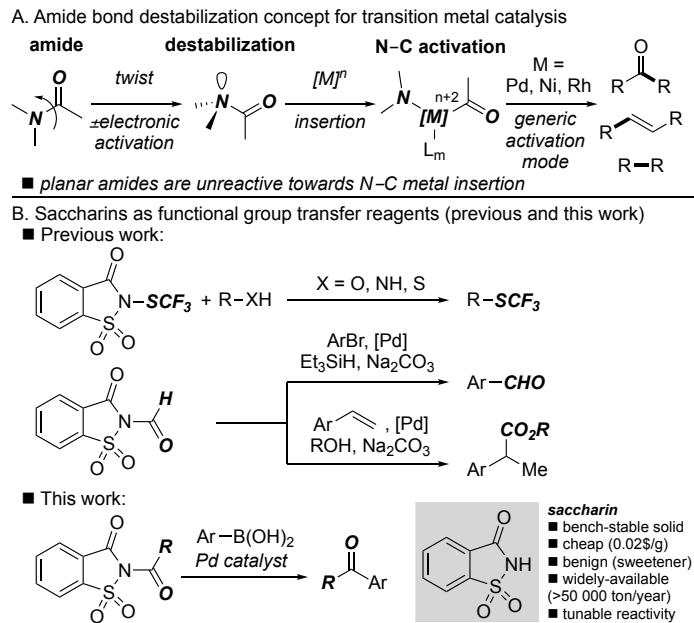


Figure 2.1.1 (a) Activation of amides by N–C cleavage. (b) Saccharins as functional

group transfer reagents: previous work and this study.

2.1.2 Reaction optimization

N-Acylsaccharins were easily synthesized in an average yield of 87% by the reaction of saccharin with acyl chlorides in *N,N*-dimethylacetamide following the known procedure¹⁸ and isolated by recrystallization.

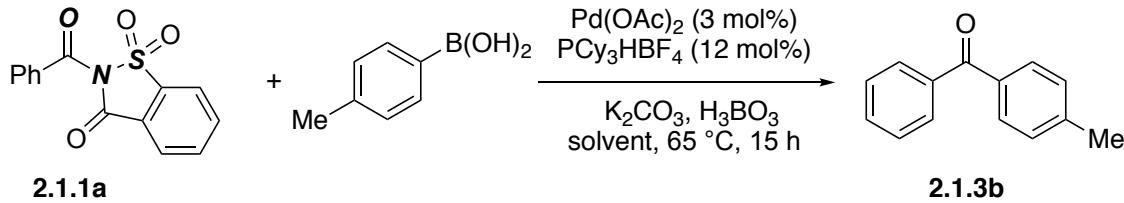
We began our catalytic studies by examining the cross-coupling of *N*-benzoylsaccharin with 4-tolylboronic acid under a variety of conditions. Table 2.1.1 summarizes key results from the optimization experiments. The desired coupling proceeded in an excellent >95% yield in the presence of Pd(OAc)₂ (3 mol %), PCy₃HBF₄ (12 mol %), K₂CO₃ (2.5 equiv), and H₃BO₃ (2.0 equiv) in THF at 65 °C (entries 1-7). THF was found to be the optimum solvent for the reaction. The screening of amines as additives (entries 13-19) and changing ligands (entry 22), demonstrated that the reaction was less efficient at room temperature. Control experiments showed that all of the reaction parameters (Pd, ligand) are essential for efficient coupling, in line with our proposal (entries 20-21). Various palladium catalysts were tested (Table 2.1.2), and Pd(OAc)₂ showed the best catalytic activity (entries 1-7). Heterogenous Pd/C was found not efficient to catalyze the cross-coupling (entry 8).

Table 2.1.3 summarizes key results on the effect of ligand in this Suzuki-Miyaura cross-coupling. A series of trialkyl phosphines were not efficient ligands for the reaction (entries 2-5). Interestingly, triaryl phosphines could be successfully employed as ligands (entries 8-15), suggesting higher reactivity of *N*-acylsaccharins than *N*-glutarimide amides.⁸ We further determined that the conditions employing PCy₂Ph proved to be the most general across the range of substrates examined, and subsequently used PCy₂Ph in

the substrate scope studies. The use of structurally related PCyPh₂ was less effective, revealing subtle features of this protocol. Furthermore, a high yield was obtained using PPh₃, indicative of facile Pd(0) insertion into the N–C bond in this class of substrates.³⁻⁶

Table 2.1.4 and Table 2.1.5 summarize key results of the effect of Pd/ligand ratio in this Suzuki-Miyaura cross-coupling from the optimization experiments. >80% yield was obtained with an equimolar Pd/ligand ratio, suggesting high reactivity of the N–C bond toward metal insertion.^{8d} Importantly, full selectivity for the N–C insertion/coupling was observed under the optimized conditions, with products resulting from C–SO₂ insertion and decarbonylation not detected.²⁰ It was important to note that we did not observe any other by-products such as decarbonylated products of over-addition products in the reaction mixture.

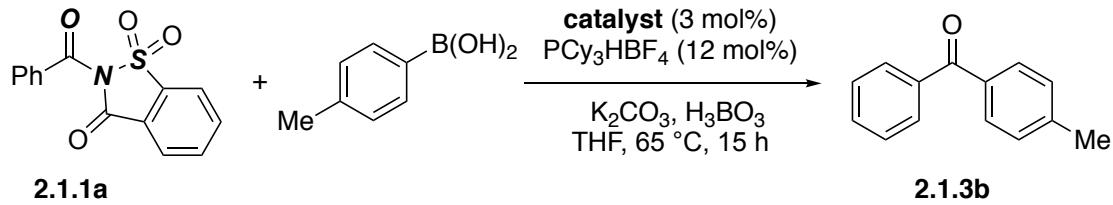
Table 2.1.1 Optimization of Pd-catalyzed Suzuki-Miyaura cross-coupling of *N*-acylsaccharins.^a



entry	R-B(OH) ₂	K ₂ CO ₃	H ₃ BO ₃	solvent	yield (%) ^a
1	2.0 equiv	2.5 equiv	2.0 equiv	THF	97
2	1.2 equiv	2.5 equiv	2.0 equiv	THF	87
3	2.0 equiv	4.0 equiv	2.0 equiv	THF	67
4	2.0 equiv	2.5 equiv	0 equiv	THF	79
5 ^b	2.0 equiv	2.5 equiv	2.0 equiv	THF	84
6	1.2 equiv	2.5 equiv	0 equiv	THF	46
7 ^c	1.2 equiv	2.5 equiv	2.0 equiv	THF	<2
8	1.2 equiv	2.5 equiv	2.0 equiv	toluene	18
9	1.2 equiv	2.5 equiv	2.0 equiv	dioxane	68
10	1.2 equiv	2.5 equiv	2.0 equiv	DCE	44
11 ^d	2.0 equiv	2.5 equiv	2.0 equiv	THF	33
12	2.0 equiv	0 equiv	2.0 equiv	THF	50
13 ^{c,e}	2.0 equiv	2.5 equiv	2.0 equiv	THF	<2
14 ^{c,f}	2.0 equiv	2.5 equiv	2.0 equiv	THF	36
15 ^{c,g}	2.0 equiv	2.5 equiv	2.0 equiv	THF	<2
16 ^{c,h}	2.0 equiv	2.5 equiv	2.0 equiv	THF	<2
17 ^{c,i}	2.0 equiv	2.5 equiv	2.0 equiv	THF	<2
18 ^{c,j}	2.0 equiv	2.5 equiv	2.0 equiv	THF	<2
19 ^{c,k}	2.0 equiv	2.5 equiv	2.0 equiv	THF	<2
20 ^l	2.0 equiv	2.5 equiv	2.0 equiv	THF	<2
21 ^{h,l}	2.0 equiv	2.5 equiv	2.0 equiv	THF	<2
22 ^{c,f,m}	2.0 equiv	2.5 equiv	2.0 equiv	THF	37

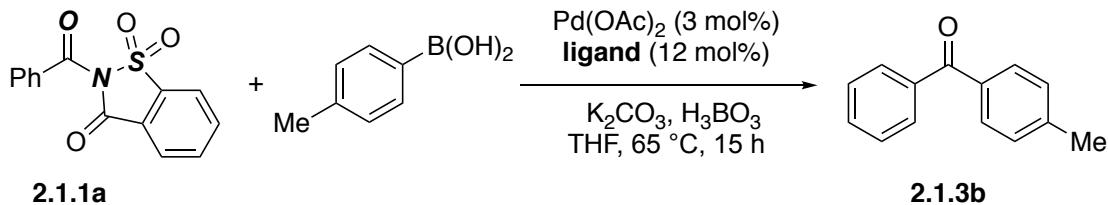
^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv), THF (0.25 M), 65 °C, 15 h. ^b120 °C. ^croom temperature. ^dH₂O (5.0 equiv). ^eEt₃N (0.1 equiv). ^fEt₃N (0.3 equiv). ^gEt₃N (0.5 equiv). ^hEt₃N (1.0 equiv). ⁱEt₃N (2.0 equiv). ^jDIPEA (0.3 equiv). ^kBu₃N (0.3 equiv). ^lwithout ligand. ^mPPh₃ as ligand.

Table 2.1.2 Effect of Pd catalyst in the Suzuki-Miyaura cross-coupling of *N*-acylsaccharins.^a



entry	catalyst	yield (%) ^a
1	Pd(OAc) ₂	97
2	PdCl ₂	61
3	Pd(dba) ₂	56
4	Pd ₂ (dba) ₃	57
5	Pd ₂ (dba) ₃ CHCl ₃	69
6	Pd(PPh ₃) ₄	77
7	Pd(PPh ₃) ₂ Cl ₂	<2
8	Pd/C	<2

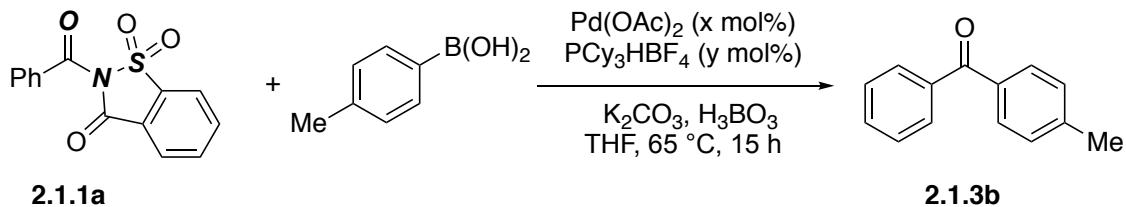
^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), catalyst (3 mol%), PCy₃BF₄ (12 mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv), THF (0.25 M), 65 °C, 15 h.

Table 2.1.3 Effect of ligand in the Suzuki-Miyaura cross-coupling of *N*-acylsaccharins.^a

entry	ligand	yield (%) ^a
1	PCy ₃ BF ₄	97
2	PMet-Bu ₂ BF ₄	36
3	PMe ₃ BF ₄	<2
4	P(<i>n</i> -Bu) ₃ BF ₄	<2
5	P(<i>t</i> -Bu) ₃ BF ₄	<2
6	PCy ₂ Ph	87
7	PCyPh ₂	<2
8	PPh ₃	91
9	P(4-MeO-C ₆ H ₄) ₃	93
10	XPhos	18
11	DPPF	9
12	DPPM	35
13	DPPP	30
14	DPPB	50
15	DPPPent	45

^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), Pd(OAc)₂ (3 mol%), ligand (12 mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv), THF (0.25 M), 65 °C, 15 h.

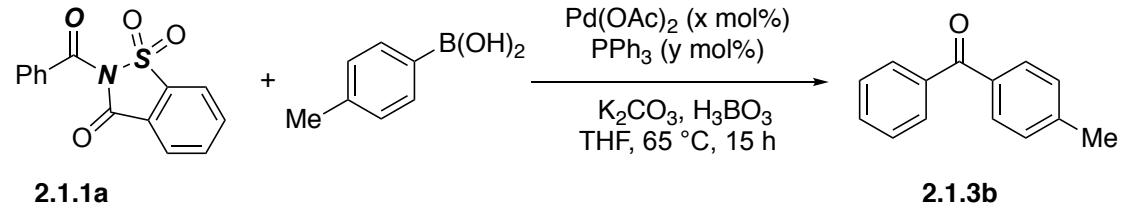
Table 2.1.4 Effect of Pd/PCy₃ ratio in the Suzuki-Miyaura cross-coupling of *N*-acylsaccharins.^a



entry	Pd(OAc) ₂ : PCy ₃ HBF ₄	yield (%) ^a
1	1:0.5	13
2	1:1	81
3	1:2	84
4	1:3	86
5	1:4	95
6	1:5	84

^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), Pd(OAc)₂ (x mol%), PCy₃HBF₄ (y mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv), THF (0.25 M), 65 °C, 15 h.

Table 2.1.5 Effect of Pd/PPh₃ ratio in the Suzuki-Miyaura cross-coupling of *N*-acylsaccharins.^a

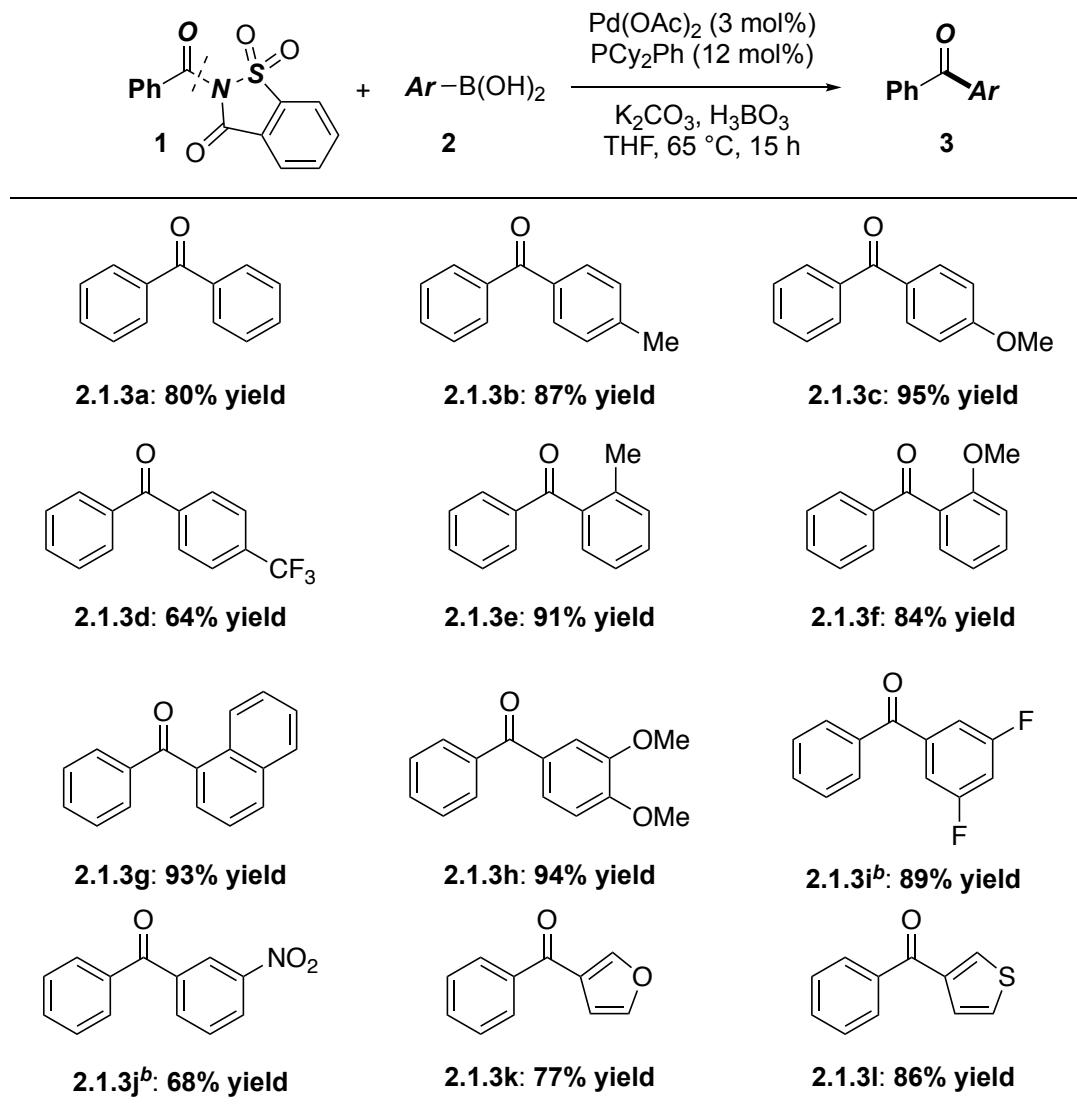


entry	Pd(OAc) ₂ : PCy ₃ HBF ₄	yield (%) ^a
1	1:1	76
2	1:2	84
3	1:3	79
4	1:4	90
5	1:5	74

^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), Pd(OAc)₂ (x mol%), PPh₃ (y mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv), THF (0.25 M), 65 °C, 15 h.

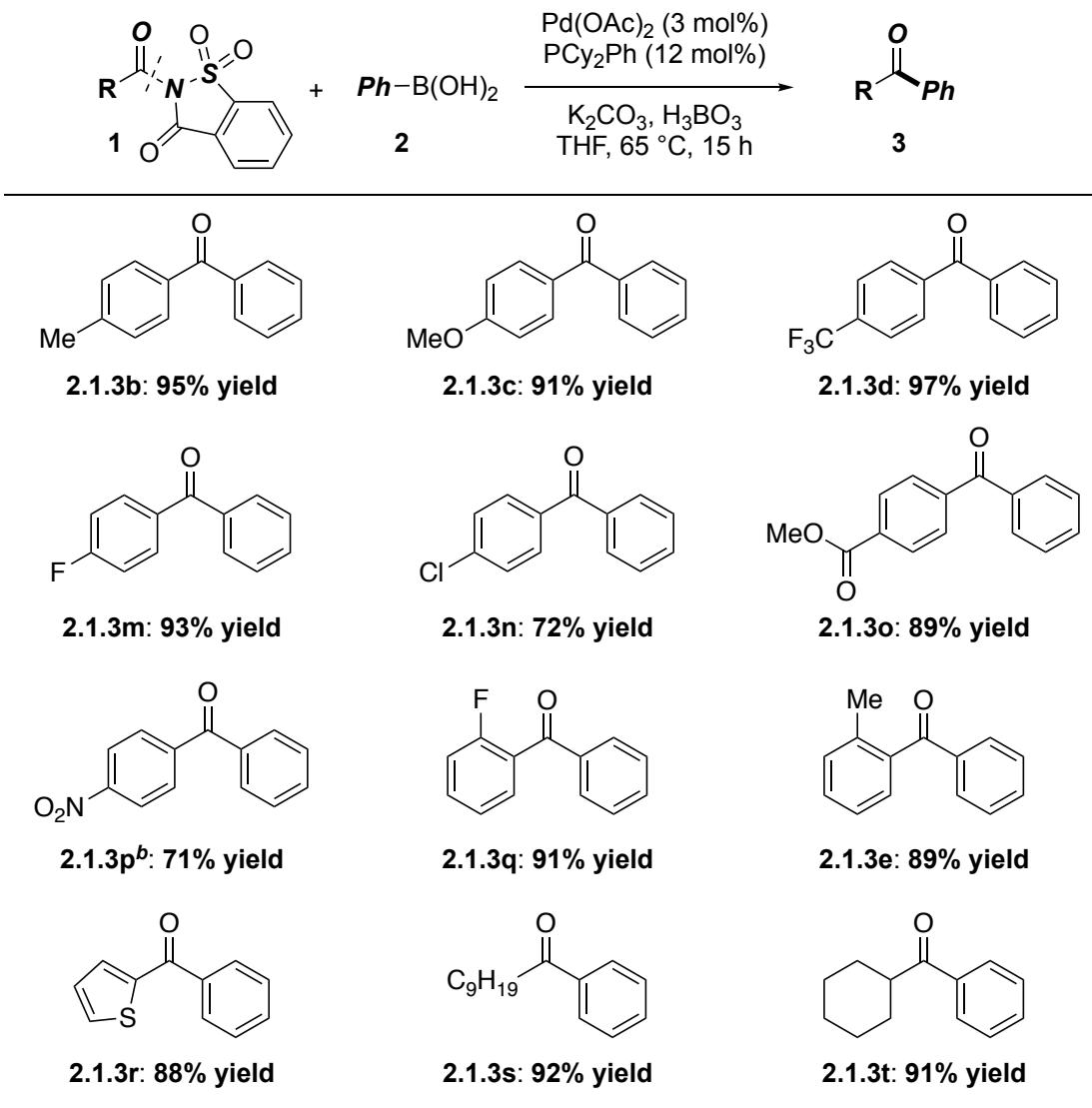
2.1.3 Substrate scope

With the optimized conditions in hand, we next investigated the scope of the reaction (Scheme 2.1.1). As shown, a variety of boronic acids could be employed, yielding the desired ketone products with high efficiency, including electron-donating (**2.1.3b-2.1.3c**), electron-withdrawing (**2.1.3d**), and sterically-hindered (**2.1.3e-2.1.3g**) boronic acids. Moreover, highly electron-rich (**2.1.3h**) and electron-deficient (**2.1.3i**) boronic acids were competent coupling partners. Of particular interest were the fact that the products containing electrophilic handles (**2.1.3j**) and medicinally relevant heterocycles were tolerated (**2.1.3k-2.1.3l**). The scope of the amide component was also broad. Electron-rich (**2.1.3b'-2.1.3c'**) and electron-deficient (**2.1.3d'**) *N*-acylsaccharins provided the desired product in high yield. Notably, electrophilic functional handles such as fluoro- (**2.1.3m**), chloro- (**2.1.3n**), ester- (**2.1.3o**), and nitro- (**2.1.3p**) at the para-position were perfectly accommodated. Moreover, ortho-coordinating (**2.1.3q**), sterically hindered (**2.1.3e'**), and heterocyclic (**2.1.3r**) amides underwent smooth acylation. Finally, 1° (**2.1.3s**) and 2° (**2.1.3t**) alkyl amides were also efficient coupling partners, affording the valuable alkyl aryl ketones in good yields. Overall, the scope of the cross-coupling of *N*-acylsaccharins compared very favorably with other examples of Suzuki-Miyaura cross-coupling by the amide N–C cleavage reported at the time.^{8,9} Importantly, this process was advantageous in terms of economy and availability of saccharin as an acyl-transfer reagent.^{1,2,16}



^aConditions: amide (1.0 equiv), ArB(OH)₂ (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₂Ph (12 mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv), THF (0.25 M), 65 °C, 15 h; ^b120 °C.

Scheme 2.1.1 Boronic acid scope in Suzuki-Miyaura cross-coupling of *N*-acylsaccharins.^a

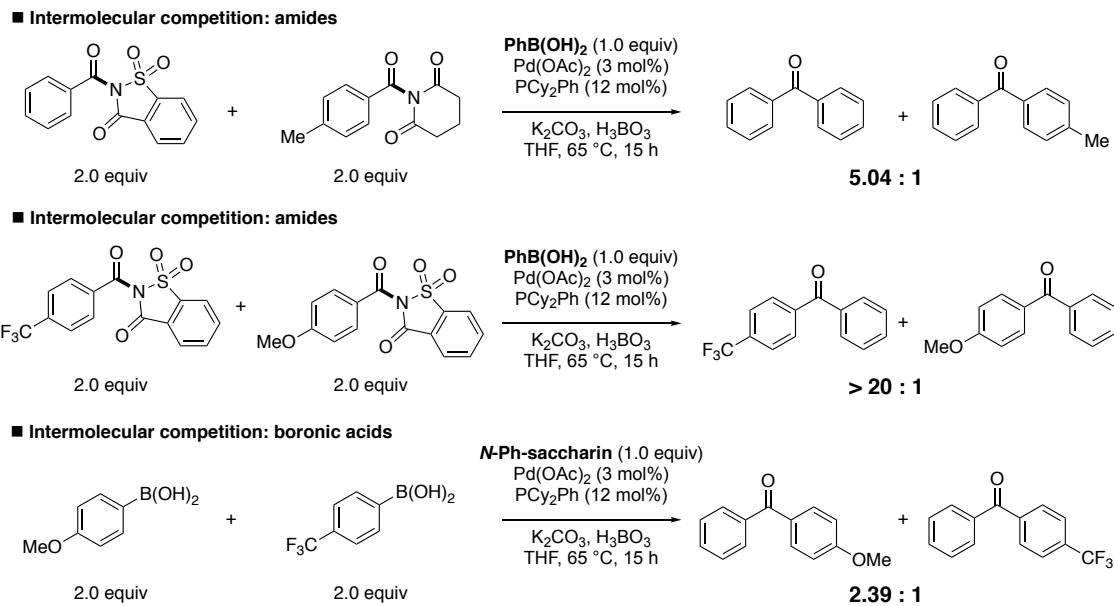


^aConditions: amide (1.0 equiv), PhB(OH)₂ (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₂Ph (12 mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv), THF (0.25 M), 65 °C, 15 h; ^bPCy₃HBF₄ as ligand.

Scheme 2.1.2 Amide scope in Suzuki-Miyaura cross-coupling of *N*-acylsaccharins.^a

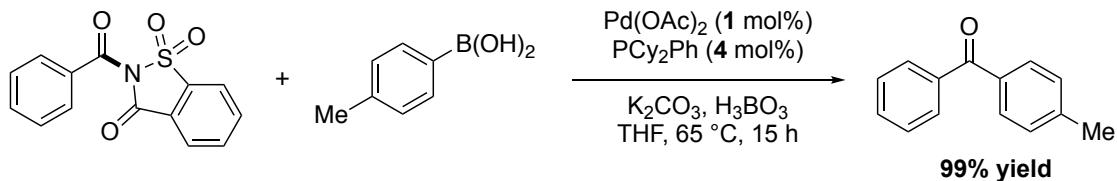
2.1.4 Mechanistic studies

Selectivity studies were next conducted (Scheme 2.1.3 and Scheme 2.1.4): (1) Intermolecular competitions established that electron-deficient aromatic amides were inherently more reactive ($4\text{-CF}_3/4\text{-MeO} > 20:1$). (2) Electron-rich nucleophiles coupled preferentially ($4\text{-MeO}/4\text{-CF}_3 = 2.4:1$). (3) An approximately 2-fold increase in yield was observed when PhB(OH)_2 and K_2CO_3 were doubled at low conversion. These effects suggested that transmetalation was most likely the rate-determining step.¹⁵ (4) A turnover number of >300 was determined. (5) Intermolecular competition studies showed higher reactivity of *N*-acylsaccharins as compared with *N*-glutarimides,⁸ suggesting significant potential of *N*-acylsaccharins as acyl-transfer reagents in a broad range of organometallic manifolds.

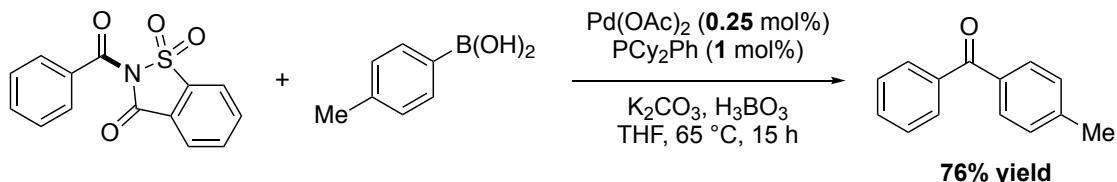


Scheme 2.1.3 Mechanistic studies in Suzuki-Miyaura cross-coupling of *N*-acylsaccharins.

■ TON 99 at 1 mol% catalyst loading



■ TON 304 at 0.25 mol% catalyst loading



Scheme 2.1.4 TON studies in Suzuki-Miyaura cross-coupling of *N*-acylsaccharins.

2.1.5 Conclusion

In conclusion, in this project we have developed *N*-acylsaccharins as new, amide-based, electrophilic reagents for transition-metal-catalyzed acyl transfer reactions by selective N–C bond cleavage. These reagents are shelf-stable, easy-to-use, and readily available from the cheap and benign saccharin. The high reactivity was demonstrated in the Pd-catalyzed Suzuki-Miyaura cross-coupling to give a variety of functionalized ketones. Mechanistic studies supported the amide bond distortion as a chemoselectivity-determining feature in N–C cleavage.

2.1.6 Experimental section

General methods. All experiments involving transition-metals were performed using Schlenk or glovebox techniques under argon or nitrogen atmosphere unless stated otherwise. All solvents were purchased at the highest commercial grade and used as

received or after purification by passing through activated alumina columns or distillation from sodium/benzophenone under nitrogen. All chemicals were purchased at the highest commercial grade and used as received. Reaction glassware was oven-dried at 140 °C for at least 24 h or flame-dried prior to use, allowed to cool under vacuum and purged with argon (three cycles). ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 on Bruker spectrometers at 500 (^1H NMR) and 125 MHz (^{13}C NMR). All shifts are reported in parts per million (ppm) relative to residual CHCl_3 peak (7.27 and 77.2 ppm, ^1H NMR and ^{13}C NMR, respectively). All coupling constants (J) are reported in hertz (Hz). Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; brs, broad singlet. GC-MS chromatography was performed using Agilent HP6890 GC System and Agilent 5973A inert XL EI/CI MSD using helium as the carrier gas at a flow rate of 1 mL/min and an initial oven temperature of 50 °C. High-resolution mass spectra (HRMS) were measured on a 7T Bruker Daltonics FT-MS instrument. All flash chromatography was performed using silica gel, 60 Å, 300 mesh. TLC analysis was carried out on glass plates coated with silica gel 60 F254, 0.2 mm thickness. The plates were visualized using a 254 nm ultraviolet lamp or aqueous potassium permanganate solutions.

General Procedure for Amide Synthesis. An oven-dried flask (25 mL) equipped with a stir bar was charged with amine (typically, 3.0 mmol, 1.0 equiv), triethylamine (typically, 1.0 equiv) and *N,N*-dimethylacetamide (DMAc, typically, 0.75 mL), placed under a positive pressure of argon, and subjected to three evacuation/ backfilling cycles under high vacuum. Acyl chloride (typically, 1.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 1 h at room temperature. After the indicated time, the reaction mixture was diluted with H_2O (5

mL) and filtered. The solid was collected by filtration, washed with Et₂O (1 x 10 mL), and dried. The crude product was purified by recrystallization (methanol or toluene) to give analytically pure product.

General procedure for Suzuki-Miyaura Cross-Coupling of Amides. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv), boronic acid (typically, 2.0 equiv), Pd(OAc)₂ (typically, 3 mol%), and PCy₂Ph (typically, 12 mol%), potassium carbonate (typically, 2.5 equiv), boric acid (typically, 2.0 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Tetrahydrofuran (0.20 M) were added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 65 °C, and stirred for the indicated time at 65 °C. After the indicated time, the reaction mixture was diluted with CH₂Cl₂ (10 mL), filtered, and concentrated. The sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate) afforded the title product.

2.1.1a. White solid. ¹H NMR (500 MHz, CDCl₃) δ 8.16-8.15 (d, *J* = 7.7 Hz, 1 H), 8.05-8.01 (m, 2 H), 7.96-7.94 (t, *J* = 7.9 Hz, 1 H), 7.80-7.78 (d, *J* = 8.3 Hz, 2 H), 7.70-7.67 (t, *J* = 7.1 Hz, 1 H), 7.55-7.52 (t, *J* = 7.7 Hz, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 166.39, 157.47, 138.51, 136.43, 134.91, 133.93, 132.40, 129.60, 128.46, 126.42, 125.56, 121.28.

2.1.1b. White solid. ¹H NMR (500 MHz, CDCl₃) δ 8.16-8.14 (d, *J* = 7.7 Hz, 1 H), 8.02-8.00 (m, 2 H), 7.95-7.92 (m, 1 H), 7.72-7.71 (d, *J* = 8.1 Hz, 2 H), 7.33-7.32 (d, *J* = 7.9 Hz,

2 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.15, 157.66, 145.34, 138.49, 136.37, 134.89, 129.96, 129.56, 129.23, 126.37, 125.66, 121.24, 21.90.

2.1.1c. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.16-8.15 (d, $J = 7.7$ Hz, 1 H), 8.01-8.00 (d, $J = 4.2$ Hz, 2 H), 7.95-7.92 (m, 1 H), 7.85-7.83 (d, $J = 8.8$ Hz, 2 H), 7.00-6.99 (d, $J = 8.8$ Hz, 2 H), 3.91 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.15, 164.72, 157.97, 138.52, 136.28, 134.85, 132.78, 126.31, 125.84, 124.41, 121.23, 113.96, 55.67.

2.1.1d. White solid. Mp = 161-163 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.17-8.15 (d, $J = 7.7$ Hz, 1 H), 8.06-8.05 (d, $J = 4.0$ Hz, 2 H), 7.99-7.95 (m, 1 H), 7.87-7.85 (d, $J = 8.2$ Hz, 2 H), 7.80-7.78 (d, $J = 8.2$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.48, 157.23, 138.42, 136.75, 135.68, 135.13, 134.85 (q, $J^F = 32.8$ Hz), 129.59, 126.57, 125.49 (q, $J^F = 3.7$ Hz), 125.15, 123.38 (d, $J^F = 271.2$ Hz), 121.40. ^{19}F NMR (471 MHz, CDCl_3) δ -63.22. HRMS calcd for $\text{C}_{15}\text{H}_8\text{O}_4\text{NSF}_3\text{Na}$ ($\text{M}^+ + \text{Na}$) 378.0018, found 378.0030.

2.1.1e. White solid. Mp = 107-108 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.17-8.15 (d, $J = 7.7$ Hz, 1 H), 8.04-8.03 (d, $J = 3.9$ Hz, 2 H), 7.97-7.94 (m, 1 H), 7.85-7.82 (t, $J = 8.6$ Hz, 2 H), 7.22-7.19 (t, $J = 8.6$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.24, 165.19 (d, $J^F = 2.4$ Hz), 157.57, 138.43, 136.54, 135.00, 132.58 (d, $J^F = 9.6$ Hz), 128.55, 126.46, 125.46, 121.32, 115.89 (d, $J^F = 22.3$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -102.58. HRMS calcd for $\text{C}_{14}\text{H}_8\text{O}_4\text{NFNa}$ ($\text{M}^+ + \text{Na}$) 328.0050, found 328.0054.

2.1.1f. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.17-8.16 (d, $J = 7.7$ Hz, 1 H), 8.04-8.03 (d, $J = 4.1$ Hz, 2 H), 7.98-7.94 (m, 1 H), 7.74-7.73 (d, $J = 8.3$ Hz, 2 H), 7.51-7.50 (d, $J = 8.4$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.42, 157.45, 140.57, 138.46, 136.56, 135.00, 131.90, 131.02, 128.89, 126.49, 125.40, 121.33.

2.1.1g. White solid. Mp = 138-139 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.24-8.23 (d, J = 7.7 Hz, 1 H), 8.19-8.17 (d, J = 8.3 Hz, 2 H), 8.16-8.14 (d, J = 7.8 Hz, 1 H), 8.05-8.04 (d, J = 3.4 Hz, 2 H), 7.82-7.80 (d, J = 8.3 Hz, 2 H), 3.99 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.89, 157.21, 138.46, 136.64, 135.05, 134.37, 130.54, 130.05, 129.57, 129.16, 126.54, 125.26, 121.35, 52.60. HRMS calcd for $\text{C}_{16}\text{H}_{11}\text{O}_6\text{NSNa}$ ($\text{M}^+ + \text{Na}$) 368.0199, found 368.0212.

2.1.1h. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.39-8.37 (d, J = 8.7 Hz, 2 H), 8.17-8.16 (d, J = 7.7 Hz, 1 H), 8.08-8.07 (d, J = 3.6 Hz, 2 H), 8.00-7.97 (m, 1 H), 7.91-7.89 (d, J = 8.7 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.96, 162.55, 138.42, 137.85, 136.92, 135.22, 133.93, 130.09, 126.66, 124.95, 123.63, 121.47.

2.1.1i. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.10-8.09 (d, J = 7.7 Hz, 1 H), 8.04-8.00 (m, 2 H), 7.94-7.91 (t, J = 6.2 Hz, 1 H), 7.50-7.47 (t, J = 7.6 Hz, 1 H), 7.43-7.42 (d, J = 7.6 Hz, 1 H), 7.34-7.30 (m 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.87, 156.75, 138.39, 136.56, 134.97, 133.06, 131.79, 130.94, 127.71, 126.39, 125.71, 125.29, 121.30, 19.39.

2.1.1j. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.15-8.13 (d, J = 7.7 Hz, 1 H), 8.06-8.01 (m, 2 H), 7.96-7.93 (t, J = 6.7 Hz, 1 H), 7.72-7.69 (t, J = 7.5 Hz, 1 H), 7.65-7.61 (m, 1 H), 7.36-7.33 (t, J = 7.6 Hz, 1 H), 7.18-7.14 (t, J = 9.6 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.45, 158.75, 156.62, 138.47, 136.57, 134.97, 134.80 (d, J^F = 8.7 Hz), 130.76, 126.47, 125.17, 124.76 (d, J^F = 3.4 Hz), 124.74, 121.34, 115.87 (d, J^F = 21.2 Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -112.532.

2.1.1k. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.21-8.20 (d, $J = 7.7$ Hz, 1 H), 8.02-8.01 (d, $J = 4.0$ Hz, 2 H), 7.99-7.98 (d, $J = 3.9$ Hz, 1 H), 7.97-7.94 (m, 1 H), 7.87-7.86 (d, $J = 4.9$ Hz, 1 H), 7.23-7.21 (t, $J = 4.8$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.63, 157.86, 138.40, 136.98, 136.34, 135.68, 134.93, 128.21, 126.39, 125.78, 121.32.

2.1.1l. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.18-8.17 (d, $J = 7.6$ Hz, 1 H), 8.02-7.99 (m, 2 H), 7.95-7.92 (m, 1 H), 3.07-3.04 (t, $J = 7.5$ Hz, 2 H), 1.80-1.76 (m, 2 H), 1.46-1.41 (m, 2 H), 1.35-1.30 (m, 10 H), 0.92-0.89 (t, $J = 6.3$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.41, 157.64, 138.30, 136.40, 134.86, 126.25, 125.16, 121.23, 38.16, 31.87, 29.39, 29.31, 29.25, 28.91, 23.53, 22.67, 14.12.

2.1.1m. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.18-8.16 (d, $J = 7.6$ Hz, 1 H), 8.01-7.97 (m, 2 H), 7.95-7.91 (m, 1 H), 3.45-3.39 (m, 1 H), 2.02-2.00 (d, $J = 12.3$ Hz, 2 H), 1.89-1.86 (d, $J = 13.2$ Hz, 2 H), 1.76-1.74 (d, $J = 12.8$ Hz, 1 H), 1.65-1.57 (m, 2 H), 1.45-1.37 (m, 2 H), 1.34-1.29 (t, $J = 12.5$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 174.36, 157.43, 138.31, 136.36, 134.86, 126.23, 125.18, 121.19, 45.10, 28.43, 25.63, 25.34.

2.1.3a. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.83 (d, $J = 8.2$ Hz, 4 H), 7.63-7.60 (t, $J = 6.7$ Hz, 2 H), 7.53-7.50 (t, $J = 7.6$ Hz, 4 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.79, 137.62, 132.43, 130.08, 128.29.

2.1.3b. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.82-7.80 (d, $J = 8.1$ Hz, 2 H), 7.76-7.74 (d, $J = 8.0$ Hz, 2 H), 7.62-7.59 (t, $J = 7.5$ Hz, 1 H), 7.52-7.49 (t, $J = 7.6$ Hz, 2 H), 7.32-7.30 (d, $J = 7.9$ Hz, 2 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.54, 143.25, 137.98, 134.90, 132.17, 130.33, 129.95, 128.99, 128.22, 21.68.

2.1.3c. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.85 (d, $J = 8.7$ Hz, 2 H), 7.79-7.77 (d, $J = 8.2$ Hz, 2 H), 7.61-7.58 (t, $J = 6.8$ Hz, 1 H), 7.51-7.48 (t, $J = 7.6$ Hz, 2 H), 7.00-6.98 (d, $J = 8.7$ Hz, 2 H), 3.92 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.59, 163.24, 138.31, 132.58, 131.90, 130.19, 129.75, 128.20, 113.57, 55.52.

2.1.3d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.93-7.91 (d, $J = 8.0$ Hz, 2 H), 7.84-7.82 (d, $J = 8.2$ Hz, 2 H), 7.79-7.77 (d, $J = 8.1$ Hz, 2 H), 7.67-7.64 (t, $J = 7.6$ Hz, 1 H), 7.55-7.52 (t, $J = 7.7$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.56, 140.74, 136.75, 134.13, 133.49 (q, $J^F = 32.4$ Hz), 130.16, 130.12, 128.55, (q, $J^F = 3.7$ Hz), 124.77, 122.24 (d, $J^F = 90.2$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -63.00.

2.1.3e. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.82 (d, $J = 8.3$ Hz, 2 H), 7.62-7.59 (t, $J = 7.5$ Hz, 1 H), 7.50-7.47 (t, $J = 7.9$ Hz, 2 H), 7.43-7.40 (t, $J = 7.5$ Hz, 1 H), 7.35-7.31 (t, $J = 7.8$ Hz, 2 H), 7.29-7.26 (t, $J = 7.5$ Hz, 1 H), 2.36 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.67, 138.63, 137.76, 136.77, 133.14, 131.01, 130.25, 130.15, 128.53, 128.47, 125.21, 20.00.

2.1.3f. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.85-7.83 (d, $J = 7.7$ Hz, 2 H), 7.59-7.56 (t, $J = 7.5$ Hz, 1 H), 7.51-7.48 (t, $J = 7.4$ Hz, 1 H), 7.47-7.44 (t, $J = 7.2$ Hz, 2 H), 7.39-7.38 (d, $J = 7.7$ Hz, 1 H), 7.08-7.05 (t, $J = 7.2$ Hz, 1 H), 7.03-7.01 (d, $J = 7.7$ Hz, 1 H), 3.75 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.48, 157.37, 137.83, 132.93, 131.88, 129.85, 129.61, 128.88, 128.22, 120.50, 111.46, 55.62.

2.1.3g. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.13-8.11 (d, $J = 8.2$ Hz, 1 H), 8.05-8.03 (d, $J = 8.1$ Hz, 1 H), 7.96-7.95 (d, $J = 7.9$ Hz, 1 H), 7.90-7.89 (d, $J = 8.3$ Hz, 2 H), 7.64-7.60 (m, 2 H), 7.58-7.52 (m, 3 H), 7.50-7.47 (t, $J = 7.6$ Hz, 2 H). ^{13}C NMR (125

MHz, CDCl₃) δ 198.05, 138.34, 136.38, 133.74, 133.25, 131.28, 130.97, 130.43, 128.46, 128.42, 127.78, 127.27, 126.48, 125.71, 124.35.

2.1.3h. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.79-7.78 (d, *J* = 8.1 Hz, 2 H), 7.61-7.58 (t, *J* = 6.9 Hz, 1 H), 7.52-7.49 (t, *J* = 7.7 Hz, 3 H), 7.41-7.40 (d, *J* = 8.4 Hz, 1 H), 6.93-6.91 (d, *J* = 8.3 Hz, 1 H), 3.99 (s, 3 H), 3.97 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 195.61, 153.04, 149.03, 138.31, 131.90, 130.24, 129.74, 128.19, 125.53, 112.13, 109.74, 56.11, 56.07.

2.1.3i. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.83-7.81 (d, *J* = 7.2 Hz, 2 H), 7.67-7.64 (t, *J* = 7.5 Hz, 1 H), 7.55-7.52 (t, *J* = 7.8 Hz, 2 H), 7.35-7.34 (d, *J* = 5.7 Hz, 2 H), 7.09-7.05 (t, *J* = 8.5 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 193.95, 163.70 (d, *J*^F = 11.7 Hz), 161.70 (d, *J*^F = 11.6 Hz), 136.40, 133.16, 129.98, 128.59, 112.95 (q, *J*^F = 6.4 Hz), 107.72 (t, *J*^F = 25.4 Hz). ¹⁹F NMR (471 MHz, CDCl₃) δ -108.15.

2.1.3j. White solid. ¹H NMR (500 MHz, CDCl₃) δ 8.65 (s, 1 H), 8.48-8.47 (d, *J* = 8.2 Hz, 1 H), 8.18-8.16 (d, *J* = 7.7 Hz, 1 H), 7.84-7.82 (d, *J* = 8.2 Hz, 2 H), 7.75-7.72 (t, *J* = 8.0 Hz, 1 H), 7.70-7.67 (t, *J* = 7.5 Hz, 1 H), 7.58-7.55 (t, *J* = 7.8 Hz, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 194.20, 148.11, 139.09, 136.28, 135.46, 133.39, 130.04, 129.66, 128.76, 126.75, 124.75.

2.1.3k. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.95 (s, 1 H), 7.89-7.88 (d, *J* = 7.2 Hz, 2 H), 7.63-7.60 (t, *J* = 7.5 Hz, 1 H), 7.54-7.50 (t, *J* = 8.0 Hz, 3 H), 6.94 (s, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 189.46, 148.58, 143.98, 138.85, 132.50, 128.85, 128.57, 126.54, 110.24.

2.1.3l. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.96 (s, 1 H), 7.88-7.87 (d, $J = 8.1$ Hz, 2 H), 7.64-7.60 (m, 2 H), 7.53-7.50 (t, $J = 7.7$ Hz, 2 H), 7.42-7.41 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 190.03, 141.33, 138.66, 133.93, 132.32, 129.39, 128.64, 128.40, 126.22.

2.1.3m. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.89-7.86 (t, $J = 5.5$ Hz, 2 H), 7.80-7.79 (d, $J = 8.2$ Hz, 2 H), 7.64-7.61 (t, $J = 7.5$ Hz, 1 H), 7.53-7.50 (t, $J = 7.7$ Hz, 2 H), 7.21-7.17 (t, $J = 8.6$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.30, 165.41 (d, $J^F = 252.5$ Hz), 137.52, 133.82 (d, $J^F = 2.9$ Hz), 132.69 (d, $J^F = 9.1$ Hz), 132.49, 129.90, 128.38, 115.48 (d, $J^F = 21.7$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -105.99.

2.1.3n. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.81-7.78 (t, $J = 7.3$ Hz, 4 H), 7.64-7.62 (t, $J = 7.5$ Hz, 1 H), 7.53-7.48 (m, 4 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.52, 138.92, 137.27, 135.89, 132.66, 131.48, 129.95, 128.66, 128.42.

2.1.3o. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.18-8.17 (d, $J = 8.1$ Hz, 2 H), 7.88-7.86 (d, $J = 8.1$ Hz, 2 H), 7.84-7.82 (d, $J = 8.2$ Hz, 2 H), 7.66-7.63 (t, $J = 7.5$ Hz, 1 H), 7.54-7.51 (t, $J = 7.7$ Hz, 2 H), 3.99 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.07, 166.34, 141.34, 136.97, 133.24, 132.97, 130.12, 129.80, 129.52, 128.48, 52.49.

2.1.3p. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.38-8.36 (d, $J = 8.7$ Hz, 2 H), 7.98-7.96 (d, $J = 8.7$ Hz, 2 H), 7.84-7.82 (d, $J = 8.2$ Hz, 2 H), 7.70-7.67 (t, $J = 7.5$ Hz, 1 H), 7.57-7.54 (t, $J = 7.8$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 194.83, 149.86, 142.91, 136.31, 133.50, 130.72, 130.12, 128.71, 123.57.

2.1.3q. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.86 (d, $J = 7.9$ Hz, 2 H), 7.64-7.61 (t, $J = 7.4$ Hz, 1 H), 7.60-7.54 (m, 2 H), 7.52-7.49 (t, $J = 7.8$ Hz, 2 H), 7.31-7.28 (t, J

δ = 7.5 Hz, 1 H), 7.21-7.17 (t, J = 9.2 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 193.50, 160.11 (d, J^F = 250.8 Hz), 137.41, 133.43, 133.08 (d, J^F = 8.2 Hz), 130.77 (d, J^F = 2.9 Hz), 129.83, 128.48, 127.06 (d, J^F = 14.7 Hz), 124.30 (d, J^F = 3.6 Hz), 116.29 (d, J^F = 21.6 Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -111.03.

2.1.3r. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.90-7.89 (d, J = 8.2 Hz, 2 H), 7.76-7.75 (d, J = 4.9 Hz, 1 H), 7.68-7.67 (d, J = 3.7 Hz, 1 H), 7.64-7.61 (t, J = 7.5 Hz, 1 H), 7.54-7.51 (t, J = 7.7 Hz, 2 H), 7.20-7.19 (t, J = 4.8 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 188.26, 143.67, 138.18, 134.86, 134.22, 132.28, 129.20, 128.43, 127.97.

2.1.3s. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.99-7.98 (d, J = 8.2 Hz, 2 H), 7.59-7.56 (t, J = 7.6 Hz, 1 H), 7.50-7.47 (t, J = 7.7 Hz, 2 H), 3.00-2.97 (t, J = 7.6 Hz, 2 H), 1.79-1.73 (m, 2 H), 1.43-1.29 (m, 12 H), 0.92-0.89 (t, J = 6.1 Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 200.66, 137.12, 132.86, 128.56, 128.07, 38.66, 31.89, 29.50, 29.49, 29.40, 29.30, 24.41, 22.68, 14.12.

2.1.3t. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.98-7.96 (d, J = 8.2 Hz, 2 H), 7.58-7.56 (t, J = 7.5 Hz, 1 H), 7.50-7.47 (t, J = 7.7 Hz, 2 H), 3.31-3.27 (t, J = 11.5 Hz, 1 H), 1.93-1.86 (m, 4 H), 1.78-1.75 (d, J = 11.7 Hz, 1 H), 1.54-1.49 (t, J = 13.4 Hz, 2 H), 1.46-1.39 (m, 2 H), 1.34-1.31 (d, J = 12.5 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 203.92, 136.38, 132.73, 128.59, 128.27, 45.65, 29.44, 25.98, 25.88.

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2.2 N-Ms amides and their reactivity in acyl Suzuki-Miyaura cross-coupling

Parts of this section were adapted with permission from the article “Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling of *N*-Mesylamides by N–C Cleavage: Electronic Effect of the Mesyl Group” (*Org. Lett.* **2017**, *19*, 1434). Copyright ©2017, American Chemical Society.

2.2.1 Introduction

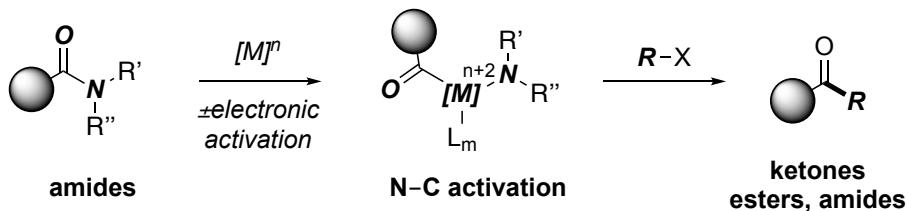
At the start of this project, amide bond N–C cross-coupling reactions have emerged as a powerful tool for the construction of carbon–carbon and carbon–heteroatom bonds (Figure 2.2.1A).^{1–3} Among many advantages of using amides as electrophilic cross-coupling partners is the availability of various activation methods of the amide bond.¹ In particular, a combination of steric and electronic destabilization in common amides has provided new opportunities in chemoselective synthesis while utilizing bench-stable amide precursors of potential biomedical relevance.⁴ Nitrogen substitution has enabled controlled access to generic acyl-metal intermediates⁵ to accomplish rational variation of sterics and amidic resonance.⁶ The highly attractive nitrogen geometry has enabled controlled variation of sterics and electronics of the amide bond, which is not easily available in acyl halides,⁷ esters,⁸ and thioesters,⁹ further adding to the advantages of using amides as cross-coupling partners. Moreover, progress has been achieved using low cost, nucleophilic Ni catalysis.^{1c} Despite the advances,¹⁰ at the start of this project, only few classes of amides have been identified that enable selective carbon–carbon bond formation by metal insertion into the N–C amide bond,¹¹ and no general activating group featuring high atom economy in acyclic amides was available.

At the same time, we recognized that significant progress has been reported in the use of aryl mesylates as cross-coupling partners (Figure 2.2.1B).^{12,13} The key advantages include higher atom economy, lower cost, and higher stability as compared to the related aryl tosylates or unstable triflates.¹² Moreover, the methanesulfonic acid by-product undergoes natural biodegradation,¹⁴ adding to the environmentally friendly profile of these precursors. However, the major challenge in cross-coupling of mesylates is the relatively poor leaving group ability.^{13a}

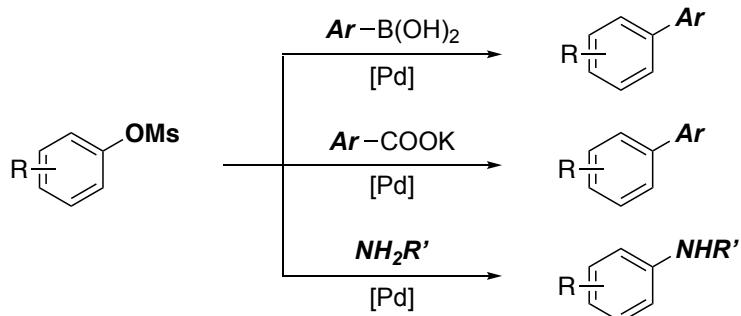
Based on our experience in amide bond cross-coupling and inspired by the highly desirable features of the mesyl substituent, we proposed to use the mesyl group as a trigger for amide bond activation in common acyclic amides. Similar to the properties of aryl mesylates, metal insertion into the N–C(O) amide bond *N*-activated by mesyl is more challenging than into the related *N*-tosyl.¹⁵ The nitrogen leaving group ability is similar to that observed in the mesylate series.¹⁶

In this project, we have developed the first general palladium-catalyzed Suzuki-Miyaura cross-coupling of *N*-mesylamides with arylboronic acids (Figure 2.2.1C).¹⁷ Of significant interest, our studies established the use of *N*-mesylamides as precursors for the controlled generation of acyl–metal intermediates from amides under catalytic conditions.⁵ The reaction delivered functionalized arylated products with a range of useful functional groups, including aldehyde, ketone, ester, nitro, and cyano, with high efficiency. In this study, we have also demonstrated the first examples of Suzuki-Miyaura cross-coupling in acyclic amides tolerating an aryl chloride¹⁸ and a sterically hindered di-ortho-substituted arylboronic acid nucleophile.¹⁹

■ A. Cross-coupling of amides (limitations: R'R'' groups)



■ B. Cross-coupling of aryl mesylates: Percec, Buchwald, Kwong, Molander, etc



■ C. This study: cross-coupling of *N*-mesyl-activated amides

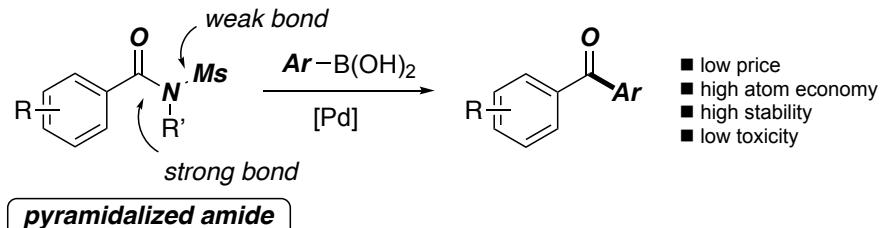


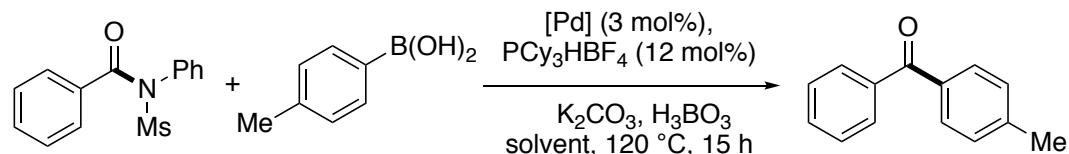
Figure 2.2.1 (a) Metal-catalyzed activation of amides and derivatives. (b) Cross-coupling of aryl mesylates. (c) Cross-coupling of *N*-mesylamides.

2.2.2 Reaction optimization

For optimization, we selected *N*-Ms-amide and 4-tolylboronic acid (see Table 2.2.1). As we expected, our optimized conditions for the cross-coupling of highly reactive *N*-glutarimide amides^{10h} provided the coupling product in negligible quantities (<10%). After extensive screening of various parameters (temperature, solvent, Pd source), the yield could be improved to 53%. The key finding involved identifying Na₂CO₃ as a competent base in the absence of added H₃BO₃. Boric acid was routinely used in previous studies to prevent protodeboronation and induce switchable N-/O-activation of the amide bond. In the cross-coupling of *N*-Ms-amides, the addition of boric acid shut down the reaction in agreement with the relative reactivity of the amide bond. Other bases, such as NaHCO₃ and KHCO₃, also gave the desired product, albeit in lower yields (see Table 2.2.2). Exploration of different Pd sources, ligands, and Pd/ligand stoichiometry (see Table 2.2.3) resulted in identifying the optimum conditions for the cross-coupling (>98% yield: Pd₂(dba)₃ (3 mol %), PCy₃HBF₄ (12 mol %), Na₂CO₃, dioxane, 120 °C).

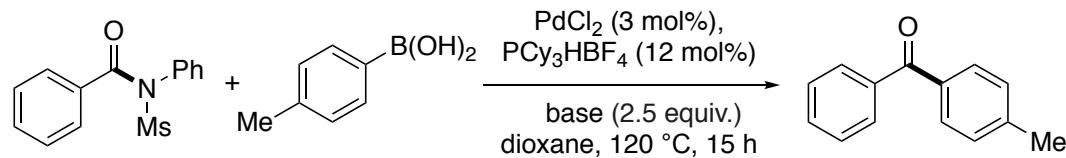
Importantly, we established that the cross-coupling could occur at temperatures as low as 80 °C (37% yield), providing an entry point for future studies. Similarly, even when the amount of boronic acid was decreased to 1.2-1.5 equiv, the desired product was still obtained in good yields (72-84%), consistent with efficient insertion/transmetalation in the catalytic cycle. Table 2.2.4 summarizes the effect of ligand in the Suzuki-Miyaura cross-coupling of *N*-Ms-amides; we have identified PCy₃HBF₄ as the best ligand.

Table 2.2.1 Optimization of Pd-catalyzed Suzuki-Miyaura cross-coupling of *N*-mesylamides.^a



entry	catalyst	K ₂ CO ₃	H ₃ BO ₃	solvent	temp	yield (%) ^a
1	Pd(OAc) ₂	2.5 equiv	1.5 equiv	THF	60 °C	7
2	Pd(OAc) ₂	2.5 equiv	1.5 equiv	THF	120 °C	27
3	Pd(OAc) ₂	2.5 equiv	1.5 equiv	dioxane	120 °C	40
4	PdCl ₂	2.5 equiv	1.0 equiv	dioxane	120 °C	28
5	PdCl ₂	2.5 equiv	1.5 equiv	dioxane	120 °C	53
6	PdCl ₂	2.5 equiv	2.0 equiv	dioxane	120 °C	38
7 ^b	PdCl ₂	2.5 equiv	1.5 equiv	dioxane	120 °C	<2
8 ^b	PdCl ₂	2.5 equiv	--	dioxane	120 °C	82

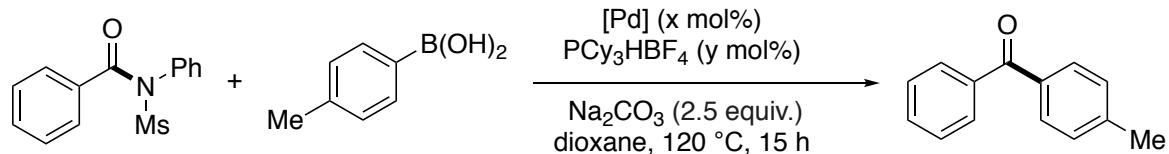
^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), catalyst (3 mol%), ligand (12 mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (x equiv), dioxane (0.25 M), 15 h. ^bNa₂CO₃.

Table 2.2.2 Effect of base in Suzuki-Miyaura cross-coupling of *N*-mesylamides.^a

entry	base	yield (%) ^a
1	Li_2CO_3	<2
2	LiOH	<2
3	Na_2CO_3	82
4	NaHCO_3	60
5	NaOH	<2
6	NaOAc	<2
7	K_2CO_3	<2
8	KHCO_3	44
9	KOH	<2
10	KOAc	<2
11	K_3PO_4	<2
12	K_2HPO_4	12
13	KH_2PO_4	<2
14	CaCO_3	<2
15	Cs_2CO_3	<2

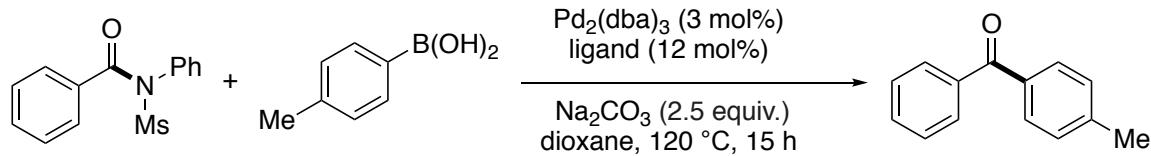
^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), PdCl₂ (3 mol%), PCy₃HBF₄ (12 mol%), base (2.5 equiv), dioxane (0.25 M), 120 °C, 15 h.

Table 2.2.3 Optimization of Pd-catalyzed Suzuki-Miyaura cross-coupling of *N*-mesylamides.^a



entry	catalyst	ligand	ratio	yield (%) ^a
1	3 mol% Pd(OAc) ₂	12 mol% PCy ₃ HBF ₄	1:4	84
2	3 mol% PdCl ₂	12 mol% PCy ₃ HBF ₄	1:4	82
3	3 mol% Pd(dba) ₂	12 mol% PCy ₃ HBF ₄	1:4	83
4	3 mol% Pd ₂ (dba) ₃	12 mol% PCy ₃ HBF ₄	1:4	99
5	3 mol% Pd(PPh ₃) ₄	12 mol% PCy ₃ HBF ₄	1:4	62
6	3 mol% Pd(OAc) ₂	6 mol% PCy ₃ HBF ₄	1:2	63
7	3 mol% PdCl ₂	6 mol% PCy ₃ HBF ₄	1:2	35
8	3 mol% Pd ₂ (dba) ₃	6 mol% PCy ₃ HBF ₄	1:2	<2
9	3 mol% Pd ₂ (dba) ₃	18 mol% PCy ₃ HBF ₄	1:6	97
10	3 mol% Pd ₂ (dba) ₃	24 mol% PCy ₃ HBF ₄	1:8	68
11	2 mol% Pd ₂ (dba) ₃	8 mol% PCy ₃ HBF ₄	1:4	87
12	1 mol% Pd ₂ (dba) ₃	4 mol% PCy ₃ HBF ₄	1:4	83
13	0.25 mol% Pd ₂ (dba) ₃	1 mol% PCy ₃ HBF ₄	1:4	42
14 ^b	3 mol% Pd ₂ (dba) ₃	12 mol% PCy ₃ HBF ₄	1:4	<2
15 ^c	3 mol% Pd ₂ (dba) ₃	12 mol% PCy ₃ HBF ₄	1:4	37
16 ^d	3 mol% Pd ₂ (dba) ₃	12 mol% PCy ₃ HBF ₄	1:4	90
17 ^e	3 mol% Pd ₂ (dba) ₃	12 mol% PCy ₃ HBF ₄	1:4	84
18 ^f	3 mol% Pd ₂ (dba) ₃	12 mol% PCy ₃ HBF ₄	1:4	72

^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), catalyst (x mol%), ligand (y mol%), Na₂CO₃ (2.5 equiv), dioxane (0.25 M), 120 °C, 15 h. ^b60 °C. ^c80 °C. ^d100 °C. ^eR-B(OH)₂ (1.50 equiv). ^fR-B(OH)₂ (1.20 equiv).

Table 2.2.4 Effect of ligand in Suzuki-Miyaura cross-coupling of *N*-mesylamides.^a

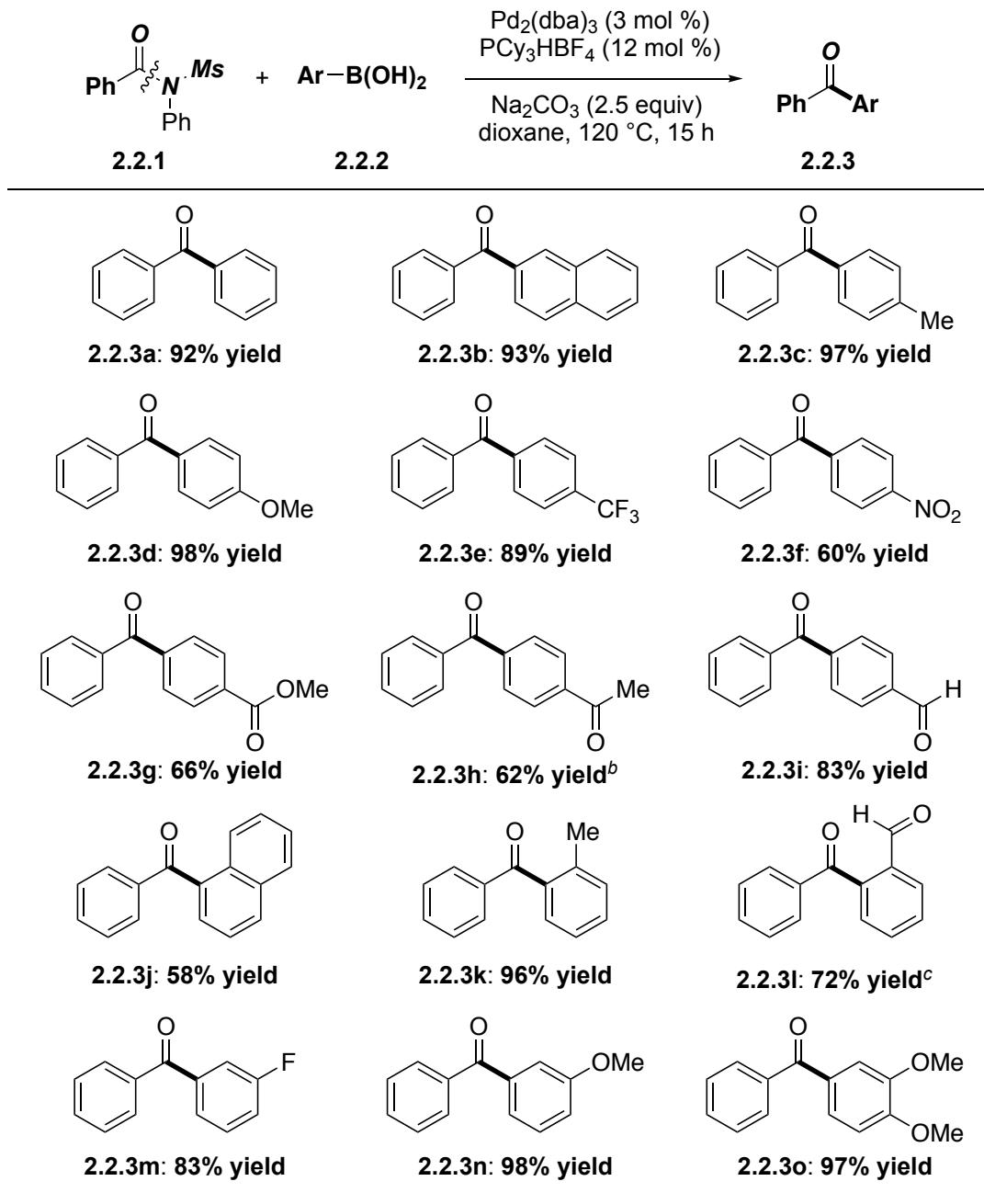
entry	base	yield (%) ^a
1	PCy ₃ HBF ₄	99
2	PCy ₂ Ph	37
3	PCyPh ₂	58
4	PPh ₃	29
5	Pt-Bu ₃ HBF ₄	<2
6	DPPB	<2
7	DPPF	<2
8	XantPhos	<2

^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), Pd₂(dba)₃ (3 mol%), ligand (12 mol%), Na₂CO₃ (2.5 equiv), dioxane (0.25 M), 120 °C, 15 h.

2.2.3 Substrate scope

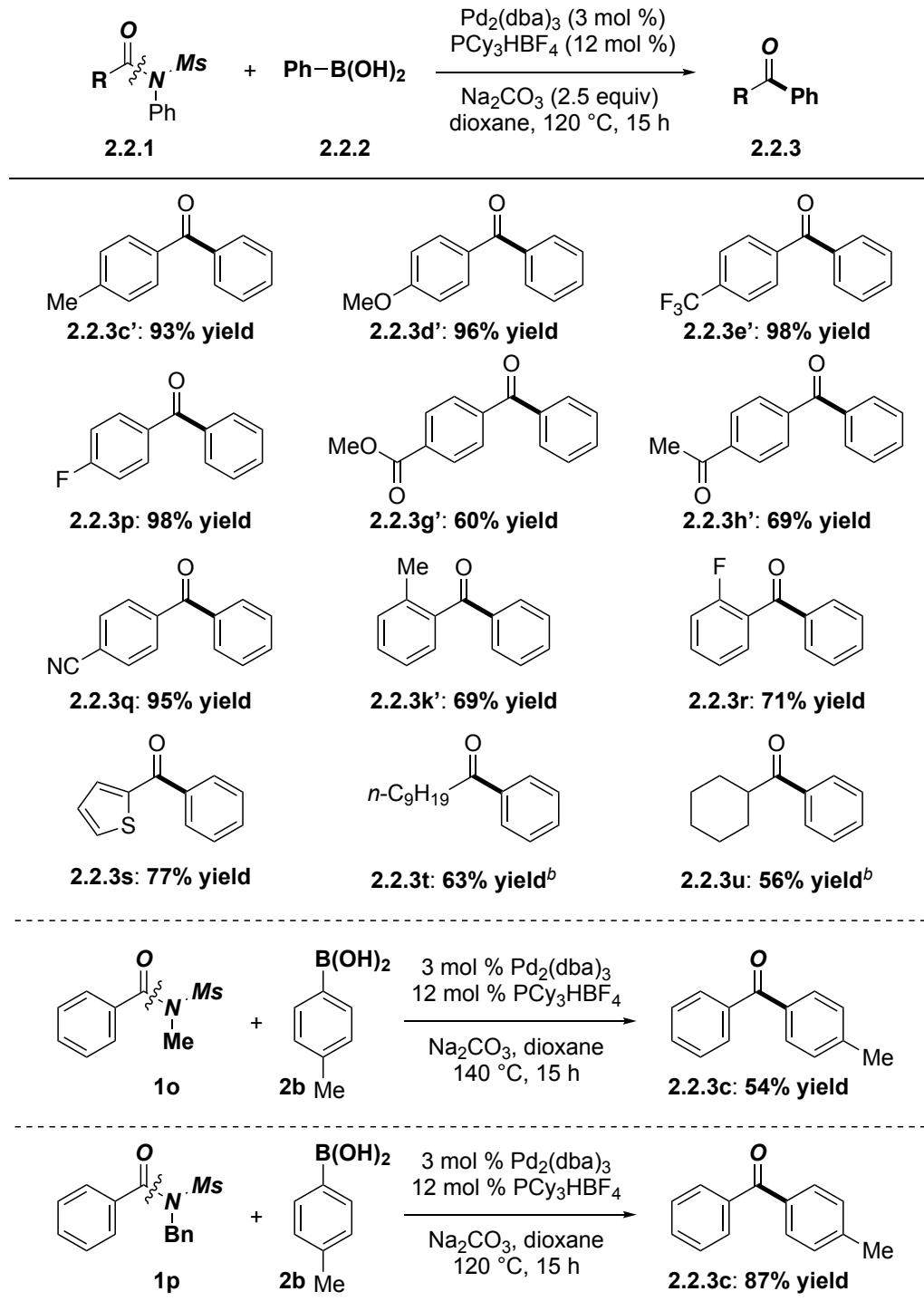
Next, using the standard conditions, we have explored the scope of the reaction with respect to the boronic acid component (Scheme 2.2.1). As shown, the reaction tolerated a range of electronically varied boronic acids (**2.2.3a-2.2.3e**). Sensitive functional groups, including nitro (**2.2.3f**), ester (**2.2.3g**), ketone (**2.2.3h**), and aldehyde groups (**2.2.3i**), were well-accommodated. It is worth noting that these groups are not tolerated in the classic Weinreb amide synthesis,²⁰ providing an important advantage. Moreover, polyarenes (**2.2.3j**), ortho-steric hindrance (**2.2.3k-2.2.3l**), electronically diverse substitution at the meta position (**2.2.3m-2.2.3n**) and highly electron-rich (**2.2.3o**) functional groups were compatible with the reaction conditions.

Next, the substrate scope with respect to the amide coupling partner was explored (Scheme 2.2.2). As shown, a variety of functional groups were well-tolerated, including electron-donating (**2.2.3c'-2.2.3d'**) and electron-poor (**2.2.3e'-2.2.3p**) substituents at the conjugating para-position. Sensitive functional groups, such as ester (**2.2.3g'**), ketone (**2.2.3h'**) and nitrile (**2.2.3q**), were well-tolerated. Ortho-substituted (**2.2.3k'-2.2.3r**) and heterocyclic amides (**2.2.3s**) were competent coupling partners. Finally, primary (**2.2.3t**) and secondary aliphatic amides (**2.2.3u**) could be coupled, albeit in modest yields. The reactions of these amides were conducted at slightly higher temperature to obtain best results. The challenging *N*-Ms/alkylamides were also viable coupling partners.



^aConditions: amide (1.0 equiv), ArB(OH)₂ (2.0 equiv), Pd₂(dba)₃ (3 mol%), PCy₃HBF₄ (12 mol%), Na₂CO₃ (2.5 equiv), dioxane (0.25 M), 120 °C, 15 h; ^bPd(OAc)₂ as catalyst; ^c140 °C.

Scheme 2.2.1 Boronic acid scope in Suzuki-Miyaura cross-coupling of *N*-mesylamides.^a



^aConditions: amide (1.0 equiv), ArB(OH)₂ (2.0 equiv), Pd₂(dba)₃ (3 mol%), PCy₃HBF₄ (12 mol%), Na₂CO₃ (2.5 equiv), dioxane (0.25 M), 120 °C, 15 h; ^b140 °C.

Scheme 2.2.2 Amide scope in Suzuki-Miyaura cross-coupling of *N*-mesylamides.^a

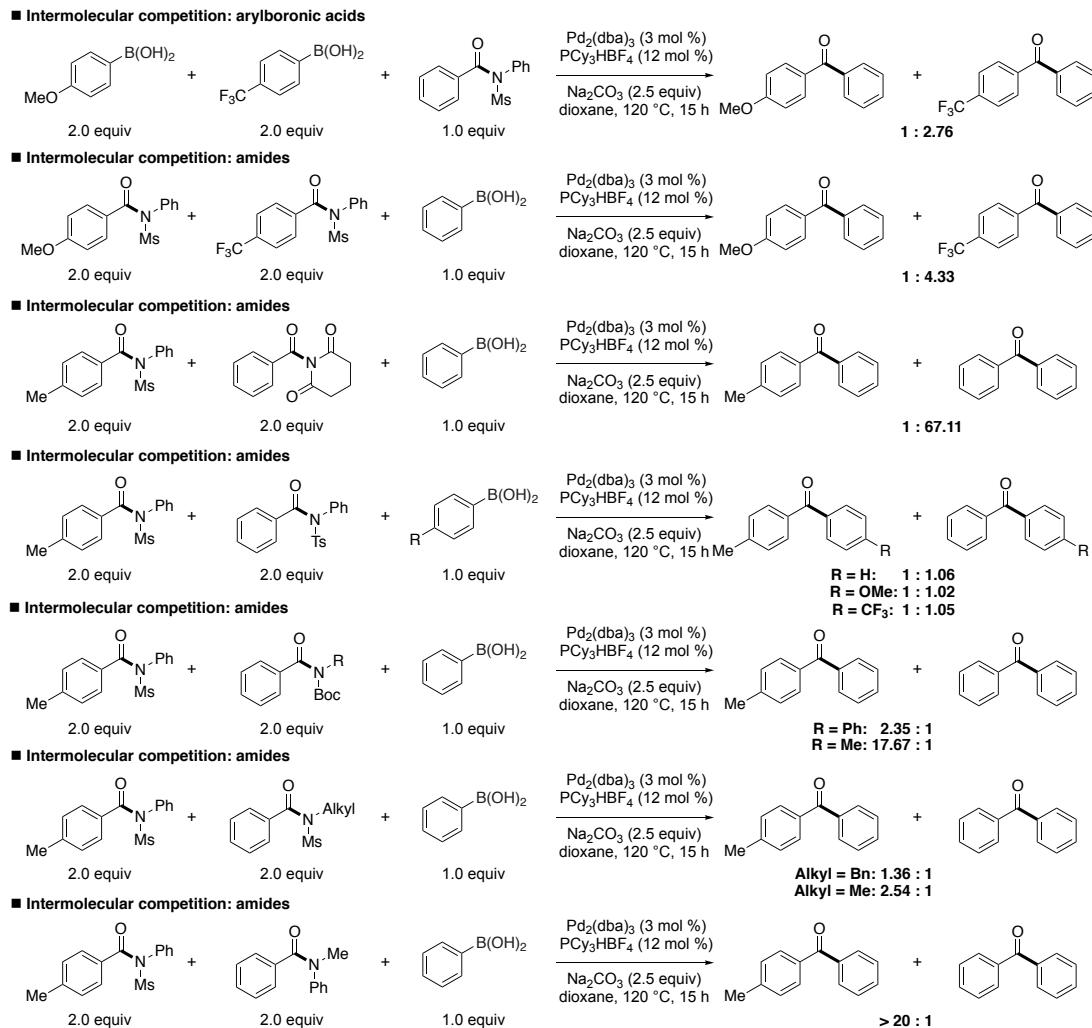
2.2.4 Mechanistic studies

To gain insight into the mechanism, we conducted competition experiments (Scheme 2.2.3). (1) Electron-deficient amides were inherently more reactive ($4\text{-CF}_3/4\text{-MeO} = 4.3:1$). (2) Electron-deficient nucleophiles reacted preferentially ($4\text{-CF}_3/4\text{-MeO} = 2.8:1$). (3) The reactivity order with respect to the amide activating group was determined to be as follows: *N*-glutarimide \gg *N*-R/Ts \approx *N*-R/Ms \gg *N*-Ar/R (anilide). High cross-coupling selectivity between these amides demonstrated the advantage of the amide *N*-activation platform.¹⁰ (4) The reactivity order of *N*-Ms/R substituents was determined to be as follows: R = Ph > R = alkyl (R = Bn, 1.4:1.0). This trend was consistent with the nitrogen leaving group ability.

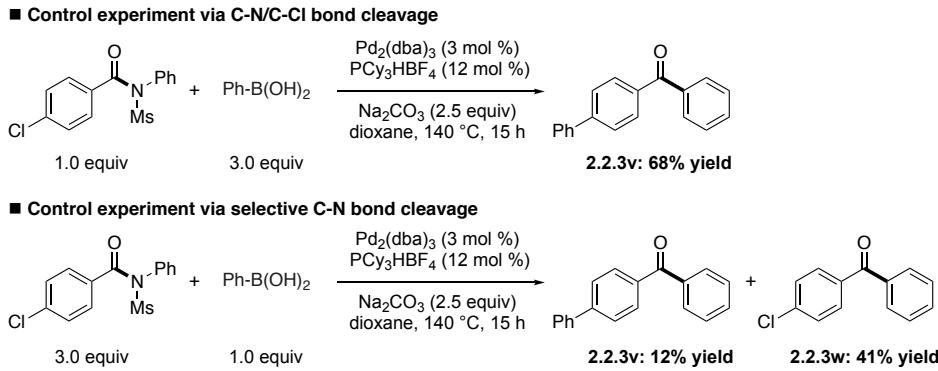
Studies to determine the order of amide vs halide selectivity were conducted (Scheme 2.2.4). Interestingly, we found that the cross-coupling of amide **2.2.1n** in the presence of a chloro substituent was possible. While the yield was moderate, prior to our study the cross-coupling of acyclic amides in the presence of halides, including *N*-Ts-amides, was not feasible.¹⁰ The cross-coupling of **2.2.1n** with a di-ortho-substituted boronic acid was also feasible (Scheme 2.2.5). Notably, this was the first example of the amide N–C bond cross-coupling using a di-ortho-substituted arylboronic acid nucleophile, providing an entry point for further studies.

The structural and mechanistic studies showed that *N*-Ms-amides were less destabilized than *N*-Ts-amides, as expected. However, the lower steric hindrance of the *N*-Ms group favored amide rotation. In several examples, the *N*-Ms group allowed for new amide

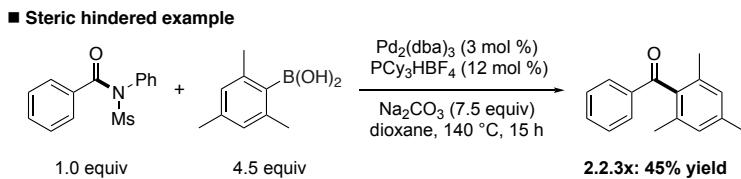
bond reactivity, which we proposed to be due to more facile insertion and/or transmetalation.



Scheme 2.2.3 Competition experiments in Suzuki-Miyaura cross-coupling of *N*-mesylamides.



Scheme 2.2.4 Control experiments in Suzuki-Miyaura cross-coupling of *N*-mesylamides.



Scheme 2.2.5 Hindered boronic acid in Suzuki-Miyaura cross-coupling of *N*-mesylamides.

2.2.5 Conclusion

In summary, we have developed the first palladium-catalyzed Suzuki-Miyaura cross-coupling of *N*-mesyl-activated amides with arylboronic acids. Using a Pd/PCy₃ catalyst system and Na₂CO₃ as a base, we have obtained high yields for the selective N–C(O) metal insertion/cross-coupling in the presence of various sensitive functional groups. The mesyl group featured highly desirable properties, including high atom economy, low cost, high stability, and low toxicity. Our method demonstrated the beneficial effect of the *N*-Ms substituent on the chemoselectivity of amide cross-coupling. *N*-Mesylamides could enable other reactions of amides by selective N–C activation, in particular when high atom economy or low steric hindrance is required.

2.2.6 Experimental section

General Procedure for Amide Synthesis. An oven-dried flask (25 mL) equipped with a stir bar was charged with aniline (typically, 5.0 mmol, 1.0 equiv), pyridine (typically, 2.5 equiv) and dichloromethane (typically, 0.50 M), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Methanesulfonyl chloride (typically, 1.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 2 h at room temperature. After the indicated time, the reaction mixture was diluted with ethyl acetate (30 mL). The reaction mixture was washed with HCl (1 x 10 mL), brine (1 x 10 mL), H₂O (1 x 10 mL), dried, and concentrated to get crude first-step product. Then an oven-dried flask (25 mL) equipped with a stir bar was charged with crude first-step product (typically, 5.0 mmol, 1.0 equiv), 4-(dimethylamino)pyridine (typically, 0.005 equiv), triethylamine (typically, 1.0 equiv) and dichloromethane (typically, 0.50 M), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acyl chloride (typically, 1.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. After the indicated time, the reaction mixture was diluted with ethyl acetate (30 mL). The reaction mixture was washed with HCl (1 x 10 mL), brine (1 x 10 mL), H₂O (1 x 10 mL), dried, and concentrated. The crude product was purified by recrystallization (toluene) to give analytically pure product.

General Procedure for Suzuki-Miyaura Cross-Coupling of Amides. An oven-dried vial equipped with a stir bar was charged with amide substrate (neat, 1.0 equiv), boronic acid (typically, 2.0 equiv), Pd₂(dba)₃ (typically, 3 mol%), PCy₃HBF₄ (typically, 12 mol%)

and Na₂CO₃ (typically, 2.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 1,4-Dioxane (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 120 °C, and stirred for the indicated time at 120 °C. After the indicated time, the reaction mixture was diluted with CH₂Cl₂ (10 mL), filtered, and concentrated. The sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate) afforded the title product.

2.2.1a. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.57-7.56 (d, *J* = 7.2 Hz, 2 H), 7.38-7.28 (m, 6 H), 7.26-7.23 (t, *J* = 7.9 Hz, 2 H), 3.46 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 171.10, 136.96, 133.14, 132.24, 129.82, 129.68, 129.47, 129.26, 128.21, 40.39.

2.2.1b. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.49-7.48 (d, *J* = 8.2 Hz, 2 H), 7.35-7.32 (m, 3 H), 7.31-7.29 (m, 2 H), 7.06-7.04 (d, *J* = 8.1 Hz, 2 H), 3.45 (s, 3 H), 2.30 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 171.05, 143.18, 137.24, 130.17, 129.98, 129.71, 129.45, 129.12, 128.93, 40.29, 21.56.

2.2.1c. White solid. Mp = 150-152 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.60-7.59 (d, *J* = 8.7 Hz, 2 H), 7.36-7.31 (m, 5 H), 6.75-6.73 (d, *J* = 8.8 Hz, 2 H), 3.78 (s, 3 H), 3.43 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 170.52, 162.88, 137.54, 132.40, 129.53, 129.49, 129.05, 124.94, 113.57, 55.38, 40.16. HRMS calcd for C₁₅H₁₅NO₄SNa (M⁺ + Na) 328.0614, found 328.0606.

2.2.1d. White solid. Mp = 158-159 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.67-7.65 (d, J = 8.2 Hz, 2 H), 7.52-7.51 (d, J = 8.2 Hz, 2 H), 7.36-7.35 (m, 3 H), 7.29-7.28 (m, 2 H), 3.49 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.73, 136.60, 136.29, 133.49 (q, J^F = 32.7 Hz), 130.55, 129.83, 129.81, 129.74, 125.27 (q, J^F = 3.7 Hz), 123.28 (q, J^F = 271.1 Hz), 40.56. ^{19}F NMR (471 MHz, CDCl_3) δ -63.28. HRMS calcd for $\text{C}_{15}\text{H}_{12}\text{F}_3\text{NO}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 366.0382, found 366.0392.

2.2.1e. White solid. Mp = 141-143 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.62-7.60 (t, J = 6.8 Hz, 2 H), 7.35 (s, 3 H), 7.30-7.28 (d, J = 5.5 Hz, 2 H), 6.96-6.92 (t, J = 7.9 Hz, 2 H), 3.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.94, 164.81 (d, J^F = 253.6 Hz), 136.96, 132.42 (d, J^F = 9.3 Hz), 129.65, 129.62, 129.38, 129.18 (d, J^F = 3.3 Hz), 115.55 (d, J^F = 22.0 Hz), 40.32. ^{19}F NMR (471 MHz, CDCl_3) δ -105.10. HRMS calcd for $\text{C}_{14}\text{H}_{12}\text{FNO}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 316.0414, found 316.0420.

2.2.1f. White solid. Mp = 132-134 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.62 (d, J = 7.7 Hz, 2 H), 7.56-7.54 (d, J = 7.8 Hz, 2 H), 7.36-7.36 (d, J = 2.7 Hz, 3 H), 7.27-7.26 (d, J = 3.3 Hz, 2 H), 3.49 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.28, 137.29, 136.06, 132.01, 129.88, 129.83, 129.80, 117.53, 115.51, 40.61. HRMS calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 323.0461, found 323.0457.

2.2.1g. White solid. Mp = 184-186 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.91-7.90 (d, J = 7.7 Hz, 2 H), 7.60-7.59 (d, J = 7.8 Hz, 2 H), 7.32 (s, 3 H), 7.27 (s, 2 H), 3.89 (s, 3 H), 3.49 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.24, 165.86, 137.19, 136.41, 132.97, 129.85, 129.61, 129.58, 129.37, 129.34, 52.45, 40.55. HRMS calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_5\text{SNa}$ ($\text{M}^+ + \text{Na}$) 356.0563, found 356.0570.

2.2.1h. White solid. Mp = 101-104 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.83-7.81 (d, J = 7.5 Hz, 2 H), 7.64-7.62 (d, J = 7.6 Hz, 2 H), 7.34 (s, 3 H), 7.29 (s, 2 H), 3.50 (s, 3 H), 2.56 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.07, 170.15, 139.25, 137.18, 136.40, 129.83, 129.68, 129.65, 129.61, 127.99, 40.56, 26.74. HRMS calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_4\text{SNa}$ ($\text{M}^+ + \text{Na}$) 340.0614, found 340.0618.

2.2.1i. White solid. Mp = 123-125 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.39-7.36 (t, J = 7.2 Hz, 1 H), 7.29-7.29 (d, J = 2.9 Hz, 6 H), 7.07-7.04 (t, J = 7.5 Hz, 1 H), 6.92-6.89 (t, J = 9.3 Hz, 1 H), 3.55 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.36, 158.33 (d, J^F = 250.7 Hz), 135.25, 132.92 (d, J^F = 8.4 Hz), 129.99, 129.68, 129.34 (d, J^F = 2.3 Hz), 129.17, 124.10 (d, J^F = 3.6 Hz), 123.33, 115.95 (d, J^F = 21.0 Hz), 41.21. ^{19}F NMR (471 MHz, CDCl_3) δ -111.88. HRMS calcd for $\text{C}_{14}\text{H}_{12}\text{FNO}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 316.0414, found 316.0421.

2.2.1j. White solid. Mp = 114-116 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.30-7.26 (m, 3 H), 7.22-7.19 (m, 3 H), 7.17-7.14 (t, J = 7.6 Hz, 1 H), 7.10-7.08 (d, J = 7.6 Hz, 1 H), 7.01-6.98 (t, J = 7.5 Hz, 1 H), 3.56 (s, 3 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.57, 136.06, 135.99, 133.85, 130.71, 130.39, 129.63, 129.42, 129.27, 127.87, 125.20, 41.35, 19.70. HRMS calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 312.0665, found 312.0673.

2.2.1k. White solid. Mp = 99-101 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.55-7.48 (m, 4 H), 7.44-7.43 (d, J = 7.7 Hz, 2 H), 7.08-7.08 (d, J = 3.9 Hz, 1 H), 6.90-6.88 (t, J = 4.2 Hz, 1 H), 3.53 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 163.16, 136.06, 135.99, 135.42, 134.29, 130.59, 130.40, 129.85, 127.44, 41.42. HRMS calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_3\text{S}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 304.0073, found 304.0078.

2.2.1l. White solid. Mp = 90-92 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.51 (t, J = 3.1 Hz, 3 H), 7.32-7.30 (m, 2 H), 3.49 (s, 3 H), 2.12-2.09 (t, J = 7.4 Hz, 2 H), 1.60-1.58 (t, J = 6.8 Hz, 2 H), 1.31-1.27 (m, 2 H), 1.23-1.21 (m, 10 H), 0.90-0.87 (t, J = 6.9 Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 174.36, 135.57, 130.11, 129.98, 129.87, 42.15, 36.68, 31.83, 29.30, 29.24, 29.20, 28.87, 24.34, 22.65, 14.11. HRMS calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 348.1604, found 348.1608.

2.2.1m. White solid. Mp = 109-111 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.53-7.51 (m, 3 H), 7.32-7.31 (m, 2 H), 3.45 (s, 3 H), 2.12-2.06 (m, 1 H), 1.76-1.68 (m, 4 H), 1.58-1.48 (m, 3 H), 1.23-1.14 (m, 1 H), 1.00-0.92 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 177.48, 135.52, 130.07, 129.89, 129.81, 43.76, 41.93, 29.02, 25.34, 25.13. HRMS calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 304.0978, found 304.0980.

2.2.1n. White solid. Mp = 137-139 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.51 (d, J = 7.6 Hz, 2 H), 7.37-7.36 (d, J = 4.5 Hz, 3 H), 7.29 (s, 2 H), 7.24-7.23 (d, J = 7.6 Hz, 2 H), 3.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.02, 138.69, 136.76, 131.47, 131.12, 129.68, 129.66, 129.48, 128.62, 40.37. HRMS calcd for $\text{C}_{14}\text{H}_{12}\text{ClNO}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 332.0119, found 332.0114.

2.2.1o. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.63-7.62 (d, J = 7.1 Hz, 2 H), 7.58-7.55 (t, J = 7.4 Hz, 1 H), 7.50-7.47 (t, J = 7.8 Hz, 2 H), 3.39 (s, 3 H), 3.30 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 172.21, 133.65, 132.27, 128.74, 128.20, 40.96, 35.96.

2.2.1p. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.67-7.66 (d, J = 7.1 Hz, 2 H), 7.60-7.57 (t, J = 7.5 Hz, 1 H), 7.51-7.48 (t, J = 7.8 Hz, 2 H), 7.36-7.32 (m, 3 H), 7.20-7.19 (d,

$J = 6.1$ Hz, 2 H), 5.02 (s, 2 H), 3.07 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 172.60, 135.65, 133.85, 132.31, 128.95, 128.87, 128.36, 128.35, 128.07, 52.19, 42.95.

2.2.3a. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.83 (d, $J = 8.2$ Hz, 4 H), 7.63-7.60 (t, $J = 6.7$ Hz, 2 H), 7.53-7.50 (t, $J = 7.6$ Hz, 4 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.78, 137.62, 132.43, 130.08, 128.29.

2.2.3b. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.30 (s, 1 H), 7.98 (s, 2 H), 7.96-7.94 (d, $J = 8.0$ Hz, 2 H), 7.90-7.89 (d, $J = 7.4$ Hz, 2 H), 7.65 (s, 2 H), 7.60-7.53 (m, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.78, 137.93, 135.29, 134.85, 132.40, 132.28, 131.89, 130.12, 129.44, 128.36, 128.34, 128.32, 127.84, 126.82, 125.81.

2.2.3c. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.82-7.80 (d, $J = 8.1$ Hz, 2 H), 7.76-7.74 (d, $J = 8.0$ Hz, 2 H), 7.62-7.59 (t, $J = 7.5$ Hz, 1 H), 7.51-7.48 (t, $J = 7.6$ Hz, 2 H), 7.32-7.28 (d, $J = 7.9$ Hz, 2 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.53, 143.26, 137.98, 134.90, 132.17, 130.33, 129.95, 128.99, 128.22, 21.68.

2.2.3d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.85 (d, $J = 8.7$ Hz, 2 H), 7.79-7.77 (d, $J = 8.2$ Hz, 2 H), 7.61-7.58 (t, $J = 6.8$ Hz, 1 H), 7.51-7.48 (t, $J = 7.6$ Hz, 2 H), 7.00-6.98 (d, $J = 8.7$ Hz, 2 H), 3.92 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.59, 163.24, 138.31, 132.58, 131.90, 130.19, 129.75, 128.20, 113.57, 55.52.

2.2.3e. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.93-7.91 (d, $J = 8.0$ Hz, 2 H), 7.84-7.82 (d, $J = 8.2$ Hz, 2 H), 7.79-7.77 (d, $J = 8.1$ Hz, 2 H), 7.67-7.64 (t, $J = 7.6$ Hz, 1 H), 7.55-7.52 (t, $J = 7.7$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.55, 140.74, 136.75, 133.74 ($q, J^F = 32.5$ Hz), 133.11, 130.15, 130.12, 128.55, 125.37 ($q, J^F = 3.7$ Hz), 123.69 ($q, J^F = 270.9$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -63.00.

2.2.3f. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.38-8.36 (d, $J = 8.7$ Hz, 2 H), 7.98-7.96 (d, $J = 8.7$ Hz, 2 H), 7.84-7.82 (d, $J = 8.2$ Hz, 2 H), 7.70-7.67 (t, $J = 7.5$ Hz, 1 H), 7.57-7.54 (t, $J = 7.8$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 194.83, 149.86, 142.91, 136.31, 133.50, 130.72, 130.12, 128.71, 123.57.

2.2.3g. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.18-8.16 (d, $J = 8.1$ Hz, 2 H), 7.87-7.86 (d, $J = 8.1$ Hz, 2 H), 7.83-7.82 (d, $J = 8.2$ Hz, 2 H), 7.66-7.63 (t, $J = 7.5$ Hz, 1 H), 7.54-7.51 (t, $J = 7.7$ Hz, 2 H), 3.99 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.07, 166.34, 141.34, 136.97, 133.24, 132.97, 130.12, 129.80, 129.52, 128.48, 52.49.

2.2.3h. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.09-8.08 (d, $J = 8.3$ Hz, 2 H), 7.90-7.88 (d, $J = 8.3$ Hz, 2 H), 7.84-7.82 (d, $J = 7.1$ Hz, 2 H), 7.66-7.63 (t, $J = 7.5$ Hz, 1 H), 7.55-7.51 (t, $J = 7.8$ Hz, 2 H), 2.70 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.54, 195.98, 141.35, 139.58, 136.93, 133.01, 130.12, 130.07, 128.50, 128.18, 26.92.

2.2.3i. White solid. ^1H NMR (500 MHz, CDCl_3) δ 10.16 (s, 1 H), 8.04-8.02 (d, $J = 8.3$ Hz, 2 H), 7.96-7.95 (d, $J = 8.2$ Hz, 2 H), 7.84-7.83 (d, $J = 7.1$ Hz, 2 H), 7.68-7.65 (t, $J = 7.5$ Hz, 1 H), 7.55-7.52 (t, $J = 7.9$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.85, 191.65, 142.59, 138.49, 136.76, 133.16, 130.35, 130.14, 129.52, 128.56.

2.2.3j. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.13-8.11 (d, $J = 8.2$ Hz, 1 H), 8.05-8.03 (d, $J = 8.1$ Hz, 1 H), 7.96-7.95 (d, $J = 7.9$ Hz, 1 H), 7.90-7.89 (d, $J = 8.3$ Hz, 2 H), 7.64-7.60 (m, 2 H), 7.58-7.52 (m, 3 H), 7.50-7.47 (t, $J = 7.6$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.05, 138.34, 136.38, 133.74, 133.25, 131.28, 130.97, 130.43, 128.46, 128.42, 127.78, 127.27, 126.48, 125.71, 124.35.

2.2.3k. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.82 (d, $J = 8.3$ Hz, 2 H), 7.62-7.59 (t, $J = 7.5$ Hz, 1H), 7.50-7.47 (t, $J = 7.9$ Hz, 2 H), 7.43-7.40 (t, $J = 7.5$ Hz, 1 H), 7.35-7.31 (t, $J = 7.8$ Hz, 2 H), 7.29-7.26 (t, $J = 7.5$ Hz, 1 H), 2.36 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.67, 138.63, 137.76, 136.77, 133.14, 131.01, 130.25, 130.15, 128.53, 128.47, 125.21, 20.00.

2.2.3l. Orange solid. ^1H NMR (500 MHz, CDCl_3) δ 10.05 (s, 1 H), 8.07-8.05 (m, 1 H), 7.83-7.82 (d, $J = 7.2$ Hz, 2 H), 7.72-7.71 (t, $J = 3.4$ Hz, 2 H), 7.65-7.62 (t, $J = 7.4$ Hz, 1 H), 7.54-7.53 (m, 1 H), 7.51-7.48 (t, $J = 7.9$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.53, 190.61, 141.42, 137.08, 135.42, 133.69, 133.36, 130.63, 130.07, 129.98, 128.90, 128.68.

2.2.3m. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.83-7.82 (d, $J = 7.5$ Hz, 2 H), 7.65-7.59 (m, 2 H), 7.54-7.47 (m, 4 H), 7.33-7.30 (t, $J = 8.3$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.59, 162.51 (d, $J^F = 246.78$ Hz), 137.05, 132.79, 130.03, 130.01, 129.95, 128.44, 125.83 (d, $J^F = 2.9$ Hz), 119.44 (d, $J^F = 21.4$ Hz), 116.77 (d, $J^F = 22.3$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -111.99.

2.2.3n. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.83 (d, $J = 7.1$ Hz, 2 H), 7.63-7.60 (t, $J = 7.4$ Hz, 1 H), 7.52-7.49 (t, $J = 7.8$ Hz, 2 H), 7.42-7.36 (m, 3 H), 7.17-7.15 (m, 1 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.54, 159.59, 138.92, 137.64, 132.44, 130.06, 129.23, 128.27, 122.89, 118.88, 114.33, 55.49.

2.2.3o. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.78 (d, $J = 8.1$ Hz, 2 H), 7.61-7.58 (t, $J = 6.9$ Hz, 1 H), 7.52-7.49 (t, $J = 7.7$ Hz, 3 H), 7.41-7.40 (d, $J = 8.4$ Hz, 1 H), 6.93-6.91 (d, $J = 8.3$ Hz, 1 H), 3.99 (s, 3 H), 3.97 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ

195.61, 153.04, 149.03, 138.31, 131.90, 130.24, 129.74, 128.19, 125.53, 112.13, 109.74, 56.11, 56.07.

2.2.3p. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.89-7.86 (t, $J = 5.5$ Hz, 2 H), 7.80-7.79 (d, $J = 8.2$ Hz, 2 H), 7.64-7.61 (t, $J = 7.5$ Hz, 1 H), 7.53-7.50 (t, $J = 7.7$ Hz, 2 H), 7.21-7.17 (t, $J = 8.6$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.30, 165.41 (d, $J^F = 252.5$ Hz), 137.52, 133.82 (d, $J^F = 2.9$ Hz), 132.69 (d, $J^F = 9.1$ Hz), 132.49, 129.90, 128.38, 115.48 (d, $J^F = 21.7$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -105.99.

2.2.3q. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.91-7.89 (d, $J = 7.7$ Hz, 2 H), 7.82-7.81 (m, 4 H), 7.68-7.65 (t, $J = 7.6$ Hz, 1 H), 7.56-7.53 (t, $J = 7.4$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.06, 141.25, 136.35, 133.35, 132.19, 130.26, 130.09, 128.66, 118.03, 115.69.

2.2.3r. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.86 (d, $J = 7.9$ Hz, 2 H), 7.64-7.61 (t, $J = 7.4$ Hz, 1 H), 7.60-7.54 (m, 2 H), 7.52-7.49 (t, $J = 7.8$ Hz, 2 H), 7.31-7.28 (t, $J = 7.5$ Hz, 1 H), 7.21-7.17 (t, $J = 9.2$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 193.50, 160.11 (d, $J^F = 250.8$ Hz), 137.41, 133.43, 133.08 (d, $J^F = 8.2$ Hz), 130.77 (d, $J^F = 2.9$ Hz), 129.83, 128.48, 127.06 (d, $J^F = 14.7$ Hz), 124.30 (d, $J^F = 3.6$ Hz), 116.29 (d, $J^F = 21.6$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -111.03.

2.2.3s. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.90-7.89 (d, $J = 8.2$ Hz, 2 H), 7.76-7.75 (d, $J = 4.9$ Hz, 1 H), 7.68-7.67 (d, $J = 3.7$ Hz, 1 H), 7.64-7.61 (t, $J = 7.5$ Hz, 1 H), 7.54-7.51 (t, $J = 7.7$ Hz, 2 H), 7.20-7.19 (t, $J = 4.8$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 188.26, 143.67, 138.18, 134.86, 134.22, 132.28, 129.20, 128.43, 127.97.

2.2.3t. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.99-7.98 (d, $J = 8.2$ Hz, 2 H), 7.59-7.56 (t, $J = 7.6$ Hz, 1 H), 7.50-7.47 (t, $J = 7.7$ Hz, 2 H), 3.00-2.97 (t, $J = 7.6$ Hz, 2 H), 1.79-1.73 (m, 2 H), 1.43-1.29 (m, 12 H), 0.92-0.89 (t, $J = 6.1$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 200.66, 137.12, 132.86, 128.56, 128.07, 38.66, 31.89, 29.50, 29.49, 29.40, 29.30, 24.41, 22.68, 14.12.

2.2.3u. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.98-7.96 (d, $J = 8.2$ Hz, 2 H), 7.58-7.56 (t, $J = 7.5$ Hz, 1 H), 7.50-7.47 (t, $J = 7.7$ Hz, 2 H), 3.31-3.27 (t, $J = 11.5$ Hz, 1 H), 1.93-1.86 (m, 4 H), 1.78-1.75 (d, $J = 11.7$ Hz, 1 H), 1.54-1.49 (t, $J = 13.4$ Hz, 2 H), 1.46-1.39 (m, 2 H), 1.34-1.31 (d, $J = 12.5$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 203.92, 136.38, 132.73, 128.59, 128.27, 45.65, 29.44, 25.98, 25.88.

2.2.3v. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.94-7.92 (d, $J = 7.2$ Hz, 2 H), 7.88-7.86 (d, $J = 7.5$ Hz, 2 H), 7.75-7.73 (d, $J = 7.3$ Hz, 2 H), 7.69-7.68 (d, $J = 7.7$ Hz, 2 H), 7.65-7.62 (t, $J = 7.1$ Hz, 1 H), 7.55-7.50 (m, 4 H), 7.45-7.42 (t, $J = 6.7$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.38, 145.26, 140.01, 137.79, 136.26, 132.40, 130.75, 130.02, 128.99, 128.33, 128.21, 127.33, 126.99.

2.2.3w. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.81-7.78 (t, $J = 7.3$ Hz, 4 H), 7.64-7.62 (t, $J = 7.5$ Hz, 1 H), 7.53-7.48 (m, 4 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.52, 138.92, 137.27, 135.89, 132.66, 131.48, 129.95, 128.66, 128.42.

2.2.3x. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.82 (d, $J = 7.5$ Hz, 2 H), 7.61-7.58 (t, $J = 7.3$ Hz, 1 H), 7.48-7.45 (t, $J = 7.4$ Hz, 2 H), 6.92 (s, 2 H), 2.36 (s, 3 H), 2.11 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 200.80, 138.51, 137.32, 136.89, 134.22, 133.55, 129.43, 128.80, 128.33, 21.17, 19.37.

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2.3 N-Ph/Ac amides and their reactivity in acyl Suzuki-Miyaura cross-coupling

Parts of this section were adapted with permission from the article “Acyl and Decarbonylative Suzuki Coupling of *N*-Acetyl Amides: Electronic Tuning of Twisted, Acyclic Amides in Catalytic Carbon–Nitrogen Bond Cleavage” (*ACS Catal.* **2018**, *8*, 9131). Copyright ©2018, American Chemical Society.

2.3.1 Introduction

At the start of this project, cross-coupling reactions of amides have been established as a powerful route to functionalization of the ubiquitous amide bond essential in organic synthesis.^{1,2} Direct insertion of a transition metal into the traditionally-inert amide bond has been demonstrated to generate versatile acyl-metal intermediate as a new platform for chemical synthesis.^{3,4} Amides are particularly attractive targets for metal-induced functional-group interconversion⁵ due to their fundamental significance as versatile synthetic intermediates and central role as key building blocks in the production of biologically-active compounds.^{6,7} As a result, converting common amides into high value functional groups has a transformative effect on organic synthesis.

In principle, transformations at the C(acyl) amide bond have relied on the steric and electronic fine-tuning of amidic resonance that further benefits from nitrogen geometry enabling controlled variation of sterics and amidicity.⁸⁻¹⁰ The development of well-defined amide precursors permits a rational approach to cross-coupling reactions of amides and sets the stage for methodological advances.¹¹⁻¹⁶ One main challenge is that the cleavage of the N–X bond (X = Ts, Boc) is a major side reaction in Pd(0) and Ni(0)-

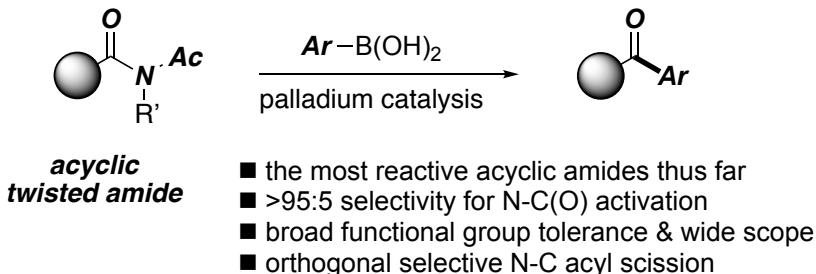
catalyzed amide N–C(O) cross-coupling.¹⁷⁻²² The development of new amide precursors that are compatible with various reaction pathways is critical to fully utilize the potential of amides in cross-coupling.¹⁻⁴

In this project, we have developed the first Pd-catalyzed acyl Suzuki-Miyaura cross-coupling of *N*-acetyl-amides with arylboronic acids (Figure 2.3.1).²³ Most crucially, the presented results introduced *N*-acetyl-amides as the most reactive acyclic amides in the transition-metal-catalyzed amide cross-coupling. Notable features of our study included: (1) unprecedented N–C(O) cleavage reactivity induced by the acyl group, (2) exceptionally high stability under the reaction conditions that avoided N–X scission, (3) reagent-controlled fully chemoselective divergent²⁴ acyl coupling, (4) in contrast to the previously reported precursors, versatile synthesis from secondary and primary amides that gave a broad generality of this reactivity platform. As a key design element, structural and mechanistic studies pointed to fine-tuning of amidic resonance^{9,10} and amide bond twist⁸ as selectivity determining features in a strategy for cross-coupling of acyclic amides. We proposed *N*-acetyl amides as generic precursors in amide bond cross-coupling to expand the scope of direct functionalization of amides due to the inherent steric and electronic advantages that determine the reactivity and selectivity of these reactions.^{2,9,10}

Prior to the start of this project, our laboratory introduced *N*-acyl-glutarimides for the cross-coupling reactions by N–C(O) amide cleavage.²² These cyclic amide precursors have been established as the most reactive amide derivatives in the amide bond cross-coupling manifold, enabling the development of more than 10 previously unknown catalytic modes of reactivity of the amide bond.^{1-4,22} Despite the success of *N*-acyl-

glutarimides, these precursors lack generality in that they cannot be prepared from common and readily available primary and secondary amides. A critical design feature of *N*-acyl-glutarimides is the combination of amide bond twist and resonance destabilization in a rotationally-inverted amide bond.^{9b} Building upon our mechanistic insights,^{9d} we proposed that glutarimide ring de-construction could maintain the capacity of amides to undergo facile metal insertion under mild conditions (Figure 2.3.1B), while enabling a broad range of common acyclic amides to be employed as viable precursors to acyl–metal intermediates in the coupling. To test this concept, we selected acyl Suzuki–Miyaura cross-coupling as a representative transformation.

A. Acyl amide cross-coupling of acyclic amides



B. Twist-enabled activation of amides: efficient platform for N-C coupling

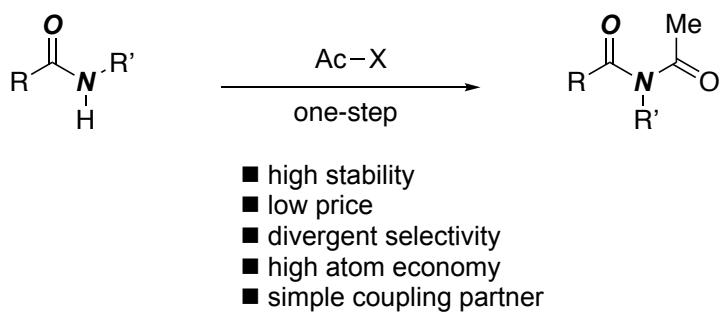


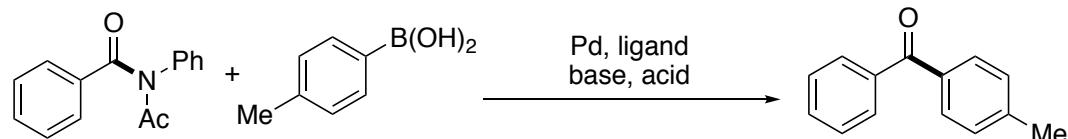
Figure 2.3.1 (a) Acyl cross-coupling of acyclic amides. (b) Twist-enabled activation of the amide bond (this study).

2.3.2 Reaction optimization

After extensive optimization, we established that the reaction of *N*-acetyl amide **2.3.1a** with 4-Tol-B(OH)₂ (2.0 equiv) in the presence of Pd(OAc)₂ (3 mol%) and PCy₃HBF₄ (12 mol%) in combination with K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv) in toluene at 60 °C resulted in a quantitative conversion to the biaryl ketone **2.3.1b** (Table 2.3.1, entry 8). Selected optimization results are summarized in Table 2.3.1. Exploration of different solvents and bases revealed that a combination of K₂CO₃ and toluene was optimal (entries 1-9). Examination of different Pd/ligand stoichiometry revealed that efficient coupling occurs with a close to 1:1 Pd:ligand ratio, consistent with facile insertion/transmetallation in the catalytic cycle (entries 10-12). Furthermore, even when the amount of boronic acid was decreased to 1.2-15 equiv, the desired ketone was obtained in good yields at 60 °C (76-83%), providing an entry point for future studies (entries 13-14). Interestingly, the reaction could provide 99% yield with as low catalyst loading as 0.25 mol% (entry 15). Finally, the reaction at 40 °C afforded **2.3.1b** in 82% yield (entry 16), demonstrating the superior reactivity of *N*-Ac-amide **2.3.1a** over other amide precursors.²

Importantly, we found that the nature of the ligand had a major impact on the coupling and PCy₃HBF₄ proved to be the most effective (Table 2.3.2, entries 1-9). This phosphine has slowly emerged as a privileged ligand in Pd-catalyzed amide bond activation, presumably due to highly electron-rich nature and well-fitted steric impact on the Pd center vs. acyl bond (cf. *t*-Bu₃P).³ Importantly, under the optimized conditions, scission of the alternative N–C bond was not observed, indicating high propensity of the *N*-acyl-amide to undergo chemoselective N–C(O) oxidative addition.

Table 2.3.1 Optimization of Pd-catalyzed Suzuki-Miyaura cross-coupling of *N*-acetyl amides.^a



entry	catalyst	ligand	base	additive	solvent	yield (%) ^a
1	Pd(OAc) ₂	PCy ₃ HBF ₄	Na ₂ CO ₃	H ₃ BO ₃	THF	92
2	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	THF	91
3	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₃ PO ₄	H ₃ BO ₃	THF	49
4	Pd(OAc) ₂	PCy ₃ HBF ₄	Na ₂ CO ₃	H ₃ BO ₃	dioxane	62
5	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	dioxane	89
6	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₃ PO ₄	H ₃ BO ₃	dioxane	53
7	Pd(OAc) ₂	PCy ₃ HBF ₄	Na ₂ CO ₃	H ₃ BO ₃	toluene	70
8	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	toluene	98
9	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₃ PO ₄	H ₃ BO ₃	toluene	72
10 ^b	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	toluene	91
11 ^c	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	toluene	84
12 ^d	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	toluene	92
13 ^e	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	toluene	76
14 ^f	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	toluene	83
15 ^g	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	toluene	99
16 ^h	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	toluene	82
17 ⁱ	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	toluene	9
18 ^{i,j}	Pd(OAc) ₂	PCy ₃ HBF ₄	K ₂ CO ₃	H ₃ BO ₃	toluene	10

^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%), base (2.5 equiv), H₃BO₃ (2.0 equiv), solvent (0.25 M), 60 °C, 15 h. ^bPd(OAc)₂ (3 mol%), PCy₃HBF₄ (3 mol%). ^cPd(OAc)₂ (3 mol%), PCy₃HBF₄ (6 mol%).

^dPd(OAc)₂ (3 mol%), PCy₃HBF₄ (9 mol%). ^eR-B(OH)₂ (1.2 equiv). ^fR-B(OH)₂ (1.5 equiv). ^gPd(OAc)₂ (0.25 mol%). ^h40 °C. ⁱ25 °C. ^jH₂O (5.0 equiv).

Table 2.3.2 Effect of ligand in Suzuki-Miyaura cross-coupling of *N*-acetyl amides.^a

entry	ligand	yield (%) ^a
1	PCy ₃ BF ₄	99
2	PCy ₂ Ph	44
3	PCyPh ₂	<2
4	PPh ₃	<2
5	P(<i>o</i> -tol) ₃	<2
6	P <i>n</i> -Bu ₃ BF ₄	89
7	P <i>t</i> -Bu ₃ BF ₄	4
8	XPhos	79
9	XantPhos	10

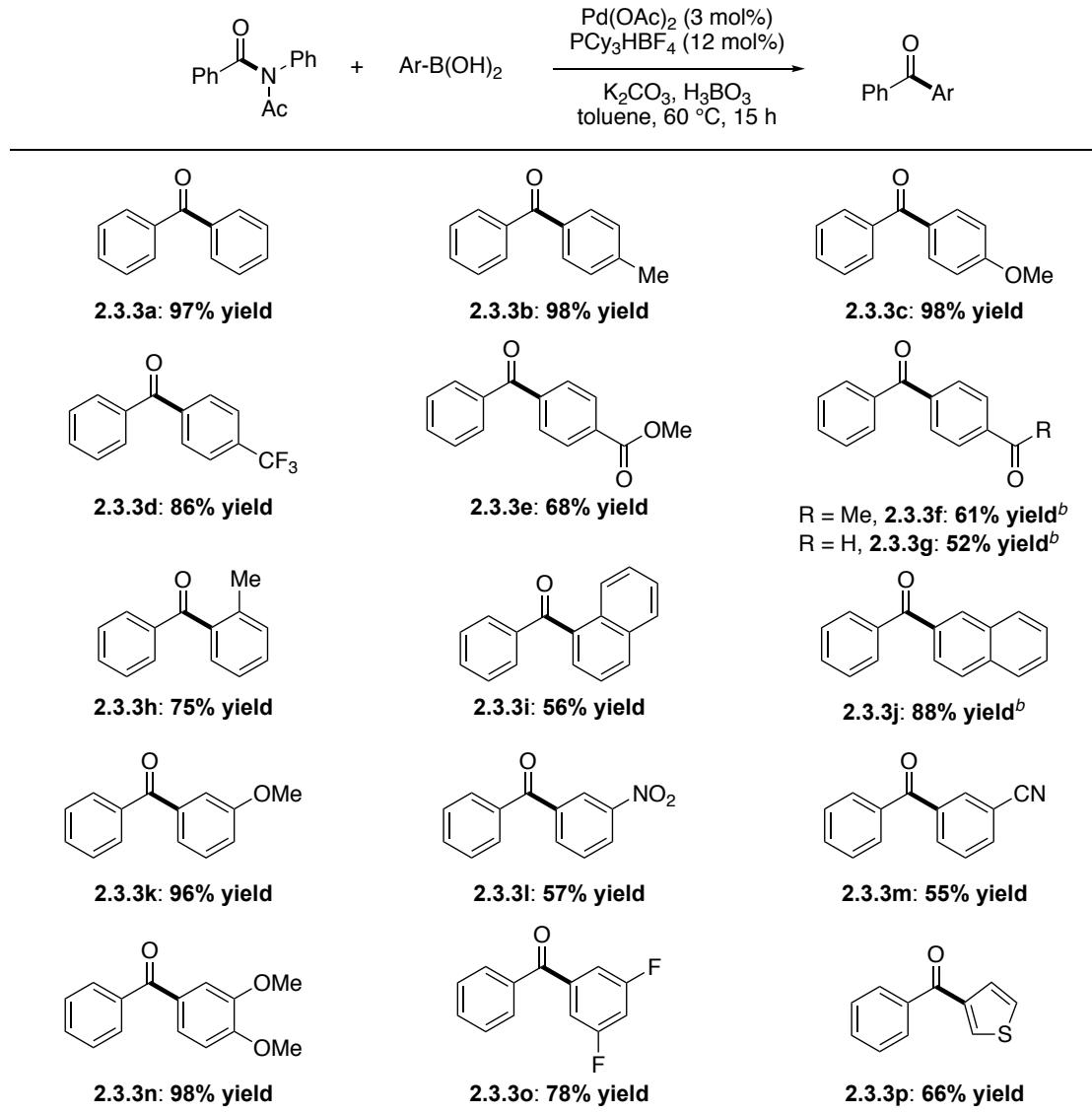
^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), Pd(OAc)₂ (3 mol%), ligand (12 mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv), toluene (0.25 M), 60 °C, 15 h.

2.3.3 Substrate scope

With optimal reaction conditions in hand, we next evaluated the scope of boronic acids that can participate in this reaction (Scheme 2.3.1). As shown, a wide range of boronic acids bearing electron-neutral (**2.3.3a**), electron-donating (**2.3.3b-2.3.3c**) and electron-withdrawing (**2.3.3d-2.3.3g**) substituents was compatible with this coupling. Particularly noteworthy was that electrophilic-functional groups that would be problematic in the classic organometallic additions,²⁵ including esters (**2.3.3e**), ketones (**2.3.3f**) and aldehydes (**2.3.3g**) were well-tolerated. Furthermore, steric-hindrance (**2.3.3h-2.3.3i**), polyaromatics (**2.3.3i-2.3.3j**) and electrophilic nitro (**2.3.3l**) and cyano groups (**2.3.3m**) could be readily employed in this coupling. Finally, fluorinated boronic acids (**2.3.3o**)

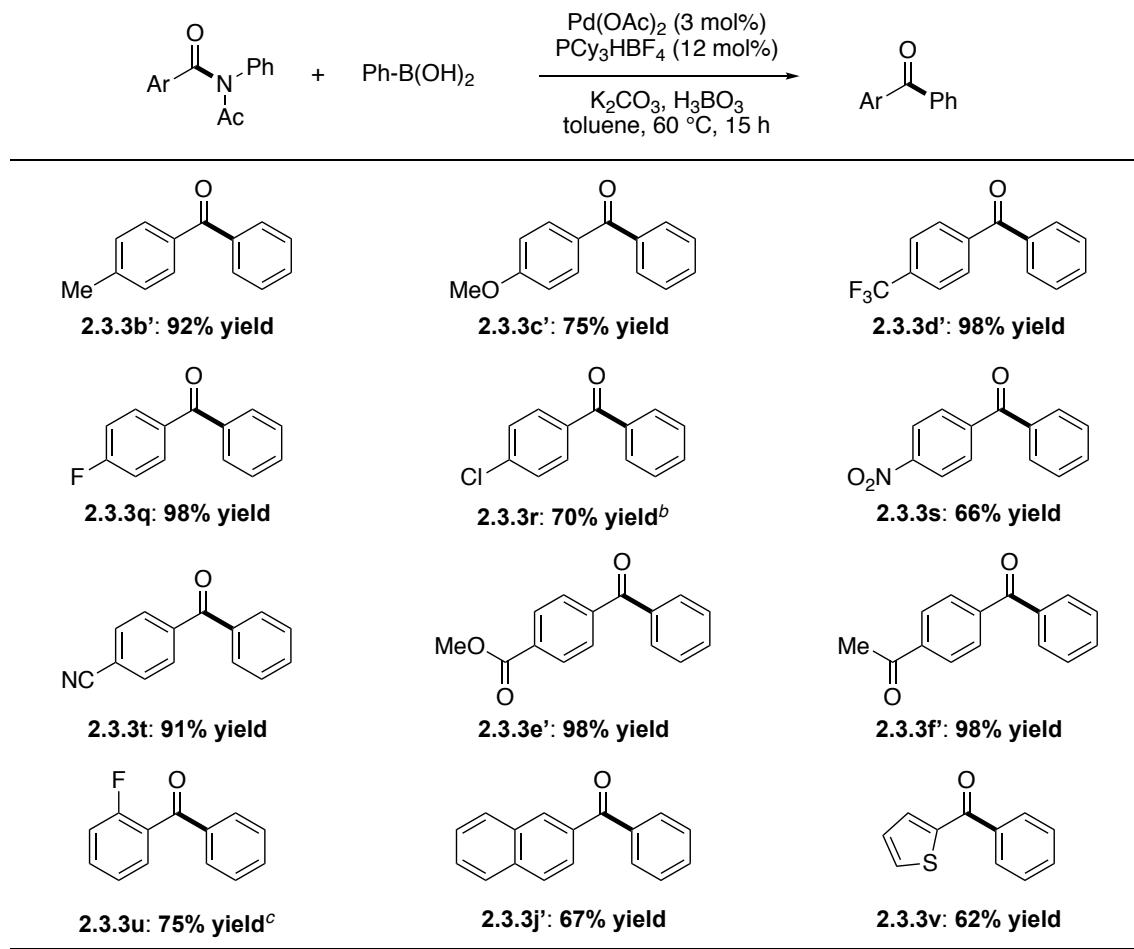
and heteroaromatics (**2.3.3p**) important from the medicinal chemistry²⁶ and functional materials standpoints²⁷ delivered the biaryl ketone products in good to excellent yields.

We next turned our attention to the scope of *N*-acetyl-amides that participate in this cross-coupling (Scheme 2.3.2). As shown, substrates with electron-donating (**2.3.3b'-2.3.3c'**) and withdrawing (**2.3.3d'-2.3.3f'**, **2.3.3q-2.3.3t**) substituents reacted well under our optimized conditions. Moreover, an aryl chloride (**2.3.3r**) was tolerated under the reaction conditions, providing handle for sequential cross-coupling. Of note, this rare selectivity²⁸ in transition-metal-catalyzed amide activation (amide > Cl) indicates high and synthetically-useful N–C(O) coupling reactivity of *N*-acetyl amides. Perhaps most notably this method could be applied to a wide variety of amides bearing electrophilic groups, including nitro (**2.3.3s**), cyano (**2.3.3t**), ester (**2.3.3e'**) and ketone (**2.3.3f'**) that would be incompatible with the classic Weinreb ketone synthesis,²⁵ demonstrating a significant synthetic advantage from the practical viewpoint. Furthermore, ortho-fluoro-substitution (**2.3.3u**) set for derivatization by S_NAr was well-tolerated. Finally, polyaromatic amides prone to decarbonylation (**2.3.3j'**) as well as heterocyclic amides (**2.3.3v**) delivered the desired product in good yields.



^aConditions: amide (1.0 equiv), ArB(OH)₂ (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv), toluene (0.20 M), 60 °C, 15 h; ^b120 °C.

Scheme 2.3.1 Boronic acid scope in Suzuki-Miyaura cross-coupling of *N*-acetyl amides.^a



^aConditions: amide (1.0 equiv), ArB(OH)₂ (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%), K₂CO₃ (2.5 equiv), H₃BO₃ (2.0 equiv), toluene (0.20 M), 60 °C, 15 h; ^bPhB(OH)₂ (1.2 equiv); ^cPhB(OH)₂ (3.0 equiv), K₂CO₃, (4.5 equiv), 120 °C.

Scheme 2.3.2 Amide scope in Suzuki-Miyaura cross-coupling of *N*-acetyl amides.^a

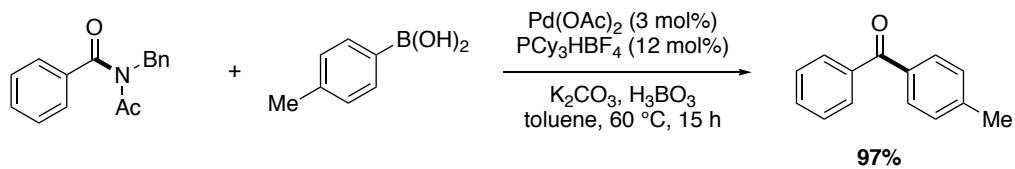
2.3.4 Mechanistic studies

We conducted mechanistic studies to gain insight into the reaction. We were pleased to find that the method could also be applied to the coupling of challenging *N*-Ac/alkyl amides (Scheme 2.3.3),² demonstrating a broad generality of this *N*-acetyl activation. Turnover number (TON) of 970 was determined for the cross-coupling of amide **1a** under 0.10 mol% Pd(OAc)₂/PCy₃ at 60 °C (Scheme 2.3.3). At the time of this project,

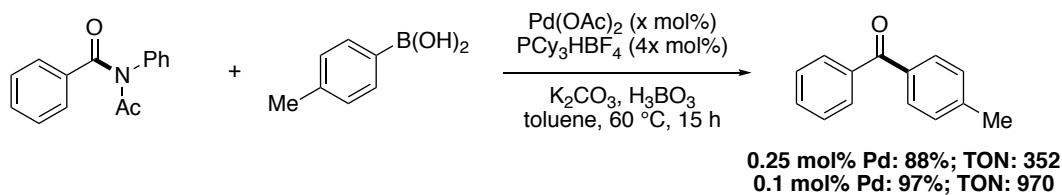
this was the highest TON determined for Pd-catalyzed amide N–C activation reported using Pd-PR₃ catalysts,²⁹ demonstrating the high activity and the advantage of *N*-acetyl-amides in the Suzuki-Miyaura cross-coupling.

To gain further insight into the mechanism, we conducted competition experiments (Scheme 2.3.4). (1) Electron-deficient amides were found to be more reactive (4-CF₃:4-MeO = 91:9). (2) Electron-rich nucleophiles reacted preferentially (4-MeO:4-CF₃ = 77:23). (3) The reactivity order, with respect to the amide activating group, was found to be as follows: *N*-Ac/R>> *N*-R/Ts, *N*-R/Boc, *N*-Ar/R (anilide). The high reactivity of *N*-acyl-amides provided the advantage in the amide bond activation platform.

■ *N*-Bn/Ac-amide for Suzuki-Miyaura coupling

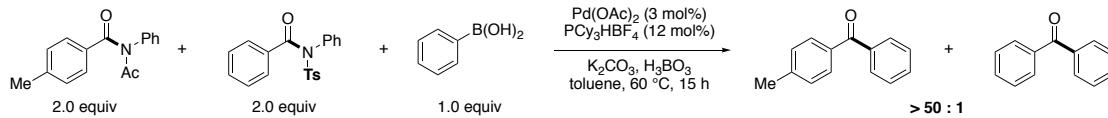


■ Large scale and TON number

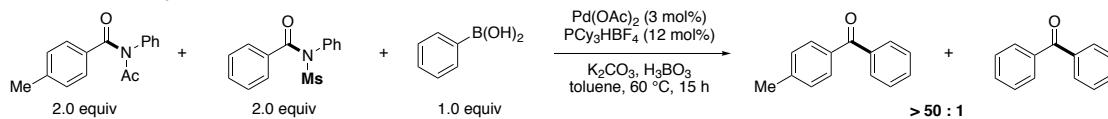


Scheme 2.3.3 Control experiments in Suzuki-Miyaura cross-coupling of *N*-acetyl amides.

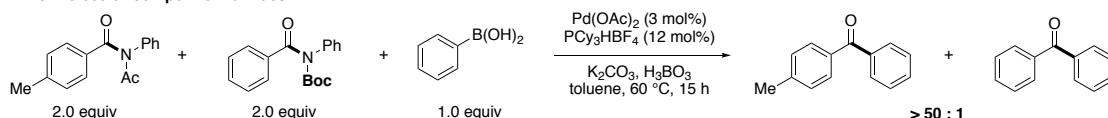
■ Intermolecular competition: amides



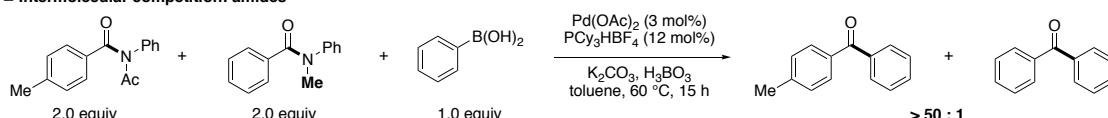
■ Intermolecular competition: amides



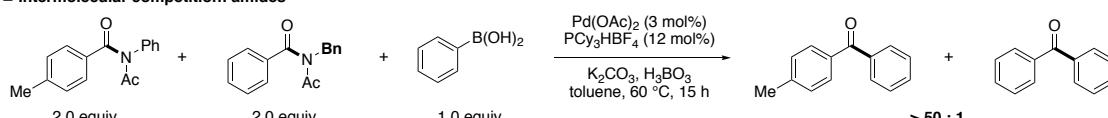
■ Intermolecular competition: amides



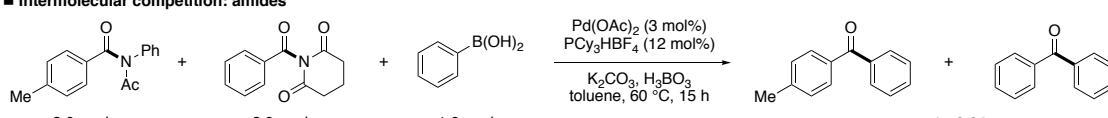
■ Intermolecular competition: amides



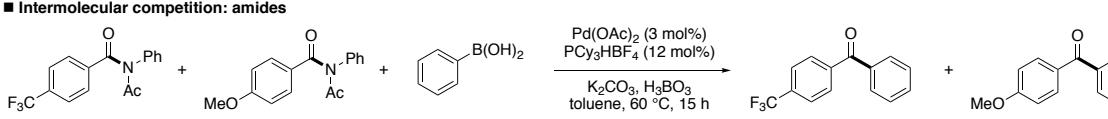
■ Intermolecular competition: amides



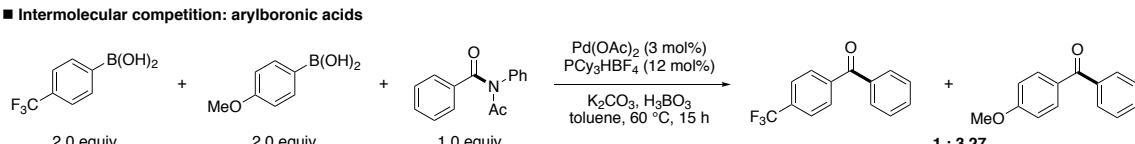
■ Intermolecular competition: amides



■ Intermolecular competition: amides



■ Intermolecular competition: arylboronic acids



Scheme 2.3.4 Competition experiments in Suzuki-Miyaura cross-coupling of *N*-

acetylamides.

2.3.5 Conclusion

In conclusion, we have developed the first Pd-catalyzed Suzuki-Miyaura cross-coupling of *N*-acetyl amides with arylboronic acids. This method introduced *N*-acetyl-amides as the most reactive acyclic amides developed in the manifold of transition-metal-catalyzed amide cross-coupling. The method allowed for a rapid access to a variety of biaryl ketones from easily accessible acyclic amides with exceptional coupling selectivity. These biaryl ketone products represented some of the most important building blocks in organic chemistry. Mechanistic studies provided evidence for fine-tuning of amidic resonance and amide bond twist as selectivity determining features in the cross-coupling of amides. We believe that this study will inspire the development of new synthetic methods and *N*-Ac-amides will be explored as generic precursors in amide bond cross-coupling enabling previously inaccessible reactivity of the amide bond.

2.3.6 Experimental section

General procedure for amide synthesis. An oven-dried flask (25 mL) equipped with a stir bar was charged with aniline (typically, 5.0 mmol, 1.0 equiv), pyridine (typically, 2.5 equiv) and dichloromethane (typically, 0.50 M), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acetyl chloride (typically, 1.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 2 h at room temperature. After the indicated time, the reaction mixture was diluted with ethyl acetate (30 mL). The reaction mixture was washed with HCl (1 x 10 mL), brine (1 x 10 mL), H₂O (1 x 10 mL), dried, and concentrated to get crude first-step product. Then an oven-dried flask (25 mL) equipped

with a stir bar was charged with crude first-step product (typically, 5.0 mmol, 1.0 equiv), 4-(dimethylamino)pyridine (typically, 0.005 equiv), triethylamine (typically, 2.0 equiv) and dichloromethane (typically, 0.50 M), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acyl chloride (typically, 1.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. After the indicated time, the reaction mixture was diluted with ethyl acetate (30 mL). The reaction mixture was washed with HCl (1 x 10 mL), brine (1 x 10 mL), H₂O (1 x 10 mL), dried, and concentrated. The crude product was purified by recrystallization (toluene) to give analytically pure product.

General Procedure for Suzuki-Miyaura Cross-Coupling of Amides. An oven-dried vial equipped with a stir bar was charged with amide substrate (neat, 1.0 equiv), boronic acid (typically, 2.0 equiv), Pd(OAc)₂ (typically, 3 mol%), PCy₃HBF₄ (typically, 12 mol%), K₂CO₃ (typically, 2.5 equiv) and H₃BO₃ (typically, 2.0 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (typically, 0.20 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 60 °C, and stirred for the indicated time at 60 °C. After the indicated time, the reaction mixture was diluted with CH₂Cl₂ (10 mL), filtered, and concentrated. The sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate) afforded the title product.

2.3.1a. Yellow solid. Mp = 55-57 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.55, 172.86, 139.14, 134.79, 132.06, 129.40, 129.24, 128.58, 128.28, 128.13, 25.69. HRMS calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 262.0838, found 262.0819.

2.3.1b. Orange oil. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.55, 172.86, 139.14, 134.79, 132.06, 129.40, 129.24, 128.58, 128.28, 128.13, 25.69. HRMS calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 276.0995, found 276.0976.

2.3.1c. Yellow solid. Mp = 35-37 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.55, 172.86, 139.14, 134.79, 132.06, 129.40, 129.24, 128.58, 128.28, 128.13, 25.69. HRMS calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_3\text{Na}$ ($\text{M}^+ + \text{Na}$) 292.0944, found 292.0926.

2.3.1d. Orange solid. Mp = 86-87 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.73, 136.60, 136.29, 133.49 (q, J^F = 32.7 Hz), 130.55, 129.83, 129.81, 129.74, 125.27 (q, J^F = 3.7 Hz), 123.28 (q, J^F = 271.1 Hz), 40.56. ^{19}F NMR (471 MHz, CDCl_3) δ -63.28. HRMS calcd for $\text{C}_{16}\text{H}_{12}\text{F}_3\text{NO}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 330.0712, found 330.0707.

2.3.1e. Orange solid. Mp = 66-67 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.94, 164.81 (d, J^F = 253.6 Hz), 136.96, 132.42 (d, J^F = 9.3 Hz), 129.65, 129.62, 129.38, 129.18 (d, J^F = 3.3 Hz), 115.55 (d, J^F = 22.0 Hz), 40.32. ^{19}F NMR (471 MHz, CDCl_3) δ -105.10. HRMS calcd for $\text{C}_{15}\text{H}_{12}\text{FNO}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 280.0744, found 280.0723.

2.3.1f. Orange solid. Mp = 77-78 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.55, 172.86, 139.14, 134.79, 132.06, 129.40, 129.24, 128.58, 128.28, 128.13, 25.69. HRMS calcd for $\text{C}_{15}\text{H}_{12}\text{ClNO}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 296.0449, found 296.0432.

2.3.1g. Yellow solid. Mp = 129-130 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.55, 172.86, 139.14, 134.79, 132.06, 129.40, 129.24, 128.58, 128.28, 128.13, 25.69. HRMS calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}^+ + \text{Na}$) 307.0689, found 307.0681.

2.3.1h. Yellow solid. Mp = 124-126 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.55, 172.86, 139.14, 134.79, 132.06, 129.40, 129.24, 128.58, 128.28, 128.13, 25.69. HRMS calcd for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 287.0791, found 287.0773.

2.3.1i. Yellow solid. Mp = 133-134 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.55, 172.86, 139.14, 134.79, 132.06, 129.40, 129.24, 128.58, 128.28, 128.13, 25.69. HRMS calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_4\text{Na}$ ($\text{M}^+ + \text{Na}$) 320.0893, found 320.0878.

2.3.1j. Yellow solid. Mp = 152-154 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.55, 172.86, 139.14, 134.79, 132.06, 129.40, 129.24, 128.58, 128.28, 128.13, 25.69. HRMS calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_3\text{Na}$ ($\text{M}^+ + \text{Na}$) 304.0944, found 304.0928.

2.3.1k. Yellow solid. Mp = 53-54 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.55-7.52 (m, 1 H), 7.41-7.33 (m, 4 H), 7.26-7.24 (d, J = 7.6 Hz, 2 H), 7.17-7.14 (t, J = 7.6 Hz, 1 H), 7.01-6.97 (t, J = 9.8 Hz, 1 H), 2.33 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 172.91, 168.43, 158.44 (d, J^F = 248.6 Hz), 138.51, 132.71 (d, J^F = 8.5 Hz), 129.88 (d, J^F = 2.4 Hz), 129.51, 128.89, 128.82, 125.00 (d, J^F = 14.2 Hz), 124.43 (d, J^F = 3.4 Hz), 115.64 (d, J^F = 21.6 Hz), 25.74. ^{19}F NMR (471 MHz, CDCl_3) δ -114.28. HRMS calcd for $\text{C}_{15}\text{H}_{12}\text{FNO}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 280.0744, found 280.0727.

2.3.1l. Yellow solid. Mp = 73-74 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.55, 172.86, 139.14, 134.79, 132.06, 129.40, 129.24, 128.58, 128.28, 128.13, 25.69. HRMS calcd for $\text{C}_{19}\text{H}_{15}\text{NO}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 312.0995, found 312.0982.

2.3.1m. Yellow solid. Mp = 77-78 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.63 (d, J = 7.1 Hz, 2 H), 7.45-7.42 (t, J = 7.4 Hz, 1 H), 7.38-7.32 (m, 4 H), 7.31-7.29 (d, J = 7.4 Hz, 1 H), 7.19-7.18 (d, J = 7.3 Hz, 2 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.55, 172.86, 139.14, 134.79, 132.06, 129.40, 129.24, 128.58, 128.28, 128.13, 25.69. HRMS calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_2\text{SNa} (\text{M}^+ + \text{Na})$ 268.0403, found 268.0384.

2.3.1n. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.59-7.55 (m, 3 H), 7.46-7.43 (t, J = 7.6 Hz, 2 H), 7.32-7.25 (m, 5 H), 5.03 (s, 2 H), 2.19 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 174.37, 173.30, 137.32, 135.79, 132.49, 128.82, 128.58, 128.41, 127.83, 127.48, 49.32, 26.44.

2.3.1o. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.36 (t, J = 7.6 Hz, 2H), 7.31- 7.21 (m, 3H), 7.16 (d, J = 8.0 Hz, 3H), 7.09 (t, J = 7.5 Hz, 1H), 2.47 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.23, 172.96, 138.78, 135.92, 135.86, 130.81, 130.07, 129.37, 128.57, 128.41, 127.13, 125.29, 26.26, 19.75.

2.3.1p. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.37 (t, J = 7.5 Hz, 2H), 7.29 (dd, J = 8.9, 5.5 Hz, 1H), 7.24 – 7.15 (m, 5H), 6.96 (d, J = 7.5 Hz, 1H), 3.77 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 173.56, 172.63, 159.37, 139.16, 135.98, 129.40, 129.29, 128.48, 128.11, 121.71, 118.38, 114.15, 55.37, 25.70. HRMS calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_3\text{Na} (\text{M}^+ + \text{Na})$ 292.0944, found 292.0924.

2.3.3a. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.83 (d, J = 8.2 Hz, 4 H), 7.63-7.60 (t, J = 6.7 Hz, 2 H), 7.53-7.50 (t, J = 7.6 Hz, 4 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.78, 137.62, 132.43, 130.08, 128.29.

2.3.3b. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.82-7.80 (d, $J = 8.1$ Hz, 2 H), 7.76-7.74 (d, $J = 8.0$ Hz, 2 H), 7.62-7.59 (t, $J = 7.5$ Hz, 1 H), 7.51-7.48 (t, $J = 7.6$ Hz, 2 H), 7.32-7.28 (d, $J = 7.9$ Hz, 2 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.53, 143.26, 137.98, 134.90, 132.17, 130.33, 129.95, 128.99, 128.22, 21.68.

2.3.3c. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.85 (d, $J = 8.7$ Hz, 2 H), 7.79-7.77 (d, $J = 8.2$ Hz, 2 H), 7.61-7.58 (t, $J = 6.8$ Hz, 1 H), 7.51-7.48 (t, $J = 7.6$ Hz, 2 H), 7.00-6.98 (d, $J = 8.7$ Hz, 2 H), 3.92 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.59, 163.24, 138.31, 132.58, 131.90, 130.19, 129.75, 128.20, 113.57, 55.52.

2.3.3d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.93-7.91 (d, $J = 8.0$ Hz, 2 H), 7.84-7.82 (d, $J = 8.2$ Hz, 2 H), 7.79-7.77 (d, $J = 8.1$ Hz, 2 H), 7.67-7.64 (t, $J = 7.6$ Hz, 1 H), 7.55-7.52 (t, $J = 7.7$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.55, 140.74, 136.75, 133.74 (q, $J^F = 32.5$ Hz), 133.11, 130.15, 130.12, 128.55, 125.37 (q, $J^F = 3.7$ Hz), 123.69 (q, $J^F = 270.9$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -63.00.

2.3.3e. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.18-8.16 (d, $J = 8.1$ Hz, 2 H), 7.87-7.86 (d, $J = 8.1$ Hz, 2 H), 7.83-7.82 (d, $J = 8.2$ Hz, 2 H), 7.66-7.63 (t, $J = 7.5$ Hz, 1 H), 7.54-7.51 (t, $J = 7.7$ Hz, 2 H), 3.99 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.07, 166.34, 141.34, 136.97, 133.24, 132.97, 130.12, 129.80, 129.52, 128.48, 52.49.

2.3.3f. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.09-8.08 (d, $J = 8.3$ Hz, 2 H), 7.90-7.88 (d, $J = 8.3$ Hz, 2 H), 7.84-7.82 (d, $J = 7.1$ Hz, 2 H), 7.66-7.63 (t, $J = 7.5$ Hz, 1 H), 7.55-7.51 (t, $J = 7.8$ Hz, 2 H), 2.70 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.54, 195.98, 141.35, 139.58, 136.93, 133.01, 130.12, 130.07, 128.50, 128.18, 26.92.

2.3.3g. White solid. ^1H NMR (500 MHz, CDCl_3) δ 10.16 (s, 1 H), 8.04-8.02 (d, J = 8.3 Hz, 2 H), 7.96-7.95 (d, J = 8.2 Hz, 2 H), 7.84-7.83 (d, J = 7.1 Hz, 2 H), 7.68-7.65 (t, J = 7.5 Hz, 1 H), 7.55-7.52 (t, J = 7.9 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.85, 191.65, 142.59, 138.49, 136.76, 133.16, 130.35, 130.14, 129.52, 128.56.

2.3.3h. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.82 (d, J = 8.3 Hz, 2 H), 7.62-7.59 (t, J = 7.5 Hz, 1 H), 7.50-7.47 (t, J = 7.9 Hz, 2 H), 7.43-7.40 (t, J = 7.5 Hz, 1 H), 7.35-7.31 (t, J = 7.8 Hz, 2 H), 7.29-7.26 (t, J = 7.5 Hz, 1 H), 2.36 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.67, 138.63, 137.76, 136.77, 133.14, 131.01, 130.25, 130.15, 128.53, 128.47, 125.21, 20.00.

2.3.3i. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.13-8.11 (d, J = 8.2 Hz, 1 H), 8.05-8.03 (d, J = 8.1 Hz, 1 H), 7.96-7.95 (d, J = 7.9 Hz, 1 H), 7.90-7.89 (d, J = 8.3 Hz, 2 H), 7.64-7.60 (m, 2 H), 7.58-7.52 (m, 3 H), 7.50-7.47 (t, J = 7.6 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.05, 138.34, 136.38, 133.74, 133.25, 131.28, 130.97, 130.43, 128.46, 128.42, 127.78, 127.27, 126.48, 125.71, 124.35.

2.3.3j. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.30 (s, 1 H), 7.98 (s, 2 H), 7.96-7.94 (d, J = 8.0 Hz, 2 H), 7.90-7.89 (d, J = 7.4 Hz, 2 H), 7.65 (s, 2 H), 7.60-7.53 (m, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.78, 137.93, 135.29, 134.85, 132.40, 132.28, 131.89, 130.12, 129.44, 128.36, 128.34, 128.32, 127.84, 126.82, 125.81.

2.3.3k. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.83 (d, J = 7.1 Hz, 2 H), 7.63-7.60 (t, J = 7.4 Hz, 1 H), 7.52-7.49 (t, J = 7.8 Hz, 2 H), 7.42-7.36 (m, 3 H), 7.17-7.15 (m, 1 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 196.54, 159.59, 138.92, 137.64, 132.44, 130.06, 129.23, 128.27, 122.89, 118.88, 114.33, 55.49.

2.3.3l. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.65 (s, 1 H), 8.48-8.47 (d, J = 8.2 Hz, 1 H), 8.18-8.16 (d, J = 7.7 Hz, 1 H), 7.84-7.82 (d, J = 8.2 Hz, 2 H), 7.75-7.72 (t, J = 8.0 Hz, 1 H), 7.70-7.67 (t, J = 7.5 Hz, 1 H), 7.58-7.55 (t, J = 7.8 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 194.20, 148.11, 139.09, 136.28, 135.46, 133.39, 130.04, 129.66, 128.76, 126.75, 124.75.

2.3.3m. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.09 (s, 1 H), 8.08-8.06 (d, J = 7.9 Hz, 1 H), 7.90-7.89 (d, J = 7.8 Hz, 1 H), 7.81-7.80 (d, J = 8.1 Hz, 2 H), 7.69-7.64 (m, 2 H), 7.57-7.54 (t, J = 7.6 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 194.40, 138.65, 136.35, 135.35, 133.84, 133.48, 133.29, 130.01, 129.41, 128.69, 117.95, 112.88.

2.3.3n. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.78 (d, J = 8.1 Hz, 2 H), 7.61-7.58 (t, J = 6.9 Hz, 1 H), 7.52-7.49 (t, J = 7.7 Hz, 3 H), 7.41-7.40 (d, J = 8.4 Hz, 1 H), 6.93-6.91 (d, J = 8.3 Hz, 1 H), 3.99 (s, 3 H), 3.97 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.61, 153.04, 149.03, 138.31, 131.90, 130.24, 129.74, 128.19, 125.53, 112.13, 109.74, 56.11, 56.07.

2.3.3o. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.83-7.81 (d, J = 7.2 Hz, 2 H), 7.67-7.64 (t, J = 7.5 Hz, 1 H), 7.55-7.52 (t, J = 7.8 Hz, 2 H), 7.35-7.34 (d, J = 5.7 Hz, 2 H), 7.09-7.05 (t, J = 8.5 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 193.95, 163.70 (d, J^F = 11.7 Hz), 161.70 (d, J^F = 11.6 Hz), 136.40, 133.16, 129.98, 128.59, 112.95 (d, J^F = 6.4 Hz), 107.72 (d, J^F = 25.4 Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -108.15.

2.3.3p. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.96 (s, 1 H), 7.88-7.87 (d, J = 8.1 Hz, 2 H), 7.64-7.60 (m, 2 H), 7.53-7.50 (t, J = 7.7 Hz, 2 H), 7.42-7.41 (m, 1 H). ^{13}C NMR

(125 MHz, CDCl₃) δ 190.03, 141.33, 138.66, 133.93, 132.32, 129.39, 128.64, 128.40, 126.22.

2.3.3q. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.89-7.86 (t, *J* = 5.5 Hz, 2 H), 7.80-7.79 (d, *J* = 8.2 Hz, 2 H), 7.64-7.61 (t, *J* = 7.5 Hz, 1 H), 7.53-7.50 (t, *J* = 7.7 Hz, 2 H), 7.21-7.17 (t, *J* = 8.6 Hz, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 195.30, 165.41 (d, *J*^F = 252.5 Hz), 137.52, 133.82 (d, *J*^F = 2.9 Hz), 132.69 (d, *J*^F = 9.1 Hz), 132.49, 129.90, 128.38, 115.48 (d, *J*^F = 21.7 Hz). ¹⁹F NMR (471 MHz, CDCl₃) δ -105.99.

2.3.3r. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.81-7.78 (t, *J* = 7.3 Hz, 4 H), 7.64-7.62 (t, *J* = 7.5 Hz, 1 H), 7.53-7.48 (m, 4 H). ¹³C NMR (125 MHz, CDCl₃) δ 195.52, 138.92, 137.27, 135.89, 132.66, 131.48, 129.95, 128.66, 128.42.

2.3.3s. White solid. ¹H NMR (500 MHz, CDCl₃) δ 8.38-8.36 (d, *J* = 8.7 Hz, 2 H), 7.98-7.96 (d, *J* = 8.7 Hz, 2 H), 7.84-7.82 (d, *J* = 8.2 Hz, 2 H), 7.70-7.67 (t, *J* = 7.5 Hz, 1 H), 7.57-7.54 (t, *J* = 7.8 Hz, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 194.83, 149.86, 142.91, 136.31, 133.50, 130.72, 130.12, 128.71, 123.57.

2.3.3t. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.91-7.89 (d, *J* = 7.7 Hz, 2 H), 7.82-7.81 (m, 4 H), 7.68-7.65 (t, *J* = 7.6 Hz, 1 H), 7.56-7.53 (t, *J* = 7.4 Hz, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 195.06, 141.25, 136.35, 133.35, 132.19, 130.26, 130.09, 128.66, 118.03, 115.69.

2.3.3u. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.87-7.86 (d, *J* = 7.9 Hz, 2 H), 7.64-7.61 (t, *J* = 7.4 Hz, 1 H), 7.60-7.54 (m, 2 H), 7.52-7.49 (t, *J* = 7.8 Hz, 2 H), 7.31-7.28 (t, *J* = 7.5 Hz, 1 H), 7.21-7.17 (t, *J* = 9.2 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 193.50, 160.11 (d, *J*^F = 250.8 Hz), 137.41, 133.43, 133.08 (d, *J*^F = 8.2 Hz), 130.77 (d, *J*^F = 2.9

Hz), 129.83, 128.48, 127.06 (d, $J^F = 14.7$ Hz), 124.30 (d, $J^F = 3.6$ Hz), 116.29 (d, $J^F = 21.6$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -111.03.

2.3.3v. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.90-7.89 (d, $J = 8.2$ Hz, 2 H), 7.76-7.75 (d, $J = 4.9$ Hz, 1 H), 7.68-7.67 (d, $J = 3.7$ Hz, 1 H), 7.64-7.61 (t, $J = 7.5$ Hz, 1 H), 7.54-7.51 (t, $J = 7.7$ Hz, 2 H), 7.20-7.19 (t, $J = 4.8$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 188.26, 143.67, 138.18, 134.86, 134.22, 132.28, 129.20, 128.43, 127.97.

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2.4 Sterically-hindered amides and their reactivity in acyl Suzuki-Miyaura cross-coupling

Parts of this section were adapted with permission from the article “Sterically Hindered Ketones via Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling of Amides by N–C(O) Activation” (*Org. Lett.* **2019**, *21*, 7976). Copyright ©2019, American Chemical Society.

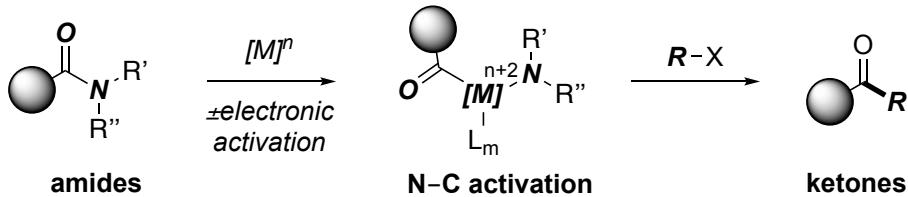
2.4.1 Introduction

The development of catalytic methods for the synthesis of sterically hindered ketones is an important objective in synthetic chemistry because bulky ketones are ubiquitous in natural products, bioactive compounds, and advanced materials and can be further explored to access functionalized derivatives by the classical carbonyl addition.¹⁻³ In this context, transition-metal-catalyzed cross-coupling of acyl electrophiles could represent an attractive method for the synthesis of sterically hindered ketones because it offers the advantages of well-controlled cross-coupling mechanisms, high levels of selectivity, and operational practicality.^{4,5} However, in contrast to the synthesis of sterically hindered biaryls by the traditional Suzuki–Miyaura cross-coupling of aryl halides,⁶ methods for the construction of sterically hindered ketones by the cross-coupling of acyl electrophiles remain largely under-developed.^{7,4} In general, very few methods for the synthesis of di-ortho, ortho'-substituted biaryl ketones by the acyl Suzuki- Miyaura cross-coupling have been developed.⁴ Mechanistically, a key difference between the two types of cross-coupling is the capacity of the acyl (ArC(O)–X) vs aryl (Ar–X) electrophile to undergo productive metal insertion, which generates the acyl-metal vs aryl-metal complex for the subsequent transmetalation step.^{8,9}

At the start of this project, we were attracted by the potential of amides¹⁰⁻¹⁵ to serve as electrophiles¹⁶⁻¹⁸ in the synthesis of sterically hindered ketones by a catalytic cross-coupling mechanism involving chemoselective metal insertion into the N–C(O) bond (Figure 2.4.1). In this study, we have developed the first general method for the synthesis of sterically hindered ketones that proceeds via Pd-catalyzed Suzuki-Miyaura cross-coupling of amides by selective N–C(O) activation (Figure 2.4.1).¹⁹

Notable features of our study included: (1) the first general protocol for the synthesis of sterically hindered ketones by the acyl Suzuki-Miyaura cross-coupling using readily available *N*-acylglutarimides as cross-coupling precursors; (2) we presented a series of mechanistic studies that demonstrated that the origin of low reactivity of sterically hindered amides is a result of minimized amide bond distortion; (3) this protocol set the stage for the development of general strategies to sterically hindered ketones by cross-coupling of unconventional amide electrophiles.

■ Cross-coupling of amides by N–C activation: new platform in catalysis



■ This study: hindered ketones via Suzuki cross-coupling of amides

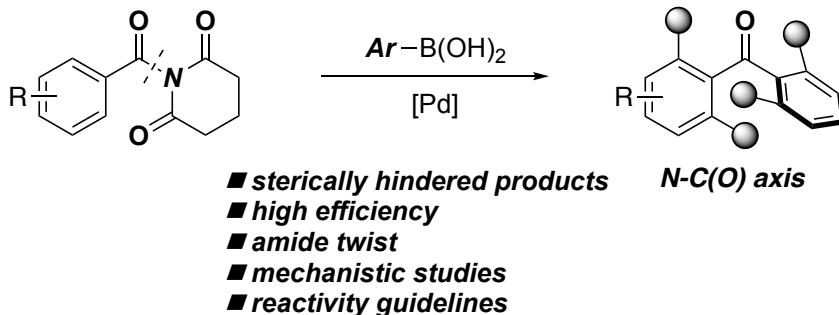


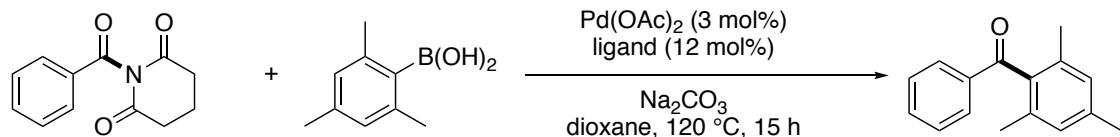
Figure 2.4.1 (a) Cross-coupling of amides by N–C activation. (b) This work: hindered ketones via Suzuki-Miyaura cross-coupling of amides.

2.4.2 Reaction optimization

We recognized that very few methods for the synthesis of sterically hindered ketones by the acyl Suzuki-Miyaura cross-coupling have been reported, likely due to low stability of acyl precursors, such aroyl chlorides or anhydrides.^{4,7,11,12} Our initial studies focused on the cross-coupling of electronically unbiased *N*-benzoylgutarimide with 2,4,6-trimethylphenylboronic acid (Table 2.4.1). Upon investigating various reaction parameters, we found that the desired cross-coupling proceeded in excellent 97% yield in the presence of Mes-B(OH)₂ (2.0 equiv) and Na₂CO₃ (2.5 equiv) in dioxane at 120 °C (Table 2.4.1, entry 3). Further improvement was realized by increasing the stoichiometry of boronic acid and base (entries 4 and 5). Pd₂(dba)₃ was identified as another promising Pd source, although it resulted in lower yield (entry 6). No cross-coupling is observed at

lower temperatures (entries 7 and 8); however, 100 °C was sufficient for the coupling (entry 9), consistent with challenging insertion and/or transmetalation steps.^{8,9} It should be noted that H₃BO₃ was not required (entries 10-12), suggesting that amide bond activation by O-protonation of the glutarimide ring was not particularly important in this cross-coupling.^{18d,20} Interestingly, K₂CO₃ was also an effective base (entry 11), while K₃PO₄ and Cs₂CO₃ were not effective for this cross-coupling (entries 13 and 14). A ligand screen revealed that PCy₃HBF₄ was the preferred phosphine ligand for this cross-coupling (entries 15-23).²¹ The best results were obtained using 3-4 equiv of the phosphine ligand with respect to Pd, while a lower ratio was insufficient for the reaction. Decreasing the electron richness in a series of PCy₃HBF₄, PCy₂Ph, PCyPh₂, and PPh₃ led to a gradual decrease of catalytic activity (entries 15-17) likely due to more challenging oxidative insertion with less σ-donating phosphine ligands. Furthermore, in the series of trialkylphosphines, PCy₃ was vastly preferred (entries 19-22) likely because the steric bulk in oxidative addition of the acyl electrophile to Pd(0) was well accommodated.^{9a,b}

Table 2.4.1 Optimization of sterically-hindered Suzuki-Miyaura cross-coupling of amides.^a



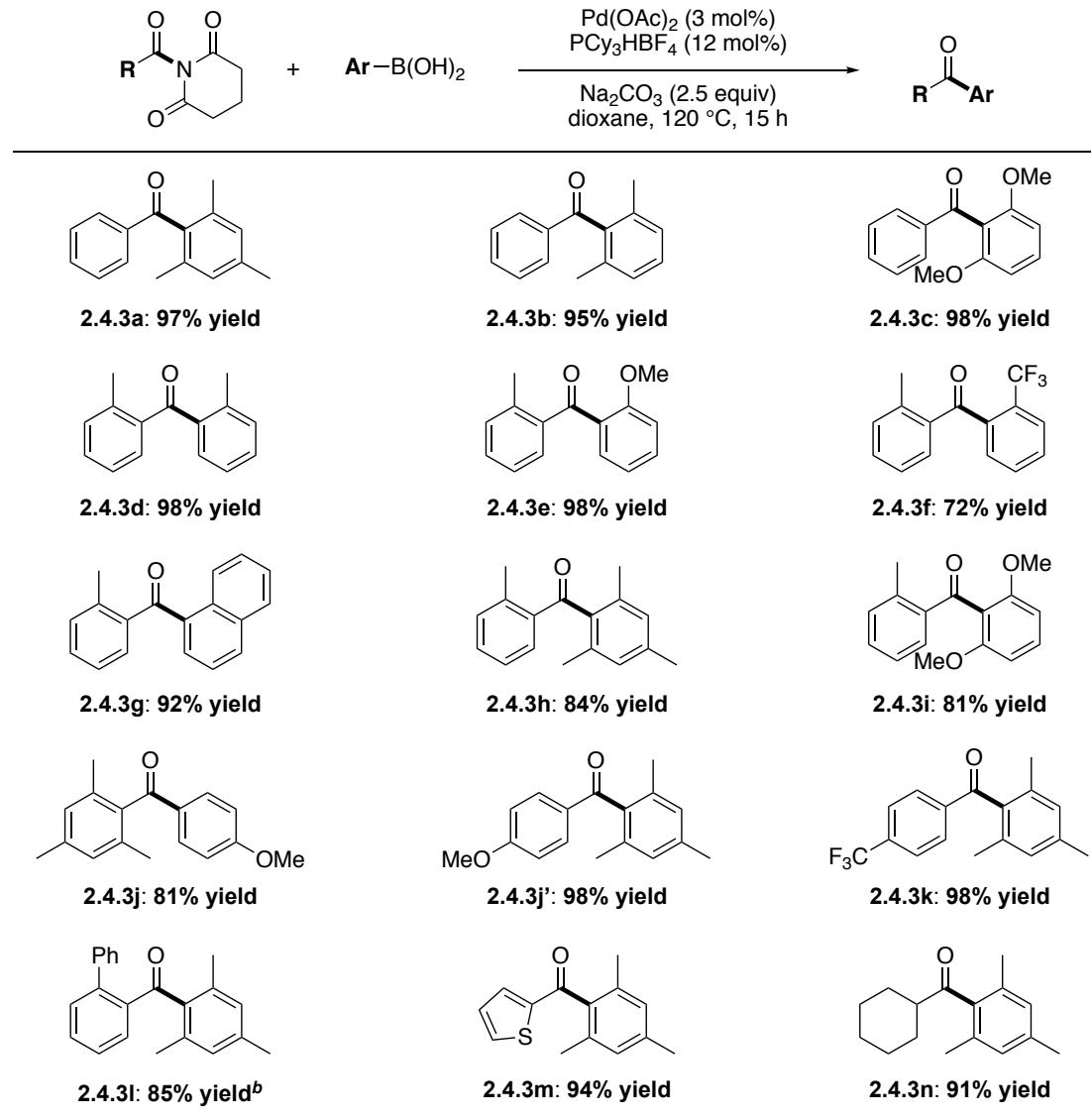
entry	catalyst	ligand	ArB(OH) ₂	Na ₂ CO ₃	temp	yield (%) ^a
1	Pd(OAc) ₂	PCy ₃ HBF ₄	1.2 equiv	1.2 equiv	120 °C	32
2	Pd(OAc) ₂	PCy ₃ HBF ₄	1.2 equiv	2.5 equiv	120 °C	21
3	Pd(OAc) ₂	PCy ₃ HBF ₄	2.0 equiv	2.5 equiv	120 °C	99
4	Pd(OAc) ₂	PCy ₃ HBF ₄	3.0 equiv	4.5 equiv	120 °C	99
5	Pd(OAc) ₂	PCy ₃ HBF ₄	4.5 equiv	7.5 equiv	120 °C	99
6	Pd ₂ (dba) ₃	PCy ₃ HBF ₄	2.0 equiv	2.5 equiv	120 °C	68
7	Pd(OAc) ₂	PCy ₃ HBF ₄	2.0 equiv	2.5 equiv	60 °C	<2
8	Pd(OAc) ₂	PCy ₃ HBF ₄	2.0 equiv	2.5 equiv	80 °C	<2
9	Pd(OAc) ₂	PCy ₃ HBF ₄	2.0 equiv	2.5 equiv	100 °C	99
10 ^b	Pd(OAc) ₂	PCy ₃ HBF ₄	2.0 equiv	2.5 equiv	120 °C	93
11 ^c	Pd(OAc) ₂	PCy ₃ HBF ₄	2.0 equiv	2.5 equiv	120 °C	92
12 ^{b,c}	Pd(OAc) ₂	PCy ₃ HBF ₄	2.0 equiv	2.5 equiv	120 °C	91
13 ^d	Pd(OAc) ₂	PCy ₃ HBF ₄	2.0 equiv	2.5 equiv	120 °C	19
14 ^e	Pd(OAc) ₂	PCy ₃ HBF ₄	2.0 equiv	2.5 equiv	120 °C	<2
15	Pd(OAc) ₂	PCy ₂ Ph	2.0 equiv	2.5 equiv	120 °C	47
16	Pd(OAc) ₂	PCyPh ₂	2.0 equiv	2.5 equiv	120 °C	24
17	Pd(OAc) ₂	PPh ₃	2.0 equiv	2.5 equiv	120 °C	10
18	Pd(OAc) ₂	P(<i>o</i> -Tol) ₃	2.0 equiv	2.5 equiv	120 °C	<2
19	Pd(OAc) ₂	PEt ₃ HBF ₄	2.0 equiv	2.5 equiv	120 °C	<2
20	Pd(OAc) ₂	P(<i>n</i> -Bu) ₃ HBF ₄	2.0 equiv	2.5 equiv	120 °C	45
21	Pd(OAc) ₂	P(<i>t</i> -Bu) ₃ HBF ₄	2.0 equiv	2.5 equiv	120 °C	<2
22	Pd(OAc) ₂	PMet-Bu ₂ HBF ₄	2.0 equiv	2.5 equiv	120 °C	19
23	Pd(OAc) ₂	DPPB	2.0 equiv	2.5 equiv	120 °C	<2

^aConditions: amide (1.0 equiv), R-B(OH)₂ (2.0 equiv), catalyst (3 mol%), ligand (12 mol%), base (2.5 equiv), dioxane (0.25 M), 60 °C, 15 h. ^bH₃BO₃ (2.0 equiv). ^cK₂CO₃ (2.5 equiv). ^dK₃PO₄ (2.5 equiv). ^eCs₂CO₃ (2.5 equiv).

2.4.3 Substrate scope

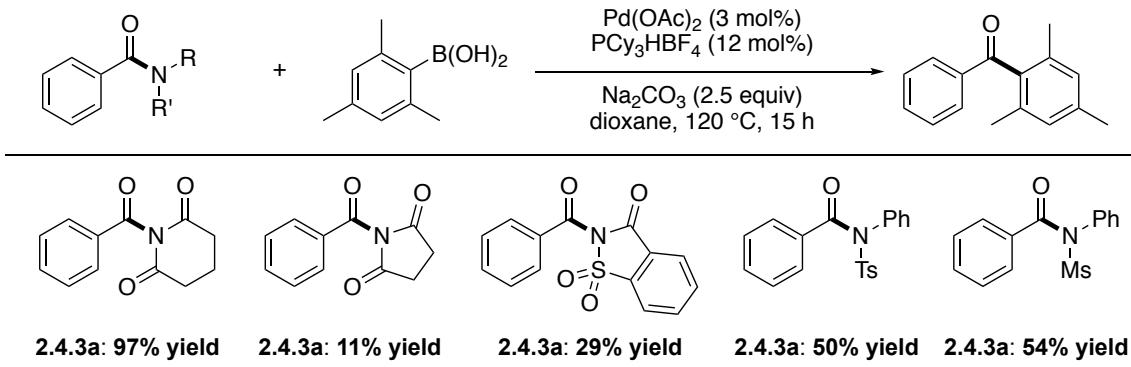
Having developed suitable conditions, we next investigated the substrate scope of this process (Scheme 2.4.1). As shown, we found that the developed conditions could be applied to the synthesis of a range of sterically hindered biaryl ketones. In addition to mesitylboronic acid (**2.4.3a**), the reaction tolerated both 2,6-dimethylphenyl (**2.4.3b**) and 2,6-dimethoxyphenylboronic acids (**2.4.3c**), furnishing ortho-disubstituted biaryl ketones in excellent yields. Products containing electronically varied ortho,ortho'-disubstitution could be synthesized in good yields (**2.4.3d-2.4.3f**). Note that this included the challenging electronically deactivated 2-trifluoromethylphenylboronic acid (**2.4.3f**). Furthermore, the cross-coupling with 1-naphthylboronic acid was possible (**2.4.3g**). Moreover, tri-ortho-substituted biaryl ketones were synthesized in excellent yields (**2.4.3h-2.4.3i**), testing the steric limits of the cross-coupling. The use of steric hindrance on the amide fragment was also feasible as illustrated by the synthesis of (**2.4.3j**). However, the reactions with di-ortho-substituted sterically hindered amides were in general more difficult. Pleasingly, the reaction seemed to be insensitive to the electronic properties of the amide electrophile, furnishing the ketone products in excellent yields (**2.4.3j'**, **2.4.3k**). The highly hindered 2-Ph-amide substrate underwent the cross-coupling in high yield (**2.4.3l**). In this instance, increasing the stoichiometry of boronic acid and base significantly improved the yield, consistent with slower transmetalation. Finally, the reaction conditions could be applied to the synthesis of sterically hindered heterocyclic (**2.4.3m**) and alkyl ketones (**2.4.3n**). Thus, the scope of the reaction was broad and superseded related methods utilizing unstable aroyl chlorides.^{4,7} Using this catalyst system, the synthesis of tetra-ortho-substituted ketones was not feasible. It was

worthwhile to note that the high reactivity of *N*-acylglutarimides resulted from a combination of minimized amidic resonance^{18d} and high stability under the reaction conditions.^{11e} Other amides, such as heteroaryl-activated amides, were not suitable coupling partners. Furthermore, we found that the reaction also proceeded with other amide electrophiles (Scheme 2.4.2). In particular, the use of *N*-Ts and *N*-Ms amides allowed to engage secondary amides as cross-coupling electrophiles in this reaction manifold.



^aConditions: amide (1.0 equiv), ArB(OH)₂ (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%), Na₂CO₃ (2.5 equiv), dioxane (0.125 M), 120 °C, 15 h; ^bArB(OH)₂ (5.0 equiv), Na₂CO₃ (7.2 equiv).

Scheme 2.4.1 Synthesis of hindered ketones by Suzuki-Miyaura cross-coupling of amides.^a



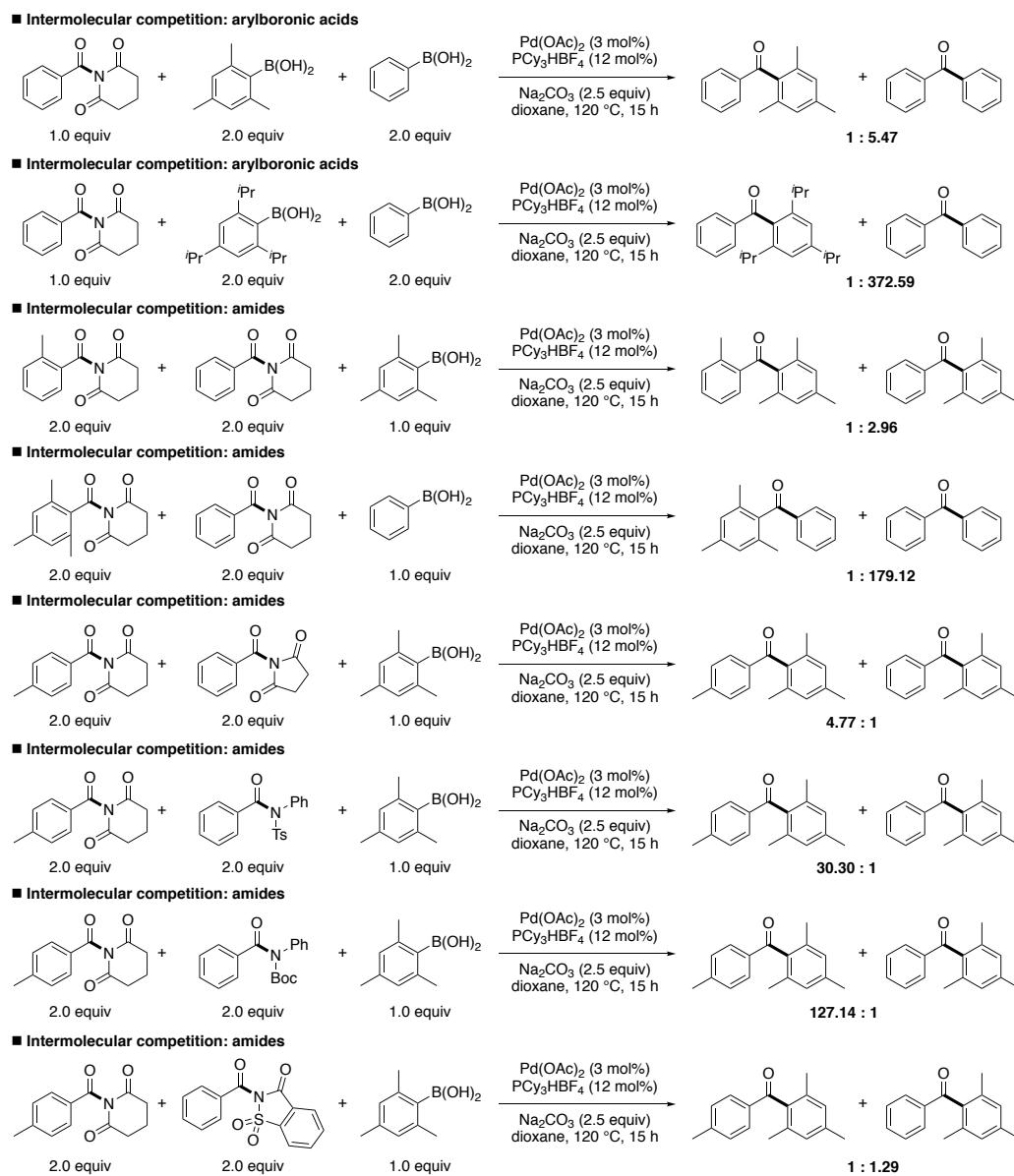
^aConditions: amide (1.0 equiv), ArB(OH)₂ (2.0 equiv), Pd(OAc)₂ (3 mol%), PCy₃HBF₄ (12 mol%), Na₂CO₃ (2.5 equiv), dioxane (0.125 M), 120 °C, 15 h.

Scheme 2.4.2 Synthesis of hindered ketones by Suzuki-Miyaura cross-coupling of amides.^a

2.4.4 Mechanistic studies

In order to gain insight into the reaction mechanism, we conducted competition experiments (Scheme 2.4.3). The cross-coupling of **2.4.1a** using phenylboronic acid was slightly preferred compared to 2,4,6-trimethylphenylboronic acid ($\text{Ph}/2,4,6\text{-Me}_3\text{C}_6\text{H}_2 = 5.5:1$). The ratio dramatically increased when more hindered 2,4,6-triisopropylphenylboronic acid ($\text{Ph}/2,4,6\text{-i-Pr}_3\text{C}_6\text{H}_2 > 200:1$) was used. Competition between 2-Me-*N*-benzoylglutarimide **2.4.1b** and the unsubstituted **2.4.1a** revealed that although the latter was inherently more reactive ($2\text{-MeC}_6\text{H}_4/\text{Ph} = 1:3.0$), the difference in reactivity was small (Scheme 2.4.3). This contrasted with the reactivity of **2.4.1c**, which was dramatically less reactive than its unsubstituted counterpart ($2,4,6\text{-Me}_3\text{C}_6\text{H}_2/\text{Ph} = 1:180$) (Scheme 2.4.3). Finally, competition between *N*-benzoylglutarimide and other amides showed that *N*-benzoylglutarimide was more reactive than *N*-benzoylsuccinimide, *N*-Ts and *N*-Boc amides (Scheme 2.4.3). Thus, our studies showed that (1) steric bulk on the amide had a significantly greater impact on the coupling than on the boronic acid,

which is opposite to the traditional Suzuki-Miyaura cross-coupling of aryl halides and consistent with a difficult metal insertion into the N–C(O) bond.^{6,8,9} (2) The results showed that cross-coupling of mono-ortho-substituted amides and di-ortho-substituted arylboronic acids was well feasible, and this was further supported by our findings with respect to the reaction scope.



Scheme 2.4.3 Competition experiments in hindered Suzuki-Miyaura coupling of amides.

2.4.5 Conclusion

In summary, we have developed the first general method for the synthesis of sterically hindered ketones via Pd-catalyzed acyl Suzuki-Miyaura cross-coupling. The reaction proceeded via selective N-C(O) activation in sterically hindered twisted amides and delivered the desired hindered ketones in good to excellent yields. Mechanistic studies showed a major impact of the steric bulk on the amide electrophile. Another key aspect involved determination of steric and electronic factors of the amide bond that lead to ground-state destabilization of sterically hindered twisted amides.

2.4.6 Experimental section

General procedure for amide synthesis. An oven-dried flask (25 mL) equipped with a stir bar was charged with glutarimide (typically, 5.0 mmol, 1.0 equiv), 4-(dimethylamino)pyridine (typically, 0.005 equiv), triethylamine (typically, 2.0 equiv) and dichloromethane (typically, 0.50 M), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acyl chloride (typically, 1.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. After the indicated time, the reaction mixture was diluted with ethyl acetate (30 mL). The reaction mixture was washed with HCl (1 x 10 mL), brine (1 x 10 mL), H₂O (1 x 10 mL), dried, and concentrated. The crude product was purified by recrystallization (toluene) to give analytically pure product.

General Procedure for Suzuki-Miyaura Cross-Coupling of Amides. An oven-dried vial equipped with a stir bar was charged with amide substrate (neat, 1.0 equiv), boronic acid (typically, 2.0 equiv), Pd(OAc)₂ (typically, 3 mol%), PCy₃HBF₄ (typically, 12 mol%) and Na₂CO₃ (typically, 2.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 1,4-Dioxane (typically, 0.125 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 120 °C, and stirred for the indicated time at 120 °C. After the indicated time, the reaction mixture was diluted with CH₂Cl₂ (10 mL), filtered, and concentrated. The sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate) afforded the title product.

2.4.1a. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.90-7.88 (d, *J* = 7.4 Hz, 2 H), 7.68-7.65 (t, *J* = 7.5 Hz, 1 H), 7.53-7.50 (t, *J* = 7.9 Hz, 2 H), 2.81-2.78 (t, *J* = 6.6 Hz, 4 H), 2.20-2.14 (m, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 171.88, 170.73, 134.96, 131.82, 130.17, 129.14, 32.42, 17.52.

2.4.1b. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.53-7.51 (d, *J* = 8.0 Hz, 1 H), 7.50-7.47 (t, *J* = 7.7 Hz, 1 H), 7.36-7.34 (d, *J* = 7.7 Hz, 1 H), 7.29-7.26 (t, *J* = 7.6 Hz, 1 H), 2.78-2.76 (t, *J* = 6.6 Hz, 4 H), 2.70 (s, 3 H), 2.17-2.11 (m, 2 H). ¹³C NMR (125 MHz, CDCl₃) δ 171.99, 170.68, 142.54, 133.76, 132.46, 131.20, 130.71, 126.21, 32.49, 21.89, 17.45.

2.4.1c. White solid. Mp = 115-117 °C. ^1H NMR (500 MHz, CDCl_3) δ 6.87 (s, 2 H), 2.73-2.70 (t, J = 6.6 Hz, 4 H), 2.38 (s, 6 H), 2.30 (s, 3 H), 2.06-2.01 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.86, 171.37, 141.16, 137.04, 132.31, 129.59, 33.19, 21.24, 20.44, 17.07. HRMS calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_3\text{Na}$ ($\text{M}^+ + \text{Na}$) 282.1101, found 282.1136.

2.4.1d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.86-7.84 (d, J = 8.9 Hz, 2 H), 6.98-6.96 (d, J = 8.9 Hz, 2 H), 3.90 (s, 3 H), 2.80-2.77 (t, J = 6.5 Hz, 4 H), 2.18-2.13 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.90, 169.50, 165.11, 132.76, 124.52, 114.50, 55.69, 32.44, 17.52.

2.4.1e. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.00-7.99 (d, J = 8.0 Hz, 2 H), 7.79-7.78 (d, J = 8.0 Hz, 2 H), 2.84-2.81 (t, J = 6.4 Hz, 4 H), 2.22-2.17 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.99, 170.19, 135.95 (q, J^F = 33.0 Hz), 134.82, 130.37, 126.22 (q, J^F = 3.6 Hz), 123.28 (q, J^F = 271.2 Hz), 32.36, 17.43. ^{19}F (471 MHz, CDCl_3) δ -63.40.

2.4.1f. White solid. Mp = 135-136 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.04-8.02 (d, J = 7.7 Hz, 1 H), 7.62-7.59 (t, J = 6.8 Hz, 1 H), 7.54-7.51 (t, J = 8.2 Hz, 1 H), 7.44-7.43 (m, 3 H), 7.36-7.35 (m, 2 H), 7.29-7.27 (m, 1 H), 2.24-2.22 (t, J = 6.3 Hz, 4 H), 1.52-1.47 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.50, 170.69, 142.47, 140.59, 132.97, 132.23, 131.77, 131.72, 128.97, 128.33, 128.03, 127.78, 32.49, 16.15. HRMS calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4\text{Na}$ ($\text{M}^+ + \text{CH}_3\text{OH} + \text{Na}$) 348.1206, found 348.1232.

2.4.1g. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.78 (dd, J = 4.9, 5.0 Hz, 1 H), 7.71-7.70 (dd, J = 3.9, 3.9 Hz, 1 H), 7.17-7.15 (dd, J = 4.9, 4.9 Hz, 1 H), 2.78-2.76 (t, J = 6.5 Hz, 4 H), 2.15-2.10 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.67, 163.65, 137.56, 136.76, 136.00, 128.82, 32.41, 17.42.

2.4.1h. White solid. ^1H NMR (500 MHz, CDCl_3) δ 2.69-2.66 (t, $J = 6.5$ Hz, 4 H), 2.65-2.61 (m, 1 H), 2.07-1.99 (m, 4 H), 1.84-1.81 (m, 2 H), 1.69-1.66 (m, 1 H), 1.52-1.45 (m, 2 H), 1.31-1.18 (m, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 180.84, 171.84, 48.74, 32.37, 28.05, 25.56, 25.37, 17.39.

2.4.1i. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.88-7.87 (d, $J = 7.9$ Hz, 2 H), 7.71-7.68 (t, $J = 7.4$ Hz, 1 H), 7.54-7.51 (t, $J = 7.8$ Hz, 2 H), 2.96 (s, 4 H). ^{13}C NMR (125 MHz, CDCl_3) δ 174.56, 167.64, 135.16, 131.41, 130.54, 128.98, 29.08.

2.4.1j. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.16-8.15 (d, $J = 7.7$ Hz, 1 H), 8.05-8.01 (m, 2 H), 7.96-7.94 (t, $J = 7.9$ Hz, 1 H), 7.80-7.78 (d, $J = 8.3$ Hz, 2 H), 7.70-7.67 (t, $J = 7.1$ Hz, 1 H), 7.55-7.52 (t, $J = 7.7$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.39, 157.47, 138.51, 136.43, 134.91, 133.93, 132.40, 129.60, 128.46, 126.42, 125.56, 121.28.

2.4.1k. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.85 (d, $J = 8.4$ Hz, 2 H), 7.47-7.46 (d, $J = 7.4$ Hz, 2 H), 7.35-7.33 (d, $J = 8.1$ Hz, 2 H), 7.31-7.29 (m, 4 H), 7.20-7.17 (m, 4 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.91, 144.83, 137.45, 135.26, 133.68, 131.75, 130.41, 129.50, 129.26, 129.12, 129.05, 128.61, 127.99, 21.74.

2.4.1l. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.57-7.56 (d, $J = 7.2$ Hz, 2 H), 7.38-7.28 (m, 6 H), 7.26-7.23 (t, $J = 7.9$ Hz, 2 H), 3.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.10, 136.96, 133.14, 132.24, 129.82, 129.68, 129.47, 129.26, 128.21, 40.39.

2.4.3a. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.82 (d, $J = 7.5$ Hz, 2 H), 7.61-7.58 (t, $J = 7.3$ Hz, 1 H), 7.48-7.45 (t, $J = 7.4$ Hz, 2 H), 6.92 (s, 2 H), 2.36 (s, 3 H), 2.11 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 200.80, 138.51, 137.32, 136.89, 134.22, 133.55, 129.43, 128.80, 128.33, 21.17, 19.37.

2.4.3b. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.82 (d, $J = 7.2$ Hz, 2 H), 7.63-7.60 (t, $J = 7.4$ Hz, 1 H), 7.49-7.46 (t, $J = 8.1$ Hz, 2 H), 7.28-7.25 (t, $J = 7.6$ Hz, 1 H), 7.11-7.10 (d, $J = 7.6$ Hz, 2 H), 2.15 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 200.51, 139.67, 137.03, 134.20, 133.70, 129.43, 128.86, 128.75, 127.58, 19.40.

2.4.3c. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 7.88-7.87 (d, $J = 7.3$ Hz, 2 H), 7.58-7.55 (t, $J = 7.4$ Hz, 1 H), 7.46-7.43 (t, $J = 7.8$ Hz, 2 H), 7.39-7.36 (t, $J = 8.4$ Hz, 1 H), 6.66-6.64 (d, $J = 8.4$ Hz, 2 H), 3.73 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 195.36, 157.65, 137.65, 133.18, 130.79, 129.44, 128.41, 117.95, 104.06, 55.89.

2.4.3d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.43-7.40 (t, $J = 7.5$ Hz, 2 H), 7.34-7.30 (m, 4 H), 7.24-7.21 (t, $J = 7.5$ Hz, 2 H), 2.47 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 200.79, 139.01, 138.18, 131.43, 131.07, 130.31, 125.42, 20.67.

2.4.3e. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.50-7.45 (m, 2 H), 7.39-7.34 (m, 2 H), 7.28-7.27 (d, $J = 7.2$ Hz, 1 H), 7.20-7.17 (t, $J = 7.5$ Hz, 1 H), 7.05-7.02 (t, $J = 7.5$ Hz, 1 H), 6.99-6.98 (d, $J = 8.4$ Hz, 1 H), 3.72 (s, 3 H), 2.51 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.38, 158.24, 139.22, 138.05, 132.75, 131.24, 130.82, 130.66, 130.13, 129.68, 125.18, 120.43, 111.80, 55.73, 20.78.

2.4.3f. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.81-7.79 (m, 1 H), 7.63-7.62 (m, 2 H), 7.47-7.44 (t, $J = 7.4$ Hz, 1 H), 7.41-7.40 (m, 1 H), 7.35-7.34 (d, $J = 7.5$ Hz, 1 H), 7.31-7.29 (m, 1 H), 7.22-7.19 (t, $J = 7.4$ Hz, 1 H), 2.64 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.40, 140.39, 139.99, 136.07, 132.61, 132.45, 132.01, 131.42, 130.02, 128.83, 128.20 (q, $J^F = 32.1$ Hz), 126.78 (q, $J^F = 4.9$ Hz), 125.37, 123.63 (q, $J^F = 272.3$ Hz),

21.45. ^{19}F (471 MHz, CDCl_3) δ -58.06. HRMS calcd for $\text{C}_{15}\text{H}_{11}\text{F}_3\text{O} (\text{M}^+)$ 264.0757, found 264.0756.

2.4.3g. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.58-8.56 (d, $J = 8.3$ Hz, 1 H), 8.04-8.03 (d, $J = 8.2$ Hz, 1 H), 7.96-7.94 (d, $J = 8.2$ Hz, 1 H), 7.63-7.58 (m, 3 H), 7.49-7.42 (m, 2 H), 7.40-7.39 (d, $J = 7.6$ Hz, 1 H), 7.35-7.33 (d, $J = 7.7$ Hz, 1 H), 7.25-7.22 (t, $J = 7.5$ Hz, 1 H), 2.50 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 200.31, 139.60, 138.27, 136.50, 133.91, 132.55, 131.39, 131.12, 131.02, 130.48, 130.30, 128.48, 127.86, 126.52, 125.86, 125.43, 124.35, 20.70.

2.4.3h. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.43-7.40 (t, $J = 8.4$ Hz, 1 H), 7.38-7.36 (d, $J = 7.7$ Hz, 1 H), 7.34-7.32 (d, $J = 7.6$ Hz, 1 H), 7.19-7.16 (t, $J = 7.5$ Hz, 1 H), 6.90 (s, 2 H), 2.70 (s, 3 H), 2.34 (s, 3 H), 2.11 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 202.69, 139.97, 138.51, 138.49, 137.01, 134.38, 132.22, 132.20, 131.89, 128.49, 125.91, 21.80, 21.16, 19.42.

2.4.3i. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.49-7.47 (d, $J = 7.9$ Hz, 1 H), 7.40-7.37 (t, $J = 7.2$ Hz, 1 H), 7.36-7.32 (t, $J = 8.4$ Hz, 1 H), 7.29-7.28 (m, 1 H), 7.19-7.16 (t, $J = 7.5$ Hz, 1 H), 6.63-6.61 (d, $J = 8.4$ Hz, 2 H), 3.73 (s, 6 H), 2.70 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.43, 157.44, 139.81, 137.44, 131.76, 131.73, 131.71, 130.57, 125.46, 120.11, 104.13, 55.95, 21.69.

2.4.3j. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 7.80-7.79 (d, $J = 7.9$ Hz, 2 H), 6.94-6.93 (d, $J = 8.9$ Hz, 2 H), 6.91 (s, 2 H), 3.89 (s, 3 H), 2.35 (s, 3 H), 2.11 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 199.32, 163.94, 138.23, 137.18, 134.10, 131.82, 130.54, 128.26, 113.98, 55.51, 21.16, 19.31.

2.4.3k. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.94-7.92 (d, $J = 8.1$ Hz, 2 H), 7.74-7.73 (d, $J = 8.2$ Hz, 2 H), 6.94 (s, 2 H), 2.37 (s, 3 H), 2.09 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 199.70, 139.94, 139.10, 136.04, 134.75 (q, $J^F = 32.5$ Hz), 134.26, 129.67, 128.55, 125.92 (q, $J^F = 3.7$ Hz), 123.61 (q, $J^F = 271.1$ Hz), 21.19, 19.39. ^{19}F (471 MHz, CDCl_3) δ -63.11.

2.4.3l. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.60-7.55 (m, 2 H), 7.41-7.38 (t, $J = 7.5$ Hz, 1 H), 7.37-7.35 (d, $J = 7.6$ Hz, 1 H), 7.33-7.29 (m, 3 H), 7.28-7.27 (m, 2 H), 6.75 (s, 2 H), 2.26 (s, 3 H), 2.11 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 200.63, 143.00, 141.40, 138.91, 138.21, 137.34, 135.24, 131.84, 131.77, 130.99, 128.73, 128.48, 127.70, 127.56, 126.91, 21.06, 20.31.

2.4.3m. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.73-7.72 (d, $J = 4.9$ Hz, 1 H), 7.36-7.36 (d, $J = 3.1$ Hz, 1 H), 7.11-7.10 (t, $J = 4.0$ Hz, 1 H), 6.91 (s, 2 H), 2.35 (s, 3 H), 2.19 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 192.86, 145.11, 138.72, 136.96, 134.97, 134.72, 134.18, 128.35, 128.31, 21.18, 19.30.

2.4.3n. White solid. ^1H NMR (500 MHz, CDCl_3) δ 6.85 (s, 2 H), 2.73-2.67 (m, 1 H), 2.30 (s, 3 H), 2.21 (s, 6 H), 1.96-1.93 (d, $J = 13.0$ Hz, 2 H), 1.85-1.82 (m, 2 H), 1.72-1.70 (m, 1 H), 1.48-1.40 (m, 2 H), 1.31-1.22 (m, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 213.69, 139.19, 138.24, 133.30, 128.57, 52.29, 28.23, 25.91, 21.04, 19.67.

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Chapter 3

Cross-Coupling of Amides by Aryl-Metal Intermediates

3.1 Decarbonylative Heck cross-coupling of *N*-acylsaccharins by palladium catalysis

Parts of this section were adapted with permission from the article “*N*-Acylsaccharins as Amide-Based Arylating Reagents via Chemoselective N–C Cleavage: Pd-Catalyzed Decarbonylative Heck Reaction” (*J. Org. Chem.* **2016**, *81*, 12023). Copyright ©2016, American Chemical Society.

3.1.1 Introduction

The ability to perform selective functionalization and interconversion reactions represents an important goal of organic synthesis. Since the original report in 1968, the Heck reaction has been established as one of the most powerful transition-metal-catalyzed transformations in organic synthesis.^{1,2} The classic Heck reaction affords functionalized olefins that represent essential structural motifs for the synthesis of pharmaceuticals, organic materials, agrochemicals, and complex natural products in both academic and industrial settings.³ In particular, the use of feedstock alkenes as nucleophilic coupling partners in the Heck reaction has become a central tool for industrial synthesis due to lowering the cost associated with olefin prefunctionalization.⁴ At the beginning of this project, methods for the cross-coupling of aryl halides,^{5a-d} triflates,^{5e} pseudohalides,^{5f} and diazonium salts have been reported.^{5g,h} While oxidative Heck reactions of carboxylic acids,^{6a} phosphonic acids,^{6b} and hydrocarbons^{6c} have also been developed, these methods require stoichiometric oxidants and proceed with limited scope or low regioselectivity.²

Furthermore, we realized that decarbonylative Heck reactions of stable aryl electrophiles, such as amides, represent a major challenge due to amidic resonance (Figure 3.1.1).⁷ However, there are several major advantages of using amides as aryl electrophiles in comparison with typical cross-coupling partners, including (1) low cost; (2) high stability; (3) ready availability of orthogonal precursors; and (4) potential for unconventional cross-couplings with new selectivity controlled by the facility of metal insertion into the C–N bond, which is not possible with less stable aryl halides or anhydrides. Mechanistically, metal insertion into a weakened C(O)–N bond leads to decarbonylation of the initially formed acyl-metal species under appropriate reaction conditions.⁸ However, despite the significant progress in the development of aryl ester electrophiles for Heck reactions,^{7c,d} amides have not been well explored as electrophilic coupling partners in this important process.^{2f,9} The main challenge in activating the amide bond toward metal insertion is the amide $n_N \rightarrow \pi^*_{C=O}$ resonance (planar amides, ca. 15–20 kcal/mol).¹⁰

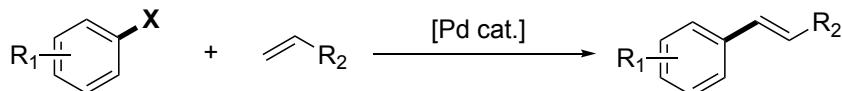
We realized that a general use of amides as electrophilic coupling partners in the Heck reaction could extend to functionalization of biomolecules and large scale industrial processes using bench-stable, chemoselective, low-cost acid amide reagents. We also kept in mind that our group has established the first decarbonylative Heck reaction of amides using *N*-glutarimides as coupling partners by steric distortion (Figure 3.1.2A).¹¹ Furthermore, our laboratory has also established the first decarbonylative Suzuki and direct decarbonylative C–H activation of *N*-glutarimide amides using Ni and Rh catalysis.¹² Moreover, at the start of this project, Ni-catalyzed decarbonylative borylation of amides by N–C cleavage has been accomplished.^{13,14} These reactions proceeded via

selective N–C insertion/decarbonylation, in which the facility of metal insertion was controlled by amide destabilization.¹⁵ Studies on amide geometry provided additional evidence for the gradual distortion of amides undergoing metal insertion.¹⁶ To expand the generality of decarbonylative Heck reactions by N–C cleavage, we proposed to use *N*-acylsaccharins as bench-stable, amide-based, electrophilic coupling partners.¹⁷ Recently, *N*-acylsaccharins have emerged as efficient functional group transfer reagents in metal-catalyzed formylation^{18a} and alkoxy carbonylation.^{18b} We have also developed conditions for the Suzuki-Miyaura cross-coupling of *N*-acylsaccharins to yield ketones with exclusive RC(O) coupling selectivity (acyl transfer, Figure 3.1.2B).^{18c}

In this project, we have developed the first Pd-catalyzed decarbonylative Heck reaction of *N*-acylsaccharins as electrophilic coupling partners by highly chemoselective N–C bond cleavage/decarbonylation. The following features of our study were noteworthy: (1) low-price, availability, benign nature of saccharin; (2) bench-stability and ease of crystallization of *N*-acylsaccharins, which allowed to avoid sensitive intermediates during cross-couplings; (3) excellent functional group tolerance and wide range of electronically-diverse amide and olefin coupling partners that could undergo this transformation; (4) operationally-simple, base-free, ligand-free conditions; (5) the development of the first example of iterative Heck cross-couplings using carbonyl electrophiles by site-selective C–N/C–Br cleavage. Overall, this study introduced readily available, bench-stable, cheap *N*-acylsaccharins as aryl transfer reagents for metal-catalyzed transformations via metal-insertion/decarbonylation to access versatile aryl metal intermediates. In this study, we have also demonstrated the highest reactivity of *N*-

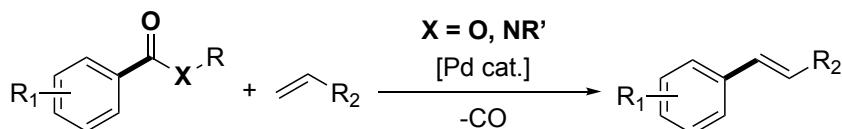
acylsaccharins out of all other amide precursors in decarbonylative cross-coupling by N–C cleavage.^{18c}

A. Classic electrophiles in the Heck Reaction



■ X = Hal (I, Br, Cl, F), OTs, N₂, OTf

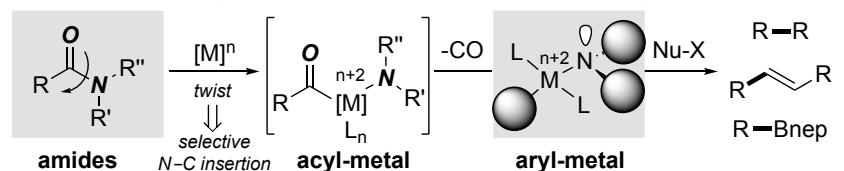
B. Unexplored: the Heck reaction of stable aryl equivalents (esters, amides)



■ low-price ■ availability ■ orthogonal cross-coupling ■ high tolerance

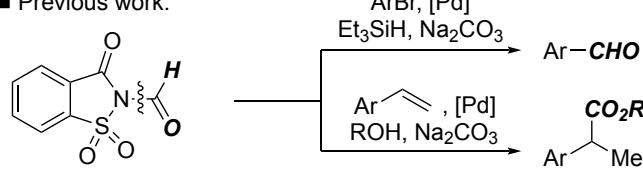
Figure 3.1.1 Classic and aryl equivalents in the Heck reaction.

A. Activation of amides by N–C bond cleavage /decarbonylation ■ amides = aryl source unexplored manifold in catalysis

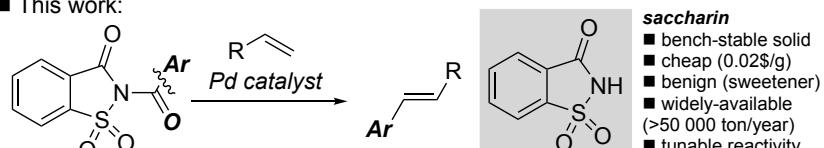


B. Saccharins as functional group transfer reagents (previous and this work)

■ Previous work:



■ This work:



✓selective aryl transfer (cf. acyl) ✓orthogonal C–X/C–N coupling ✓high reactivity

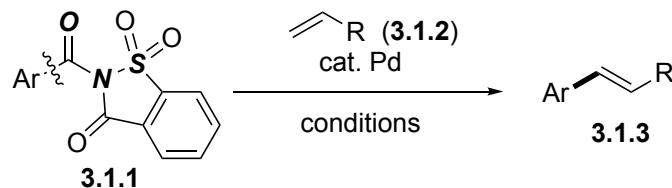
saccharin
■ bench-stable solid
■ cheap (0.02\$/g)
■ benign (sweetener)
■ widely-available (>50 000 ton/year)
■ tunable reactivity

Figure 3.1.2 (a) Decarbonylative N–C cleavage in amides. (b) Saccharins as electrophilic functional group transfer reagents.

3.1.2 Reaction optimization

We first investigated the Heck cross-coupling of *N*-benzoylsaccharin with *n*-butyl acrylate as a model reaction to identify the most active catalyst system. Selected key optimization results obtained during the optimization studies are summarized in Table 3.1.1. Under our standard conditions, *N*-benzoylsaccharin underwent the decarbonylative N–C coupling in excellent 98% yield (entry 1). Notably, we found that the presence of halide salts had a negative impact on the reaction efficiency (entries 2-15).¹⁹ Similarly, the use of external nucleophiles⁷ (entries 4 and 13) and other solvents (entries 5-6 and 11-12) resulted in a diminished yield of the arylation product. We hypothesized that these effects are consistent with high electrophilicity of *N*-acylsaccharins and competing nucleophilic addition. Mechanistically, we found that the reaction ensues at 80 °C with complete aryl- vs acyl-selectivity (entries 8-9 and 14-15), consistent with the high propensity of the N–C bond in *N*-acylsaccharins for metal insertion/decarbonylation.^{18a-c} Furthermore, we were pleased to find that after small adjustment of the reaction conditions, the process could be extended to valuable styrene nucleophiles (entries 16-18). The use of other Pd precursors, including Pd(OAc)₂, PdBr₂, and PdI₂ resulted in low reaction efficiency. Importantly, under the optimized conditions, products resulting from the acyl-transfer (cf. arylation) were not observed,^{18a} demonstrating efficient decarbonylation under these conditions.⁸ Furthermore, cleavage of the alternative C–SO₂ bond was not observed.²⁰ Overall, the optimized conditions compared quite favorably with other methods for the decarbonylative Heck reactions in terms of operational simplicity and reaction efficiency.^{7,11}

Table 3.1.1 Optimization of Pd-catalyzed decarbonylative Heck reaction of *N*-acylsaccharins.^a



entry	catalyst	ligand	solvent	yield (%) ^a
1	PdCl ₂		NMP	98
2	PdCl ₂	LiBr	NMP	63
3 ^b	PdCl ₂	LiBr	NMP	41
4 ^c	PdCl ₂	LiBr	NMP	<5
5	PdCl ₂	LiBr	toluene	<5
6	PdCl ₂	LiBr	dioxane	19
7 ^d	PdCl ₂	LiBr	NMP	43
8 ^e	PdCl ₂	LiBr	NMP	28
9 ^f	PdCl ₂	LiBr	NMP	<5
10 ^b	PdCl ₂		NMP	53
11	PdCl ₂		toluene	26
12	PdCl ₂		dioxane	36
13 ^c	PdCl ₂		NMP	25
14 ^d	PdCl ₂		NMP	50
15 ^e	PdCl ₂		NMP	40
16 ^g	PdCl ₂	LiBr	NMP	<5
17 ^{g,h,i}	PdCl ₂		NMP	75
18 ^{g,i,j}	PdCl ₂		NMP	92

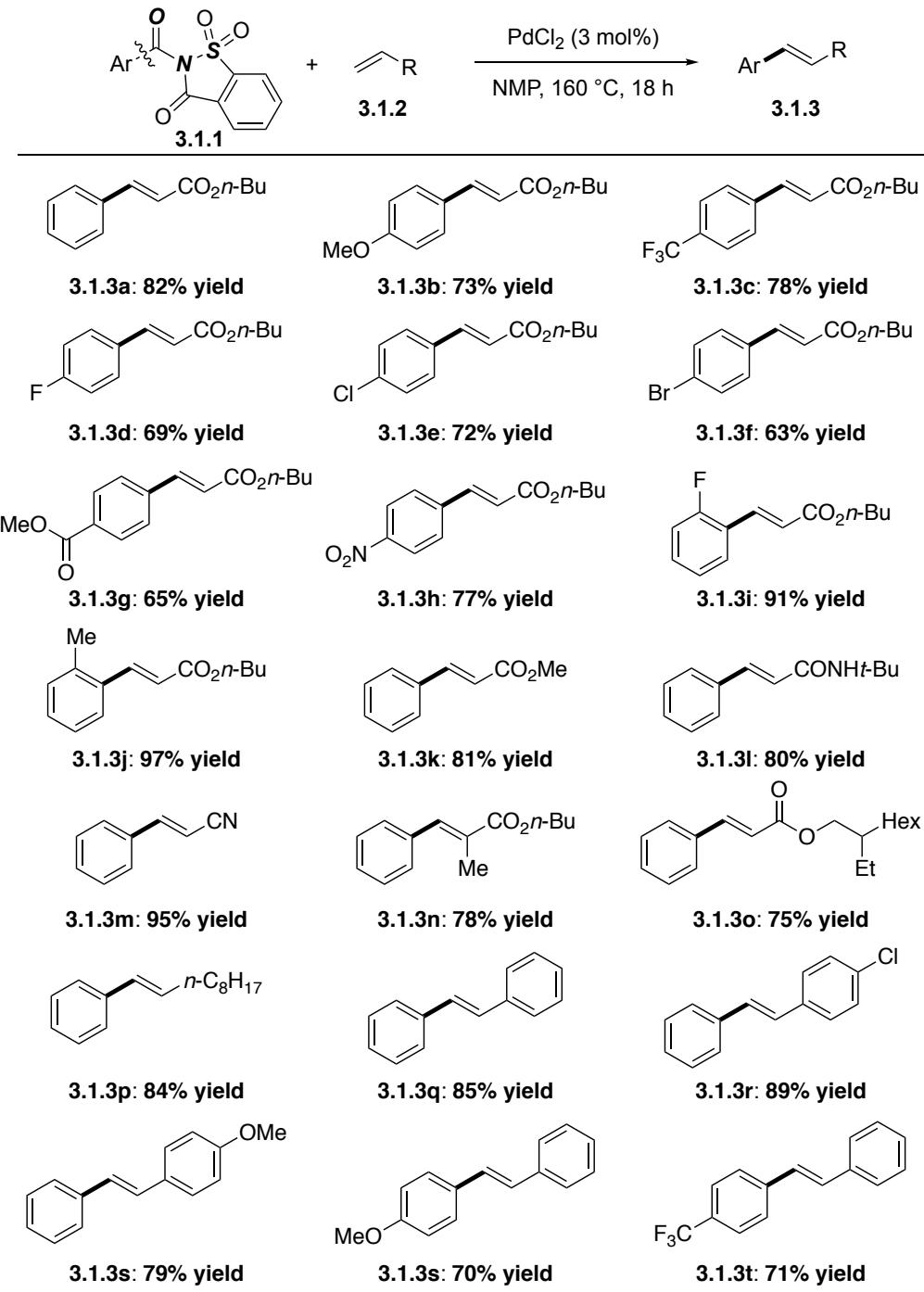
^aConditions: amide (1.0 equiv), R-CH=CH₂ (2.0 equiv), catalyst (3 mol%), ligand (9 mol%), solvent (0.25 M), 160 °C, 18 h. R = CO₂n-Bu. ^b R-CH=CH₂ (1.2 equiv). ^c Isoquinoline (0.1 equiv). ^d 120 °C. ^e 80 °C. ^f ligand (1.0 equiv). ^g R = Ph. ^h 180 °C. ⁱ catalyst (5 mol%). ^j R-CH=CH₂ (3.0 equiv).

3.1.3 Substrate scope

With the optimized conditions in hand, we next investigated the substrate scope of this reaction (Scheme 3.1.1). As shown, a wide range of electronically varied substrates containing diverse functional groups underwent the cross-coupling in high yields and with generally excellent regioselectivity (entries 1-21). Neutral (**3.1.3a**), electron-rich (**3.1.3b**), electron-poor (**3.1.3c**), fluoro- (**3.1.3d**), chloro- (**3.1.3e**), bromo- (**3.1.3f**), ester- (**3.1.3g**), and nitro-containing substrates (**3.1.3h**) were perfectly tolerated, affording the corresponding olefins in 63-82% yields. Debromination was not observed. Moreover, ortho-substituted *N*-acylsaccharins (**3.1.3i**, **3.1.3j**) coupled in high yields. The scope of the reaction with respect to the olefin component was also broad and encompassed α,β -unsaturated esters (**3.1.3k**, **3.1.3o**), amides (**3.1.3l**), and nitriles (**3.1.3m**). Disubstituted olefins were suitable coupling partners (**3.1.3n**).^{21a} Aliphatic alkenes could also be used (**3.1.3p**); however, these substrates afforded mixture of isomers, as expected.^{21b,7c} Finally, electronically diverse styrenes underwent coupling in good yields and with high regioselectivity. For these substrates a higher catalyst loading (5 mol%) was used to obtain optimum results. Only monoarylation products were observed in all examples examined.^{7d,e} In all cases, exclusive formation of *E* isomers was found. The reaction enabled synthesis of olefins with diverse electrophilic functional handles for further manipulation. Of note was the synthesis of a common UV-B sunscreen produced industrially (**3.1.3o**).^{4a} While the reaction employed NMP as a polar solvent to achieve optimum yields, the process did not require expensive oxidants and the scope of the reaction was not limited to ortho-substituted substrates as in the case of oxidative Heck reactions.⁶⁻⁸ To further the utility of the process, we performed the coupling on a 2.0

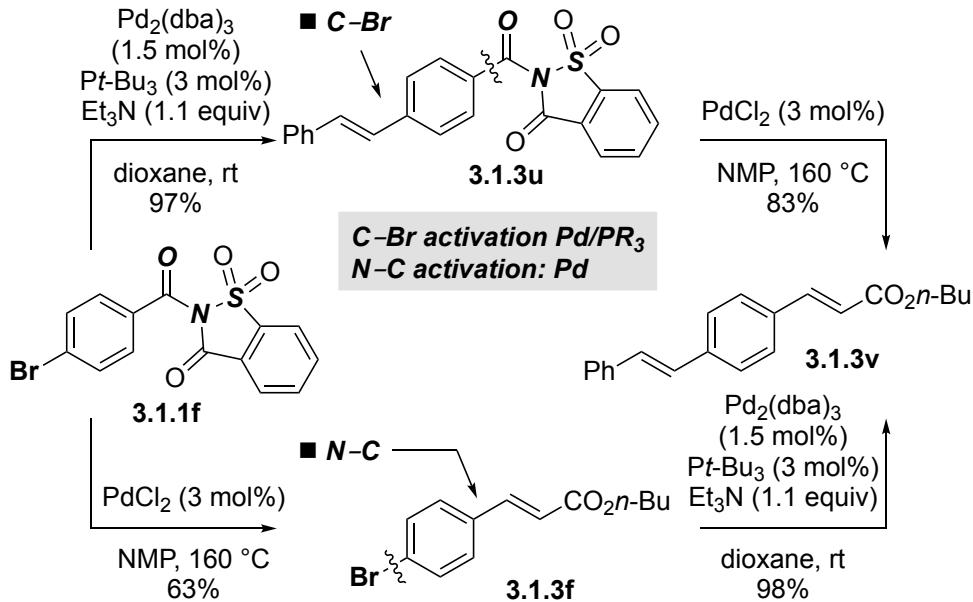
mmol scale using *n*-butyl acrylate and styrene, and gave **3.1.3a** and **3.1.3q** in 79% ($>20:1$ selectivity) and 87% (92:8 selectivity) isolated yields, respectively, attesting to the synthetic utility of the method.

We highlighted the synthetic utility of *N*-acylsaccharins as orthogonal cross-coupling partners in iterative site-specific C–N/C–Br cross-coupling (Scheme 3.1.2).²³ The Heck cross-coupling of aryl bromides could be achieved by Pd/*Pt*-Bu₃-catalysis,^{5d,22c} leaving the amide bond in *N*-acylsaccharins intact (Scheme 3.1.2, top). Alternatively, the amide N–C cross-coupling could be followed by the C–Br cleavage (Scheme 3.1.2, bottom). To our knowledge, this was the first sequential cross-coupling involving any decarbonylative process of amide bonds.^{2,3,7} The iterative cross-coupling was facilitated by the high reactivity of *N*-acylsaccharins¹⁸ and the ease of purification of intermediates by recrystallization.¹⁷



^aConditions: amide (1.0 equiv), R-CH=CH₂ (2.0 equiv), PdCl₂ (3 mol%), NMP (0.25 M), 160 °C, 18 h, selectivity: > 20:1; ^bselectivity: 5.80:2.20:1.00; ^cisomers (8.44:2.72:5.99:1.00); ^damide (1.0 equiv), R-CH=CH₂ (3.0 equiv), PdCl₂ (5 mol%), 2,1/1,2:91:9 (**3.1.3q**), 95:5 (**3.1.3r**), 81:19 (**3.1.3s**), 75:25 (**3.1.3s'**), 92:8 (**3.1.3t**).

Scheme 3.1.1 Scope of decarbonylative Heck reaction of *N*-acylsaccharins.^a



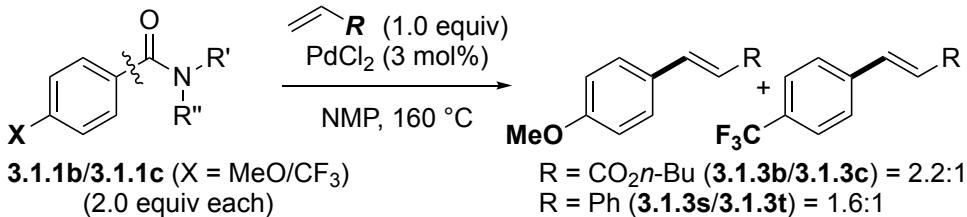
Scheme 3.1.2 Iterative Heck cross-coupling of *N*-acylsaccharins: C–N vs C–Br cleavage.

3.1.4 Mechanistic studies

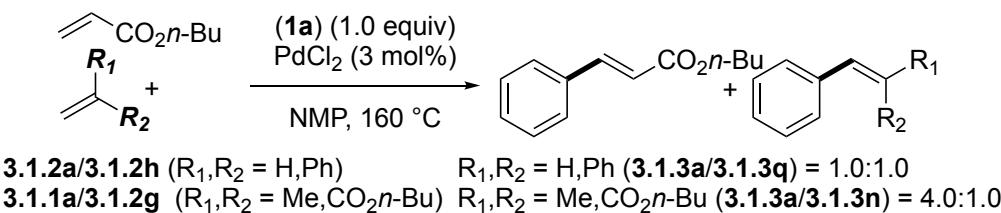
Intrigued by the high reactivity of *N*-acylsaccharins (twisted amide bond: $\tau = 23.0^\circ$, $\chi_N = 12.5^\circ$),^{18c} we conducted selectivity studies to gain insight into the reaction mechanism (Scheme 3.1.3).²² (1) Intermolecular competition experiments between differently substituted *N*-acylsaccharins indicated that electron-deficient substrates reacted preferentially (Scheme 3.1.3A). (2) Experiments with different olefins established the following reactivity order: $H_2C=CH-CO_2n-Bu \approx H_2C=CH-Ph > H_2C=C-MeCO_2n-Bu$ (Scheme 3.1.3B). (3) Experiments with aryl electrophiles revealed the following order of reactivity: *N*-acylsaccharins $>$ *N*-glutarimides \approx $(Ar-CO)_2O \gg Ar-CO_2R$ (Scheme 3.1.3C). (4) Electronic effects observed in the regioselectivity of the arylation with styrenes (styrene: Hammett ρ -value of 1.21, $R^2 = 0.99$; amide: ρ^+ -value of 0.46, $R^2 = 0.90$) indicated an increase in the arylation regioselectivity of electron-deficient olefins and

electron-deficient amides. These studies were consistent with the initial metal insertion into the amide N–C bond;⁹ olefin insertion might be a relevant step in the reaction.^{22b} The high reactivity of *N*-acylsaccharins (cf. glutarimides)¹¹ compared favorably with other amides for potential applications in decarbonylative cross-coupling by N–C cleavage.

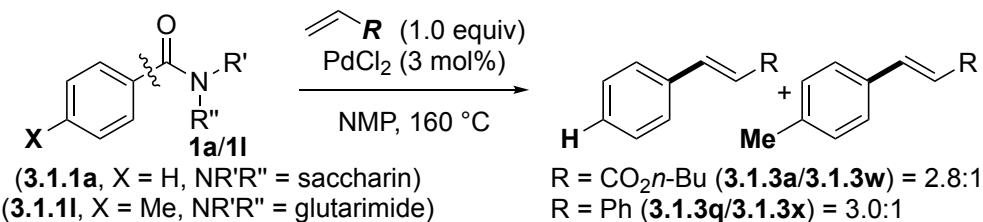
A) Intermolecular competition: amides 1



B) Intermolecular competition: olefins 2



C) Intermolecular competition: amides 3



Scheme 3.1.3 Mechanistic studies of decarbonylative Heck reaction of *N*-acylsaccharins.

3.1.5 Conclusion

In summary, we have developed the first Pd-catalyzed decarbonylative Heck cross-coupling of *N*-acylsaccharins by chemoselective N–C cleavage. We found that a variety of amide and olefin substrates were suitable for this reaction. The sequential Heck coupling of C–Br and C–N bonds was demonstrated for the first time. *N*-Acylsaccharins

represent an attractive class of air-stable, crystalline solids that showed comparable reactivity to *N*-glutarimide amides. The discovery that *N*-acylsaccharins could readily undergo aryl transfer could enable the development of new metal-catalyzed transformations of amides.

3.1.6 Experimental section

General procedure for amide synthesis. An oven-dried flask (25 mL) equipped with a stir bar was charged with aniline (typically, 5.0 mmol, 1.0 equiv), pyridine (typically, 2.5 equiv) and dichloromethane (typically, 0.50 M), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acetyl chloride (typically, 1.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 2 h at room temperature. After the indicated time, the reaction mixture was diluted with ethyl acetate (30 mL). The reaction mixture was washed with HCl (1 x 10 mL), brine (1 x 10 mL), H₂O (1 x 10 mL), dried, and concentrated to get crude first-step product. Then an oven-dried flask (25 mL) equipped with a stir bar was charged with crude first-step product (typically, 5.0 mmol, 1.0 equiv), 4-(dimethylamino)pyridine (typically, 0.005 equiv), triethylamine (typically, 2.0 equiv) and dichloromethane (typically, 0.50 M), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acyl chloride (typically, 1.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. After the indicated time, the reaction mixture was diluted with ethyl acetate (30 mL). The reaction mixture was washed with HCl (1 x 10 mL), brine (1 x 10 mL), H₂O (1 x 10 mL), dried,

and concentrated. The crude product was purified by recrystallization (toluene) to give analytically pure product.

General Procedure for Suzuki-Miyaura Cross-Coupling of Amides. An oven-dried vial equipped with a stir bar was charged with amide substrate (neat, 1.0 equiv), boronic acid (typically, 2.0 equiv), Pd(OAc)₂ (typically, 3 mol%), PCy₃HBF₄ (typically, 12 mol%), K₂CO₃ (typically, 2.5 equiv) and H₃BO₃ (typically, 2.0 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (typically, 0.20 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 60 °C, and stirred for the indicated time at 60 °C. After the indicated time, the reaction mixture was diluted with CH₂Cl₂ (10 mL), filtered, and concentrated. The sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate) afforded the title product.

3.1.3a. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.72-7.69 (d, *J* = 16.0 Hz, 1 H), 7.56-7.55 (d, *J* = 4.9 Hz, 2 H), 7.41-7.40 (t, *J* = 1.9 Hz, 3 H), 6.49-6.45 (d, *J* = 15.9 Hz, 1 H), 4.25-4.23 (t, *J* = 6.6 Hz, 2 H), 1.75-1.69 (m, 2 H), 1.51-1.43 (m, 2 H), 1.01-0.98 (t, *J* = 7.4 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 167.14, 144.57, 134.50, 130.22, 128.89, 128.06, 118.32, 64.46, 30.79, 19.22, 13.77.

3.1.3b. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.68-7.65 (d, *J* = 16.0 Hz, 1 H), 7.51-7.49 (d, *J* = 8.7 Hz, 2 H), 6.94-6.92 (d, *J* = 8.6 Hz, 2 H), 6.35-6.32 (d, *J* = 16.0 Hz, 1 H), 4.24-4.21 (t, *J* = 6.7 Hz, 2 H), 3.86 (s, 3 H), 1.74-1.68 (m, 2 H), 1.50-1.43 (m, 2 H), 1.00-

0.97 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.47, 161.33, 144.22, 129.70, 127.24, 115.80, 114.32, 64.29, 55.39, 30.83, 19.23, 13.78.

3.1.3c. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.73-7.70 (d, $J = 16.1$ Hz, 1 H), 7.68-7.64 (t, $J = 9.3$ Hz, 4 H), 6.55-6.52 (d, $J = 16.1$ Hz, 1 H), 4.27-4.24 (t, $J = 6.6$ Hz, 2 H), 1.75-1.70 (m, 2 H), 1.51-1.43 (m, 2 H), 1.01-0.98 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.54, 142.68, 137.87, 131.72 (q, $J^F = 32.5$ Hz), 128.17, 125.87 (q, $J^F = 3.7$ Hz), 123.84 (d, $J^F = 270.4$ Hz), 120.89, 64.75, 30.74, 19.20, 13.75. ^{19}F NMR (471 MHz, CDCl_3) δ -62.86.

3.1.3d. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.68-7.65 (d, $J = 16.0$ Hz, 1 H), 7.55-7.52 (t, $J = 7.5$ Hz, 2 H), 7.12-7.08 (t, $J = 8.3$ Hz, 2 H), 6.40-6.37 (d, $J = 16.0$ Hz, 1 H), 4.25-4.22 (t, $J = 6.6$ Hz, 2 H), 1.74-1.68 (m, 2 H), 1.50-1.43 (m, 2 H), 1.00-0.97 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.01, 163.88 (d, $J^F = 249.0$ Hz), 143.26, 130.72, 129.92 (d, $J^F = 8.5$ Hz), 118.07 (d, $J^F = 2.3$ Hz), 116.04 (d, $J^F = 21.7$ Hz), 64.50, 30.78, 19.21, 13.76. ^{19}F NMR (471 MHz, CDCl_3) δ -109.78.

3.1.3e. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.66-7.63 (d, $J = 16.0$ Hz, 1 H), 7.49-7.47 (d, $J = 8.0$ Hz, 2 H), 7.39-7.37 (d, $J = 8.0$ Hz, 2 H), 6.45-6.42 (d, $J = 16.1$ Hz, 1 H), 4.25-4.22 (t, $J = 6.6$ Hz, 2 H), 1.74-1.68 (m, 2 H), 1.50-1.42 (m, 2 H), 1.00-0.97 (t, $J = 7.3$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.87, 143.11, 136.12, 132.98, 129.22, 129.17, 118.91, 64.57, 30.77, 19.20, 13.76.

3.1.3f. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.65-7.61 (d, $J = 16.0$ Hz, 1 H), 7.55-7.53 (d, $J = 8.2$ Hz, 2 H), 7.42-7.40 (d, $J = 8.3$ Hz, 2 H), 6.47-6.43 (d, $J = 16.0$ Hz, 1 H), 4.25-4.22 (t, $J = 6.6$ Hz, 2 H), 1.74-1.68 (m, 2 H), 1.50-1.42 (m, 2 H), 1.00-0.97 (t, $J =$

7.4 Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.85, 143.17, 133.41, 132.14, 129.44, 124.46, 119.02, 64.58, 30.76, 19.20, 13.75.

3.1.3g. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.08-8.06 (d, $J = 7.9$ Hz, 2 H), 7.73-7.69 (d, $J = 16.1$ Hz, 1 H), 7.61-7.60 (d, $J = 7.9$ Hz, 2 H), 6.56-6.52 (d, $J = 16.1$ Hz, 1 H), 4.26-4.23 (t, $J = 6.6$ Hz, 2 H), 3.95 (s, 3 H), 1.74-1.69 (m, 2 H), 1.50-1.43 (m, 2 H), 1.00-0.97 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.63, 166.47, 143.12, 138.71, 131.33, 130.10, 127.90, 120.72, 64.67, 52.29, 30.74, 19.20, 13.75.

3.1.3h. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.28-8.26 (d, $J = 8.4$ Hz, 2 H), 7.74-7.71 (d, $J = 17.4$ Hz, 1 H), 7.71-7.69 (d, $J = 8.9$ Hz, 2 H), 6.60-6.57 (d, $J = 16.0$ Hz, 1 H), 4.27-4.25 (t, $J = 6.6$ Hz, 2 H), 1.75-1.70 (m, 2 H), 1.50-1.43 (m, 2 H), 1.01-0.98 (t, $J = 7.5$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.14, 148.49, 141.59, 140.61, 128.63, 124.18, 122.63, 64.93, 30.70, 19.18, 13.73.

3.1.3i. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.85-7.82 (d, $J = 16.2$ Hz, 1 H), 7.58-7.55 (t, $J = 7.6$ Hz, 1 H), 7.40-7.36 (m, 1 H), 7.20-7.17 (t, $J = 7.6$ Hz, 1 H), 7.14-7.10 (t, $J = 9.8$ Hz, 1 H), 6.58-6.55 (d, $J = 16.2$ Hz, 1 H), 4.26-4.23 (t, $J = 6.6$ Hz, 2 H), 1.75-1.69 (m, 2 H), 1.50-1.43 (m, 2 H), 1.01-0.98 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.95, 161.35 (d, $J^F = 252.3$ Hz), 137.17, 131.62 (d, $J^F = 8.7$ Hz), 129.07 (d, $J^F = 2.8$ Hz), 124.43 (d, $J^F = 3.6$ Hz), 122.57 (d, $J^F = 11.6$ Hz), 120.90 (d, $J^F = 6.5$ Hz), 116.20 (d, $J^F = 21.8$ Hz), 64.57, 30.77, 19.21, 13.76.

3.1.3j. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.02-7.98 (d, $J = 15.9$ Hz, 1 H), 7.59-7.57 (d, $J = 7.7$ Hz, 1 H), 7.31-7.28 (t, $J = 7.2$ Hz, 1 H), 7.25-7.22 (t, $J = 6.9$ Hz, 2 H), 6.40-6.37 (d, $J = 15.9$ Hz, 1 H), 4.26-4.23 (t, $J = 6.7$ Hz, 2 H), 2.47 (s, 3 H), 1.75-1.69 (m,

2 H), 1.51-1.43 (m, 2 H), 1.01-0.98 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.20, 142.27, 137.64, 133.47, 130.79, 129.96, 126.41, 126.33, 119.33, 64.44, 30.80, 19.81, 19.23, 13.78.

3.1.3k. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.74-7.71 (d, $J = 16.0$ Hz, 1 H), 7.55-7.55 (d, $J = 2.9$ Hz, 2 H), 7.42-7.41 (t, $J = 2.5$ Hz, 3 H), 6.49-6.46 (d, $J = 16.0$ Hz, 1 H), 3.84 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.46, 144.90, 134.40, 130.32, 128.91, 128.09, 117.82, 51.73.

3.1.3l. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.61-7.58 (d, $J = 15.6$ Hz, 1 H), 7.51-7.50 (d, $J = 7.0$ Hz, 2 H), 7.40-7.37 (t, $J = 6.6$ Hz, 3 H), 6.36-6.33 (d, $J = 15.5$ Hz, 1 H), 5.45 (s, 1 H), 1.46 (s, 9 H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.17, 140.30, 135.00, 129.48, 128.78, 127.72, 121.94, 51.54, 28.89.

3.1.3m. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.49-7.45 (t, $J = 11.2$ Hz, 5 H), 7.43-7.42 (d, $J = 8.2$ Hz, 1 H), 5.93-5.90 (d, $J = 16.7$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.62, 133.54, 131.24, 129.14, 127.37, 118.16, 96.38.

3.1.3n. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.71-7.42 (s, 1 H), 7.42-7.42 (d, $J = 3.4$ Hz, 4 H), 7.36-7.33 (m, 1 H), 4.26-4.23 (t, $J = 6.6$ Hz, 2 H), 2.14 (s, 3 H), 1.76-1.71 (m, 2 H), 1.52-1.44 (m, 2 H), 1.02-0.99 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 168.80, 138.64, 136.00, 129.65, 129.03, 128.36, 128.24, 64.82, 30.80, 19.30, 14.07, 13.79.

3.1.3o. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.72-7.69 (d, $J = 16.0$ Hz, 1 H), 7.56-7.55 (d, $J = 4.9$ Hz, 2 H), 7.41-7.41 (t, $J = 3.2$ Hz, 3 H), 6.49-6.46 (d, $J = 16.0$ Hz, 1 H), 4.16-4.14 (t, $J = 5.1$ Hz, 2 H), 1.70-1.66 (m, 1 H), 1.48-1.42 (m, 2 H), 1.38-1.34 (m, 6

H), 0.97-0.91 (m, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.25, 144.51, 134.51, 130.21, 128.88, 128.07, 118.37, 67.02, 38.88, 30.49, 28.98, 23.87, 23.00, 14.08, 11.05.

3.1.3q. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.56-7.54 (d, $J = 7.7$ Hz, 4 H), 7.41-7.38 (t, $J = 7.7$ Hz, 4 H), 7.31-7.28 (t, $J = 7.1$ Hz, 2 H), 7.14 (s, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 137.35, 128.71, 128.70, 127.64, 126.53.

3.1.3r. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.54-7.53 (d, $J = 7.7$ Hz, 2 H), 7.48-7.46 (d, $J = 8.1$ Hz, 2 H), 7.41-7.38 (t, $J = 7.7$ Hz, 2 H), 7.36-7.35 (d, $J = 8.2$ Hz, 2 H), 7.32-7.29 (t, $J = 6.8$ Hz, 1 H), 7.13-7.06 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 137.00, 135.86, 133.19, 129.33, 128.86, 128.75, 127.89, 127.67, 127.38, 126.56.

3.1.3s. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.53-7.51 (d, $J = 7.8$ Hz, 2 H), 7.49-7.48 (d, $J = 8.3$ Hz, 2 H), 7.39-7.36 (t, $J = 7.6$ Hz, 2 H), 7.28-7.25 (t, $J = 8.0$ Hz, 1 H), 7.11-6.99 (q, $J = 16.3$ Hz, 2 H), 6.94-6.92 (d, $J = 8.2$ Hz, 2 H), 3.86 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.32, 137.66, 130.16, 128.65, 128.22, 127.73, 127.22, 126.63, 126.26, 114.15, 55.35.

3.1.3t. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.63 (s, 4 H), 7.57-7.56 (d, $J = 7.6$ Hz, 2 H), 7.43-7.40 (t, $J = 7.5$ Hz, 2 H), 7.34-7.32 (t, $J = 7.3$ Hz, 1 H), 7.24-7.13 (q, $J = 16.4$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 140.82, 136.64, 131.22, 129.27 (q, $J^F = 32.5$ Hz), 128.82, 128.31, 127.14, 126.79, 126.59, 125.65 (q, $J^F = 3.6$ Hz), 124.24 (d, $J^F = 270.0$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.45.

3.1.3u. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.72-7.68 (d, $J = 16.0$ Hz, 1 H), 7.55 (s, 6 H), 7.41-7.38 (t, $J = 7.2$ Hz, 2 H), 7.32-7.29 (t, $J = 7.0$ Hz, 1 H), 7.22-7.11 (q, $J = 16.4$ Hz, 2 H), 6.49-6.46 (d, $J = 16.0$ Hz, 1 H), 4.26-4.23 (t, $J = 6.5$ Hz, 2 H), 1.75-1.70

(m, 2 H), 1.51-1.44 (m, 2 H), 1.01-0.98 (t, $J = 7.2$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.20, 144.04, 139.33, 136.98, 133.70, 130.08, 128.77, 128.51, 128.04, 127.80, 126.92, 126.69, 117.87, 64.45, 30.81, 19.23, 13.78.

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3.2 Decarbonylative phosphorylation of amides by palladium and nickel catalysis

Parts of this section were adapted with permission from the article “Decarbonylative Phosphorylation of Amides by Palladium and Nickel Catalysis: The Hirao Cross-Coupling of Amide Derivatives” (*Angew. Chem. Int. Ed.* **2017**, *56*, 12718). Copyright ©2017, Thieme Gruppe.

3.2.1 Introduction

Organophosphorus compounds are essential structures in chemical synthesis, and have seen key applications as drug pharmacophores, agrochemicals and flame retardants (Figure 3.2.1A).^{1,2} The capacity of phosphorus to coordinate to transition metals and biological receptors has enabled design of novel reactions and control of numerous biological functions.^{3,4} Considering the importance of organophosphorus compounds in modern chemistry, the development of new methods for their synthesis is particularly significant.

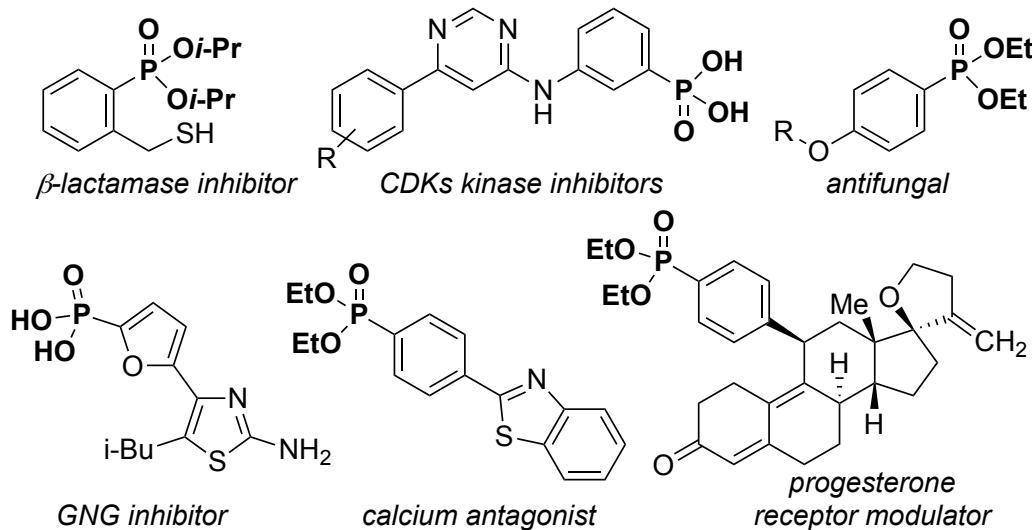
Since its discovery in 1981, the Hirao cross-coupling has become a central C–P bond forming reaction in organic synthesis (Figure 3.2.1B).^{5,6} In this context, aryl halides,⁷ sulfonates,⁸ diazonium salts,⁹ boronic acids,¹⁰ silanes,¹¹ organobismuth compounds,¹² pivalates,¹³ and sulfides¹⁴ via C–X, C–O, C–N, C–B, C–Bi, C–Si and C–S bond cleavage have found wide application in organic synthesis using Pd,⁷⁻¹² Ni¹³⁻¹⁵ and Cu¹⁶ catalysis.^{7j-q} These methods have significantly expanded a range of organic coupling partners to participate in the construction of C–P bonds. Additionally, chemical methods for the synthesis of C–P bonds using conventional Grignard or organolithium reagents

and the Michaelis-Arbuzov reaction have been established; however, these protocols suffer from toxicity, substrate and efficiency limitations.^{17,18} Furthermore, new methods for the construction of C–P bonds by C–H activation¹⁹ and photoredox pathways²⁰ continue to evolve.

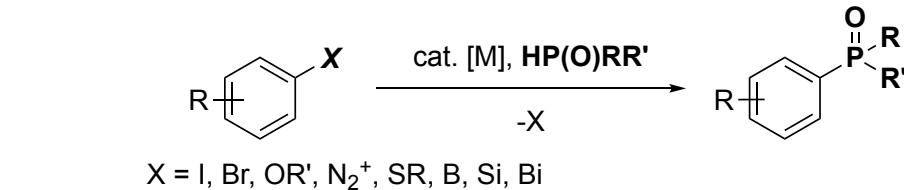
At the same time, amide bond cross-coupling has emerged as a powerful tool for the construction of organic molecules.²¹⁻²⁴ As demonstrated,²⁵⁻³³ a unique amide bond activation mode utilizing amide bond n_N to $\pi^*_{C=O}$ resonance destabilization³⁴ can be successfully employed to accomplish direct metal insertion into the typically inert N–C(O) moiety.²¹ The ability to utilize amides as precursors to form C–O, C–N, C–C, C–B, and C–H bonds with high predictability and chemoselectivity via acyl and decarbonylative pathways has been demonstrated.³⁵ Such bond forming reactions of readily accessible, bench-stable amides²² significantly expand the portfolio of electrophiles available for cross-coupling under synthetically attractive redox-neutral conditions, wherein the reactivity is controlled by geometry and *N*-substitution of the amide bond.^{26,29} Moreover, the versatile amide electrophiles (1) are traditionally derived from different precursors than halides, phenols and anilines; (2) are easy to prepare; and (3) are inert to a variety of conditions allowing for ring prefunctionalization. Despite the significant progress, the intrinsic limitation is the reactivity of the N–C(O) amide bond for oxidative insertion and control of the relative reactivity of the acyl-metal intermediate towards decarbonylation.³⁶ In light of the importance of amides as key building blocks in peptides and versatile bench-stable intermediates in organic synthesis,²² we proposed to use amides as cross-coupling partners in the synthesis of C–P bonds.

In this project, we have developed a catalytic deamidative phosphorylation of a wide range of amides using palladium or nickel catalysis to give aryl phosphonates in good to excellent yields (Figure 3.2.1C). The reaction represented the first example of a transition-metal-catalyzed generation of C–P bonds from amides. The method tolerated a wide range of functional groups. Given the importance of amides and phosphonates as synthetic intermediates, we proposed that this Pd and Ni-catalyzed C–P bond forming method could find broad utility in the construction of organic molecules. In this context, the method also represented a two-step approach to aryl phosphorus compounds from ubiquitous carboxylic acids^{35a} which is a highly desirable transformation that at the start of this project could not be readily accomplished by other methods.

A. Examples of pharmaceutically-relevant organophosphorus compounds



B. Traditional metal-catalyzed synthesis of organophosphorus compounds



C. Decarbonylative phosphorylation of amides by Pd and Ni catalysis: *this study*

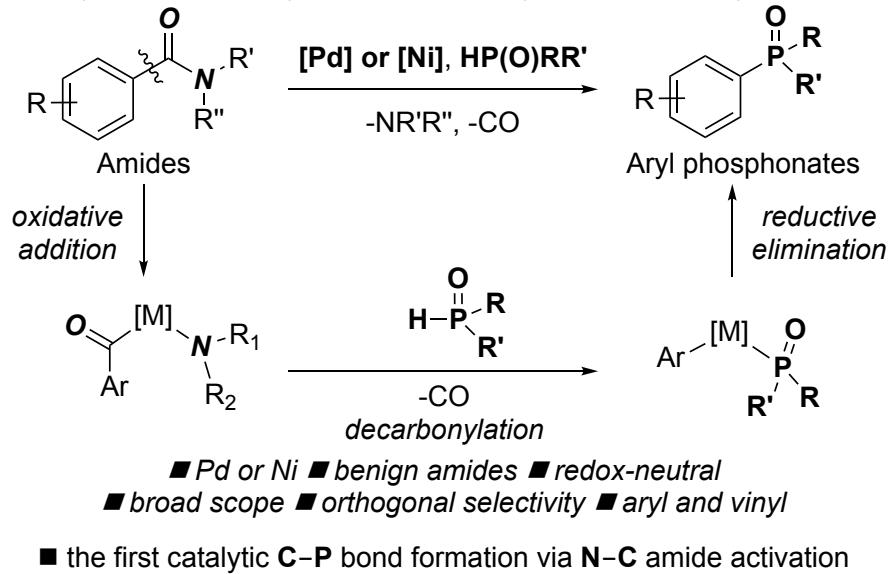
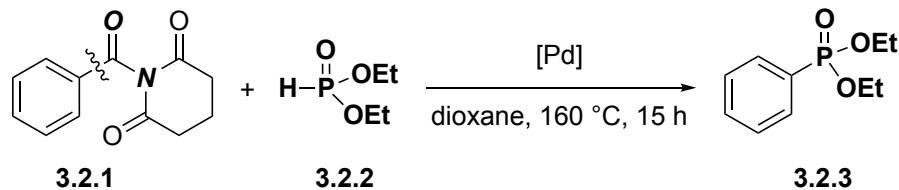


Figure 3.2.1 (a) Pharmaceutically important organophosphorus compounds. (b) Conventional synthesis of organophosphorus compounds (Hirao coupling). (c) Pd- and Ni-catalyzed decarbonylative phosphorylation of amides (*this study*).

3.2.2 Reaction optimization

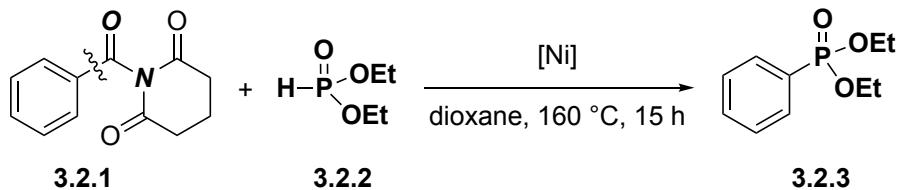
We realized that redox-neutral phosphorylation of ubiquitous carboxylic acid derivatives remained a challenging goal.³⁵ In an effort to demonstrate the utility of the amide bond activation platform, at the beginning we explored a practical palladium-catalyzed²³ decarbonylative coupling between N–C(O) electrophiles and dialkyl phosphites. We reasoned that the nucleophilic character of the phosphorus anion might render these couplings susceptible to decarbonylation when using an appropriate ligand.^{6b} The phosphorylation of *N*-benzoylglutarimide with diethylphosphite was first evaluated using palladium catalysts under various conditions (Table 3.2.1). After extensive investigation, we were delighted to identify that the proposed deamidative coupling in the presence of HP(O)(OEt)₂, Pd(OAc)₂ (5 mol %), Xantphos or DPPB (10 mol %) and Et₃N (1.5 equiv) in dioxane at 160 °C, provided the desired aryl phosphonate product in quantitative yield.

In consideration of the economic advantages offered by nickel catalysis,³⁷ we also proposed that nickel catalysis might be employed to promote the C–P bond formation by the uncommon cleavage of the N–C amide bond. In general, very limited success using both Pd and Ni to promote a single reaction of amides through N–C activation has been achieved. To our delight, after very extensive investigation we discovered that an inexpensive, bench-stable Ni(dppp)Cl₂ in the presence of Na₂CO₃ as a base promoted the desired coupling. Summary of key optimization results using Ni catalysis is presented in Table 3.2.2.

Table 3.2.1 Optimization of Pd-catalyzed decarbonylative phosphorylation of amides.^a

entry	catalyst	ligand	phosphite	base	yield (%) ^a
1			1.0 equiv		<2
2	Pd(OAc) ₂	XantPhos	1.0 equiv		27
3	Pd(OAc) ₂	XantPhos	1.0 equiv	Et ₃ N	56
4	Pd(OAc) ₂	XantPhos	1.0 equiv	Na ₂ CO ₃	13
5	Pd(OAc) ₂	XantPhos	1.0 equiv	K ₂ CO ₃	<2
6	PdCl ₂	XantPhos	1.0 equiv	Et ₃ N	28
7	Pd(dba) ₂	XantPhos	1.0 equiv	Et ₃ N	10
8	Pd ₂ (dba) ₃	XantPhos	1.0 equiv	Et ₃ N	36
9	Pd(OAc) ₂	XantPhos	0.5 equiv	Et ₃ N	>95
10	Pd(OAc) ₂	DPEPhos	0.5 equiv	Et ₃ N	49
11	Pd(OAc) ₂	DavePhos	0.5 equiv	Et ₃ N	30
12	Pd(OAc) ₂	BINAP	0.5 equiv	Et ₃ N	45
13	Pd(OAc) ₂	dppb	0.5 equiv	Et ₃ N	>95
14	Pd(OAc) ₂	dppf	0.5 equiv	Et ₃ N	78
15	Pd(OAc) ₂	PCy ₃ HBF ₄	0.5 equiv	Et ₃ N	74
16	Pd(OAc) ₂	PCy ₂ Ph	0.5 equiv	Et ₃ N	84
17	Pd(OAc) ₂	PCyPh ₂	0.5 equiv	Et ₃ N	47
18	Pd(OAc) ₂	PPh ₃	0.5 equiv	Et ₃ N	40

^aConditions: amide (1.0 equiv), HP(O)(OEt)₂ (0.5 equiv), catalyst (5 mol%), ligand (10 mol%), base (1.5 equiv), dioxane (0.25 M), 160 °C, 15 h.

Table 3.2.2 Optimization of Ni-catalyzed decarbonylative phosphorylation of amides.^a

entry	catalyst	ligand	base	yield (%) ^a
1	5 mol% Ni(PCy ₃) ₂ Cl ₂		Na ₂ CO ₃	<5
2	5 mol% Ni(PCy ₃) ₂ Cl ₂		K ₂ CO ₃	<2
3	5 mol% Ni(PCy ₃) ₂ Cl ₂		Cs ₂ CO ₃	<2
4	5 mol% Ni(PPh ₃) ₂ Cl ₂		Na ₂ CO ₃	<2
5	5 mol% Ni(dppf)Cl ₂		Na ₂ CO ₃	<2
6	5 mol% Ni(acac) ₂		Na ₂ CO ₃	<2
7	5 mol% Ni(acac) ₂	10 mol% dppb	Na ₂ CO ₃	<2
8	5 mol% Ni(dppe)Cl ₂		Na ₂ CO ₃	57
9	10 mol% Ni(dppe)Cl ₂		Na ₂ CO ₃	57
10	5 mol% Ni(dppp)Cl ₂		Na ₂ CO ₃	72
11	10 mol% Ni(dppp)Cl ₂		Na ₂ CO ₃	95

^aConditions: amide (1.0 equiv), HP(O)(OEt)₂ (1.5 equiv), catalyst (5 mol%), ligand (10 mol%), base (1.5 equiv), dioxane (0.25 M), 160 °C, 15 h.

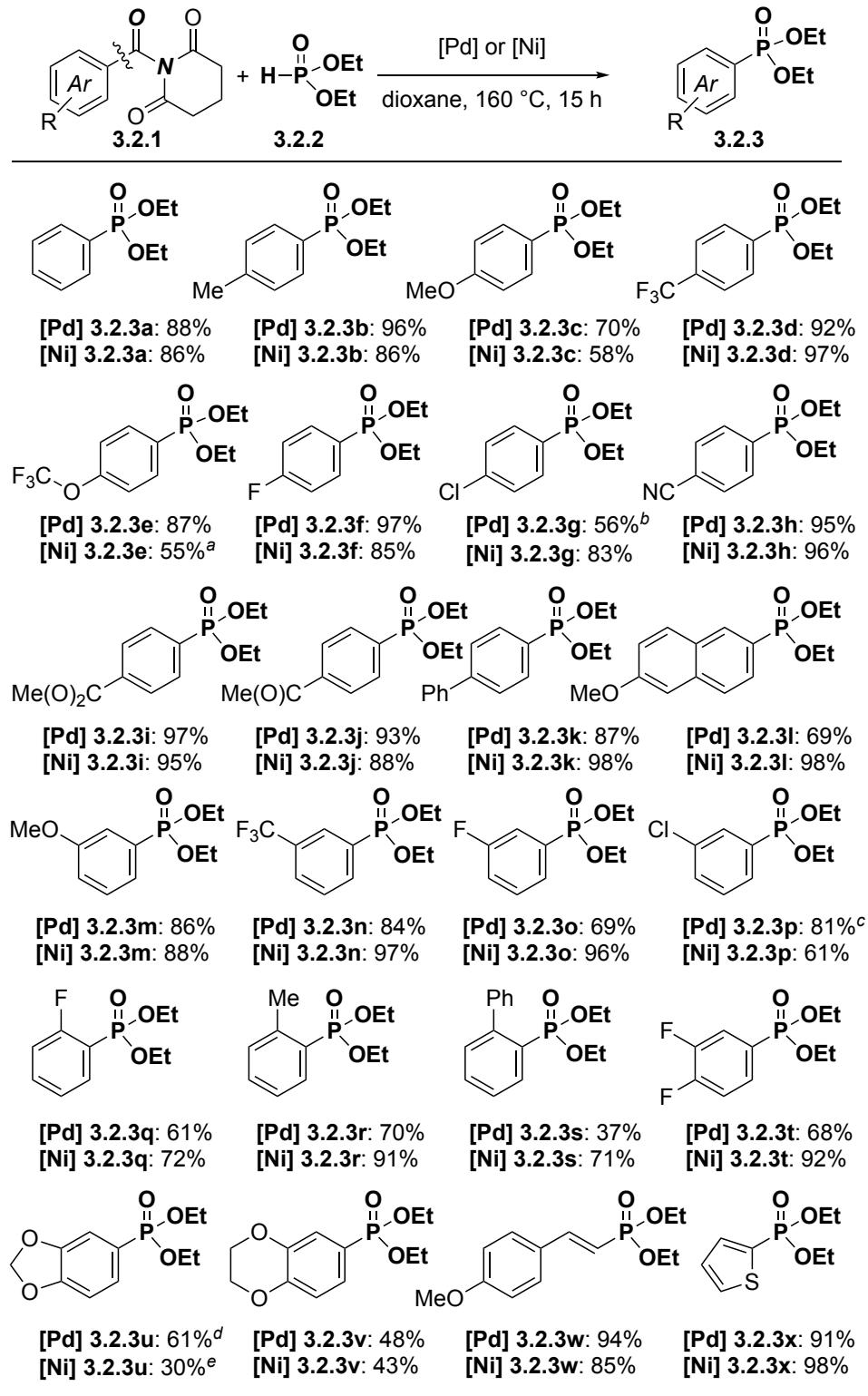
3.2.3 Substrate scope

With the optimized conditions in hand, we next investigated the scope of this new method for C–P bond construction. As shown in Scheme 3.2.1, the scope of the reaction was very broad and accommodated a wide range of functional groups. As shown, the reaction conditions were compatible with a wide range of electronically- and sterically-diverse substrates, featuring various functional groups and synthetic handles, including aryl halides, ethers, nitriles, esters, ketones, naphthalenes, biaryls, dioxolanes, dioxanes, vinyl amides, and thiophenes. In general, Ni-catalysis resulted in comparable yields in the vast majority of examples examined. However, the transformation was more efficient for conjugated and sterically-hindered substrates, consistent with higher nucleophilicity of Ni.³⁷ Moreover, while with respect to the phosphite, dibutylphosphite and diisopropylphosphite also readily participated in this coupling, diphenylphosphine could be employed to afford the corresponding phosphine (Scheme 3.2.2). Overall, the developed process employed air-stable, inexpensive Ni catalyst, which was economically advantageous over Pd, with the complementary scope to the Pd-catalyzed C–P bond formation. We noted that a careful control of the reaction stoichiometry was essential to control reactivity of the acylmetal intermediate, in particular in the case of acylpalladium, which decarbonylated more slowly than acylnickel.^{28,29} The observed selectivity of the amide coupling in the presence of Ar–Cl or Ar–CN bonds was consistent with the facility of metal insertion into the resonance destabilized amides.²⁶⁻³³

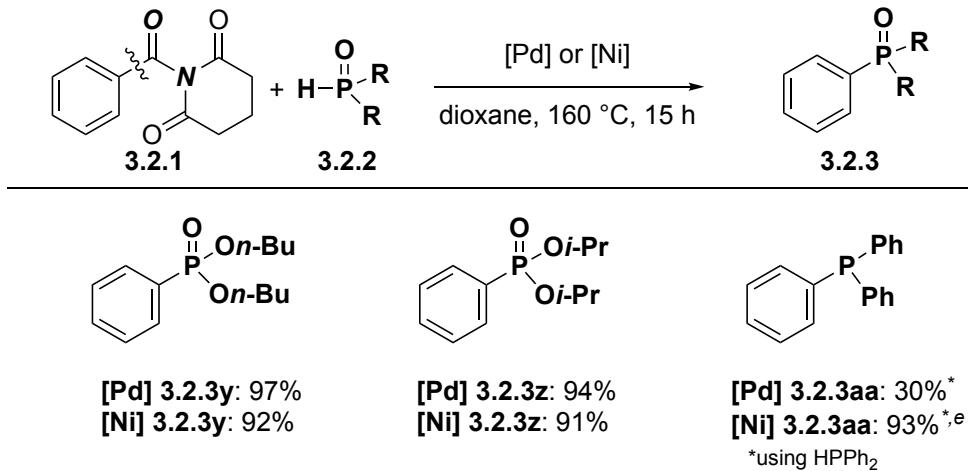
Notably, this transformation was compatible with functional groups that are prone to metal-catalyzed C–O cleavage, such as aryl esters and aryl sulfonates (Scheme 3.2.3),

highlighting the potential to achieve high selectivity using amide electrophiles under orthogonal cross-coupling conditions.

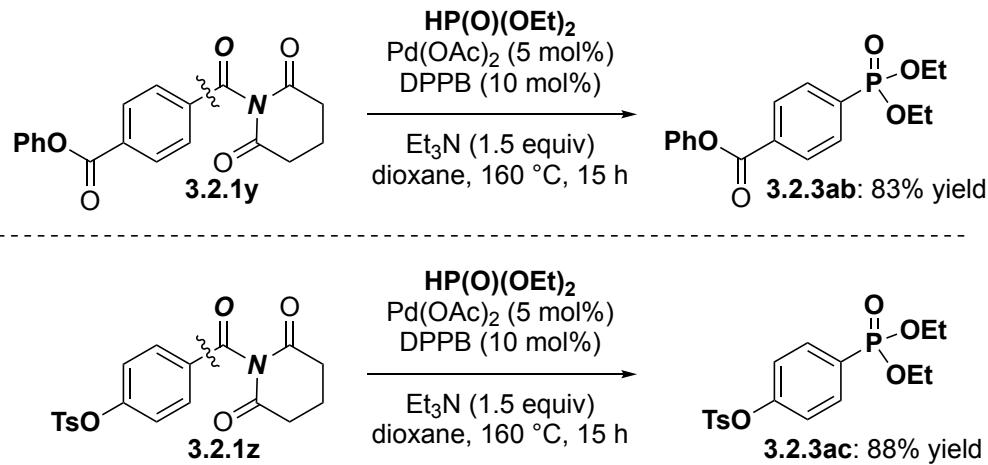
We were further pleased to identify that acyclic *N*-Ts amides served as suitable cross-coupling partners in this new C–P bond forming protocol (Scheme 3.2.4). Notably, these amide precursors could be prepared directly from secondary amides,²⁶ thus demonstrating the ability of this protocol to generate C–P bonds from common acyclic amides. The coupling of atom-economic *N*-Ms amide proceeded with excellent efficiency (Scheme 3.2.5). This result demonstrated the potential to engage different amide precursors in decarbonylative N–C coupling.



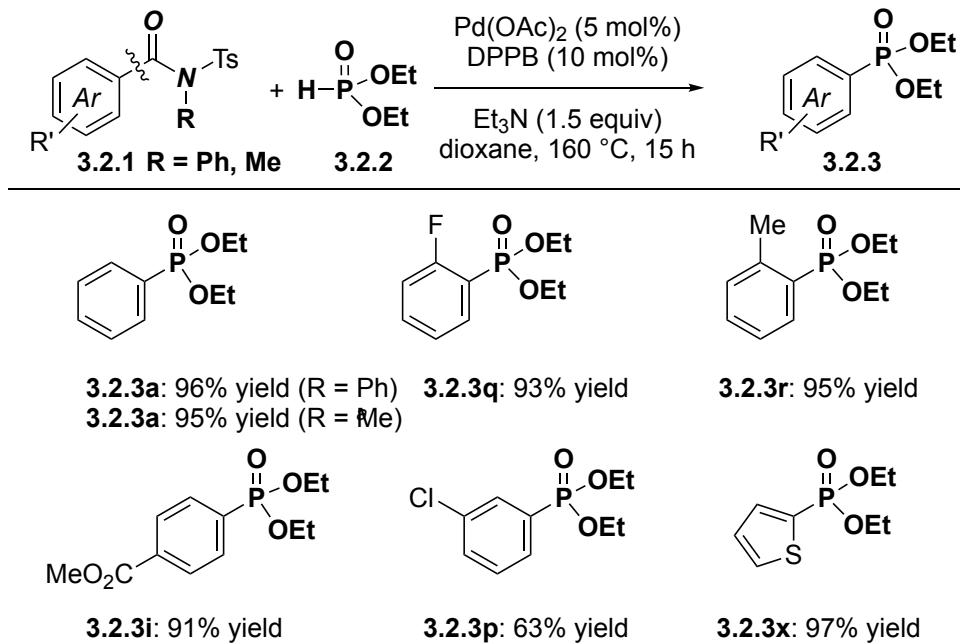
Scheme 3.2.1 Amide scope in decarbonylative phosphorylation of amides.



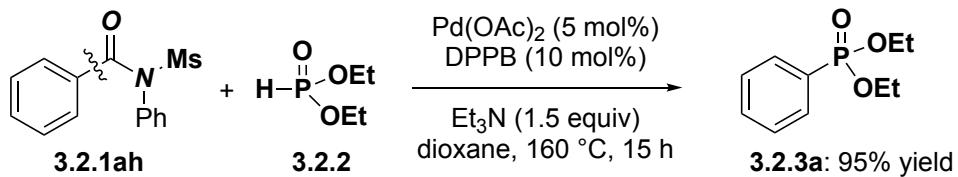
Scheme 3.2.2 Phosphite scope in decarbonylative phosphorylation of amides.



Scheme 3.2.3 Selective deamidative phosphorylation in the presence of O-electrophiles.



Scheme 3.2.4 Decarbonylative phosphorylation of *N*-Ts amides.

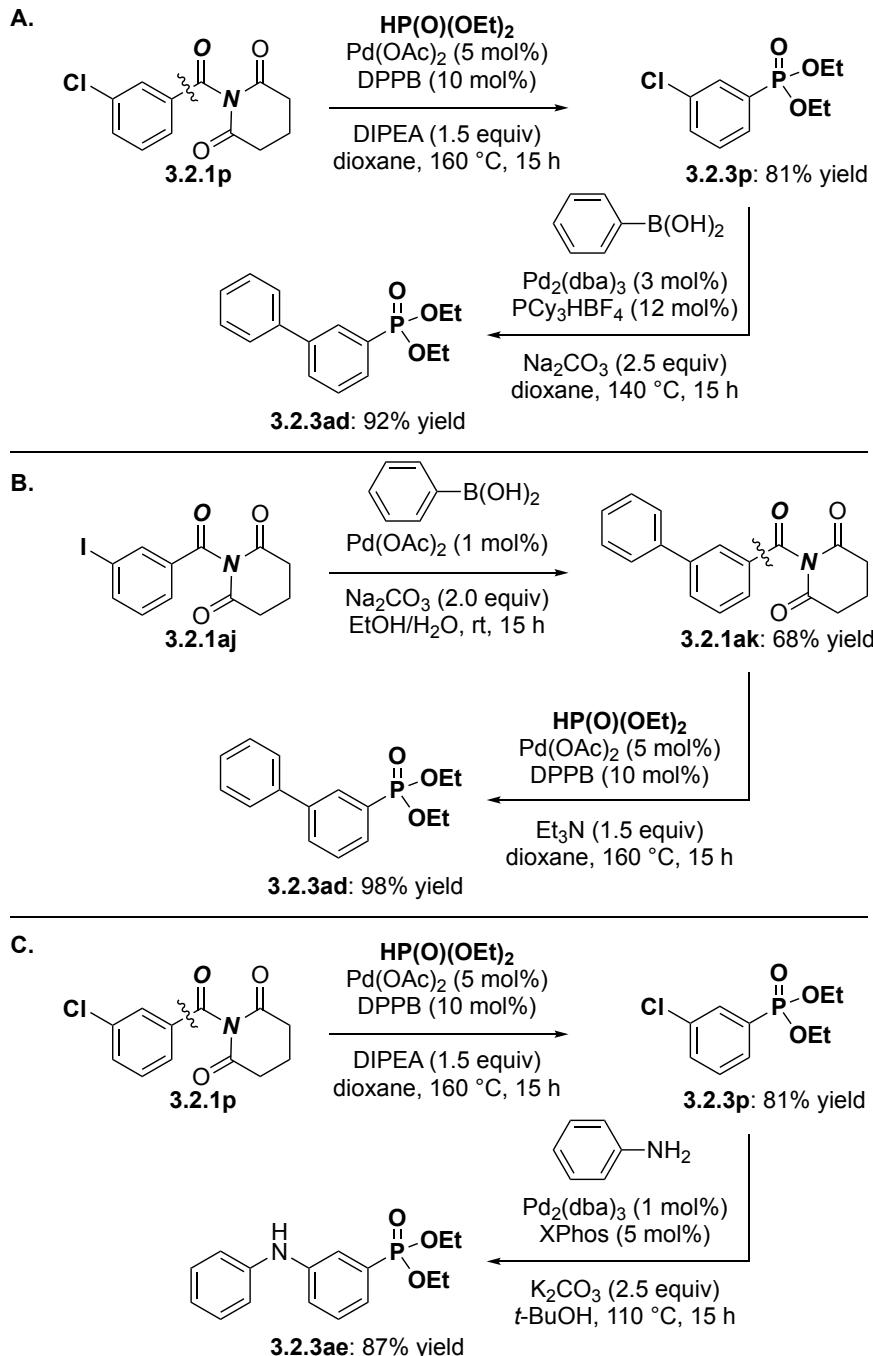


Scheme 3.2.5 Decarbonylative phosphorylation of *N*-Ms amide.

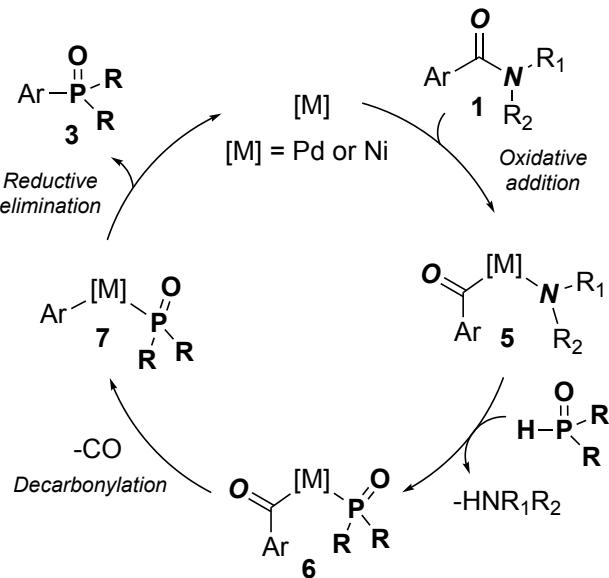
3.2.4 Synthetic applications

To gain insight into selectivity of this new C–P bond forming method, we have conducted a series of experiments. First, we showcased the utility of this new phosphorylation reaction to site-selectively construct C–P and C–C or C–N bonds in sequential orthogonal cross-couplings (Scheme 3.2.6). Second, we performed selectivity studies to investigate factors controlling the Pd- and Ni-catalyzed deamidative phosphorylation protocol (not

shown).³⁸ We concluded that the key step involved metal insertion into the amide N–C bond and transmetalation under both Pd and Ni catalytic conditions (Scheme 3.2.7).



Scheme 3.2.6 Selective cross-coupling/deamidative phosphorylation.



Scheme 3.2.7 Proposed mechanism of decarbonylative phosphorylation of amides.

3.2.5 Conclusion

In summary, in this project we have developed the first deamidative phosphorylation of amides by palladium and nickel catalysis. The reaction constituted the first example of a transition-metal-catalyzed generation of C–P bonds from amides. This new process provided an alternative to the classic Hirao cross-coupling reaction and used carboxylic acid derived electrophiles. This versatile method tolerated a wide range of functional groups and accommodated cyclic and acyclic *N*-activating groups. Mechanistic studies have provided support for the oxidative addition/transmetallation pathway, in which transmetallation proceeded prior to decarbonylation under both Pd and Ni catalytic conditions. Considering the ubiquity of organophosphorus compounds in modern organic synthesis, this Pd and Ni-catalyzed C–P bond forming method could be of general interest.

3.2.6 Experimental section

General procedure for amide synthesis. A previously published procedure was followed. An oven-dried vial (20 mL) equipped with a stir bar was charged with secondary amine (5.0 mmol, 1.0 equiv), dimethylaminopyridine (typically, 0.005 equiv), triethylamine (typically, 1.0 equiv), and dichloromethane (typically, 10 mL), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acyl chloride (typically, 1.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred 12 h at room temperature. After the indicated time, the reaction mixture was diluted with ethyl acetate (50 mL), extracted with 1 M HCl solution (20 mL), brine (20 mL), water (20 mL). Then the organic layer was dried, filtrated and concentrated. Unless stated otherwise, the crude product was purified by recrystallization (toluene) to give analytically pure product.

Method A: General Procedure for Ni Catalyzed Phosphorylation Reaction of Amides. An oven-dried vial equipped with a stir bar was charged with amide (neat, 1.0 equiv), phosphite (neat, 1.5 equiv), Ni(dppp)Cl₂ (typically, 10 mol%), and Na₂CO₃ (typically, 1.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 160 °C, and stirred for the indicated time at 160 °C.

Method B: General Procedure for Pd Catalyzed Phosphorylation Reaction of Amides. An oven-dried vial equipped with a stir bar was charged with phosphite (neat,

1.0 equiv), amide (neat, 2.0 equiv), Pd(OAc)₂ (typically, 5 mol%), ligand (typically, 10 mol%), and triethylamine (typically, 1.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.125 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 160 °C, and stirred for the indicated time at 160 °C.

3.2.1a. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.90-7.88 (d, $J = 7.8$ Hz, 2 H), 7.68-7.65 (t, $J = 7.5$ Hz, 1 H), 7.53-7.50 (t, $J = 7.7$ Hz, 2 H), 2.81-2.78 (t, $J = 6.6$ Hz, 4 H), 2.20-2.14 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.88, 170.73, 134.96, 131.82, 130.17, 129.14, 32.42, 17.52.

3.2.1b. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.78-7.77 (d, $J = 8.0$ Hz, 2 H), 7.31-7.29 (d, $J = 8.0$ Hz, 2 H), 2.79-2.77 (t, $J = 6.6$ Hz, 4 H), 2.44 (s, 3 H), 2.18-2.13 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.92, 170.44, 146.34, 130.33, 129.89, 129.24, 32.41, 21.89, 17.51.

3.2.1c. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.86-7.84 (d, $J = 7.5$ Hz, 2 H), 6.98-6.96 (d, $J = 7.5$ Hz, 2 H), 3.90 (s, 3 H), 2.80-2.77 (t, $J = 6.6$ Hz, 4 H), 2.18-2.13 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.90, 169.50, 165.11, 132.76, 124.52, 114.50, 55.69, 32.44, 17.52.

3.2.1d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.00-7.99 (d, $J = 8.1$ Hz, 2 H), 7.79-7.78 (d, $J = 8.0$ Hz, 2 H), 2.84-2.81 (t, $J = 6.5$ Hz, 4 H), 2.22-2.17 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.99, 170.19, 135.95 (q, $J^F = 36.7$ Hz), 134.82, 130.37, 126.22 (q, $J^F = 3.5$ Hz), 123.28 (q, $J^F = 272.4$ Hz), 32.36, 17.43. ^{19}F (471 MHz, CDCl_3) δ -63.40.

3.2.1e. Orange solid. $M_p = 96\text{-}98^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3) δ 7.95-7.93 (d, $J = 8.5$ Hz, 2 H), 7.34-7.32 (d, $J = 8.2$ Hz, 2 H), 2.82-2.80 (t, $J = 6.5$ Hz, 4 H), 2.20-2.15 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.91, 169.58, 153.93, 132.28, 130.03, 120.72, 120.29, 32.39, 17.47. ^{19}F NMR (471 MHz, CDCl_3) δ -57.57. HRMS calcd for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{NO}_4\text{Na}$ ($\text{M}^+ + \text{Na}$) 324.0454, found 324.0445.

3.2.1f. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.92-7.89 (t, $J = 8.5$ Hz, 2 H), 7.19-7.15 (t, $J = 8.4$ Hz, 2 H), 2.78-2.77 (t, $J = 6.5$ Hz, 4 H), 2.15-2.13 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.98 (d, $J^F = 6.9$ Hz), 169.64 (d, $J^F = 7.9$ Hz), 166.84 (d, $J^F = 256.7$ Hz), 133.02 (d, $J^F = 9.9$ Hz), 128.31 (d, $J^F = 2.9$ Hz), 116.53 (d, $J^F = 22.3$ Hz), 32.35, 17.44. ^{19}F (471 MHz, CDCl_3) δ -101.29.

3.2.1g. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.82-7.80 (d, $J = 8.6$ Hz, 2 H), 7.48-7.47 (d, $J = 8.6$ Hz, 2 H), 2.79-2.77 (t, $J = 6.5$ Hz, 4 H), 2.17-2.12 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.95, 170.00, 141.68, 131.46, 130.31, 129.56, 32.36, 17.45.

3.2.1h. Orange solid. ^1H NMR (500 MHz, CDCl_3) δ 7.98-7.96 (d, $J = 8.5$ Hz, 2 H), 7.83-7.81 (d, $J = 8.5$ Hz, 2 H), 2.84-2.81 (t, $J = 6.5$ Hz, 4 H), 2.22-2.17 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.91, 169.89, 135.25, 132.88, 130.32, 117.98, 117.49, 32.39, 17.43.

3.2.1i. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.17-8.15 (d, $J = 8.5$ Hz, 2 H), 7.94-7.93 (d, $J = 8.2$ Hz, 2 H), 3.98 (s, 3 H), 2.83-2.80 (t, $J = 6.5$ Hz, 4 H), 2.21-2.16 (m, 2 H). ^{13}C NMR (125 MHz CDCl_3) δ 171.91, 170.40, 165.77, 135.43, 135.20, 130.22, 129.96, 52.64, 32.40, 17.47.

3.2.1j. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.07-8.06 (d, $J = 8.2$ Hz, 2 H), 7.97-7.96 (d, $J = 8.2$ Hz, 2 H), 2.83-2.81 (t, $J = 6.5$ Hz, 4 H), 2.67 (s, 3 H), 2.22-2.17 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.03, 171.89, 170.35, 141.42, 135.15, 130.28, 128.84, 32.41, 26.95, 17.47.

3.2.1k. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.96-7.95 (d, $J = 8.5$ Hz, 2 H), 7.73-7.72 (d, $J = 8.2$ Hz, 2 H), 7.64-7.62 (d, $J = 8.2$ Hz, 2 H), 7.52-7.49 (t, $J = 8.2$ Hz, 2 H),

7.46-7.43 (t, $J = 8.2$ Hz, 1 H), 2.84-2.82 (t, $J = 6.5$ Hz, 4 H), 2.22-2.17 (m, 2 H). ^{13}C NMR (125 MHz CDCl₃) δ 172.04, 170.54, 147.78, 139.45, 130.78, 130.44, 129.05, 128.65, 127.84, 127.38, 32.42, 17.52.

3.2.1l. White solid. ^1H NMR (500 MHz, CDCl₃) δ 8.28 (s, 1H), 7.91-7.89 (d, $J = 8.5$ Hz, 1H), 7.84-7.82 (d, $J = 8.8$ Hz, 1H), 7.80-7.78 (d, $J = 8.7$ Hz, 1H), 7.22-7.20 (d, $J = 8.7$ Hz, 1H), 7.16 (s, 1H), 3.96 (s, 3H), 2.82 (s, 4H), 2.18 (s, 2H). ^{13}C NMR (125 MHz, CDCl₃) δ 172.09, 170.71, 160.60, 138.39, 132.55, 131.46, 127.83, 127.02, 125.62, 120.18, 105.89, 55.51, 32.48, 17.55.

3.2.1m. White Solid. ^1H NMR (500 MHz, CDCl₃) δ 7.46 (s, 1 H), 7.37 (s, 2 H), 7.18 (s, 1 H), 3.84 (s, 3 H), 2.78-2.74 (m, 4 H), 2.15-2.11 (m, 2 H). ^{13}C NMR (125 MHz, CDCl₃) δ 172.07, 170.88, 160.12, 133.04, 130.17, 122.63, 121.50, 114.41, 55.56, 32.32, 17.45.

3.2.1n. White Solid. ^1H NMR (500 MHz, CDCl₃) δ 8.13 (s, 1 H), 8.04-8.02 (d, $J = 7.9$ Hz, 1 H), 7.92-7.91 (d, $J = 7.8$ Hz, 1 H), 7.68-7.65 (t, $J = 7.8$ Hz, 1 H), 2.83-2.80 (t, $J = 6.5$ Hz, 4 H), 2.20-2.15 (m, 2 H). ^{13}C NMR (125 MHz, CDCl₃) δ 171.99, 170.00, 133.11, 132.67, 131.90 (q, $J^F = 32.5$ Hz), 131.32 (q, $J^F = 6.3$ Hz), 129.92, 126.79 (q, $J^F = 7.5$ Hz), 123.32 (d, $J^F = 270.0$ Hz), 32.36, 17.44. ^{19}F NMR (471 MHz, CDCl₃) δ -62.95.

3.2.1o. White solid. ^1H NMR (500 MHz, CDCl₃) δ 7.67-7.66 (d, $J = 8.5$ Hz, 1 H), 7.57-7.56 (d, $J = 8.2$ Hz, 1 H), 7.52-7.48 (q, $J = 8.2$ Hz, 1 H), 7.39-7.35 (t, $J = 8.2$ Hz, 1 H), 2.82-2.79 (t, $J = 6.5$ Hz, 4 H), 2.20-2.15 (m, 2 H). ^{13}C NMR (125 MHz CDCl₃) δ 171.93, 169.94, 169.91, 162.87 (d, $J^F = 247.4$ Hz), 133.92 (d, $J^F = 7.1$ Hz), 130.90 (d, $J^F = 7.8$ Hz), 125.86 (d, $J^F = 3.0$ Hz), 122.11 (d, $J^F = 21.3$ Hz), 116.81 (d, $J^F = 23.0$ Hz), 32.35, 17.44. ^{19}F NMR (471 MHz, CDCl₃) δ -111.06.

3.2.1p. White solid. Mp = 133-135 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.83 (s, 1 H), 7.77-7.75 (d, J = 8.2 Hz, 1 H), 7.64-7.62 (d, J = 8.2 Hz, 1 H), 7.48-7.44 (t, J = 8.2 Hz, 1 H), 2.82-2.79 (t, J = 6.5 Hz, 4 H), 2.18-2.16 (m, 2 H). ^{13}C NMR (125 MHz CDCl_3) δ 171.91, 169.87, 135.41, 134.90, 133.53, 130.45, 129.98, 128.18, 32.37, 17.45. HRMS calcd for $\text{C}_{12}\text{H}_{10}\text{ClNO}_3\text{Na}$ ($\text{M}^+ + \text{Na}$) 274.0241, found 274.0230.

3.2.1q. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.12-8.09 (m, 1 H), 7.65-7.62 (q, J = 1.8 Hz, 1 H), 7.34-7.31 (t, J = 6.5 Hz, 1 H), 7.15-7.11 (m, 1 H), 2.78-2.75 (t, J = 6.5 Hz, 4 H), 2.16-2.10 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.70, 166.87 (d, J^F = 1.5 Hz), 161.86 (d, J^F = 255.8 Hz), 136.80 (d, J^F = 10.0 Hz), 132.97, 125.11 (d, J^F = 3.5 Hz), 120.37 (d, J^F = 8.0 Hz), 117.10 (d, J^F = 23.6 Hz), 32.41, 17.24. ^{19}F NMR (471 MHz, CDCl_3) δ -113.53.

3.2.1r. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.53-7.51 (d, J = 7.6 Hz, 1 H), 7.50-7.47 (t, J = 7.6 Hz, 1 H), 7.36-7.34 (d, J = 7.6 Hz, 1 H), 7.29-7.26 (t, J = 7.6 Hz, 1 H), 2.78-2.76 (t, J = 6.6 Hz, 4 H), 2.70 (s, 3 H), 2.17-2.11 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.99, 170.68, 142.54, 133.76, 132.46, 131.20, 130.71, 126.21, 32.49, 21.89, 17.45.

3.2.1s. Orange solid. ^1H NMR (500 MHz, CDCl_3) δ 8.04-8.02 (d, J = 7.7 Hz, 1 H), 7.62-7.59 (t, J = 6.8 Hz, 1 H), 7.54-7.51 (t, J = 8.2 Hz, 1 H), 7.44-7.43 (m, 3 H), 7.36-7.35 (m, 2 H), 7.29-7.27 (m, 1 H), 2.24-2.22 (t, J = 6.3 Hz, 4 H), 1.52-1.47 (m, 2 H). ^{13}C NMR (125 MHz CDCl_3) δ 171.50, 170.69, 142.47, 140.59, 132.97, 132.23, 131.77, 131.72, 128.97, 128.33, 128.03, 127.78, 32.49, 16.15.

3.2.1t. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 7.74-7.67 (m, 2 H), 7.35-7.28 (m, 1 H), 2.82-2.79 (m, 4 H), 2.19-2.17 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.87, 168.96, 152.78 ($q, J^F = 243.8$ Hz), 152.67 ($q, J^F = 237.5$ Hz), 129.08 (d, $J^F = 18.8$ Hz), 127.36 (d, $J^F = 18.8$ Hz), 119.44 (d, $J^F = 18.8$ Hz), 118.26 (d, $J^F = 17.5$ Hz), 32.37, 17.43. ^{19}F NMR (471 MHz, CDCl_3) δ -125.77 (d, $J^l = 18.8$ Hz), -134.80 (d, $J^l = 18.8$ Hz).

3.2.1u. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.47-7.45 (d, $J = 8.2$ Hz, 1 H), 7.36 (s, 1 H), 6.90-6.88 (d, $J = 8.2$ Hz, 1 H), 6.11 (s, 2 H), 2.81-2.78 (t, $J = 6.4$ Hz, 4 H), 2.19-2.14 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.85, 169.24, 153.62, 148.63, 127.30, 126.26, 109.61, 108.56, 102.40, 32.44, 17.50.

3.2.1v. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.44-7.42 (d, $J = 8.5$ Hz, 1 H), 7.39 (s, 1 H), 6.95-6.94 (d, $J = 8.5$ Hz, 1 H), 4.34 (s, 2 H), 4.29 (s, 2 H), 2.79-2.77 (t, $J = 6.5$ Hz, 4 H), 2.18-2.13 (m, 2 H). ^{13}C NMR (125 MHz CDCl_3) δ 171.88, 169.42, 149.85, 143.68, 125.16, 124.58, 119.70, 117.99, 64.82, 64.00, 32.39, 17.49.

3.2.1w. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.67-7.64 (d, $J = 15.8$ Hz, 1H), 7.54-7.52 (d, $J = 8.4$ Hz, 2H), 6.94-6.92 (d, $J = 8.3$ Hz, 2H), 6.59-6.56 (d, $J = 15.7$ Hz, 1H), 3.88 (s, 3H), 2.77-2.75 (t, $J = 6.6$ Hz, 4H), 2.12-2.07 (m, 2H). ^{13}C NMR (500 MHz, CDCl_3) δ 171.75, 169.27, 162.53, 148.56, 130.94, 126.36, 118.77, 114.52, 55.48, 32.54, 17.40.

3.2.1x. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.78 (dd, $J = 5.0, 3.9$ Hz, 1 H), 7.71-7.70 (dd, $J = 3.9, 3.9$ Hz, 1 H), 7.17-7.15 (dd, $J = 4.9, 3.9$ Hz, 1 H), 2.78-2.76 (t, $J = 6.6$ Hz, 4 H), 2.15-2.10 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.67, 163.65, 137.56, 136.74, 136.00, 128.82, 32.41, 17.42.

3.2.1y. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.32-8.30 (d, $J = 8.5$ Hz, 2 H), 7.99-7.98 (d, $J = 8.2$ Hz, 2 H), 7.46-7.43 (t, $J = 8.2$ Hz, 2 H), 7.31-7.28 (t, $J = 8.2$ Hz, 1 H), 7.23-7.21 (d, $J = 8.5$ Hz, 2 H), 2.82-2.79 (t, $J = 6.5$ Hz, 4 H), 2.18-2.15 (m, 2 H). ^{13}C NMR (125 MHz CDCl_3) δ 171.98, 170.46, 163.90, 150.65, 135.74, 134.84, 130.77, 130.08, 129.63, 126.27, 121.53, 32.38, 17.45.

3.2.1z. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.81-7.79 (d, $J = 8.5$ Hz, 2 H), 7.72-7.70 (d, $J = 8.2$ Hz, 2 H), 7.34-7.32 (d, $J = 8.2$ Hz, 2 H), 7.13-7.11 (d, $J = 8.2$ Hz, 2 H), 2.78-2.76 (t, $J = 6.5$ Hz, 4 H), 2.46 (s, 3 H), 2.16-2.13 (m, 2 H). ^{13}C NMR (125 MHz CDCl_3) δ 171.97, 169.79, 154.29, 146.02, 131.99, 131.88, 130.41, 130.07, 128.46, 122.99, 32.33, 21.77, 17.42.

3.2.1aa. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.85 (d, $J = 8.3$ Hz, 2 H), 7.47-7.46 (d, $J = 8.3$ Hz, 2 H), 7.35-7.33 (d, $J = 8.1$ Hz, 2 H), 7.31-7.29 (m, 4 H), 7.20-7.17 (m, 4 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.91, 144.83, 137.45, 135.26, 133.68, 131.75, 130.41, 129.50, 129.26, 129.12, 129.05, 128.61, 127.99, 21.74.

3.2.1ab. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.86-7.85 (d, $J = 8.5$ Hz, 2 H), 7.57-7.56 (d, $J = 8.2$ Hz, 2 H), 7.53-7.50 (t, $J = 8.2$ Hz, 1 H), 7.44-7.41 (t, $J = 8.2$ Hz, 2 H), 7.36-7.34 (d, $J = 8.2$ Hz, 2 H), 3.30 (s, 3 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz CDCl_3) δ 171.50, 144.93, 135.22, 134.53, 131.97, 129.64, 128.50, 128.43, 128.31, 35.61, 21.68.

3.2.1ac. White solid. $M_p = 157\text{-}158$ °C. ^1H NMR (500 MHz, CDCl_3) δ 7.93-7.92 (d, $J = 8.5$ Hz, 2 H), 7.37-7.36 (d, $J = 8.2$ Hz, 2 H), 7.27-7.26 (d, $J = 8.2$ Hz, 4 H), 7.21-7.20 (d, $J = 8.2$ Hz, 3 H), 6.99-6.96 (t, $J = 8.2$ Hz, 1 H), 6.83-6.79 (t, $J = 8.2$ Hz, 1 H), 2.48 (s, 3 H). ^{13}C NMR (125 MHz CDCl_3) δ 166.11, 158.17 (d, $J^F = 250.5$ Hz), 145.21, 135.55 (d,

$J^F = 72.2$ Hz), 132.62 (d, $J^F = 8.2$ Hz), 130.43, 129.52, 129.48, 129.40, 129.38, 129.35, 128.93, 123.94 (d, $J^F = 3.4$ Hz), 123.67 (d, $J^F = 15.4$ Hz), 115.79 (d, $J^F = 21.1$ Hz), 21.76. ^{19}F NMR (471 MHz, CDCl_3) δ -111.82. HRMS calcd for $\text{C}_{20}\text{H}_{16}\text{FNO}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 392.0727, found 392.0723.

3.2.1ad. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.95-7.93 (d, $J = 8.5$ Hz, 2 H), 7.38-7.37 (d, $J = 8.2$ Hz, 2 H), 7.29-7.26 (m, 3 H), 7.15-7.15 (d, $J = 8.2$ Hz, 2 H), 7.12-7.08 (m, 2 H), 7.02-7.00 (d, $J = 8.2$ Hz, 1 H), 6.96-6.93 (t, $J = 8.2$ Hz, 1 H), 2.50 (s, 3 H), 2.25 (s, 3 H). ^{13}C NMR (125 MHz CDCl_3) δ 170.19, 144.96, 136.56, 135.71, 135.67, 134.45, 130.43, 130.08, 129.92, 129.37, 129.33, 129.26, 129.03, 127.64, 124.98, 21.76, 19.40.

3.2.1ae. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.88-7.84 (m, 4 H), 7.49-7.48 (d, $J = 8.5$ Hz, 2 H), 7.36-7.35 (d, $J = 8.2$ Hz, 2 H), 7.32-7.29 (m, 3 H), 7.18-7.15 (m, 2 H), 3.87 (s, 3 H), 2.49 (s, 3 H). ^{13}C NMR (125 MHz CDCl_3) δ 169.04, 165.96, 145.14, 137.82, 136.93, 134.99, 132.52, 130.43, 129.53, 129.37, 129.29, 129.17, 127.27, 121.70, 52.39, 21.75.

3.2.1af. White solid. Mp = 143-144 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.86-7.84 (d, $J = 8.5$ Hz, 2 H), 7.46 (s, 1 H), 7.36-7.33 (m, 5 H), 7.29-7.26 (m, 2 H), 7.17-7.16 (d, $J = 8.5$ Hz, 2 H), 7.12-7.09 (t, $J = 8.5$ Hz, 1 H), 2.48 (s, 3 H). ^{13}C NMR (125 MHz CDCl_3) δ 168.45, 145.09, 137.03, 135.45, 134.97, 134.24, 131.73, 130.36, 129.53, 129.51, 129.37, 129.34, 129.31, 129.24, 127.35, 21.75. HRMS calcd for $\text{C}_{20}\text{H}_{16}\text{ClNO}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 408.0432, found 408.0427.

3.2.1ag. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.94-7.92 (d, $J = 8.4$ Hz, 2 H), 7.55-7.52 (m, 1 H), 7.50-7.47 (m, 2 H), 7.42-7.41 (m, 1 H), 7.38-7.35 (m, 4 H), 6.97-6.96 (m, 1 H), 6.83-6.81 (m, 1 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz CDCl_3) δ 161.97, 144.94, 136.72, 136.44, 135.75, 134.96, 133.72, 131.06, 130.26, 129.61, 129.52, 129.35, 127.23, 21.74.

3.2.1ah. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.57-7.56 (d, $J = 7.2$ Hz, 2 H), 7.38-7.28 (m, 6 H), 7.26-7.23 (t, $J = 7.9$ Hz, 2 H), 3.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 171.10, 136.96, 133.14, 132.24, 129.82, 129.68, 129.47, 129.26, 128.21, 40.39.

3.2.1ai. White solid. $M_p = 137\text{-}139$ °C. ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.51 (d, $J = 7.6$ Hz, 2 H), 7.37-7.36 (d, $J = 4.5$ Hz, 3 H), 7.29 (s, 2 H), 7.24-7.23 (d, $J = 7.6$ Hz, 2 H), 3.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.02, 138.69, 136.76, 131.47, 131.12, 129.68, 129.66, 129.48, 128.62, 40.37. HRMS calcd for $\text{C}_{14}\text{H}_{12}\text{ClNO}_3\text{SNa}$ ($\text{M}^+ + \text{Na}$) 332.0119, found 332.0114.

3.2.1aj. White solid. $M_p = 159\text{-}161$ °C. ^1H NMR (500 MHz, CDCl_3) δ 8.20 (s, 1 H), 7.99-7.97 (d, $J = 8.2$ Hz, 1 H), 7.82-7.81 (d, $J = 8.2$ Hz, 1 H), 7.27-7.24 (t, $J = 8.2$ Hz, 1 H), 2.81-2.80 (m, 4 H), 2.17-2.16 (m, 2 H). ^{13}C NMR (125 MHz CDCl_3) δ 171.93, 171.87, 143.67, 138.75, 133.66, 130.69, 129.18, 94.54, 32.37, 17.46. HRMS calcd for $\text{C}_{12}\text{H}_{10}\text{INO}_3\text{Na}$ ($\text{M}^+ + \text{Na}$) 365.9598, found 365.9587.

3.2.1ak. White solid. $M_p = 167\text{-}169$ °C. ^1H NMR (500 MHz, CDCl_3) δ 8.13 (s, 1 H), 7.88-7.86 (d, $J = 8.2$ Hz, 1 H), 7.82-7.80 (d, $J = 8.2$ Hz, 1 H), 7.61-7.56 (m, 3 H), 7.51-7.48 (t, $J = 8.2$ Hz, 2 H), 7.44-7.41 (t, $J = 8.2$ Hz, 1 H), 2.82-2.79 (t, $J = 6.5$ Hz, 4 H), 2.19-2.14 (m, 2 H). ^{13}C NMR (125 MHz CDCl_3) δ 172.01, 170.87, 142.49, 139.69,

133.74, 132.33, 129.60, 129.02, 128.86, 128.82, 128.07, 127.26, 32.41, 17.53. HRMS calcd for C₁₈H₁₅NO₃Na (M⁺ + Na) 316.0944, found 316.0935.

3.2.3a. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.86-7.82 (m, 2 H), 7.59-7.56 (t, *J* = 7.3 Hz, 1 H), 7.51-7.47 (m, 2 H), 4.24-4.07 (m, 4 H), 1.36-1.34 (t, *J* = 7.0 Hz, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 132.39, 132.37, 131.79 (d, *J*^P = 9.8 Hz), 128.48 (d, *J*^P = 14.9 Hz), 62.11 (d, *J*^P = 5.3 Hz), 16.35 (d, *J*^P = 6.6 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 18.81.

3.2.3b. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.74-7.69 (m, 2 H), 7.28 (s, 2 H), 4.18-4.03 (m, 4 H), 2.42 (s, 3 H), 1.34-1.31 (t, *J* = 6.9 Hz, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 142.96 (d, *J*^P = 2.9 Hz), 131.85 (d, *J*^P = 10.3 Hz), 129.23 (d, *J*^P = 15.3 Hz), 125.00 (d, *J*^P = 189.0 Hz), 62.00 (d, *J*^P = 5.3 Hz), 21.66, 16.33 (d, *J*^P = 6.5 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 19.57.

3.2.3c. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.79-7.75 (m, 2 H), 7.00-6.98 (d, *J* = 8.6 Hz, 2 H), 4.18-4.03 (m, 4 H), 3.88 (s, 3 H), 1.35-1.32 (t, *J* = 6.8 Hz, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 162.85 (d, *J*^P = 3.2 Hz), 133.80 (d, *J*^P = 11.3 Hz), 119.59 (d, *J*^P = 193.6 Hz), 114.02 (d, *J*^P = 16.0 Hz), 61.91 (d, *J*^P = 5.3 Hz), 55.34, 16.35 (d, *J*^P = 6.5 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 19.72.

3.2.3d. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.99-7.95 (m, 2 H), 7.76-7.74 (m, 2 H), 4.24-4.09 (m, 4 H), 1.38-1.35 (t, *J* = 7.1 Hz, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 132.25 (d, *J*^P = 10.0 Hz), 125.40 (q, *J*^P = 3.6 Hz), 125.28 (q, *J*^P = 3.8 Hz), 62.52 (d, *J*^P = 5.5 Hz), 16.35 (d, *J*^P = 6.4 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 16.27. ¹⁹F NMR (471 MHz, CDCl₃) δ -63.28.

3.2.3e. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.91-7.87 (m, 2 H), 7.33-7.32 (d, J = 7.7 Hz, 2 H), 4.23-4.08 (m, 4 H), 1.37-1.34 (t, J = 7.0 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 152.23, 133.85 (d, J^P = 10.9 Hz), 128.55 (q, J^P = 147.2 Hz), 120.49 (d, J^P = 15.6 Hz), 120.31 (d, J^P = 257.1 Hz), 62.36 (d, J^P = 5.5 Hz), 16.35 (d, J^P = 6.4 Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.04. ^{19}F NMR (471 MHz, CDCl_3) δ -57.62.

3.2.3f. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.82 (m, 2 H), 7.19-7.16 (t, J = 8.4 Hz, 2 H), 4.21-4.06 (m, 4 H), 1.36-1.33 (t, J = 6.9 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 134.43 (d, J^P = 9.0 Hz), 134.34 (d, J^P = 9.0 Hz), 115.93 (d, J^P = 16.2 Hz), 115.76 (d, J^P = 16.2 Hz), 62.22 (d, J^P = 5.4 Hz), 16.34 (d, J^P = 6.5 Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.81. ^{19}F NMR (471 MHz, CDCl_3) δ -106.04.

3.2.3g. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.75 (m, 2 H), 7.48-7.46 (m, 2 H), 4.19-4.06 (m, 4 H), 1.36-1.33 (t, J = 6.8 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 138.97 (d, J^P = 4.0 Hz), 133.22 (d, J^P = 10.6 Hz), 128.86 (d, J^P = 15.6 Hz), 127.80, 62.29 (d, J^P = 5.4 Hz), 16.34 (d, J^P = 6.4 Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.62.

3.2.3h. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.97-7.93 (m, 2 H), 7.79-7.77 (m, 2 H), 4.25-4.10 (m, 4 H), 1.38-1.35 (t, J = 6.9 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 134.00 (d, J^P = 186.7 Hz), 132.29 (d, J^P = 9.8 Hz), 132.02 (d, J^P = 14.9 Hz), 117.88, 116.01, 62.70 (d, J^P = 5.6 Hz), 16.36 (d, J^P = 6.3 Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 15.34.

3.2.3i. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.15-8.14 (m, 2 H), 7.94-7.90 (m, 2 H), 4.24-4.09 (m, 4 H), 3.97 (s, 3 H), 1.37-1.34 (t, J = 7.0 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.27, 133.81 (d, J^P = 64.0 Hz), 133.05 (d, J^P = 118.1 Hz), 131.81 (d, J^P =

10.0 Hz), 129.44 (d, $J^P = 14.9$ Hz), 62.43 (d, $J^P = 5.5$ Hz), 52.49, 16.35 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.01.

3.2.3j. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.06-8.04 (m, 2 H), 7.97-7.93 (m, 2 H), 4.24-4.09 (m, 4 H), 2.67 (s, 3 H), 1.37-1.35 (t, $J = 6.9$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.54, 139.85 (d, $J^P = 3.1$ Hz), 133.43 (d, $J^P = 185.5$ Hz), 132.10 (d, $J^P = 10.0$ Hz), 128.07 (d, $J^P = 15.0$ Hz), 62.45 (d, $J^P = 5.5$ Hz), 26.84, 16.36 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.86.

3.2.3k. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.93-7.89 (m, 2 H), 7.72-7.70 (m, 2 H), 7.64-7.63 (d, $J = 7.4$ Hz, 2 H), 7.51-7.48 (t, $J = 7.3$ Hz, 2 H), 7.44-7.41 (t, $J = 6.8$ Hz, 1 H), 4.26-4.10 (m, 4 H), 1.39-1.36 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.20 (d, $J^P = 3.1$ Hz), 140.01, 132.32 (d, $J^P = 10.1$ Hz), 128.96, 128.17, 127.30, 127.19 (d, $J^P = 15.3$ Hz), 126.19, 62.15 (d, $J^P = 5.5$ Hz), 16.39 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.97.

3.2.3l. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.38-8.35 (d, $J = 15.3$ Hz, 1 H), 7.86-7.81 (m, 2 H), 7.77-7.73 (t, $J = 10.6$ Hz, 1 H), 7.25-7.23 (d, $J = 8.9$ Hz, 1 H), 7.18 (s, 1 H), 4.24-4.08 (m, 4 H), 3.97 (s, 3 H), 1.37-1.34 (t, $J = 6.9$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.49, 136.65, 133.82, 133.74, 130.51, 127.87 (d, $J^P = 17.0$ Hz), 127.23 (d, $J^P = 6.0$ Hz), 127.13 (d, $J^P = 10.5$ Hz), 119.82, 105.69, 62.08 (d, $J^P = 5.1$ Hz), 55.43, 16.39 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 19.72.

3.2.3m. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.42-7.35 (m, 3 H), 7.11-7.10 (m, 1 H), 4.21-4.06 (m, 4 H), 3.87 (s, 3 H), 1.37-1.34 (t, $J = 6.9$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.46 (d, $J^P = 18.5$ Hz), 129.83, 129.69, 123.99 (d, $J^P = 9.2$ Hz), 118.80 (d, J^P

$= 3.0$ Hz), 116.37 (d, $J^P = 11.3$ Hz), 62.18 (d, $J^P = 5.4$ Hz), 55.45, 16.35 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.67.

3.2.3n. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.11-8.08 (d, $J = 13.7$ Hz, 1 H), 8.05-8.01 (m, 1 H), 7.84-7.82 (d, $J = 7.7$ Hz, 1 H), 7.65-7.62 (m, 1 H), 4.25-4.10 (m, 4 H), 1.38-1.35 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 135.03 (d, $J^P = 9.2$ Hz), 130.06 (q, $J^P = 17.1$ Hz), 130.86, 129.35, 129.13, 129.01, 128.62, 62.54 (d, $J^P = 5.6$ Hz), 16.35 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.30. ^{19}F NMR (471 MHz, CDCl_3) δ -62.84.

3.2.3o. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.65-7.61 (m, 1 H), 7.55-7.45 (m, 2 H), 7.29-7.25 (m, 1 H), 4.23-4.08 (m, 4 H), 1.37-1.34 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.43 (dd, $J^P = 21.5$ Hz), 131.81 (d, $J^P = 6.1$ Hz), 130.46 (dd, $J^P = 7.4$ Hz), 127.50 (dd, $J^P = 3.1$ Hz), 119.54 (dd, $J^P = 2.9$ Hz), 118.62 (dd, $J^P = 10.4$ Hz), 62.40 (d, $J^P = 5.4$ Hz), 16.34 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.63 (d, $J = 8.6$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -111.55 (d, $J = 8.5$ Hz).

3.2.3p. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.82-7.80 (d, $J = 13.8$ Hz, 1 H), 7.74-7.70 (m, 1 H), 7.55-7.54 (d, $J = 7.9$ Hz, 1 H), 7.46-7.42 (m, 1 H), 4.23-4.08 (m, 4 H), 1.38-1.35 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 134.81 (d, $J^P = 20.2$ Hz), 132.51 (d, $J^P = 2.9$ Hz), 131.68 (d, $J^P = 10.7$ Hz), 130.80 (d, $J^P = 186.8$ Hz), 129.94 (d, $J^P = 16.4$ Hz), 129.82 (d, $J^P = 9.3$ Hz), 62.43 (d, $J^P = 5.5$ Hz), 16.35 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.55.

3.2.3q. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.92-7.86 (m, 1 H), 7.59-7.55 (m, 1 H), 7.28-7.25 (m, 1 H), 7.17-7.13 (m, 1 H), 4.27-4.13 (m, 4 H), 1.38-1.35 (t, $J = 7.1$ Hz, 6

H). ^{13}C NMR (125 MHz, CDCl_3) δ 163.40 (d, $J^P = 251.3$ Hz), 134.97 (dd, $J^P = 3.6$ Hz), 134.83 (dd, $J^P = 2.2$ Hz), 124.14 (dd, $J^P = 3.5$ Hz), 116.24 (d, $J^P = 8.0$ Hz), 116.06 (d, $J^P = 8.0$ Hz), 62.53 (d, $J^P = 5.6$ Hz), 16.32 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 13.67. ^{19}F NMR (471 MHz, CDCl_3) δ -103.73.

3.2.3r. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.96-7.91 (m, 1 H), 7.46-7.43 (t, $J = 7.6$ Hz, 1 H), 7.30-7.27 (m, 2 H), 4.22-4.07 (m, 4 H), 2.60 (s, 3 H), 1.37-1.34 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 141.83 (d, $J^P = 10.1$ Hz), 133.94 (d, $J^P = 10.2$ Hz), 132.44 (d, $J^P = 3.0$ Hz), 131.20 (d, $J^P = 14.9$ Hz), 126.86 (d, $J^P = 182.8$ Hz), 125.38 (d, $J^P = 14.8$ Hz), 61.88 (d, $J^P = 5.5$ Hz), 21.24 (d, $J^P = 3.5$ Hz), 16.34 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 19.47.

3.2.3s. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.09-8.04 (m, 1 H), 7.60-7.57 (t, $J = 7.6$ Hz, 1 H), 7.48-7.45 (m, 4 H), 7.43-7.38 (m, 3 H), 7.37-7.34 (t, $J = 6.4$ Hz, 1 H), 3.99-3.91 (m, 2 H), 3.89-3.81 (m, 2 H), 1.16-1.13 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 146.06 (d, $J^P = 9.8$ Hz), 141.48 (d, $J^P = 4.1$ Hz), 133.83 (d, $J^P = 9.6$ Hz), 131.94 (d, $J^P = 2.9$ Hz), 131.37 (d, $J^P = 14.0$ Hz), 130.50 (d, $J^P = 23.0$ Hz), 129.35, 128.78 (d, $J^P = 10.3$ Hz), 127.47 (d, $J^P = 6.2$ Hz), 126.88 (d, $J^P = 14.5$ Hz), 61.80 (d, $J^P = 6.1$ Hz), 16.07 (d, $J^P = 6.8$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.11.

3.2.3t. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.68-7.58 (m, 2 H), 7.28 (s, 2 H), 4.22-4.07 (m, 4 H), 1.37-1.34 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 128.82, 126.63 (t, $J^P = 3.9$ Hz), 125.10 (t, $J^P = 4.4$ Hz), 121.20 (d, $J^P = 11.5$ Hz), 121.06 (d, $J^P = 11.3$ Hz), 117.92 (t, $J^P = 17.6$ Hz), 62.50 (d, $J^P = 5.5$ Hz), 16.33 (d, $J^P = 6.4$ Hz). ^{31}P

NMR (202 MHz, CDCl₃) δ 15.77 (d, *J* = 6.6 Hz). ¹⁹F NMR (471 MHz, CDCl₃) δ -130.87 (d, *J* = 20.8 Hz), -136.15 (q, *J* = 6.5 Hz).

3.2.3u. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.39 (m, 1 H), 7.24-7.22 (d, *J* = 12.8 Hz, 1 H), 6.92-6.90 (m, 1 H), 6.05 (s, 2 H), 4.19-4.04 (m, 4 H), 1.36-1.33 (t, *J* = 6.8 Hz, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 151.18 (d, *J*^P = 3.1 Hz), 147.85 (d, *J*^P = 22.4 Hz), 127.50 (d, *J*^P = 11.0 Hz), 121.33 (d, *J*^P = 192.0 Hz), 111.27 (d, *J*^P = 12.1 Hz), 108.61 (d, *J*^P = 18.6 Hz), 101.59, 62.06 (d, *J*^P = 5.2 Hz), 16.34 (d, *J*^P = 6.5 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 18.96.

3.2.3v. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.36-7.34 (m, 1 H), 7.33-7.31 (m, 1 H), 6.97-6.94 (m, 1 H), 4.34-4.29 (m, 4 H), 4.17-4.05 (m, 4 H), 1.35-1.33 (t, *J* = 7.1 Hz, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 125.51, 125.43, 121.17, 121.08, 117.71, 117.57, 64.37 (d, *J*^P = 49.8 Hz), 62.00 (d, *J*^P = 5.2 Hz), 16.34 (d, *J*^P = 6.6 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 18.98.

3.2.3w. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.52-7.44 (m, 3 H), 6.93-6.92 (d, *J* = 7.7 Hz, 2 H), 6.15-6.08 (t, *J* = 17.6 Hz, 1 H), 4.18-4.11 (m, 4 H), 3.86 (s, 3 H), 1.39-1.36 (t, *J* = 6.8 Hz, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 148.46 (d, *J*^P = 7.1 Hz), 129.35, 127.78, 114.25, 111.67, 110.14, 61.74 (d, *J*^P = 5.4 Hz), 55.40, 16.43 (d, *J*^P = 6.5 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 20.45.

3.2.3x. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.72-7.69 (m, 1 H), 7.28-7.27 (d, *J* = 5.6 Hz, 1 H), 7.20 (s, 1 H), 4.23-4.09 (m, 4 H), 1.38-1.35 (t, *J* = 6.7 Hz, 6 H). ¹³C NMR (125 MHz, CDCl₃) δ 136.76, 136.66, 133.37 (d, *J*^P = 7.4 Hz), 128.06 (d, *J*^P = 18.4 Hz), 62.66 (d, *J*^P = 5.3 Hz), 16.29 (d, *J*^P = 6.6 Hz). ³¹P NMR (202 MHz, CDCl₃) δ 11.91.

3.2.3y. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.86-7.82 (m, 2 H), 7.57-7.53 (m, 1 H), 7.49-7.45 (m, 2 H), 4.74-4.68 (m, 2 H), 1.40-1.39 (d, $J = 6.2$ Hz, 6 H), 1.26-1.24 (d, $J = 6.2$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 132.04 (d, $J^P = 3.2$ Hz), 131.79, 131.71, 128.30 (d, $J^P = 14.8$ Hz), 70.70 (d, $J^P = 5.5$ Hz), 24.10 (d, $J^P = 4.0$ Hz), 23.85 (d, $J^P = 4.9$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.62.

3.2.3z. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.85-7.81 (m, 2 H), 7.59-7.56 (t, $J = 7.5$ Hz, 1 H), 7.49-7.48 (m, 2 H), 4.13-3.99 (m, 4 H), 1.70-1.65 (m, 4 H), 1.45-1.38 (m, 4 H), 0.94-0.91 (t, $J = 7.4$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 132.33, 132.30, 131.79 (d, $J^P = 9.8$ Hz), 128.44 (d, $J^P = 14.9$ Hz), 65.81 (d, $J^P = 5.7$ Hz), 32.46 (d, $J^P = 6.5$ Hz), 18.75, 13.60. ^{31}P NMR (202 MHz, CDCl_3) δ 18.78.

3.2.3aa. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.32 (m, 15 H). ^{13}C NMR (125 MHz, CDCl_3) δ 133.76 (d, $J^P = 19.3$ Hz), 128.72, 128.53, 128.48. ^{31}P NMR (202 MHz, CDCl_3) δ -5.40.

3.2.3ab. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.33-8.30 (m, 2 H), 8.01-7.97 (m, 2 H), 7.49-7.46 (t, $J = 7.7$ Hz, 2 H), 7.34-7.31 (t, $J = 7.5$ Hz, 1 H), 7.25-7.24 (d, $J = 7.6$ Hz, 2 H), 4.26-4.12 (m, 4 H), 1.39-1.36 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.38, 150.74, 132.03, 131.95, 130.05, 129.93, 129.61, 126.18, 121.57, 62.51 (d, $J^P = 5.5$ Hz), 16.38 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.71. HRMS calcd for $\text{C}_{17}\text{H}_{19}\text{O}_5\text{PNa} (\text{M}^+ + \text{Na})$ 357.0862, found 357.0857.

3.2.3ac. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.73 (m, 4 H), 7.36-7.34 (d, $J = 8.1$ Hz, 2 H), 7.13-7.11 (m, 2 H), 4.20-4.06 (m, 4 H), 2.48 (s, 3 H), 1.36-1.33 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 152.59, 145.78, 133.53 (d, $J^P = 10.8$ Hz),

132.15, 129.93, 128.50, 128.36, 122.52 (d, $J^P = 15.8$ Hz), 62.36 (d, $J^P = 5.5$ Hz), 21.76, 16.34 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.13.

3.2.3ad. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.08-8.05 (d, $J = 14.0$ Hz, 1 H), 7.83-7.79 (m, 2 H), 7.64-7.63 (d, $J = 7.6$ Hz, 2 H), 7.59-7.55 (m, 1 H), 7.50-7.47 (t, $J = 7.5$ Hz, 2 H), 7.42-7.39 (t, $J = 7.3$ Hz, 1 H), 4.27-4.10 (m, 4 H), 1.39-1.36 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 140.03, 131.08 (d, $J^P = 3.1$ Hz), 130.55, 130.49 (d, $J^P = 2.1$ Hz), 130.41, 129.03, 128.92, 128.29, 127.85, 127.23, 62.20 (d, $J^P = 5.4$ Hz), 16.40 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.72.

3.2.3ae. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.86-7.82 (m, 1 H), 7.59-7.56 (t, $J = 7.5$ Hz, 1 H), 7.51-7.47 (m, 2 H), 7.38-7.31 (m, 2 H), 7.28-7.26 (m, 1 H), 7.13-7.11 (d, $J = 8.0$ Hz, 1 H), 7.03-7.00 (t, $J = 7.3$ Hz, 1 H), 5.86 (s, 1 H), 4.21-4.07 (m, 4 H), 1.37-1.34 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.67 (d, $J^P = 17.9$ Hz), 142.08, 132.38 (d, $J^P = 3.0$ Hz), 131.79 (d, $J^P = 9.8$ Hz), 129.50, 128.47 (d, $J^P = 14.9$ Hz), 123.54 (d, $J^P = 9.2$ Hz), 122.00, 120.26 (d, $J^P = 47.5$ Hz), 118.70, 62.14 (d, $J^P = 5.2$ Hz), 16.36 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.91. HRMS calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_3\text{PNa}$ ($\text{M}^+ + \text{Na}$) 328.1079, found 328.1098.

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3.3 Decarbonylation of thioesters to thioethers by nickel catalysis

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3.3.1 Introduction

The thioether functional group represents one of the privileged structural motifs in the synthesis of pharmaceuticals (Figure 3.3.1A).^{1,2} Most synthetic disconnections for the synthesis of aryl thioethers focus on transition-metal-catalyzed cross-coupling of aryl halides or pseudohalides with thiols (Figure 3.3.1B).^{3,4} Significant progress has been made in the development of transition-metal- catalyzed decarbonylative processes that utilize ubiquitous carboxylic acids as ultimate cross-coupling precursors in the oxidant free, redox-neutral decarbonylative pathway.⁵ In this context, carboxylic acids are among the most appealing chemical building blocks in organic synthesis.^{5b} Of note, carboxylic acids are (1) cheaper and there are more carboxylic acids commercially available than aryl halides; (2) derived from a different pool of precursors than aryl halides and pseudohalides; (3) inert to a variety of reaction conditions allowing for ring prefunctionalization.⁶ Similarly, significant effort has been made in the cross-coupling of inert C–S bonds.⁷ Notably, Morandi and co-workers have developed a versatile method for carbon–sulfur bond metathesis,⁸ while Yorimitsu and co-workers have shown that Pd–NHC systems catalyze the coupling of aromatic thioethers with N- and C-nucleophiles.⁹ In another important development, Niwa, Hosoya and co-workers established the feasibility of Rh-catalyzed decarbonylative borylation of thioesters.¹⁰ The

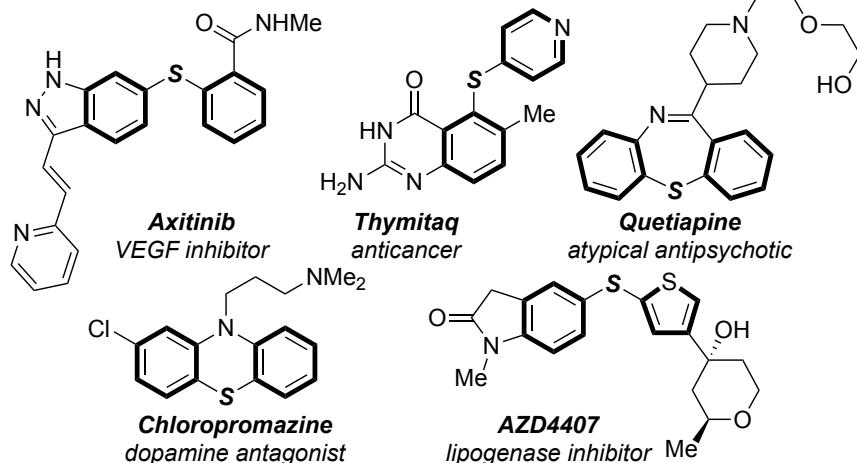
recent emergence of efforts to use sulfur intermediates in metal-free pathways¹¹ provided and additional appeal to assembling thioethers from carboxylic acid-based substrates using robust, operationally-simple protocols that could be widely employed in various areas of chemical science.

Simultaneously, in the past decade, there has been an increasing interest in nickel catalysis due to more facile oxidative addition, abundance and economic advantages compared with Pd catalysis.¹² In general, the use of air- and moisture-stable precatalysts is strongly preferred in modern cross-coupling applications.¹³ In this context, the groups of Monteiro,¹⁴ Percec,¹⁵ Buchwald,¹⁶ Jamison,¹⁷ Doyle,¹⁸ Monfette¹⁹ and others¹⁵⁻¹⁹ have reported well-defined Ni(II) precatalysts, which enable a variety of cross-coupling transformations. The fact is that the use of robust, bench-stable Ni(II) precatalysts enables broad applications of metal catalysis in industrial research¹³ instead of rather limited options available with air-sensitive and capricious Ni(0)-complexes.

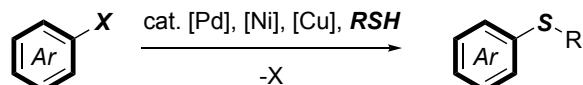
In this project, we have been inspired by our recent studies in decarbonylative olefination,²⁰ arylation,²¹ cyanation²² and phosphorylation²³ of amides.²⁴ In one of the avenues of research we explored thioesters as viable precursors to acyl-metal intermediates by selective oxidative addition into the acyl C(O)–X bond. In this study, we have developed decarbonylative thioetherification of aryl thioesters by selective C–S cleavage enabled by user-friendly, air- and moisture-stable nickel precatalysts (Figure 3.3.1C). While this project was in progress, a Ni(0)-catalyzed decarbonylative thioether synthesis by C–S cleavage using a combination of air-sensitive Ni(cod)₂ (10 mol%) and PCy₃ (20 mol%) was reported.²⁵ Our method (1) utilized Ni(II) precatalysts that are air-stable, easy to handle and manipulate, (2) was significantly broader in scope, and (3)

enabled the use of operationally-simple and robust decarbonylative thioetherification for wide applications within both industry and academia, providing a general protocol of will be of general interest to the broad synthetic community.^{1-4,13}

A. Examples of pharmaceutically-relevant aryl thioethers

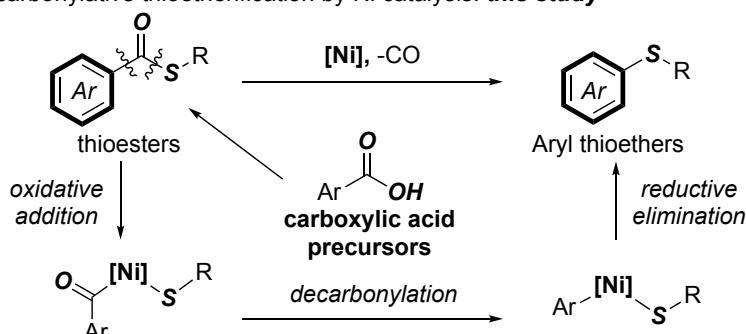


B. Traditional metal-catalyzed synthesis of aryl thioethers



$\text{X} = \text{I}, \text{Br}, \text{Cl}, \text{OR}', \text{N}_2^+, \text{B}, \text{Si}$

C. Decarbonylative thioetherification by Ni catalysis: *this study*



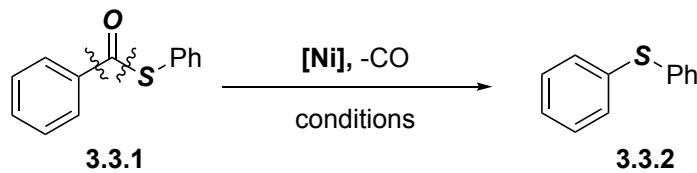
■ selective C–S cleavage ■ modular, air-stable Ni precatalyst
■ carboxylic acid precursors ■ broad tolerance ■ high generality

Decarbonylative Coupling via Selective C–S Cleavage

Figure 3.3.1 (a) Examples of pharmaceutically important aryl thioethers. (b) Conventional synthesis. (c) Intramolecular decarbonylation of thioesters by nickel catalysis (this study).

3.3.2 Reaction optimization

We optimized the reaction using *S*-phenyl benzothioate as a model substrate. Key optimization experiments are summarized in Table 3.3.1. Using our optimized conditions, Ni(dppp)Cl₂, (10 mol%), Na₂CO₃ (1.5 equiv), dioxane, 160 °C, *S*-phenyl benzothioate underwent selective C–S insertion/CO extrusion in excellent yield (entry 1). Under these conditions, Ni(PCy₃)₂Cl₂ was also a highly effective catalyst (entry 2). As expected, no reaction was observed in the absence of base (entries 3 and 4) or nickel precatalyst (entry 5). Examination of various reaction parameters revealed a significant dependence on the Ni(II) complex used (entries 6-10), with Ni(dppp)Cl₂, Ni(dppe)Cl₂, and Ni(PCy₃)₂Cl₂ showing similar performance. As expected, no reaction was observed in the absence of phosphine ligand (entry 11). An extensive screen of bases revealed that the best results were obtained with Na₂CO₃ (entries 12-14). Dioxane was identified as the optimal solvent (entries 15-17). We were pleased to find that decreasing the nickel loading to 5 mol% delivered the product under the optimized conditions (entries 18 and 19). Low conversions were observed in the presence of oxygen. Finally, we note that substantial conversion was observed at 120 °C, consistent with facile decarbonylation by this catalytic system (entry 20).

Table 3.3.1 Optimization of Ni-catalyzed intramolecular decarbonylation of thioesters.^a

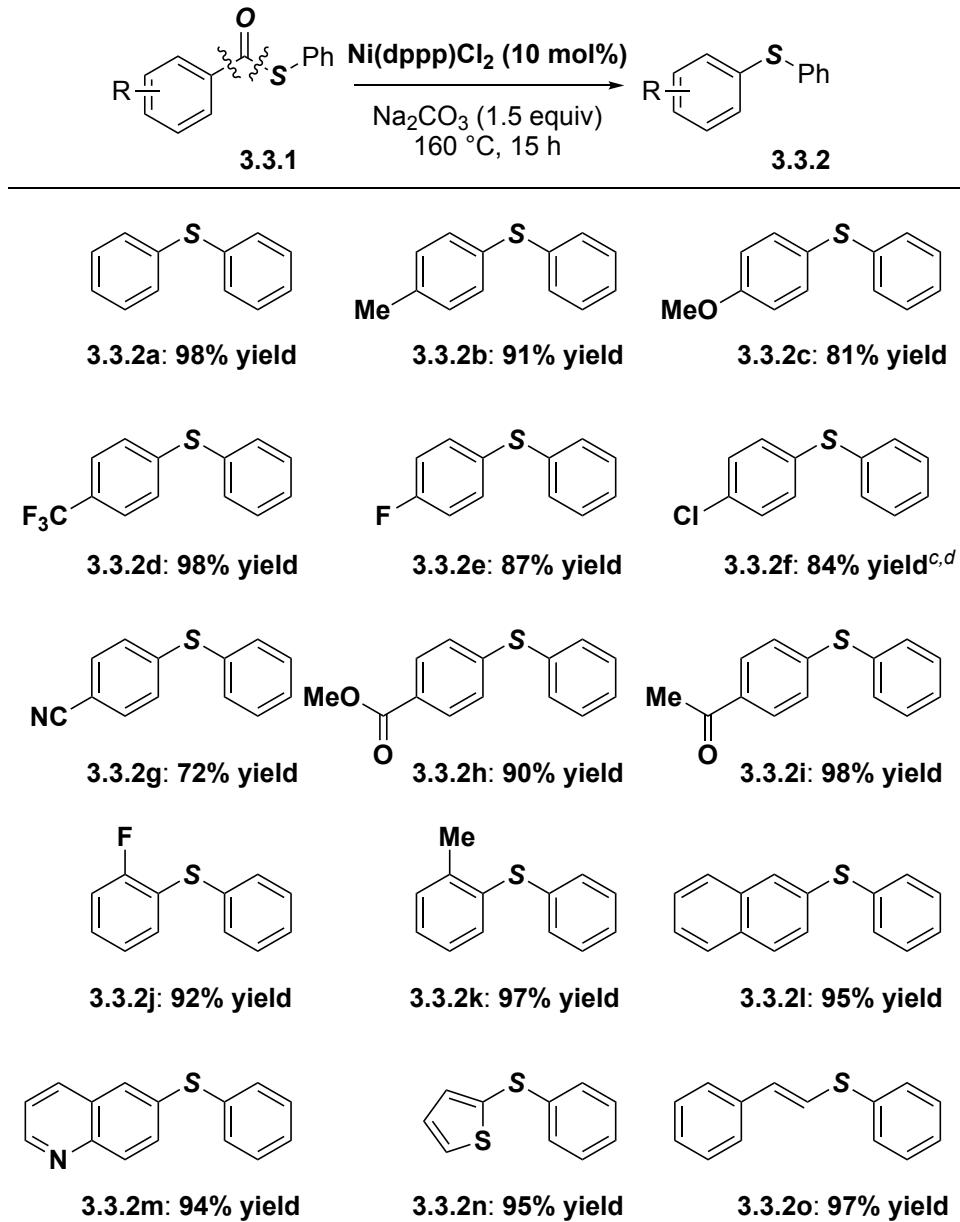
entry	catalyst	base	T (°C)	yield (%) ^b
1	Ni(dppp)Cl ₂	Na ₂ CO ₃	160	>95
2	Ni(PCy ₃) ₂ Cl ₂	Na ₂ CO ₃	160	>95
3	Ni(dppp)Cl ₂		160	<2
4	Ni(PCy ₃) ₂ Cl ₂		160	<2
5		Na ₂ CO ₃	160	<2
6	Ni(dppp)Cl ₂	Na ₂ CO ₃	140	>95
7 ^c	Ni(PCy ₃) ₂ Cl ₂	Na ₂ CO ₃	140	>95
8	Ni(PPh ₃) ₂ Cl ₂	Na ₂ CO ₃	140	43
9	Ni(dppe)Cl ₂	Na ₂ CO ₃	140	>95
10	Ni(dppf)Cl ₂	Na ₂ CO ₃	140	18
11	Ni(OAc) ₂	Na ₂ CO ₃	140	<5
12	Ni(PCy ₃) ₂ Cl ₂	K ₂ CO ₃	140	27
13	Ni(PCy ₃) ₂ Cl ₂	Cs ₂ CO ₃	140	<5
14	Ni(PCy ₃) ₂ Cl ₂	K ₃ PO ₄	140	15
15 ^c	Ni(PCy ₃) ₂ Cl ₂	Na ₂ CO ₃	140	87
16 ^d	Ni(PCy ₃) ₂ Cl ₂	Na ₂ CO ₃	140	>95
17 ^e	Ni(PCy ₃) ₂ Cl ₂	Na ₂ CO ₃	140	>95
18 ^f	Ni(PCy ₃) ₂ Cl ₂	Na ₂ CO ₃	140	27
19 ^f	Ni(PCy ₃) ₂ Cl ₂	Na ₂ CO ₃	160	>95
20	Ni(PCy ₃) ₂ Cl ₂	Na ₂ CO ₃	120	52

^aConditions: thioester (1.0 equiv), catalyst (10 mol%), base (1.5 equiv), dioxane (0.20 M), T, 15 h. ^bGC/¹H NMR yields. ^ctoluene. ^dCH₃CN. ^eDMF. ^fcatalyst (5 mol%).

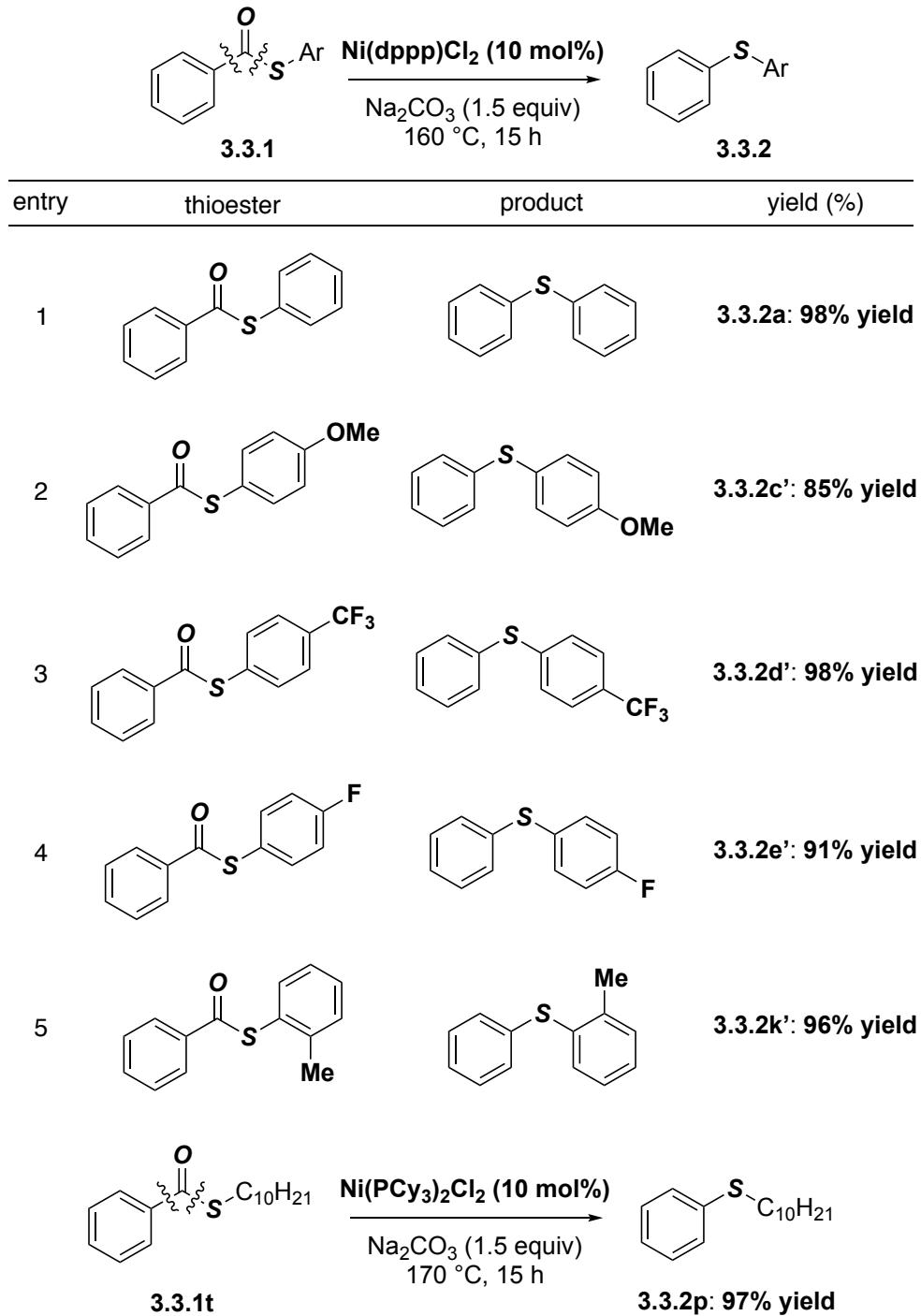
3.3.3 Substrate scope

We found that this decarbonylative reaction shows broad substrate scope (Scheme 3.3.1). Electron-rich (**3.3.2b-c**) and electron-deficient (**3.3.2d**) substrates performed well in this protocol. Notable examples included halides (**3.3.2e-f**) and electrophilic functional groups (**3.3.2g-i**), providing handles for further functionalization. Substitution at the ortho-position was well-tolerated under these conditions (**3.3.2j-k**). Furthermore, this protocol could be extended to polyaromatic (**3.3.2l**), heterocyclic (**3.3.2m-n**) and vinyl substrates (**3.3.2o**), providing the desired products in good to excellent yields. Finally, the scope of the thiol component was briefly examined (Scheme 3.3.2). A selection of electron-rich (entry 2), electron-deficient (entry 3), halide-containing (entry 4) and sterically-hindered (entry 5) substrates were converted into the desired thioethers in high yields. Importantly from a practical point of view, all of these reactions were conveniently set-up on a bench-top, which provided a very attractive feature of this protocol.¹³⁻¹⁹ Furthermore, the scope superseded the Ni(cod)₂ system²⁵ in that cyanides, ketones, halides, unprotected anilines and aryl esters were readily tolerated.

We further demonstrated that cross-coupling of an aryl-alkyl thioester was also feasible (Scheme 3.3.2), providing another advantage of this user-friendly method. Note that alkyl thioesters were not tolerated using air-sensitive Ni(cod)₂.²⁵



Scheme 3.3.1 Scope of Ni-catalyzed intramolecular decarbonylation of thioesters.



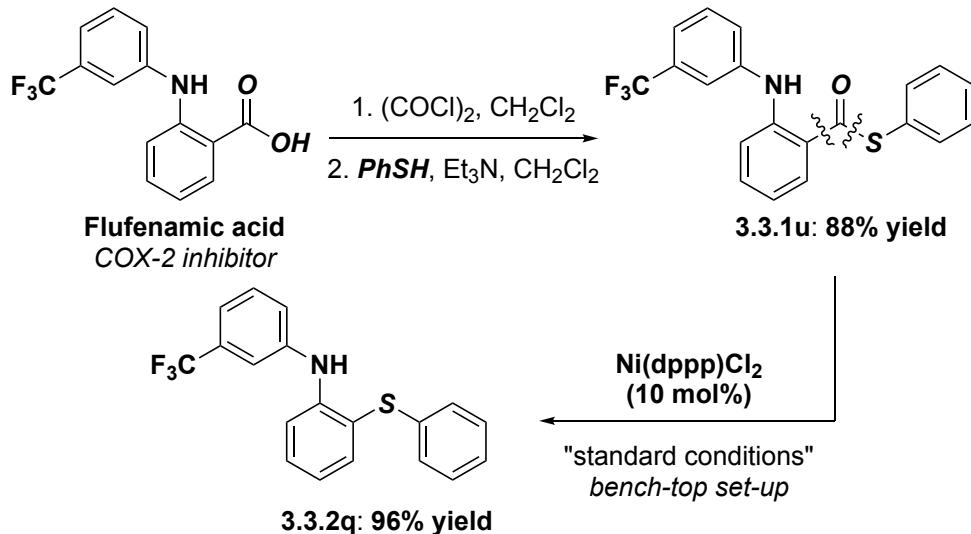
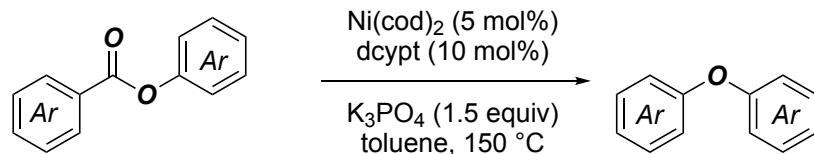
Scheme 3.3.2 Scope of Ni-catalyzed intramolecular decarbonylation of thioesters.

3.3.4 Synthetic applications

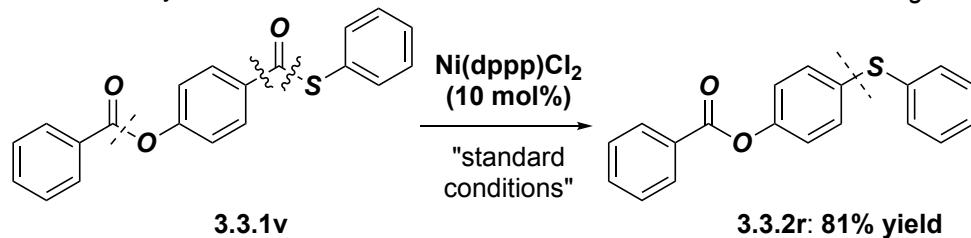
To investigate the potential utility of this novel cross-coupling method, we tested this protocol in the rapid derivatization of flufenamic acid, a selective COX-2 inhibitor (Scheme 3.3.3).²⁶ As shown, the reaction proceeded readily under the developed reaction conditions, delivering the desired thioether product in high overall yield.¹⁰

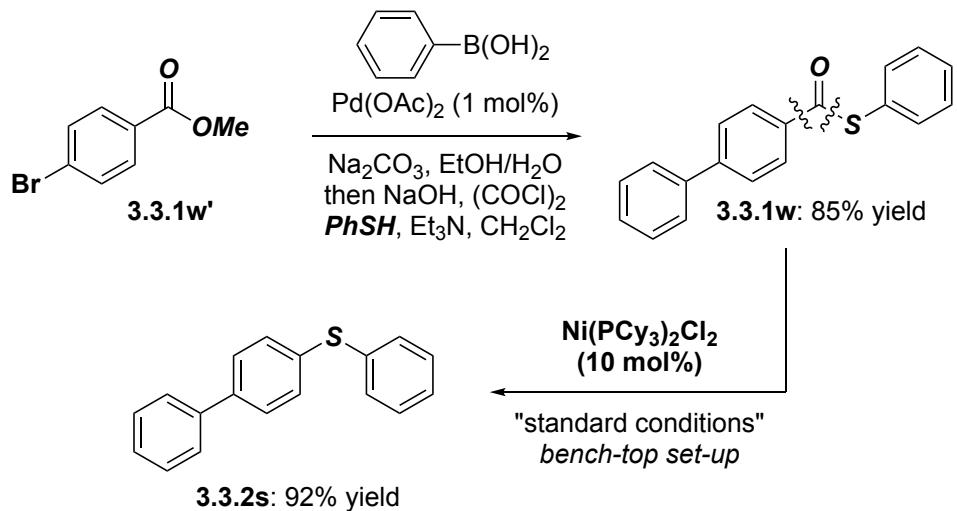
We further realized that Yamaguchi, Itami and co-workers recently reported a Ni-catalyzed decarbonylative diaryl ether synthesis by C–O cleavage.²⁷ We were intrigued to find that the present coupling proceeded in the presence of the sensitive aryl ester linkage (Scheme 3.3.4), demonstrating high chemoselectivity of the present method.

To further showcase the utility of this new thioetherification, we investigated sequential orthogonal cross-couplings (Scheme 3.3.5). The developed sequence highlighted the potential of decarbonylative thioetherification to selectively generate thioethers from readily available carboxylic acids.^{5,6,10}

**Scheme 3.3.3** Facile synthesis of flufenamic acid thioether.**A:** Decarbonylative etherification, Yamaguchi, Itami et al.**B:** Decarbonylative thioetherification, this work

selective C-S cleavage

**Scheme 3.3.4** Selective decarbonylative thioetherification.



Scheme 3.3.5 Site-selective cross-coupling/decarboxylative thioetherification.

3.3.5 Conclusion

In conclusion, in this project we have developed a general method for decarbonylative thioetherification by C–S cleavage using a commercially-available, user-friendly, inexpensive, air- and moisture-stable nickel(II) precatalyst. The process provided a synthetic entry to the biologically-relevant thioether functional group exploiting abundant carboxylic acids as ultimate cross-coupling precursors. In view of the synthetic utility of thioethers and Ni(II) precatalysts, the method should enable further applications of decarbonylative thioetherification.

3.3.6 Experimental section

General Procedure for Thioester Synthesis. An oven-dried flask (25 mL) equipped with a stir bar was charged with thiophenol (typically, 5.0 mmol, 1.0 equiv), acyl chloride (typically, 1.0 equiv), 4-(dimethylamino)pyridine (typically, 0.005 equiv), and dichloromethane (typically, 0.50 M), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Triethylamine (typically, 2.0 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. After the indicated time, the reaction mixture was diluted with ethyl acetate (30 mL). The reaction mixture was washed with HCl (1 x 10 mL), brine (1 x 10 mL), H₂O (1 x 10 mL), dried, and concentrated. The crude product was washed with hexane to give analytically pure product.

General Procedure for Decarbonylation of Thioester. An oven-dried vial equipped with a stir bar was charged with thioester substrate (neat, 1.0 equiv), Ni(dppp)Cl₂ (typically, 10 mol%) and Na₂CO₃ (typically, 1.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 1,4-Dioxane (typically, 0.20 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 160 °C, and stirred for the indicated time at 160 °C. After the indicated time, the reaction mixture was diluted with CH₂Cl₂ (10 mL), filtered, and concentrated. The sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate) afforded the title product.

3.3.1a. Yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 8.19 (s, 2 H), 7.68 (s, 2 H), 7.64-7.62 (d, *J* = 6.2 Hz, 1 H), 7.53 (s, 5 H). ¹³C NMR (125 MHz, CDCl₃) δ 189.90, 136.80, 135.32, 133.90, 129.70, 129.47, 129.00, 127.67.

3.3.1b. White solid. ¹H NMR (500 MHz, CDCl₃) δ 8.05-8.03 (d, *J* = 7.6 Hz, 2 H), 7.97-7.95 (d, *J* = 7.7 Hz, 1 H), 7.54 (s, 1 H), 7.48 (s, 2 H), 7.31-7.30 (d, *J* = 7.4 Hz, 2 H), 2.46 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 189.75, 144.61, 135.15, 134.11, 130.28, 129.43, 129.24, 129.22, 127.59, 21.78.

3.3.1c. Yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 8.06-8.04 (d, *J* = 8.8 Hz, 2 H), 7.57-7.54 (m, 2 H), 7.51-7.46 (m, 3 H), 7.00-6.98 (d, *J* = 8.8 Hz, 2 H), 3.90 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 188.60, 164.04, 135.23, 132.38, 129.75, 129.41, 129.21, 127.70, 113.97, 55.58.

3.3.1d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.16 (s, 2 H), 7.79 (s, 2 H), 7.55 (s, 2 H), 7.51 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.40, 139.47, 135.01, 134.95 (q, $J^2 = 32.9$ Hz), 129.89, 129.44, 127.84, 126.59, 125.87 (q, $J^3 = 3.4$ Hz), 123.51 (q, $J^1 = 270.7$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -63.06.

3.3.1e. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.10-8.07 (m, 2 H), 7.55-7.53 (m, 2 H), 7.50-7.48 (t, $J = 3.3$ Hz, 3 H), 7.21-7.18 (t, $J = 8.5$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 188.72, 166.10 (d, $J^1 = 253.9$ Hz), 135.12, 132.99 (d, $J^4 = 3.0$ Hz), 130.09 (d, $J^3 = 9.3$ Hz), 129.67, 129.32, 127.08, 115.95 (d, $J^2 = 22.0$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -104.10.

3.3.1f. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 8.00 (s, 2 H), 7.54 (s, 2 H), 7.49 (s, 5 H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.08, 140.10, 135.08, 134.99, 129.72, 129.35, 129.10, 128.85, 126.93.

3.3.1g. Orange solid. ^1H NMR (500 MHz, CDCl_3) δ 8.15-8.13 (d, $J = 8.3$ Hz, 2 H), 7.83-7.81 (d, $J = 8.3$ Hz, 2 H), 7.55-7.51 (m, 5 H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.11, 139.82, 134.96, 132.65, 130.04, 129.51, 127.93, 126.23, 117.79, 116.92.

3.3.1h. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.18-8.17 (d, $J = 8.4$ Hz, 2 H), 8.11-8.09 (d, $J = 8.3$ Hz, 2 H), 7.56-7.54 (m, 2 H), 7.50-7.49 (m, 3 H), 3.99 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.75, 166.09, 139.98, 135.01, 134.44, 129.99, 129.79, 129.39, 127.42, 126.83, 52.56.

3.3.1i. Orange solid. ^1H NMR (500 MHz, CDCl_3) δ 8.14-8.12 (d, $J = 8.4$ Hz, 2 H), 8.09-8.07 (d, $J = 8.2$ Hz, 2 H), 7.56-7.54 (m, 2 H), 7.51-7.50 (d, $J = 3.1$ Hz, 3 H), 2.68 (s, 3 H).

¹³C NMR (125 MHz, CDCl₃) δ 197.29, 189.70, 140.65, 139.94, 135.00, 129.82, 129.41, 128.65, 127.71, 126.79, 26.92.

3.3.1j. Yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 7.96-7.93 (t, *J* = 7.8 Hz, 1 H), 7.60-7.55 (m, 3 H), 7.50-7.49 (t, *J* = 3.8 Hz, 3 H), 7.30-7.27 (t, *J* = 7.2 Hz, 1 H) 7.24-7.20 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 187.17, 160.53 (d, *J*³ = 256.6 Hz), 135.01, 134.64 (d, *J*³ = 8.8 Hz), 129.90, 129.73, 129.31, 127.27 (d, *J*³ = 4.2 Hz), 125.18 (d, *J*³ = 11.5 Hz), 124.37 (d, *J*³ = 3.6 Hz), 117.01 (d, *J*³ = 22.0 Hz). ¹⁹F NMR (471 MHz, CDCl₃) δ -109.71.

3.3.1k. Yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 8.09 (s, 1 H), 7.67 (s, 2 H), 7.56-7.50 (m, 4 H), 7.40-7.36 (m, 2 H), 2.64 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 192.09, 137.54, 136.88, 135.07, 132.20, 131.94, 129.60, 129.42, 128.80, 128.42, 126.06, 20.99.

3.3.1l. White solid. ¹H NMR (500 MHz, CDCl₃) δ 8.65 (s, 1 H), 8.07-8.02 (m, 2 H), 7.96-7.92 (m, 2 H), 7.67-7.59 (m, 4 H), 7.52-7.51 (m, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 190.09, 135.92, 135.17, 133.97, 132.50, 129.64, 129.57, 129.31, 129.04, 128.68, 128.67, 127.88, 127.48, 127.04, 123.30.

3.3.1m. White solid. Mp = 116-118 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.06-9.05 (d, *J* = 4.1 Hz, 1 H), 8.61 (s, 1 H), 8.34-8.29 (m, 2 H), 8.23-8.21 (d, *J* = 8.8 Hz, 1 H), 7.59-7.58 (m, 2 H), 7.54-7.50 (m, 4 H). ¹³C NMR (125 MHz, CDCl₃) δ 189.60, 152.83, 150.39, 137.56, 135.11, 134.48, 130.39, 129.75, 129.39, 128.77, 127.52, 127.07, 127.01, 122.18. HRMS calcd for C₁₆H₁₁NOSNa (M⁺ + Na) 288.0454, found 288.0442.

3.3.1n. Orange solid. ¹H NMR (500 MHz, CDCl₃) δ 7.95 (s, 1 H), 7.65 (s, 1 H), 7.60 (s, 2 H), 7.49 (s, 3 H). 7.15 (s, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 182.00, 141.39, 135.18, 133.56, 131.86, 129.79, 129.41, 129.27, 128.26, 127.09.

3.3.1o. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 7.73-7.69 (d, $J = 15.8$ Hz, 1 H), 7.60-7.59 (m, 2 H), 7.54-7.52 (m, 2 H), 7.49-7.41 (m, 6 H), 6.84-6.81 (d, $J = 15.8$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 187.98, 141.55, 134.64, 134.05, 130.78, 129.47, 129.23, 129.03, 128.52, 127.65, 124.17.

3.3.1p. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 8.06-8.05 (d, $J = 7.7$ Hz, 2 H), 7.64-7.61 (t, $J = 7.2$ Hz, 1 H), 7.52-7.49 (t, $J = 7.5$ Hz, 2 H), 7.46-7.44 (d, $J = 8.6$ Hz, 2 H), 7.03-7.01 (d, $J = 8.6$ Hz, 2 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 191.07, 160.82, 136.66, 133.58, 130.60, 128.74, 127.48, 117.91, 115.00, 55.41.

3.3.1q. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.06-8.05 (d, $J = 8.1$ Hz, 2 H), 7.75-7.73 (d, $J = 8.2$ Hz, 2 H), 7.69-7.65 (m, 3 H), 7.55-7.52 (t, $J = 7.7$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 188.92, 136.25, 135.23, 134.07, 132.19, 131.47 (q, $J^2 = 32.6$ Hz), 128.91, 127.59, 126.02 (q, $J^3 = 3.7$ Hz), 123.86 (q, $J^1 = 270.8$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.78.

3.3.1r. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.10-8.08 (d, $J = 8.1$ Hz, 2 H), 7.62-7.59 (t, $J = 7.3$ Hz, 1 H), 7.54-7.47 (m, 4 H), 7.19-7.16 (t, $J = 8.6$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.81, 163.68 (d, $J^1 = 248.4$ Hz), 137.29 (d, $J^3 = 8.5$ Hz), 136.47, 133.91, 128.92, 127.58, 122.87 (d, $J^4 = 3.4$ Hz), 116.58 (d, $J^2 = 21.9$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -110.55.

3.3.1s. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.12-8.11 (d, $J = 8.0$ Hz, 2 H), 7.67-7.64 (t, $J = 7.4$ Hz, 1 H), 7.55-7.52 (m, 3 H), 7.43-7.42 (m, 2 H), 7.34-7.31 (t, $J = 7.4$ Hz, 1 H), 2.46 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.66, 142.71, 136.85, 136.47, 133.63, 130.89, 130.28, 128.79, 127.60, 126.87, 126.73, 20.89.

3.3.1t. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 8.00-7.99 (d, $J = 7.5$ Hz, 2 H), 7.60-7.57 (t, $J = 7.4$ Hz, 1 H), 7.48-7.45 (t, $J = 7.6$ Hz, 2 H), 3.11-3.08 (t, $J = 7.2$ Hz, 2 H), 1.73-1.67 (m, 2 H), 1.46-1.42 (m, 2 H), 1.32-1.29 (m, 12 H), 0.92-0.89 (t, $J = 5.9$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 192.16, 137.31, 133.19, 128.56, 127.19, 31.91, 29.58, 29.56, 29.53, 29.32, 29.18, 29.08, 28.97, 22.70, 14.13.

3.3.1u. Orange oil. ^1H NMR (500 MHz, CDCl_3) δ 8.05-8.03 (d, $J = 7.3$ Hz, 1 H), 7.69-7.58 (m, 2 H), 7.54-7.53 (m, 2 H), 7.47 (s, 3 H), 7.42-7.35 (m, 5 H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.66, 141.56, 137.59, 135.03, 134.79, 134.51, 133.53, 133.22, 131.44 (q, $J^2 = 63.0$ Hz), 130.56, 129.99, 129.69 (q, $J^2 = 30.9$ Hz), 129.43, 129.36, 129.20, 127.56 (q, $J^1 = 270.2$ Hz), 123.71 (q, $J^1 = 3.3$ Hz), 123.04 (q, $J^1 = 3.7$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.52. HRMS calcd for $\text{C}_{20}\text{H}_{14}\text{F}_3\text{NOSNa} (\text{M}^+ + \text{Na})$ 396.0640, found 396.0629.

3.3.1v. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 8.25-8.24 (d, $J = 7.9$ Hz, 2 H), 8.16-8.14 (d, $J = 8.4$ Hz, 2 H), 7.71-7.68 (t, $J = 7.4$ Hz, 1 H), 7.58-7.55 (m, 4 H), 7.50 (s, 3 H), 7.40-7.39 (d, $J = 8.4$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.06, 164.56, 155.14, 135.13, 134.23, 133.99, 130.31, 129.63, 129.31, 129.16, 129.01, 128.72, 127.19, 122.17.

3.3.1w. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 8.14-8.13 (d, $J = 8.2$ Hz, 2 H), 7.75-7.73 (d, $J = 8.2$ Hz, 2 H), 7.68-7.66 (d, $J = 7.6$ Hz, 2 H), 7.58-7.56 (m, 2 H), 7.53-7.50 (m, 5 H), 7.46-7.43 (t, $J = 7.3$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 189.69, 146.45, 139.76, 135.35, 135.14, 129.55, 129.29, 129.02, 128.37, 128.08, 127.40, 127.31.

3.3.2a. Yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.36 (d, $J = 7.2$ Hz, 4 H), 7.34-7.31 (t, $J = 7.2$ Hz, 4 H), 7.28-7.25 (t, $J = 7.0$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 135.80, 131.05, 129.20, 127.05.

3.3.2b. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.29 (m, 6 H), 7.25-7.12 (m, 3 H), 2.37 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 137.62, 137.13, 132.29, 131.29, 130.08, 129.79, 129.05, 126.42, 21.15.

3.3.2c. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.45-7.43 (d, $J = 8.4$ Hz, 2 H), 7.28-7.24 (t, $J = 7.5$ Hz, 2 H), 7.20-7.15 (m, 3 H), 6.93-6.92 (d, $J = 8.4$ Hz, 2 H), 3.85 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.85, 138.61, 135.38, 128.94, 128.22, 125.77, 124.33, 115.00, 55.38.

3.3.2d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.51-7.46 (m, 5 H), 7.42-7.38 (m, 3 H), 7.30 (s, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 142.84, 133.55, 131.03, 129.69, 129.02 (q, $J^2 = 63.0$ Hz), 128.66, 128.29, 125.82 (q, $J^3 = 3.8$ Hz), 124.09 (q, $J^l = 270.1$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.42.

3.3.2e. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.42-7.39 (m, 2 H), 7.36-7.29 (m, 4 H), 7.26-7.23 (m, 1 H), 7.07-7.03 (t, $J = 8.6$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.42 (d, $J^l = 246.2$ Hz), 136.64, 134.10 (d, $J^3 = 8.1$ Hz), 131.05, 129.96, 129.19, 126.77, 116.42 (d, $J^2 = 21.8$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -113.99.

3.3.2f. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.39-7.25 (m, 9 H). ^{13}C NMR (125 MHz, CDCl_3) δ 132.03, 131.48, 131.34, 131.18, 129.36, 129.33, 129.32, 127.46.

3.3.2g. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.54 (s, 2 H), 7.51-7.49 (d, J = 8.3 Hz, 2 H), 7.46-7.46 (d, J = 2.7 Hz, 3 H), 7.20-7.18 (d, J = 8.3 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.75, 134.53, 132.39, 130.86, 129.94, 129.42, 127.34, 118.82, 108.73.

3.3.2h. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.93-7.91 (d, J = 8.4 Hz, 2 H), 7.52-7.51 (m, 2 H), 7.44-7.39 (m, 3 H), 7.24-7.22 (d, J = 8.4 Hz, 2 H), 3.91 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.70, 144.39, 133.71, 132.40, 130.10, 129.65, 128.67, 127.59, 127.50, 52.10.

3.3.2i. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.85-7.84 (d, J = 8.4 Hz, 2 H), 7.53-7.52 (m, 2 H), 7.45-7.40 (m, 3 H), 7.25-7.22 (d, J = 8.4 Hz, 2 H), 3.91 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.14, 144.93, 134.51, 133.89, 132.12, 129.70, 128.91, 128.81, 127.49, 26.49.

3.3.2j. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.30 (m, 6 H), 7.28-7.27 (m, 1 H), 7.14-7.08 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 161.16 (d, J^1 = 245.6 Hz), 134.19, 133.43 (d, J^6 = 0.9 Hz), 130.95, 130.13 (d, J^2 = 231.9 Hz), 129.35 (d, J^4 = 7.8 Hz), 129.28, 127.30, 124.72 (d, J^5 = 3.8 Hz), 115.95 (d, J^3 = 22.0 Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -108.67.

3.3.2k. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.28 (m, 3 H), 7.26-7.16 (m, 6 H), 2.41 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 140.00, 136.17, 133.77, 133.01, 130.61, 129.65, 129.14, 127.92, 126.73, 126.36, 20.61.

3.3.2l. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.88 (s, 1 H), 7.85-7.84 (d, J = 6.4 Hz, 1 H), 7.81-7.80 (d, J = 8.6 Hz, 1 H), 7.78-7.76 (d, J = 8.3 Hz, 1 H), 7.52-7.50 (t, J = 3.8 Hz, 2 H), 7.46-7.42 (m, 3 H), 7.37-7.34 (t, J = 7.3 Hz, 2 H), 7.31-7.28 (t, J = 7.3 Hz, 1 H).

¹³C NMR (125 MHz, CDCl₃) δ 135.89, 133.83, 133.05, 132.33, 131.00, 129.92, 129.27, 128.90, 128.79, 127.77, 127.46, 127.10, 126.63, 126.24.

3.3.2m. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.90-8.89 (d, *J* = 3.8 Hz, 1 H), 8.05-8.02 (t, *J* = 6.1 Hz, 2 H), 7.73-7.72 (d, *J* = 1.7 Hz, 1 H), 7.63-7.61 (m, 1 H), 7.48-7.46 (d, *J* = 7.3 Hz, 2 H), 7.42-7.33 (m, 4 H). ¹³C NMR (125 MHz, CDCl₃) δ 150.37, 147.21, 135.30, 135.25, 134.45, 132.11, 131.49, 130.30, 129.49, 128.69, 128.00, 127.85, 121.69.

3.3.2n. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.51-7.50 (d, *J* = 4.9 Hz, 1 H), 7.32 (s, 1 H), 7.29-7.26 (m, 2 H), 7.23-7.21 (m, 2 H), 7.20-7.17 (t, *J* = 7.2 Hz, 1 H), 7.11 (s, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 138.67, 136.08, 131.30, 131.16, 128.99, 127.95, 127.15, 126.07.

3.3.2o. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.46-7.44 (d, *J* = 7.5 Hz, 2 H), 7.39-7.33 (m, 6 H), 7.31-7.26 (m, 2 H), 6.94-6.91 (d, *J* = 15.5 Hz, 1 H), 6.79-6.76 (d, *J* = 15.5 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 136.55, 135.25, 131.83, 129.86, 129.18, 128.71, 127.61, 126.98, 126.05, 123.42.

3.3.2p. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.34 (d, *J* = 7.6 Hz, 2 H), 7.31-7.30 (d, *J* = 7.4 Hz, 2 H), 7.20-7.17 (t, *J* = 7.3 Hz, 1 H), 2.95-2.92 (t, *J* = 7.5 Hz, 2 H), 1.70-1.64 (m, 2 H), 1.47-1.41 (m, 2 H), 1.33-1.28 (m, 12 H), 0.92-0.89 (t, *J* = 6.8 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 137.06, 128.83, 128.81, 125.62, 33.59, 31.89, 30.95, 29.54, 29.51, 29.31, 29.17, 28.86, 22.69, 14.12.

3.3.2q. Yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 9.61 (s, 1 H), 8.19-8.17 (d, *J* = 8.1 Hz, 1 H), 7.57-7.55 (m, 2 H), 7.52-7.51 (m, 3 H), 7.45-7.42 (t, *J* = 7.5 Hz, 3 H), 7.37-7.36 (d, *J* = 8.7 Hz, 1 H), 7.33-7.31 (d, *J* = 8.4 Hz, 2 H), 6.94-6.91 (t, *J* = 8.0 Hz, 1 H). ¹³C NMR

(125 MHz, CDCl₃) δ 144.81, 141.03, 135.63, 134.92, 131.81 (q, *J*² = 32.2 Hz), 130.86, 129.92, 129.82, 129.36, 129.08, 127.44, 126.06 (q, *J*¹ = 277.3 Hz), 124.89, 120.01 (q, *J*³ = 3.8 Hz), 119.76, 118.46 (q, *J*⁴ = 3.8 Hz) 114.72. HRMS calcd for C₁₉H₁₄F₃NSNa (M⁺ + Na) 368.0691, found 368.0688.

3.3.2r. Colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 8.07-8.06 (d, *J* = 8.1 Hz, 2 H), 7.66-7.63 (t, *J* = 7.3 Hz, 1 H), 7.57-7.45 (m, 8 H), 7.36-7.27 (m, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 165.22, 151.00, 133.61, 130.77, 130.21, 129.63, 129.53, 129.50, 129.46, 129.11, 128.60, 127.54, 121.75. HRMS calcd for C₁₉H₁₄O₂SNa (M⁺ + Na) 329.0607, found 329.0611.

3.3.2s. White solid. ¹H NMR (500 MHz, CDCl₃) δ 7.61-7.60 (d, *J* = 8.0 Hz, 2 H), 7.57-7.55 (d, *J* = 8.1 Hz, 2 H), 7.48-7.42 (m, 6 H), 7.39-7.33 (m, 4 H). ¹³C NMR (125 MHz, CDCl₃) δ 140.33, 139.99, 135.69, 134.91, 131.30, 131.18, 129.27, 128.86, 127.87, 127.50, 127.17, 126.98.

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Chapter 4

Decarbonylative Cross-Coupling of Carboxylic Acids

4.1 Palladium-catalyzed decarbonylative borylation of carboxylic acids

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4.1.1 Introduction

In general, carboxylic acids are considered as ideal substrates for organic synthesis.¹⁻³ Transition-metal-catalyzed cross-coupling reactions of carboxylic acids proceed via decarboxylative or decarbonylative pathways.^{4,5} While decarboxylative cross-couplings (loss of CO₂) have been utilized to great extent to generate aryl nucleophiles,⁶ the development of decarbonylative reactions (loss of CO) to provide aryl electrophiles has met with limited success (Figure 4.1.1).^{7,8} In contrast to decarboxylative reactions which typically afford aryl nucleophiles for cross-coupling and are performed under oxidative conditions, decarbonylative manifold proceeds under redox-neutral conditions and employs readily accessible activated carboxylic acid derivatives that permit selective oxidative addition of a carboxylic acid to a low valent metal center.^{4,8} While several activating reagents have been employed (e.g. acid chlorides, anhydrides, esters, amides), all of these reagents are limited by stability to the reaction conditions, selectivity of the oxidative addition, and ease of preparation from carboxylic acids, typically necessitating

a separate step involving chromatographic purification⁹ which prevents the broad applicability of these methods.

Furthermore, the control of decarbonylation (vs. more straightforward acyl-coupling)¹⁰⁻¹² has remained a key challenge to the development of direct redox-neutral cross-coupling reactions of carboxylic acids in organic synthesis.⁴⁻⁸ Based on our experience in amide bond cross-coupling and considering the widespread availability and the remarkable potential of the direct cross-coupling of carboxylic acids, we proposed that the overall net decarbonylative-like process could be achieved by sequential C(acyl)-O bond activation and controlled decarbonylation, thus engaging carboxylic acids in a modular decarbonylative cross-coupling platform.^{4,5} We proposed that this strategy could furnish both carbon–carbon and carbon–heteroatom bonds via the classical oxidative addition mechanism¹³ under redox-neutral conditions, with the goal of providing an effective solution to the routine application of carboxylic acids as ubiquitous cross-coupling partners in chemical synthesis (Figure 4.1.1).

At the beginning of this project, we first targeted decarbonylative borylation of carboxylic acids because of the key importance of aryl–boron bonds in various areas of chemistry (Figure 4.1.2).¹⁴ Previous studies have shown that decarbonylative borylation of esters and amides with Ni and Rh catalysis is feasible;¹⁵ however, at the start of this project no method for either the versatile Pd-catalyzed borylation¹⁶ or much more broadly applicable borylation of carboxylic acids^{1,2,10-12} in any form was available, which highlighted the challenge that these substrates presented to a decarbonylative processes.

A Classic electrophiles in cross-coupling

■ X = Hal (I, Br, Cl, F), OTs, N₂, NR'₃⁺, OR', OCOR', OCONR'₂

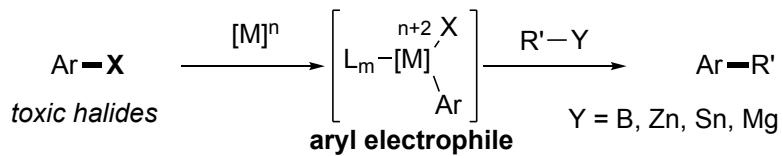
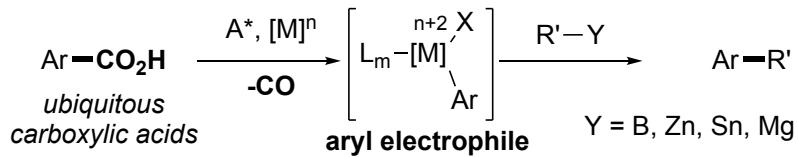
**B Decarbonylative cross-coupling**

Figure 4.1.1 Cross-coupling of aryl halides and carboxylic acids.

4.1.2 Reaction optimization

We first examined the proposed coupling using benzoic acid and B₂pin₂ as model substrates (Table 4.1.1). To our delight, we found that the combination of Pd(OAc)₂ (5 mol%) and dppb (10 mol%) in the presence of piv₂O (1.5 equiv), and Et₃N (1.5 equiv) as base delivered the desired coupling product in 95% yield on a gram scale.¹⁷ Selected optimization experiments are presented in Table 4.1.1. Importantly, in all cases examined, formation of acyl products was not detected in crude reaction mixtures, consistent with high capability of the metal catalyst system to facilitate decarbonylation.

Table 4.1.1 Optimization of Pd-catalyzed decarbonylative borylation of carboxylic acids.^a

Ph-CO₂H		+ B ₂ pin ₂		[Pd cat.]	-CO	Ph-Bpin	4.1.2a
entry	catalyst	ligand	base	additive	acid:B:base:add	yield (%) ^a	
1					1:1.5:0:0	<2	
2	Pd(OAc) ₂	DPPB	Et ₃ N		1:1.5:1.5:0	<2	
3	Pd(OAc) ₂	DPPB		Piv ₂ O	1:1.5:1.5:1.5	60	
4	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	1:1.5:1.5:1.5	95	
5	Pd(OAc) ₂	DPPB	DMAP	Piv ₂ O	1:1.5:1.5:1.5	95	
6	Pd(OAc) ₂	DPPB	Na ₂ CO ₃	Piv ₂ O	1:1.5:1.5:1.5	78	
7	Pd(OAc) ₂	DPPB	K ₂ CO ₃	Piv ₂ O	1:1.5:1.5:1.5	<2	
8	Pd(OAc) ₂	DPPB	Et ₃ N	Boc ₂ O	1:1.5:1.5:1.5	16	
9	Pd(OAc) ₂	DPPB	Et ₃ N	Ac ₂ O	1:1.5:1.5:1.5	23	
10	Pd(OAc) ₂	DPPB	Et ₃ N	PivCl	1:1.5:1.5:1.5	39	
11 ^b	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	1:1.5:1.5:1.5	76	
12 ^c	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	1:1.5:1.5:1.5	53	
13 ^d	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	1:1.5:1.5:1.5	57	
14 ^e	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	1:1.5:1.5:1.5	95	
15 ^f	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	1:1.5:1.5:1.5	92	
16	Pd(OAc) ₂	XantPhos	Et ₃ N	Piv ₂ O	1:1.5:1.5:1.5	52	
17	Pd(OAc) ₂	DPPF	Et ₃ N	Piv ₂ O	1:1.5:1.5:1.5	56	
18	Pd(OAc) ₂	PCy ₃ BF ₄	Et ₃ N	Piv ₂ O	1:1.5:1.5:1.5	9	

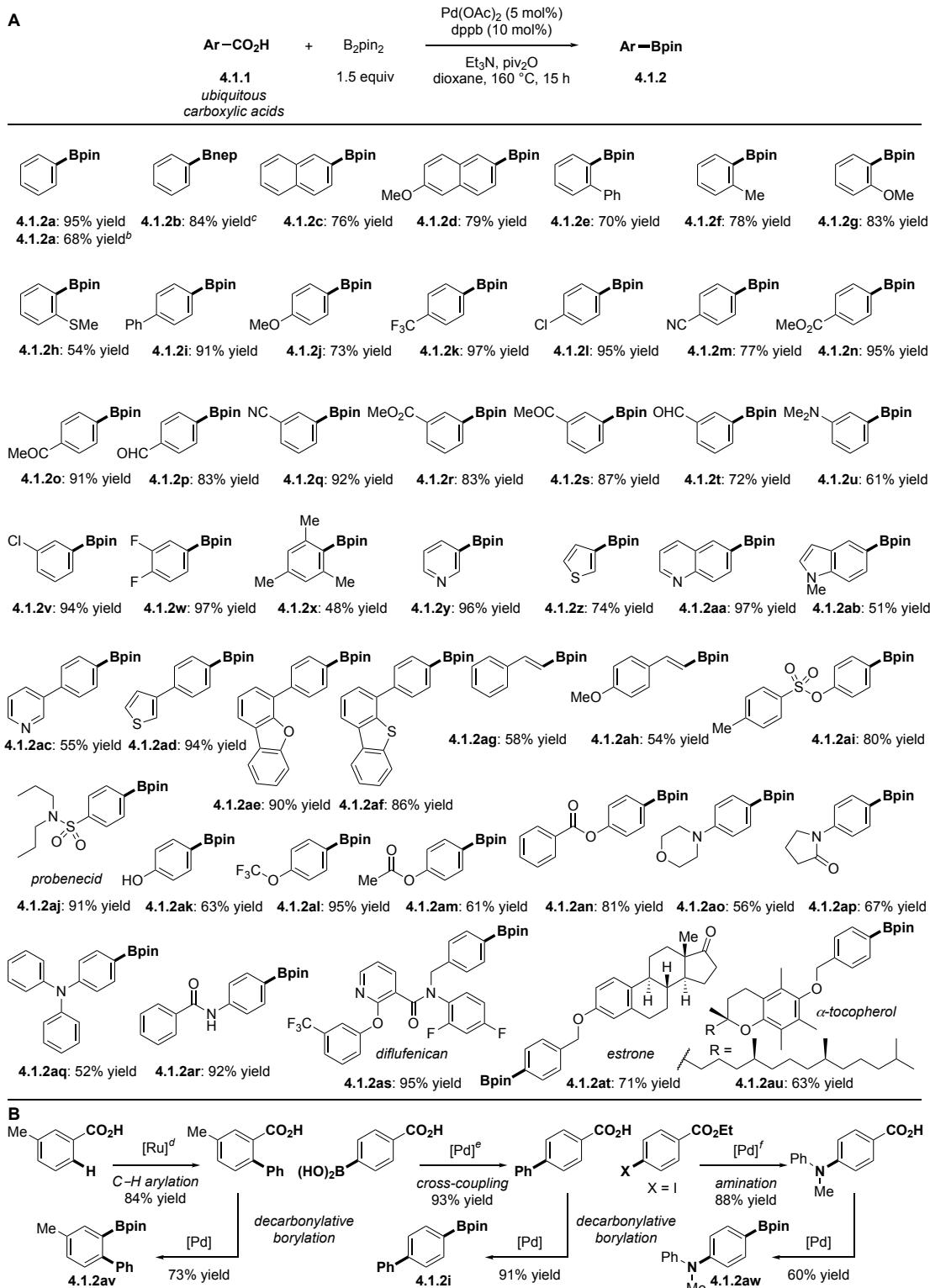
Conditions: **4.1.1a** (1.0 equiv), B₂pin₂ (1.5 equiv), Pd(OAc)₂ (5 mol%), ligand (10 mol%), Et₃N (1.5 equiv), Piv₂O (1.5 equiv), dioxane (0.20 M), 160 °C, 15 h. ^aDetermined by ¹H NMR and/or GC-MS. ^b140 °C. ^c120 °C. ^d1.0 M. ^e1 h. ^fToluene.

4.1.3 Substrate scope

Having identified the optimal conditions, we next examined the scope of this new aryl–B forming reaction using common carboxylic acids substrates (Scheme 4.1.1). As shown, the scope of the reaction was very broad and tolerated an extensive array of carboxylic acids, including simple (**4.1.2a-d**) and sterically-hindered carboxylic acids (**4.1.2e-h**, **4.1.2x**), as well as those bearing diverse neutral, electron-donating and electron-withdrawing substituents (**4.1.2d-w**). Perhaps the most notable feature of new method was the capacity to tolerate a broad range of functional groups that are poised for further manipulation or form key components in synthetic routes across all research settings, including halides (**4.1.2l**, **4.1.2v-w**), nitriles (**4.1.2m**, **4.1.2q**), esters (**4.1.2n**, **4.1.2r**, **4.1.2am**, **4.1.2an**), ketones (**4.1.2o**, **4.1.2s**, **4.1.2at**), aldehydes (**4.1.2p**, **4.1.2t**), amides (**4.1.2ap**, **4.1.2ar**), phenols (**4.1.2ak**), anilines (**4.1.2u**, **4.1.2ao**, **4.1.2aq**, **4.1.2as**), nitrogen- (**4.1.2y**, **4.1.2aa**, **4.1.2ab**, **4.1.2ac**, **4.1.2as**), sulfur- (**4.1.2z**, **4.1.2ad**, **4.1.2af**) and oxygen-heterocycles (**4.1.2ae**, **4.1.2ao**), amines (**4.1.2u**, **4.1.2ao**), lactams (**4.1.2ap**), sulfonate esters (**4.1.2ai**), sulfonamides (**4.1.2aj**), trifluoromethyl ethers (**4.1.2al**). It was particularly noteworthy that this protocol provided direct access to late-stage derivatization of drugs (probenecid, **4.1.2aj**), pesticides (diflufenican, **4.1.2as**), bioactive probes (estrone, **4.1.2at**) and natural products (tocopherol, **4.1.2au**). Clearly, the scope of these reactions was enabled by the direct utilization of the carboxylic acid functional group, and further illustrated the excellent functional group tolerance of our protocol.

As a further evidence of the synthetic utility of this new aryl–B forming method, we demonstrated illustrative protocols for sequential cross-coupling exploiting orthogonal properties of carboxylic acids to provide high-value traceless mode of reactivity,

including C–H arylation/borylation (**4.1.2av**),¹⁸ Suzuki–Miyaura cross-coupling/borylation (**4.1.2i**),¹⁹ and amination/borylation (**4.1.2aw**)²⁰ according to the Buchwald protocol (Scheme 4.1.1).



Scheme 4.1.1 Scope of decarbonylative borylation of carboxylic acids.

4.1.4 Conclusion

In conclusion, our study demonstrated that this direct borylation methodology of carboxylic acids serves as a powerful tool to control selective decarbonylative cross-coupling directly utilizing carboxylic acids. We proposed that with all the benefits that carboxylic acids bring to organic synthesis, this decarbonylative, redox-neutral approach should greatly expand the development of a wide variety of novel cross-coupling reactions.

4.1.5 Experimental section

General Procedure for Decarbonylative Borylation of Carboxylic Acids. An oven-dried vial equipped with a stir bar was charged with carboxylic acid (neat, 1.0 equiv), diboronate ester (neat, 1.5 equiv), Pd(OAc)₂ (typically, 5 mol%), ligand (typically, 10 mol%), triethylamine (typically, 1.5 equiv) and trimethylacetic anhydride (1.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.20 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 160 °C, and stirred for the indicated time at 160 °C. After the indicated time, the reaction mixture was cooled down to room temperature. Then the sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples.

4.1.2a. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.84-7.83 (d, $J = 6.9$ Hz, 2 H), 7.50-7.47 (t, $J = 7.4$ Hz, 1 H), 7.41-7.38 (t, $J = 7.6$ Hz, 2 H), 1.37 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 134.75, 131.26, 127.71, 83.78, 24.88. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2b. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.83-7.82 (d, $J = 7.2$ Hz, 2 H), 7.46-7.43 (t, $J = 7.0$ Hz, 1 H), 7.39-7.36 (t, $J = 7.4$ Hz, 2 H), 3.80 (s, 4 H), 1.05 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 133.82, 130.68, 127.59, 72.33, 31.90, 21.93. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2c. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.40 (s, 1 H), 7.92-7.90 (d, $J = 7.9$ Hz, 1 H), 7.88-7.84 (m, 3 H), 7.55-7.48 (m, 2 H), 1.42 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 136.25, 135.04, 132.83, 130.41, 128.67, 127.72, 126.98, 126.97, 125.80, 83.94, 24.94. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.31 (s, 1 H), 7.82-7.79 (m, 2 H), 7.75-7.73 (d, $J = 8.2$ Hz, 1 H), 7.17-7.15 (m, 2 H), 3.95 (s, 3 H), 1.41 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.55, 136.44, 135.99, 131.12, 130.26, 128.39, 125.92, 118.69, 105.63, 83.80, 55.30, 24.93. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2e. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.75-7.73 (d, $J = 6.6$ Hz, 1 H), 7.49-7.46 (m, 1 H), 7.43-7.34 (m, 7 H), 1.23 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 147.52, 143.26, 134.44, 130.07, 129.14, 128.97, 127.77, 126.83, 126.28, 83.73, 24.60. The

carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2f. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.77 (d, $J = 6.8$ Hz, 1 H), 7.35-7.32 (t, $J = 7.5$ Hz, 1 H), 7.19-7.17 (t, $J = 7.0$ Hz, 2 H), 2.56 (s, 3 H), 1.37 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 144.84, 135.86, 130.79, 129.78, 124.71, 83.41, 24.90, 22.22.

The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2g. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.70-7.69 (d, $J = 7.0$ Hz, 1 H), 7.43-7.40 (t, $J = 7.5$ Hz, 1 H), 6.98-6.95 (t, $J = 7.3$ Hz, 1 H), 6.89-6.87 (d, $J = 8.4$ Hz, 1 H), 3.86 (s, 3 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.17, 136.71, 132.46, 120.19, 110.46, 83.45, 55.82, 24.84. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2h. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.71-7.70 (m, 1 H), 7.41-7.37 (m, 1 H), 7.20-7.18 (d, $J = 8.0$ Hz, 1 H), 7.14-7.11 (m, 1 H), 2.48 (s, 3 H), 1.40 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.19, 135.94, 131.24, 123.91, 123.67, 84.00, 24.86, 15.75.

The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2i. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.92-7.90 (d, $J = 8.1$ Hz, 2 H), 7.65-7.63 (m, 4 H), 7.48-7.45 (t, $J = 7.5$ Hz, 2 H), 7.40-7.37 (t, $J = 7.4$ Hz, 1 H), 1.39 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.90, 141.04, 135.26, 128.78, 127.56, 127.25, 126.48, 83.84, 24.90. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2j. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.77 (d, $J = 8.6$ Hz, 2 H), 6.93-6.91 (d, $J = 8.7$ Hz, 2 H), 3.85 (s, 3 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.16, 136.52, 113.32, 83.56, 55.10, 24.87. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2k. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.94-7.93 (d, $J = 7.7$ Hz, 2 H), 7.64-7.63 (d, $J = 7.9$ Hz, 2 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 135.01, 132.83 (q, $J^F = 31.9$ Hz), 124.33 (q, $J^F = 3.7$ Hz), 124.14 (q, $J^F = 270.7$ Hz), 84.28, 24.87. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening. ^{19}F NMR (471 MHz, CDCl_3) δ -62.97.

4.1.2l. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.76-7.74 (d, $J = 8.3$ Hz, 2 H), 7.37-7.36 (d, $J = 8.3$ Hz, 2 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 137.54, 136.13, 128.02, 84.03, 24.87. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2m. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.91-7.90 (d, $J = 8.0$ Hz, 2 H), 7.67-7.66 (d, $J = 8.0$ Hz, 2 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 135.11, 131.15, 118.89, 114.56, 84.51, 24.88. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2n. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.05-8.03 (d, $J = 8.2$ Hz, 2 H), 7.90-7.88 (d, $J = 8.2$ Hz, 2 H), 3.95 (s, 3 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.16, 134.67, 132.32, 128.61, 84.19, 52.16, 24.89. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2o. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.96-7.91 (m, 4 H), 2.64 (s, 3 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.48, 139.01, 134.93, 127.30, 84.23, 26.78, 24.89. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2p. White solid. ^1H NMR (500 MHz, CDCl_3) δ 10.07 (s, 1 H), 7.99-7.98 (d, $J = 8.0$ Hz, 2 H), 7.90-7.88 (d, $J = 8.1$ Hz, 2 H), 1.39 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 192.68, 138.13, 135.23, 128.72, 84.35, 24.90. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2q. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.12 (s, 1 H), 8.03-8.02 (d, $J = 7.5$ Hz, 1 H), 7.75-7.74 (d, $J = 7.8$ Hz, 1 H), 7.51-7.48 (t, $J = 7.7$ Hz, 1 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 138.74, 138.43, 134.41, 128.39, 118.85, 112.10, 84.50, 24.87. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2r. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.49 (s, 1 H), 8.16-8.14 (d, $J = 7.8$ Hz, 1 H), 8.01-8.00 (d, $J = 7.4$ Hz, 1 H), 7.49-7.46 (t, $J = 7.6$ Hz, 1 H), 3.94 (s, 3 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.19, 139.16, 135.84, 132.31, 129.59, 127.82, 84.11, 52.04, 24.89. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2s. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.38 (s, 1 H), 8.09-8.08 (d, $J = 7.9$ Hz, 1 H), 8.02-8.01 (d, $J = 7.3$ Hz, 1 H), 7.51-7.48 (t, $J = 7.6$ Hz, 1 H), 2.66 (s, 3 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.44, 139.42, 136.54, 134.83, 130.78, 128.06,

84.17, 26.78, 24.89. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2t. White solid. ^1H NMR (500 MHz, CDCl_3) δ 10.07 (s, 1 H), 8.33 (s, 1 H), 8.09-8.07 (d, $J = 7.4$ Hz, 1 H), 8.02-8.00 (d, $J = 7.7$ Hz, 1 H), 7.57-7.54 (t, $J = 7.5$ Hz, 1 H), 1.39 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 192.59, 140.69, 137.25, 135.79, 131.31, 128.44, 84.29, 24.90. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2u. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.30-7.27 (m, 1 H), 7.21-7.20 (m, 2 H), 6.89-6.87 (m, 1 H), 2.99 (s, 6 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.16, 128.50, 123.25, 118.71, 115.83, 83.62, 40.80, 24.86. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2v. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.80 (s, 1 H), 7.69-7.68 (d, $J = 7.3$ Hz, 1 H), 7.46-7.43 (m, 1 H), 7.34-7.31 (t, $J = 7.7$ Hz, 1 H), 1.37 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 134.57, 134.05, 132.65, 131.28, 129.20, 84.15, 24.87. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2w. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.62-7.58 (t, $J = 9.1$ Hz, 1 H), 7.56-7.53 (m, 1 H), 7.19-7.14 (m, 1 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 152.70 (dd, $J^F = 250.7$ Hz), 150.23 (dd, $J^F = 247.4$ Hz), 131.37 (q, $J^F = 2.8$ Hz), 123.32 (d, $J^F = 15.5$ Hz), 116.94 (d, $J^F = 16.3$ Hz), 84.24, 24.85. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening. ^{19}F NMR (471 MHz, CDCl_3) δ -133.80, -139.46.

4.1.2x. White solid. ^1H NMR (500 MHz, CDCl_3) δ 6.79 (s, 2 H), 2.39 (s, 6 H), 2.26 (s, 3 H), 1.39 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 142.13, 138.93, 127.45, 83.46, 24.96, 22.19, 21.24. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2y. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.94 (s, 1 H), 8.67-8.66 (d, $J = 4.3$ Hz, 1 H), 8.10-8.09 (d, $J = 7.3$ Hz, 1 H), 7.33-7.30 (t, $J = 6.1$ Hz, 1 H), 1.33 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 154.29, 150.72, 143.12, 123.43, 84.35, 24.81. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2z. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.95-7.94 (d, $J = 1.9$ Hz, 1 H), 7.44-7.43 (d, $J = 4.1$ Hz, 1 H), 7.37-7.36 (m, 1 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 136.46, 132.03, 125.33, 83.66, 24.84. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2aa. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.97-8.96 (d, $J = 4.1$ Hz, 1 H), 8.37 (s, 1 H), 8.22-8.21 (d, $J = 8.2$ Hz, 1 H), 8.10 (s, 2 H), 7.44-7.42 (m, 1 H), 1.42 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 151.40, 149.77, 136.71, 136.14, 134.24, 128.51, 127.68, 121.16, 84.20, 24.94. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2ab. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.18 (s, 1 H), 7.70-7.68 (d, $J = 8.2$ Hz, 1 H), 7.35-7.33 (d, $J = 8.3$ Hz, 1 H), 7.06-7.06 (d, $J = 3.1$ Hz, 1 H), 6.53-6.52 (d, $J = 3.6$ Hz, 1 H), 3.82 (s, 3 H), 1.39 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 138.64, 128.90, 128.83, 128.22, 127.62, 108.58, 101.68, 83.40, 30.95, 24.92. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2ac. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.91-8.90 (d, $J = 1.8$ Hz, 1 H), 8.64-8.63 (m, 1 H), 7.95-7.94 (d, $J = 8.2$ Hz, 3 H), 7.63-7.61 (d, $J = 8.2$ Hz, 2 H), 7.43-7.40 (m, 1 H), 1.39 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.33, 148.01, 140.28, 136.66, 135.53, 134.77, 126.43, 123.70, 83.99, 24.89. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2ad. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.86 (d, $J = 7.7$ Hz, 2 H), 7.64-7.63 (d, $J = 7.5$ Hz, 2 H), 7.54 (s, 1 H), 7.46-7.45 (d, $J = 4.8$ Hz, 1 H), 7.42-7.41 (d, $J = 2.9$ Hz, 1 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 142.24, 138.39, 135.34, 126.34, 126.25, 125.69, 120.93, 83.81, 24.89. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2ae. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.02-8.00 (d, $J = 8.1$ Hz, 3 H), 7.98-7.94 (m, 3 H), 7.66-7.61 (m, 2 H), 7.51-7.44 (m, 2 H), 7.40-7.37 (t, $J = 7.7$ Hz, 1 H), 1.41 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.20, 153.43, 139.22, 135.09, 128.14, 127.25, 126.91, 125.82, 124.96, 124.17, 123.19, 122.78, 120.68, 119.94, 111.90, 83.87, 24.91. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2af. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.22-8.18 (m, 2 H), 8.00-7.99 (d, $J = 8.1$ Hz, 2 H), 7.87-7.85 (m, 1 H), 7.79-7.78 (d, $J = 8.2$ Hz, 2 H), 7.60-7.57 (t, $J = 7.6$ Hz, 1 H), 7.53-7.51 (m, 1 H), 7.50-7.48 (m, 2 H), 1.41 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.35, 139.61, 138.57, 136.92, 136.28, 135.75, 135.28, 127.60, 126.95, 126.82, 125.10, 124.38, 122.64, 121.73, 120.64, 83.93, 24.93. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2ag. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.51 (d, $J = 7.4$ Hz, 2 H), 7.44-7.41 (d, $J = 18.5$ Hz, 1 H), 7.39-7.30 (m, 3 H), 6.21-6.18 (d, $J = 18.5$ Hz, 1 H), 1.34 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.51, 138.65, 138.00, 128.89, 128.57, 127.06, 83.36, 24.83.

4.1.2ah. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.47-7.45 (d, $J = 8.7$ Hz, 2 H), 7.39-7.36 (d, $J = 18.4$ Hz, 1 H), 6.90-6.88 (d, $J = 8.6$ Hz, 2 H), 6.05-6.02 (d, $J = 18.4$ Hz, 1 H), 3.84 (s, 3 H), 1.33 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.30, 149.07, 130.42, 130.27, 128.48, 113.98, 83.23, 55.30, 24.82.

4.1.2ai. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.75-7.70 (m, 4 H), 7.32-7.31 (d, $J = 8.2$ Hz, 2 H), 7.00-6.99 (d, $J = 8.4$ Hz, 2 H), 2.46 (s, 3 H), 1.35 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 152.01, 145.34, 136.26, 132.37, 129.75, 128.55, 121.68, 84.09, 24.86, 21.72. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2aj. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.94-7.93 (d, $J = 8.2$ Hz, 2 H), 7.81-7.80 (d, $J = 8.3$ Hz, 2 H), 3.10-3.07 (t, $J = 7.7$ Hz, 4 H), 1.59-1.52 (m, 4 H), 1.38 (s, 12 H), 0.90-0.87 (t, $J = 7.4$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 142.37, 135.23, 126.04, 84.38, 49.96, 24.89, 21.95, 11.19. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2ak. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.85-7.84 (d, $J = 7.8$ Hz, 2 H), 7.09-7.07 (d, $J = 7.7$ Hz, 2 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 153.70, 136.12, 120.89, 83.88, 24.87. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2al. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.85 (d, $J = 8.5$ Hz, 2 H), 7.23-7.22 (d, $J = 7.9$ Hz, 2 H), 1.37 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 151.66, 136.52, 131.24 (q, $J^F = 878.8$ Hz), 119.89, 84.09, 24.87. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening. ^{19}F NMR (471 MHz, CDCl_3) δ -57.50.

4.1.2am. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.86-7.85 (d, $J = 8.4$ Hz, 2 H), 7.12-7.11 (d, $J = 8.4$ Hz, 2 H), 2.32 (s, 3 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.27, 153.19, 136.20, 120.96, 83.90, 24.86, 21.18. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2an. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.24-8.22 (d, $J = 7.1$ Hz, 2 H), 7.92-7.90 (d, $J = 8.4$ Hz, 2 H), 7.68-7.65 (t, $J = 7.5$ Hz, 1 H), 7.55-7.52 (t, $J = 7.9$ Hz, 2 H), 7.27-7.25 (d, $J = 8.5$ Hz, 2 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.97, 153.52, 136.26, 133.62, 130.21, 129.55, 128.59, 121.10, 83.93, 24.88. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2ao. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.75-7.74 (d, $J = 8.5$ Hz, 2 H), 6.91-6.90 (d, $J = 8.5$ Hz, 2 H), 3.89-3.87 (t, $J = 4.8$ Hz, 4 H), 3.26-3.24 (t, $J = 4.9$ Hz, 4 H), 1.35 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 153.38, 136.17, 114.10, 83.43, 66.80, 48.38, 24.86. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2ap. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.83-7.82 (d, $J = 8.4$ Hz, 2 H), 7.67-7.65 (d, $J = 8.5$ Hz, 2 H), 3.91-3.88 (t, $J = 7.0$ Hz, 2 H), 2.65-2.62 (t, $J = 8.1$ Hz, 2 H), 2.21-2.15 (m, 2 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 174.37, 141.99, 135.53,

118.59, 83.75, 48.58, 32.94, 24.87, 17.97. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2aq. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.69-7.68 (d, $J = 8.0$ Hz, 2 H), 7.31-7.29 (m, 1 H), 7.28-7.26 (m, 3 H), 7.14-7.12 (d, $J = 8.4$ Hz, 4 H), 7.08-7.04 (m, 4 H), 1.35 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 147.40, 135.85, 129.30, 125.00, 123.36, 121.80, 117.82, 83.57, 24.87. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2ar. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.91-7.88 (m, 3 H), 7.86-7.84 (d, $J = 8.4$ Hz, 2 H), 7.71-7.69 (d, $J = 8.4$ Hz, 2 H), 7.60-7.57 (t, $J = 7.4$ Hz, 1 H), 7.53-7.51 (t, $J = 7.8$ Hz, 2 H), 1.38 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.59, 140.60, 135.92, 131.97, 129.14, 128.86, 127.02, 118.87, 83.79, 24.89. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2as. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.04-8.03 (m, 1 H), 7.83-7.82 (d, $J = 7.4$ Hz, 1 H), 7.74-7.73 (d, $J = 8.0$ Hz, 2 H), 7.53-7.47 (m, 2 H), 7.33-7.31 (d, $J = 8.0$ Hz, 2 H), 7.16-7.14 (d, $J = 3.9$ Hz, 2 H), 7.00-6.98 (m, 1 H), 6.91-6.86 (m, 1 H), 6.69-6.65 (m, 1 H), 6.62-6.58 (t, $J = 8.8$ Hz, 1 H), 5.53-5.50 (d, $J = 14.4$ Hz, 1 H), 4.69-4.66 (d, $J = 14.6$ Hz, 1 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.15, 159.94 (q, $J^F = 250.5$ Hz), 157.41, 153.15, 148.46, 139.25, 138.71, 135.02, 131.91 (q, $J^F = 32.7$ Hz), 131.31 (q, $J^F = 10.2$ Hz), 130.04, 128.58, 128.05, 125.31 (q, $J^F = 8.1$ Hz), 124.67, 122.54, 121.66 (q, $J^F = 3.8$ Hz), 121.11, 118.75, 118.40 (q, $J^F = 3.9$ Hz), 111.44 (q, $J^F = 18.8$ Hz), 104.83 (q, $J^F = 25.8$ Hz), 83.89, 52.34, 24.88. The carbon directly attached to the boron

atom was not detected due to quadrupolar broadening. ^{19}F NMR (471 MHz, CDCl_3) δ - 62.62.

4.1.2at. White solid. $M_p = 124\text{-}127 \text{ }^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3) δ 7.85-7.83 (d, $J = 7.5 \text{ Hz}$, 2 H), 7.45-7.44 (d, $J = 7.5 \text{ Hz}$, 2 H), 7.22-7.20 (d, $J = 8.6 \text{ Hz}$, 1 H), 6.80-6.78 (d, $J = 9.0 \text{ Hz}$, 1 H), 6.74 (s, 1 H), 5.09 (s, 2 H), 2.93-2.89 (m, 2 H), 2.55-2.50 (m, 1 H), 2.42-2.40 (d, $J = 10.7 \text{ Hz}$, 1 H), 2.29-2.23 (m, 1 H), 2.20-2.13 (m, 1 H), 2.10-1.97 (m, 4 H), 1.66-1.60 (m, 2 H), 1.53-1.44 (m, 3 H), 1.37 (s, 12 H), 0.93 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.80, 140.48, 137.80, 135.01, 132.36, 126.44, 126.34, 115.00, 112.45, 83.82, 69.88, 50.45, 48.03, 44.01, 38.36, 35.89, 31.60, 29.65, 26.55, 25.91, 24.87, 21.60, 13.87. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening. HRMS calcd for $\text{C}_{31}\text{H}_{39}\text{O}_4\text{BNa}$ ($\text{M}^+ + \text{Na}$) 509.2839, found 509.2853.

4.1.2au. Orange oil. ^1H NMR (500 MHz, CDCl_3) δ 7.88-7.86 (d, $J = 7.5 \text{ Hz}$, 2 H), 7.53-7.52 (d, $J = 7.5 \text{ Hz}$, 2 H), 4.75 (s, 2 H), 2.63-2.60 (t, $J = 6.1 \text{ Hz}$, 2 H), 2.23 (s, 3 H), 2.18 (s, 3 H), 2.13 (s, 3 H), 1.88-1.77 (m, 2 H), 1.63-1.53 (m, 5 H), 1.38 (s, 12 H), 1.29-1.22 (m, 19 H), 0.90-0.87 (t, $J = 6.5 \text{ Hz}$, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.20, 134.95, 134.76, 133.67, 127.93, 127.71, 126.69, 122.94, 117.60, 83.78, 83.51, 74.59, 40.08, 39.39, 37.48, 37.44, 37.41, 37.31, 32.80, 32.72, 31.30, 28.00, 27.08, 24.89, 24.46, 23.91, 22.75, 22.66, 21.06, 20.78, 20.70, 19.78, 19.72, 12.02. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening. HRMS calcd for $\text{C}_{42}\text{H}_{67}\text{O}_4\text{BNa}$ ($\text{M}^+ + \text{Na}$) 669.5032, found 669.5035.

4.1.2av. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.55 (s, 1 H), 7.41-7.33 (m, 5 H), 7.31-7.27 (m, 3 H), 2.41 (s, 3 H), 1.24 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 144.74, 143.17, 135.77, 135.08, 130.86, 129.14, 128.99, 127.72, 126.62, 83.69, 24.61, 20.99. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

4.1.2aw. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.70-7.69 (d, $J = 7.9$ Hz, 2 H), 7.37-7.34 (t, $J = 7.5$ Hz, 2 H), 7.18-7.16 (d, $J = 8.1$ Hz, 2 H), 7.12-7.09 (t, $J = 7.4$ Hz, 1 H), 6.91-6.90 (d, $J = 7.9$ Hz, 2 H), 3.36 (s, 3 H), 1.35 (s, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 151.43, 148.37, 135.94, 129.43, 123.81, 123.47, 116.17, 83.37, 40.09, 24.85. The carbon directly attached to the boron atom was not detected due to quadrupolar broadening.

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4.2 Palladium-catalyzed decarbonylative reduction of carboxylic acids

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4.2.1 Introduction

The reduction of carboxylic acid derivatives is one of the most fundamental transformations in synthetic chemistry and catalysis.¹ Reduction reactions of carboxylic acids and derivatives are traditionally performed using stoichiometric metal hydrides.² However, these reagents suffer from major scope limitations and are inherently less safe than milder silane-based hydrides due to their pyrophoric nature.³ The reduction of carboxylic acid chlorides to aldehydes (acyl pathway) has been achieved by Rosenmund using Pd-catalysis⁴ via an oxidative insertion/transmetalation/reductive elimination mechanism,⁵ thus establishing the classic cross-coupling method for the synthesis of aldehydes from carboxylic acids (Figure 4.2.1A). More recently, a Ni-catalyzed step-down reduction of *N*-chelating amides directly to hydrocarbons has been achieved by Maiti and co-workers,⁶ while the Rueping group developed a selective methodology for the Ni-catalyzed step-down reduction of phenolic esters and *N*-acyl-glutarimides (Figure 4.2.1B),⁷ developed earlier by our group.⁸

In this project, we developed the first highly selective method for the direct step-down reduction of ubiquitous carboxylic acids to arenes by a decarbonylative pathway, which

proceeded via well-defined Pd(0)/(II) cycle (Figure 4.2.1C). The method superseded the two-step methods using less general substrates and showed much broader reaction scope owing to the versatility of Pd-catalysis.⁵

We recognized that the use of preformed carboxylic acid derivatives was the method of choice to effect the direct reduction to hydrocarbons (Figure 4.2.1B).^{6,7} However, these specifically designed and less general N- and O-derivatives (pyrazoles, glutarimides, phenolic esters) were prepared from carboxylic acids in a separate step. As such, a more straightforward approach engaging directly simple aromatic carboxylic acids would be of high synthetic value in this important reaction class using versatile Pd-catalysis (Figure 4.2.1C).

Specifically, we proposed that the direct reduction of carboxylic acids^{9,10} to hydrocarbons via previously unknown redox-neutral decarbonylative (loss of CO)¹¹⁻¹⁵ Pd(0)-catalyzed pathway would enable to use ubiquitous carboxylic acids as traceless activating groups, offering high level of predictability^{5a,b} and functional group tolerance^{5e-g} under redox-neutral conditions orthogonal to protodecarboxylation (loss of CO₂).¹⁶ Furthermore, the method could permit for a significantly more convenient approach to hydrocarbons than the reduction of designer N- and O-carboxylic acid derivatives, which are further limited by substrate scope.^{6,7} Since aromatic carboxylic acids are commercially synthesized from the corresponding and cheaper toluenes by oxidation, the method would establish Pd-promoted access to benzenes from feedstock toluenes, thus enabling to valorize oil as a mild alternative to toluene hydrodealkylation.¹⁷

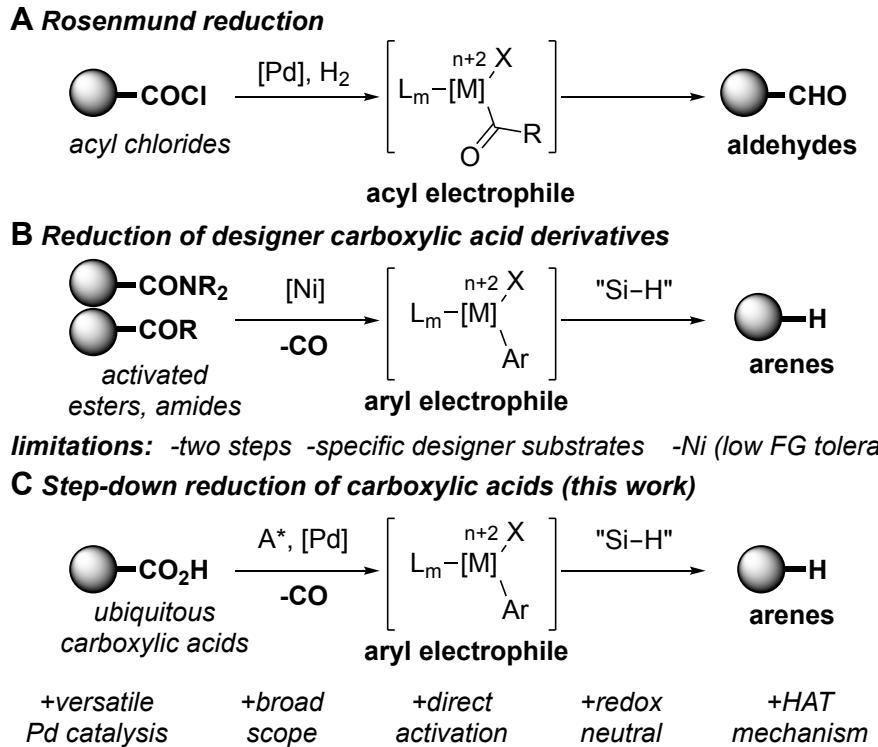
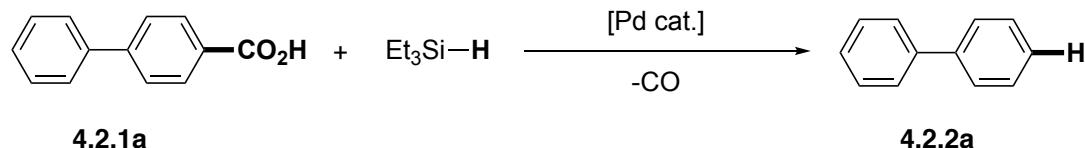


Figure 4.2.1 Transition-metal-catalyzed reduction of carboxylic acids.

4.2.2 Reaction optimization

We initiated our studies by probing the direct Pd-catalyzed reduction of electronically- and sterically-unbiased 4-phenyl benzoic acid as a model substrate. After extensive optimization (Table 4.2.1), we found that the reduction in the presence of $\text{Pd}(\text{OAc})_2$ (5 mol%), dppb (10 mol%, dppb = 1,4-bis(diphenylphosphino)butane), piv_2O (1.5 equiv, $\text{piv} = 2,2\text{-dimethylpropanoyl}$) and Et_3SiH (1.5 equiv) as a hydride source as the optimal condition afforded the desired product in 98% yield. Under the optimized conditions reduction to the aldehyde or aldehyde derived products was not observed, consistent with high facility of the catalytic system to trigger the reduction (cf. acyl pathway) under redox-neutral conditions.

Table 4.2.1 Optimization of Pd-catalyzed decarbonylative reduction of carboxylic acids.^a

entry	catalyst	ligand	base	additive	solvent	Acid:H:base:add	yield (%) ^a
1	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	dioxane	1:1.5:1.5:1.5	77
2	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	dioxane	1:2.0:1.5:1.5	73
3 ^b	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	dioxane	1:1.5:1.5:1.5	65
4 ^c	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	dioxane	1:1.5:1.5:1.5	45
5 ^d	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	dioxane	1:1.5:1.5:1.5	42
6	Pd(OAc) ₂	DPPB	Et ₃ N	Piv ₂ O	toluene	1:1.5:1.5:1.5	>98
7	Pd(OAc) ₂	DPPB	Et ₃ N	Ac ₂ O	toluene	1:1.5:1.5:1.5	89
8				Piv ₂ O	toluene	1:1.5:0:1.5	<2
9	Pd(OAc) ₂	DPPB			toluene	1:1.5:0:0	<2
10	Pd(OAc) ₂	DPPB		Piv ₂ O	toluene	1:1.5:0:1.5	>98
11	Pd(OAc) ₂			Piv ₂ O	toluene	1:1.5:0:1.5	<2
12 ^e	Pd(OAc) ₂	DPPB		Piv ₂ O	toluene	1:1.5:0:1.5	78
13 ^f	Pd(OAc) ₂	DPPB		Piv ₂ O	toluene	1:1.5:0:1.5	98
14 ^g	Pd(OAc) ₂	DPPB		Piv ₂ O	toluene	1:1.5:0:1.5	84
15 ^h	Pd(OAc) ₂	PCy ₃ HBF ₄		Piv ₂ O	toluene	1:1.5:0:1.5	63
16	Pd(OAc) ₂	XantPhos		Piv ₂ O	toluene	1:1.5:0:1.5	80
17	Pd(OAc) ₂	DPPF		Piv ₂ O	toluene	1:1.5:0:1.5	85
18	Pd(OAc) ₂	PCy ₃ HBF ₄		Piv ₂ O	toluene	1:1.5:0:1.5	31

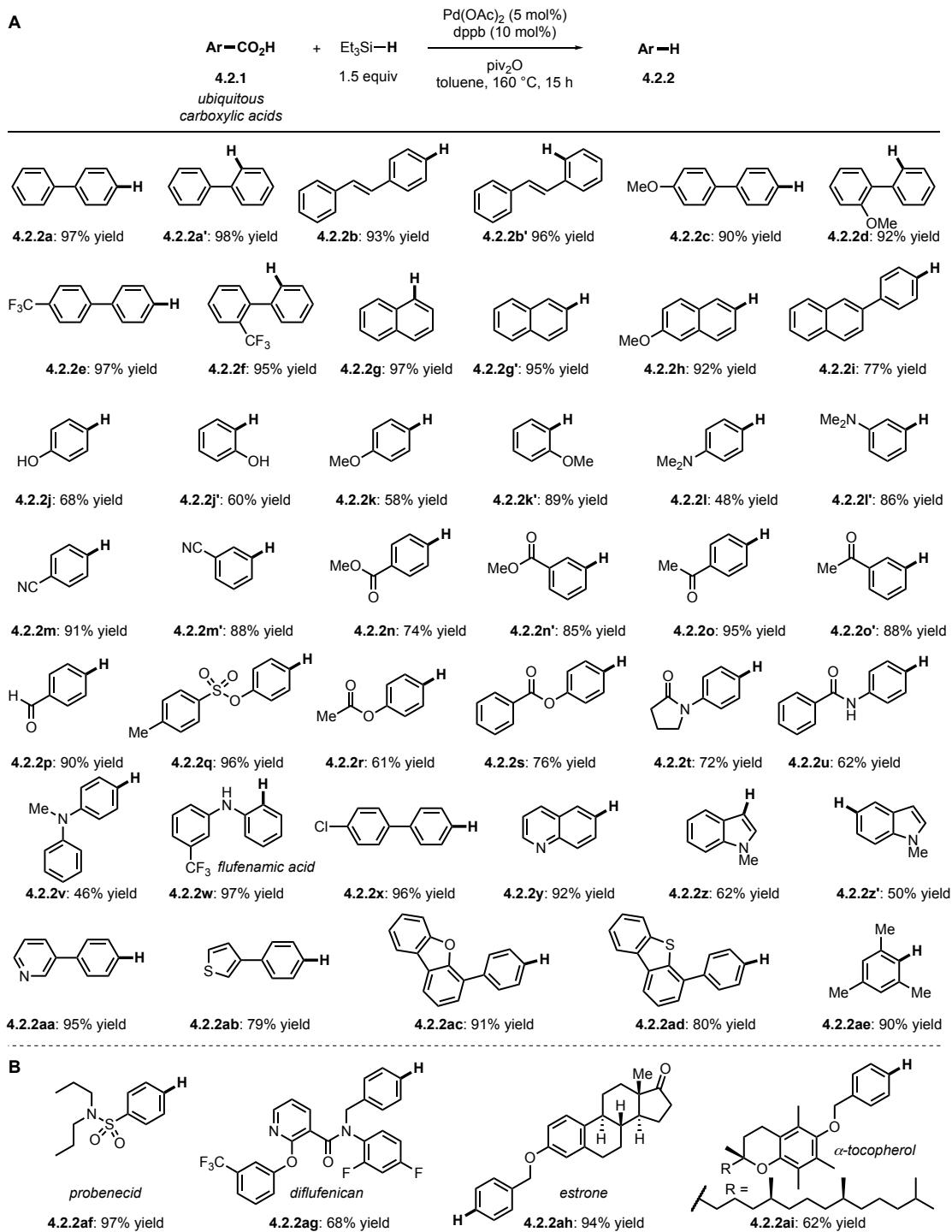
Conditions: carboxylic acid (1.0 equiv), Et₃SiH (1.5 equiv), Pd(OAc)₂ (5 mol%), ligand (10 mol%), piv₂O (1.5 equiv), toluene (0.20 M), 160 °C, 15 h. ^aDetermined by ¹H NMR and/or GC-MS. ^b140 °C. ^c120 °C. ^d100 °C. ^ePd(OAc)₂ (0.25 mol%), DPPB (0.5 mol%). ^fHMe₂Si-O-SiMe₂H. ^gEt₂SiH₂. ^hPh₂SiH₂.

4.2.3 Substrate scope

With optimal conditions in hand, we next examined the scope of the decarbonylative reduction of carboxylic acids (Scheme 4.2.1A). We were delighted to find that the scope of the reaction is very broad and compatible with a variety of functional groups. As shown, unbiased as well as sterically-hindered aryl (**4.2.2a-a'**, **4.2.2c-f**) and alkenyl (**4.2.2b-b'**) acids underwent smooth reduction. Substitution with electron-donating (**4.2.2c-d**) or electron-withdrawing (**4.2.2e-f**) groups was readily tolerated. Simple (**4.2.2g-g'**) and substituted naphthalenes (**4.2.2h-i**) were found to be competent substrates. Notably the reduction was not limited to conjugated arenes⁶ and could be applied to a broad range of benzoic acids bearing a variety of functional groups poised for further manipulation, including unprotected hydroxy (**4.2.2j-j'**), ethers (**4.2.2k-k'**), amines (**4.2.2l-l'**), nitriles (**4.2.2m-m'**), esters (**4.2.2n-n'**), ketones (**4.2.2o-o'**), aldehydes (**4.2.2p**), sulfonyl (**4.2.2q**), acyl groups (**4.2.2r-s**), amides (**4.2.2t-u**), amines (**4.2.2v-w**), and halides (**4.2.2x**). It was noteworthy that the reduction of a range of heterocycles, including quinolines (**4.2.2y**), indoles (**4.2.2z-z'**), pyridines (**4.2.2aa**), thiophenes (**4.2.2ab**), benzofurans (**4.2.2ac**) and benzothiophenes (**4.2.2ad**), as well as extremely sterically-hindered carboxylic acids (**4.2.2af**) proceeded in high yields and with full selectivity for decarbonylation. Overall, the scope of the reaction showed a number of clear advantages over other methods.^{6,7,9,10,11,16}

To demonstrate the generality and potential impact of this new reduction method, we applied this protocol to late-stage derivatization of bioactive natural products and pharmaceuticals (Scheme 4.2.1B). We were delighted to find that the decarbonylative reduction of probenecid (**4.2.2af**) as well as of carboxylic acids derived from a fluorine-

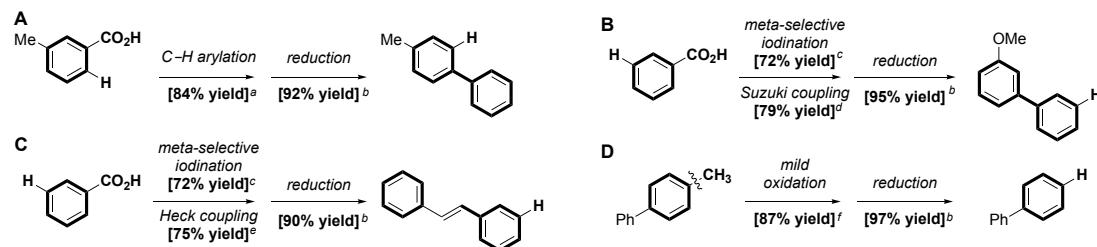
containing 18 diflufenican (**4.2.2ag**), estrone (**4.2.2ah**) and tocopherol (**4.2.2ai**) afforded the desired products in high yields, underscoring the mild conditions of our protocol.



Scheme 4.2.1 Scope of decarbonylative reduction of carboxylic acids.

4.2.4 Synthetic applications

As a further illustration of the synthetic utility of our method, we conducted a series of metal-catalyzed and metal-free reactions using carboxylic acid as a traceless directing group (Scheme 4.2.2). We were pleased to find that Ru-catalyzed ortho-arylation directed by carboxylic acid,¹⁹ electrophilic meta-iodination/Suzuki cross-coupling²⁰ and electrophilic meta-iodination/Heck cross-coupling²⁰ provided rapid access to a range of valuable products in high yields, thus highlighting the appeal of this novel method in organic synthesis. Furthermore, we showed that this decarbonylative reduction of carboxylic acids established valuable access to benzenes from feedstock toluenes (Scheme 4.2.2). In general, new valorization methods of oil processing products are of high interest from the industrial and sustainability standpoints.^{17a,b}



Scheme 4.2.2 Synthetic applications.

4.2.5 Conclusion

In conclusion, we have developed the first general method for the direct decarbonylative reduction of carboxylic acids to arenes using well-defined Pd(0)/(II) catalytic cycle. The broad scope of reactivity, tolerance to various sensitive functional groups and the potential to predictably use in functionalization of complex acids provide distinct advantages from other processes for removing carboxylic acid group in organic synthesis by catalytic reduction.^{6,7,9,10,11,16} Furthermore, this novel reduction process of carboxylic acids via a redox-neutral pathway should be benchmarked against the known methods for the reduction of carboxylic acid derivatives using Ni^{6,7} and the known methods via protodecarboxylation mechanism.¹⁶ This transformation encompasses a general manifold for decarbonylative redox-neutral cross-coupling of ubiquitous carboxylic acids via a unified mechanism that provides a range of new synthetic methods for manipulation of this privileged functional group.²⁵

4.2.6 Experimental section

General Procedure for Decarbonylative Reduction of Carboxylic Acids. An oven-dried vial equipped with a stir bar was charged with carboxylic acid (neat, 1.0 equiv), Pd(OAc)₂ (typically, 5 mol%), ligand (typically, 10 mol%), triethylsilane (typically, 1.5 equiv) and trimethylacetic anhydride (1.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (0.20 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 160 °C, and stirred for the indicated time at 160 °C. After the indicated time, the reaction mixture was cooled down to room temperature,

diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

4.2.2a. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.62 (d, $J = 7.3$ Hz, 4 H), 7.49-7.46 (t, $J = 7.5$ Hz, 4 H), 7.40-7.37 (t, $J = 7.4$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 141.26, 128.77, 127.27, 127.19.

4.2.2b. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.56-7.54 (d, $J = 7.5$ Hz, 4 H), 7.41-7.38 (t, $J = 7.5$ Hz, 4 H), 7.31-7.28 (t, $J = 7.4$ Hz, 2 H), 7.14 (s, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 137.35, 128.71, 128.70, 127.64, 126.53.

4.2.2c. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.59-7.55 (m, 4 H), 7.46-7.43 (t, $J = 7.6$ Hz, 2 H), 7.34-7.31 (t, $J = 7.4$ Hz, 1 H), 7.02-7.00 (d, $J = 8.7$ Hz, 2 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.15, 140.85, 133.80, 128.73, 128.17, 126.76, 126.67, 114.21, 55.37.

4.2.2d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.58-7.57 (d, $J = 7.6$ Hz, 2 H), 7.47-7.44 (t, $J = 7.5$ Hz, 2 H), 7.38-7.35 (t, $J = 7.1$ Hz, 3 H), 7.09-7.06 (t, $J = 7.5$ Hz, 1 H), 7.04-7.02 (d, $J = 8.6$ Hz, 1 H), 3.85 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.49, 138.57, 130.92, 130.75, 129.57, 128.64, 128.01, 126.94, 120.85, 111.25, 55.58.

4.2.2e. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.73 (s, 4 H), 7.64-7.63 (d, $J = 7.6$ Hz, 2 H), 7.52-7.49 (t, $J = 7.5$ Hz, 2 H), 7.46-7.43 (t, $J = 7.4$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 144.75, 139.79, 129.36 (q, $J^F = 32.3$ Hz), 129.01, 128.21, 127.44, 127.30, 125.73 (q, $J^F = 3.7$ Hz), 124.34 (q, $J^F = 270.2$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.39.

4.2.2f. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.78 (d, $J = 7.8$ Hz, 1 H), 7.60-7.58 (t, $J = 7.3$ Hz, 1 H), 7.51-7.48 (t, $J = 7.6$ Hz, 1 H), 7.43 (s, 3 H), 7.37 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 141.45 (q, $J^F = 1.9$ Hz), 139.87, 132.04, 131.28, 128.96 (q, $J^F = 1.4$ Hz), 128.49 (q, $J^F = 29.6$ Hz), 127.74, 127.61, 127.32, 126.05 (q, $J^F = 5.3$ Hz), 124.18 (q, $J^F = 272.2$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -56.83.

4.2.2g. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.93-7.91 (m, 4 H), 7.56-7.54 (m, 4 H). ^{13}C NMR (125 MHz, CDCl_3) δ 133.53, 127.96, 125.89.

4.2.2h. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.80-7.76 (m, 3 H), 7.48-7.45 (t, $J = 7.1$ Hz, 1 H), 7.37-7.35 (t, $J = 7.2$ Hz, 1 H), 7.19-7.17 (m, 2 H), 3.95 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 157.61, 134.58, 129.40, 128.97, 127.67, 126.75, 126.38, 123.60, 118.73, 105.76, 55.31.

4.2.2i. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.08 (s, 1 H), 7.96-7.92 (t, $J = 8.8$ Hz, 2 H), 7.91-7.89 (d, $J = 7.8$ Hz, 1 H), 7.79-7.75 (m, 3 H), 7.55-7.50 (m, 4 H), 7.43-7.40 (t, $J = 7.3$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 141.15, 138.58, 133.69, 132.63, 128.87, 128.42, 128.21, 127.66, 127.45, 127.37, 126.30, 125.94, 125.82, 125.61.

4.2.2j. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.30-7.27 (t, $J = 7.7$ Hz, 2 H), 6.99-6.96 (t, $J = 7.4$ Hz, 1 H), 6.88-6.87 (d, $J = 8.2$ Hz, 2 H), 4.99 (s, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 155.40, 129.73, 120.89, 115.34.

4.2.2k. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.31 (t, $J = 7.6$ Hz, 2 H), 6.99-6.97 (t, $J = 7.3$ Hz, 1 H), 6.95-6.93 (d, $J = 8.3$ Hz, 2 H), 3.84 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.56, 129.46, 120.66, 113.90, 55.15.

4.2.2l. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.31-7.28 (d, $J = 8.1$ Hz, 2 H), 6.81-6.76 (m, 3 H), 2.99 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.69, 129.10, 116.65, 112.69, 40.65.

4.2.2m. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.68-7.67 (d, $J = 8.3$ Hz, 2 H), 7.64-7.61 (t, $J = 7.6$ Hz, 1 H), 7.51-7.48 (t, $J = 7.9$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 132.80, 132.17, 129.15, 118.87, 112.46.

4.2.2n. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.08-8.06 (d, $J = 7.6$ Hz, 2 H), 7.59-7.57 (t, $J = 7.4$ Hz, 1 H), 7.48-7.45 (t, $J = 7.7$ Hz, 2 H), 3.94 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.14, 132.92, 130.18, 129.58, 128.37, 52.11.

4.2.2o. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.99-7.97 (d, $J = 7.4$ Hz, 2 H), 7.60-7.57 (t, $J = 7.4$ Hz, 1 H), 7.50-7.47 (t, $J = 7.8$ Hz, 2 H), 2.63 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.18, 137.14, 133.12, 128.59, 128.32, 26.63.

4.2.2p. White solid. ^1H NMR (500 MHz, CDCl_3) δ 10.05 (s, 1 H), 7.92-7.90 (d, $J = 8.3$ Hz, 2 H), 7.68-7.65 (t, $J = 7.3$ Hz, 1 H), 7.58-7.55 (t, $J = 7.7$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 192.42, 136.42, 134.48, 129.77, 129.02.

4.2.2q. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.73-7.72 (d, $J = 7.6$ Hz, 2 H), 7.33-7.25 (m, 5 H), 7.01-7.00 (d, $J = 7.8$ Hz, 2 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.67, 145.33, 132.44, 129.74, 129.61, 128.54, 127.09, 122.41, 21.73.

4.2.2r. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.42-7.39 (t, $J = 7.7$ Hz, 2 H), 7.27-7.24 (t, $J = 7.4$ Hz, 1 H), 7.12-7.11 (d, $J = 8.6$ Hz, 2 H), 2.33 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.49, 150.72, 129.44, 125.84, 121.59, 21.15.

4.2.2s. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.25-8.24 (d, $J = 8.0$ Hz, 2 H), 7.69-7.66 (t, $J = 7.3$ Hz, 1 H), 7.56-7.53 (t, $J = 7.7$ Hz, 2 H), 7.48-7.45 (t, $J = 7.8$ Hz, 2 H), 7.32-7.29 (t, $J = 7.4$ Hz, 1 H), 7.26-7.25 (d, $J = 8.2$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.21, 150.99, 133.60, 130.20, 129.62, 129.52, 128.59, 125.91, 121.74.

4.2.2t. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.62 (d, $J = 8.0$ Hz, 2 H), 7.41-7.38 (t, $J = 7.9$ Hz, 2 H), 7.18-7.15 (t, $J = 7.4$ Hz, 1 H), 3.91-3.88 (t, $J = 7.0$ Hz, 2 H), 2.65-2.62 (t, $J = 8.1$ Hz, 2 H), 2.22-2.16 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 174.23, 139.42, 128.84, 124.52, 119.98, 48.80, 32.78, 18.06.

4.2.2u. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.90-7.89 (d, $J = 7.6$ Hz, 3 H), 7.68-7.66 (d, $J = 8.1$ Hz, 2 H), 7.59-7.56 (t, $J = 7.3$ Hz, 1 H), 7.52-7.49 (t, $J = 7.7$ Hz, 2 H), 7.41-7.38 (t, $J = 7.7$ Hz, 2 H), 7.20-7.17 (t, $J = 7.4$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.75, 137.94, 135.03, 131.87, 129.13, 128.82, 127.03, 124.60, 120.21.

4.2.2v. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.29 (t, $J = 8.1$ Hz, 4 H), 7.06-7.04 (d, $J = 8.1$ Hz, 4 H), 7.00-6.97 (t, $J = 7.3$ Hz, 2 H), 3.35 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.05, 129.20, 121.26, 120.45, 40.25.

4.2.2w. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.33 (m, 3 H), 7.29 (s, 1 H), 7.22-7.21 (d, $J = 8.4$ Hz, 1 H), 7.16-7.13 (t, $J = 8.2$ Hz, 3 H), 7.06-7.03 (t, $J = 7.4$ Hz, 1 H), 5.85 (s, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 144.06, 141.78, 131.78 (q, $J^F = 31.8$ Hz), 129.84, 129.59, 124.11 (q, $J^F = 270.7$ Hz), 122.37, 119.74, 119.06, 116.94 (q, $J^F = 3.8$ Hz), 113.23 (q, $J^F = 3.9$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.87.

4.2.2x. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.60-7.58 (d, $J = 7.5$ Hz, 2 H), 7.56-7.55 (d, $J = 8.4$ Hz, 2 H), 7.50-7.44 (m, 4 H), 7.42-7.39 (t, $J = 7.3$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 140.03, 139.70, 133.41, 128.94, 128.91, 128.42, 127.62, 127.02.

4.2.2y. White solid. ^1H NMR (500 MHz, CDCl_3) δ 10.24 (s, 1 H), 9.09 (s, 1 H), 8.39-8.36 (m, 2 H), 8.26-8.22 (m, 2 H), 7.57-7.55 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 153.15, 150.94, 137.50, 134.37, 133.64, 130.87, 127.75, 126.80, 122.25.

4.2.2z. White solid. ^1H NMR (500 MHz, CDCl_3) δ 10.06 (s, 1 H), 8.18 (s, 1 H), 7.84-7.82 (d, $J = 8.6$ Hz, 1 H), 7.44-7.43 (d, $J = 8.5$ Hz, 1 H), 7.18-7.18 (d, $J = 3.0$ Hz, 1 H), 6.68-6.68 (d, $J = 2.9$ Hz, 1 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 139.96, 130.73, 129.32, 128.23, 126.47, 121.85, 109.79, 103.27, 33.16.

4.2.2aa. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.88 (s, 1 H), 8.63-8.62 (d, $J = 4.5$ Hz, 1 H), 7.91-7.90 (d, $J = 7.9$ Hz, 1 H), 7.62-7.61 (d, $J = 7.5$ Hz, 2 H), 7.53-7.50 (t, $J = 7.5$ Hz, 2 H), 7.45-7.42 (t, $J = 7.4$ Hz, 1 H), 7.41-7.38 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.49, 148.37, 137.87, 136.67, 134.39, 129.10, 128.12, 127.18, 123.56.

4.2.2ab. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.64-7.62 (d, $J = 7.5$ Hz, 1 H), 7.48-7.40 (m, 4 H), 7.39-7.36 (m, 2 H), 7.34-7.31 (t, $J = 7.3$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 142.40, 135.89, 128.81, 127.14, 126.47, 126.37, 126.20, 120.18.

4.2.2ac. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.04-8.03 (d, $J = 7.7$ Hz, 1 H), 7.99-7.96 (t, $J = 7.4$ Hz, 3 H), 7.66-7.64 (d, $J = 7.9$ Hz, 2 H), 7.61-7.58 (t, $J = 7.6$ Hz, 2 H), 7.53-7.46 (m, 3 H), 7.42-7.39 (t, $J = 7.5$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.22, 153.41, 136.48, 128.86, 128.70, 127.83, 127.26, 126.91, 125.93, 124.95, 124.26, 123.24, 122.80, 120.71, 119.70, 111.90.

4.2.2ad. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.23-8.18 (m, 2 H), 7.87-7.85 (d, J = 8.4 Hz, 1 H), 7.78-7.77 (d, J = 7.8 Hz, 2 H), 7.61-7.46 (m, 7 H). ^{13}C NMR (125 MHz, CDCl_3) δ 140.63, 139.61, 138.63, 137.06, 136.23, 135.82, 128.82, 128.29, 128.03, 126.92, 126.81, 125.12, 124.39, 122.63, 121.75, 120.46.

4.2.2af. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.83-7.82 (d, J = 7.8 Hz, 2 H), 7.58-7.56 (t, J = 7.4 Hz, 1 H), 7.53-7.50 (t, J = 7.6 Hz, 2 H), 3.11-3.08 (t, J = 7.6 Hz, 4 H), 1.61-1.53 (m, 4 H), 0.90-0.87 (t, J = 7.4 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 140.18, 132.22, 128.96, 127.03, 50.02, 22.02, 11.19.

4.2.2ag. White solid. M_p = 109-110 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.04-8.03 (d, J = 4.3 Hz, 1 H), 7.84-7.83 (d, J = 7.2 Hz, 1 H), 7.53-7.47 (m, 2 H), 7.31-7.29 (m, 5 H), 7.17-7.16 (m, 2 H), 7.01-6.98 (t, J = 5.5 Hz, 1 H), 6.91-6.90 (d, J = 6.5 Hz, 1 H), 6.69-6.66 (t, J = 9.2 Hz, 1 H), 6.63-6.60 (t, J = 7.9 Hz, 1 H), 5.48-5.45 (d, J = 14.3 Hz, 1 H), 4.73-4.70 (d, J = 14.4 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.12, 160.02 (q, J^F = 250.5 Hz), 159.9 (q, J^F = 250.5 Hz), 157.37, 153.19, 148.45, 138.69, 136.23, 131.91 (q, J^F = 32.5 Hz), 131.30 (d, J^F = 9.7 Hz), 130.02, 128.74, 128.58, 127.85, 125.37 (dd, J^F = 4.1 Hz), 124.60, 123.63 (q, J^F = 270.7 Hz), 121.62 (q, J^F = 3.7 Hz), 121.21, 118.78, 118.34 (q, J^F = 3.7 Hz), 111.42 (dd, J^F = 3.7 Hz), 104.82 (dd, J^F = 24.3 Hz), 52.37. ^{19}F NMR (471 MHz, CDCl_3) δ -62.68, -107.69, -114.19. HRMS calcd for $\text{C}_{26}\text{H}_{17}\text{O}_2\text{F}_5\text{N}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 507.1102, found 507.1104.

4.2.2ah. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.75-7.74 (d, J = 7.6 Hz, 2 H), 7.63-7.60 (t, J = 7.6 Hz, 2 H), 7.49-7.46 (t, J = 8.1 Hz, 1 H), 7.24-7.22 (d, J = 8.6 Hz, 1 H), 6.81-6.79 (m, 1 H), 6.74 (s, 1 H), 5.12 (s, 2 H), 2.93-2.90 (m, 2 H), 2.55-2.50 (m, 1 H),

2.43-2.40 (m, 1 H), 2.29-2.25 (m, 1 H), 2.20-2.13 (m, 1 H), 2.10-1.97 (m, 3 H), 1.69-1.55 (m, 3 H), 1.53-1.42 (m, 3 H), 0.93 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.88, 156.55, 142.55, 137.94, 132.66, 129.88, 129.61, 126.93, 126.45, 114.95, 112.37, 69.32, 50.43, 48.02, 44.00, 38.34, 35.89, 31.59, 29.67, 26.53, 25.92, 21.61, 13.87.

4.2.2ai. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.54-7.53 (d, $J = 7.5$ Hz, 2 H), 7.45-7.42 (t, $J = 7.4$ Hz, 2 H), 7.38-7.35 (t, $J = 7.2$ Hz, 1 H), 4.73 (s, 2 H), 2.64-2.61 (t, $J = 6.7$ Hz, 2 H), 2.25 (s, 3 H), 2.20 (s, 3 H), 2.14 (s, 3 H), 1.89-1.77 (m, 2 H), 1.61-1.53 (m, 3 H), 1.45-1.40 (m, 3 H), 1.35-1.24 (m, 12 H), 1.19-1.09 (m, 6 H), 0.91-0.87 (m, 12 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.14, 147.94, 138.08, 128.47, 127.96, 127.78, 127.72, 125.98, 122.95, 117.62, 74.85, 74.72, 40.10, 39.40, 37.62, 37.45, 37.42, 37.32, 32.81, 32.73, 31.29, 28.01, 24.83, 24.47, 23.92, 22.75, 22.66, 21.08, 20.71, 19.72, 12.89, 12.02, 11.85.

4.2.2aj. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.62-7.60 (d, $J = 7.7$ Hz, 2 H), 7.53-7.52 (d, $J = 7.9$ Hz, 2 H), 7.47-7.44 (t, $J = 7.6$ Hz, 2 H), 7.37-7.34 (t, $J = 7.3$ Hz, 1 H), 7.28-7.28 (d, $J = 4.8$ Hz, 2 H), 2.43 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 141.18, 138.38, 137.04, 129.49, 128.72, 127.01, 126.99, 21.12.

4.2.2ak. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.63-7.62 (d, $J = 7.7$ Hz, 2 H), 7.49-7.46 (t, $J = 7.5$ Hz, 2 H), 7.41-7.38 (m, 2 H), 7.23-7.21 (d, $J = 7.6$ Hz, 1 H), 7.17 (s, 1 H), 6.95-6.93 (d, $J = 8.1$ Hz, 1 H), 3.90 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.97, 142.81, 141.14, 129.76, 128.75, 127.43, 127.22, 119.71, 112.94, 112.71, 55.32.

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4.3 Palladium-catalyzed decarbonylative Suzuki-Miyaura cross-coupling of carboxylic acids

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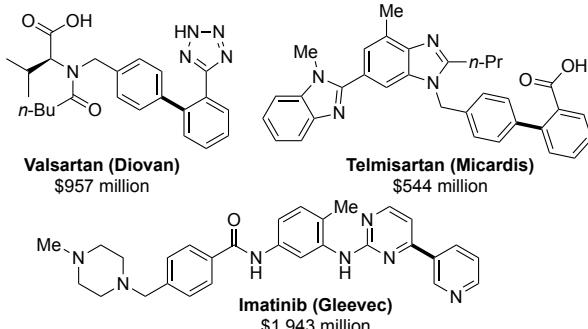
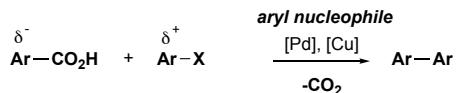
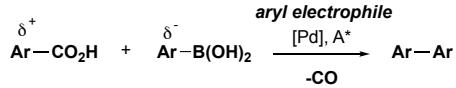
4.3.1 Introduction

The biaryl motif is a privileged subunit in chemistry.¹⁻³ The importance of biaryls is highlighted by the wide presence in pharmaceuticals, functional materials, and natural products in both industrial and academic research.^{4,5} The biaryl motif is the element of widely prescribed antihypertensive and anticancer agents, which, in addition to the major economic factor, save the lives of millions of patients annually (Figure 4.3.1A).⁶ The tremendous success of the conventional Suzuki-Miyaura cross-coupling of aryl halides has provided multiple ways to generate biaryl motifs of key significance to the chemical industry.⁷⁻¹⁰ Since the 2010 Nobel Prize in Chemistry,¹¹ more than 12,000 publications address the improvements to the conventional Suzuki-Miyaura cross-coupling,¹² highlighting the great advantage of developing this transformation. Although effective, the conventional Suzuki-Miyaura cross-coupling of aryl halides suffers from major limitations, including (1) the use of less available aryl halides, (2) the requirement for stoichiometric inorganic base to promote transmetallation, and (3) generation of toxic halide waste.

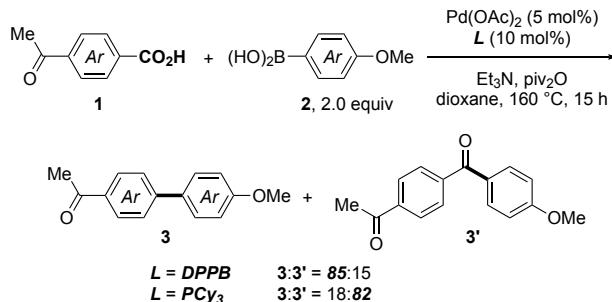
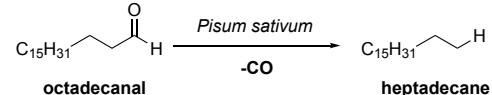
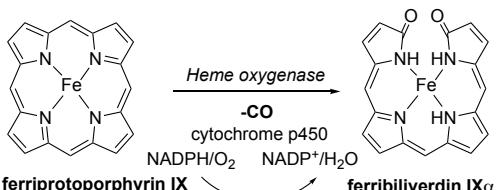
The major breakthrough in using ubiquitous carboxylic acids as substrates for the synthesis of biaryls was achieved in 2006 involving the extrusion of carbon dioxide ($-\text{CO}_2$, Figure 4.3.1B).¹³ In this carefully engineered design, the use of a copper(I) co-catalyst lowers the decarboxylation barrier and delivers aryl nucleophiles to $[\text{Ar}-\text{Pd}-\text{X}]$ intermediates ($\text{X} = \text{Cl}, \text{Br}$). Despite severe limitations mainly with respect to the reaction scope, this seminal report has sparked new interest in decarboxylative cross-couplings of ubiquitous carboxylic acids as advantageous substrates in homogeneous catalysis.^{14,15} At the same time, recent years have witnessed the development of unconventional precursors for the biaryl synthesis, including aryl ethers,¹⁶ acetates,¹⁷ pivalates,¹⁸ carbamates,¹⁹ sulfamates,¹⁹ and ammonium salts.^{20,21} Further progress has been realized in using aroyl precursors, including anhydrides,²² esters,²³ amides,^{24,25} and acyl fluorides²⁶ under Rh and Ni catalysis. In an alternative direction, the combined use of photocatalysis and Ni catalysis has effectively addressed the limitation of cross-coupling of $\text{C}(\text{sp}^3)$ centers,^{27,28} whereas fundamental studies on ligand design have addressed the challenge of enantiodivergent²⁹ and conjunctive³⁰ Pd-catalyzed Suzuki cross-coupling. However, none of these methods have the key advantage of directly engaging the ubiquitous carboxylic acid functional group in the Suzuki-Miyaura cross-coupling to generate highly useful biaryls.

In this project, we have developed a decarbonylative version of Suzuki-Miyaura cross-coupling with loss of carbon monoxide that enables to directly engage carboxylic acids in a redox-neutral pathway to generate biaryls with high selectivity using a well-defined Pd(0)/(II) catalytic cycle ($-\text{CO}$, Figure 4.3.1C).³¹

We realized that (1) significantly more carboxylic acids than aryl halides are commercially available and (2) carboxylic acids form an intrinsic part of advanced bioactive products and functional materials. As such, the direct Suzuki-Miyaura cross-coupling of carboxylic acids as electrophilic components could represent a highly attractive approach to construct biaryl building blocks. Furthermore, the orthogonal properties of carboxylic acids and the utilization of carbon monoxide loss (CO versus CO₂, carbon dioxide) would offer unique opportunities for catalysis. More generally, the C–C bond formation by cross-coupling of boronic acids is a fundamental reaction in organic synthesis that has found widespread application in various areas of chemistry. In our study, we demonstrated the first example of implementing ubiquitous carboxylic acids in the Suzuki cross-coupling for the synthesis of biaryls.

A Examples of top-selling biaryl pharmaceuticals**B Decarboxylative cross-coupling (-CO₂)****C This study: Decarbonylative cross-coupling (-CO)**

■ ubiquitous carboxylic acids ■ key biaryl building blocks ■ redox-neutral
■ orthogonal selectivity ■ inorganic base free ■ broad scope

F Development of decarbonylative Suzuki coupling of carboxylic acids**D Examples of enzymatic decarbonylation in nature**

-decarbonylation is an important enzymatic process
(decarbonylases, heme degradation)

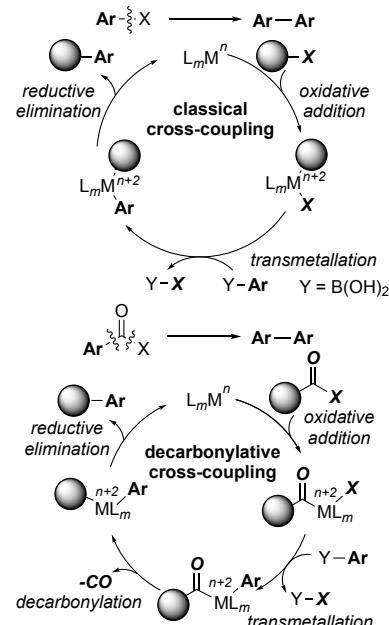
E Classic and decarbonylative Suzuki cross-coupling

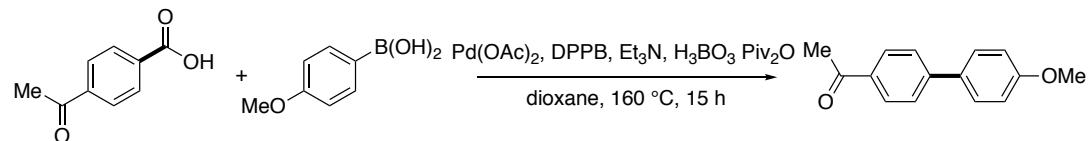
Figure 4.3.1 Background and reaction development.

4.3.2 Reaction optimization

Through extensive optimization, we identified two catalytic systems that led to vastly different outcomes in the cross-coupling of 4-acetyl-benzoic acid with 4-MeO(C₆H₄)-B(OH)₂ (2.0 equiv) as the model reaction (Table 4.3.1): (1) Pd(OAc)₂ (5 mol %)/1,4-bis(diphenylphosphino)butane [dppb] (10 mol %), piv₂O (2.0 equiv), Et₃N (2.0 equiv), dioxane, 160°C: biaryl: ketone = 85:15 selectivity (82% yield of the biaryl); (2) Pd(OAc)₂ (5 mol %)/PCy₃ (10 mol %), piv₂O (2.0 equiv), Et₃N (2.0 equiv), dioxane, 160 °C: biaryl: ketone = 18:82 selectivity (68% yield of the ketone). Selected key optimization results are presented in Table 4.3.1. It was noteworthy that an inorganic base was not required (entries 3-6), establishing a practical alternative to the Ni(0)-catalyzed method²⁶ and that there was a good correlation between the efficiency and the ligand bite angle (entries 9-15).^{8,9} We also noted that the absence of piv₂O resulted in no reaction, in agreement with our design.

Synthetically, the key advantage of this approach is that carboxylic acids are directly engaged in the synthesis of biaryls without separate preactivation steps. The released by-products in the process are CO and a mild organic acid pivOH ($pK_a = 5.0$), which diminish the potential side reactions, while at the same time this approach obviates toxic and more expensive activating reagents (e.g., TFFH [tetramethyl fluoro-formamidinium hexafluorophosphate]).²⁶ Importantly, our method is performed on the bench-top using commercially available, air- and moisture-stable reagents, which supersedes previous methods using air-sensitive Ni(0). Overall, this process results in a broadly applicable entry to the Suzuki-Miyaura cross-coupling of carboxylic acids under redox-neutral conditions.

Table 4.3.1 Optimization of decarbonylative Suzuki-Miyaura coupling of carboxylic acids.^a



entry	variation from standard conditions	yield (%) ^{a,b}
1	No change	82 (15)
2	No H ₃ BO ₃	49 (9)
3	Na ₂ CO ₃ instead of Et ₃ N	52 (15)
4	K ₂ CO ₃ instead of Et ₃ N	51 (23)
5	Added Na ₂ CO ₃	80 (12)
6	Added K ₂ CO ₃	71 (13)
7	Pyridine instead of Et ₃ N	43 (6)
8	DMAP instead of Et ₃ N	43 (<2)
9	PPh ₃ instead of dppb	24 (61)
10	PCy ₃ HBF ₄ instead of dppb	15 (68)
11	DavePhos instead of dppb	<2 (<2)
12	dppp instead of dppb	<10 (<2)
13	dpppe instead of dppb	44 (21)
14	BINAP instead of dppb	27 (27)
15	XantPhos instead of dppb	26 (3)

Conditions: carboxylic acid (1.0 equiv), Ar-B(OH)₂ (2.0 equiv), Pd(OAc)₂ (5 mol%), dppb (10 mol%), Et₃N (2.0 equiv), piv₂O (2.0 equiv), H₃BO₃ (2.0 equiv), dioxane (0.20 M), 160 °C, 15 h. ^aDetermined by ¹H NMR and/or GC-MS. ^bYields of the ketone product are shown in parentheses.

4.3.3 Substrate scope

We next examined the scope of this novel Suzuki-Miyaura cross-coupling (Scheme 4.3.1). The scope of this process is remarkably broad. In all examples, carboxylic acids were used directly without any preactivation steps. As shown in Scheme 4.3.1, a wide range of carboxylic acid substrates are compatible, including tolerance to many functional groups that could be utilized in downstream transformations. Esters (**4.3.3a**), ketones (**4.3.3b**), aldehydes (**4.3.3c**), trifluoromethyl groups (**4.3.3d**), tosylates (**4.3.3e**), and nitriles (**4.3.3f**) provided the biaryl products in high yields. Steric substitution, including ortho-alkyl (**4.3.3g**), ortho-thiomethyl (**4.3.3h**), ortho-methoxy (**4.3.3i**), as well as 1-naphthyl (**4.3.3j**), proved compatible. We noted that decarboxylative biaryl syntheses (loss of CO₂) typically require an activating substituent to favor decarboxylation,¹³⁻¹⁵ whereas this was not needed in our process. Polyaromatic (**4.3.3k**) and heterocyclic substrates (**4.3.3l-4.3.3p**), such as naphthalene, quinoline, pyridines, benzofuran, and benzothiophene, gave the cross-coupling adducts with high selectivity. Notably, owing to the activating role of carboxylic acids in the conventional cross-coupling strategies,^{8,9} our process could be readily utilized in the synthesis of terphenyls, including push-pull compounds (**4.3.3q**), and conjugated stilbenes (**4.3.3r**), which are widely used in the synthesis of functional materials.³² Furthermore, electronically unactivated carboxylic acids (**4.3.3t**) as well as reactive functional groups, such as chloro (**4.3.3u**), ester (**4.3.3v**), ketone (**4.3.3w**), trifluoromethyl ether (**4.3.3y**), and phenolic ester (**4.3.3z**), also delivered the corresponding biaryls in good to excellent yields. The latter example was particularly noteworthy as it highlighted compatibility of our process with highly activated phenolic esters, which could be reacted under forcing Ni catalysis.²³ This unique selectivity relies

on selective activation of carboxylic acid derivatives enabled by transition metal catalysis (resonance energy, PhC(O)–Opiv = 5.1 kcal/mol versus PhC(O)–OPh, 9.3 kcal/mol, barrier to rotation).³¹

We showcased the synthetic potential of this method in the direct functionalization of pharmaceuticals and bioactive natural products (Scheme 4.3.1B), including probenecid (**4.3.3aa**), flufenamic acid (**4.3.3ab**), diflufenican (**4.3.3ac**), and tocopherol (**4.3.3ad**). These examples highlighted the potential impact of the present protocol for late-stage introduction of biaryl architectures directly engaging the carboxylic acid functional group. The utility of this direct cross-coupling strategy was further emphasized by the unique capacity of carboxylic acids to act as traceless activating groups (Scheme 4.3.1C). To this end, we showed the feasibility of metal-catalyzed C–H functionalizations directed by a carboxylic acid (**4.3.3ae**) as well as metal-free electrophilic halogenation (**4.3.3af**) that significantly expanded the pool of carboxylic acid precursors available for cross-coupling.^{33,34} Moreover, the combination with decarbonylative borylation³⁵ furnished organoboranes directly from carboxylic acids (**4.3.3ag**), while valorization of toluenes (**4.3.3ah**) (Scheme 4.3.1C) offered a new opportunity for synthetic processes.

We also investigated the scope of the method with respect to the boronic acid coupling partner, as shown in Scheme 4.3.2. Pleasingly, we found that a wide range of aryl boronic acids were amenable to this biaryl Suzuki-Miyaura cross-coupling process, including deactivated electron-deficient boronic acids bearing an array of sensitive functional groups poised for further modification, such as ketones (**4.3.3ai**), esters (**4.3.3aj**), aldehydes (**4.3.3ak**), and nitriles (**4.3.3am**). Furthermore, electron-rich boronic acids that could lead to a competing ketone formation (**4.3.3an**)²⁶ as well as fluorinated (**4.3.3ao**–

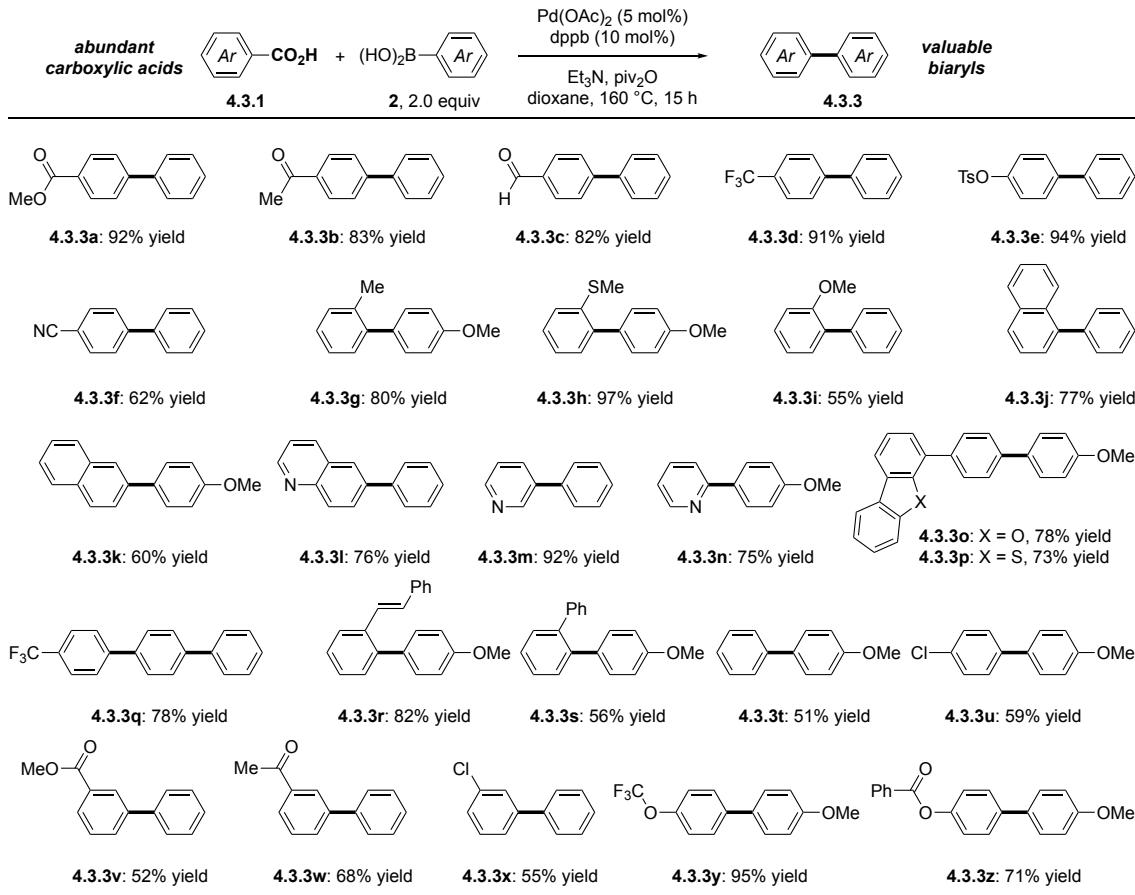
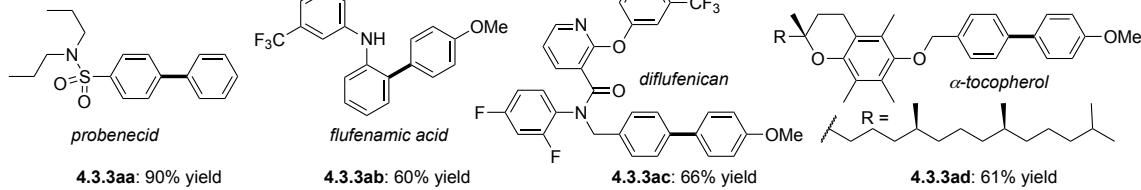
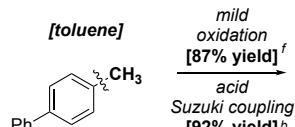
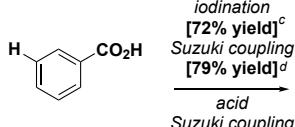
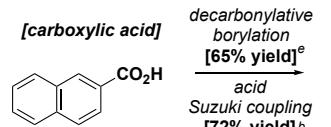
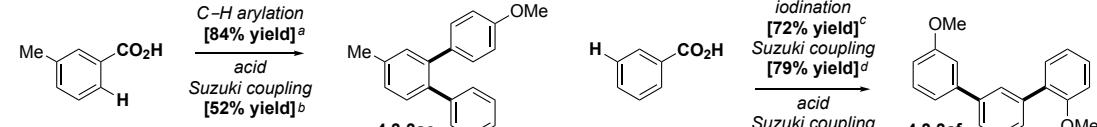
4.3.3aq)³⁶ and sterically hindered boronic acids (**4.3.3ar**) were effectively coupled in our protocol. Substitution at the unconjugated 3-position was well-tolerated (**4.3.3at-4.3.3av**). Moreover, we found that various heterocyclic as well as polyaromatic substrates cross-coupled in this redox-neutral protocol with high efficiency (**4.3.3aw-4.3.3ba**). The utility of this method was further demonstrated in the direct synthesis of biaryls bearing electrophilic carbonyl (**4.3.3bb-4.3.3bi**) and halogen handles (**4.3.3bj-4.3.3bm**) for subsequent manipulation by the traditional nucleophilic addition or cross-coupling strategies.

We also conducted studies to determine steric limits of our protocol (Scheme 4.3.2B). Ortho-substituted biaryls are important structural motifs in biologically active products and functional materials. We found that 2,6-disubstitution on the boronic acid component was well-tolerated, including various useful functional groups on the carboxylic acid cross-coupling partner (**4.3.3bn-4.3.3bs**). The steric limits of the present protocol were reached with tri-ortho-substituted biaryls (**4.3.3bu**) as well as with 2,2'-bis-ortho-substituted biaryls (**4.3.3bv**). Finally, to further demonstrate the powerful opportunity in late-stage derivatization of pharmaceuticals,³⁷ we conducted a series of direct reactions with probenecid (**4.3.3bw-4.3.3cc**) and flufenamic acid (**4.3.3cd-4.3.3ce**) that allowed for selective modification of the core motifs. Clearly, the ubiquity of the carboxylic acid moiety in biologically active molecules highlighted the advantage of this direct decarbonylative biaryl cross-coupling strategy.

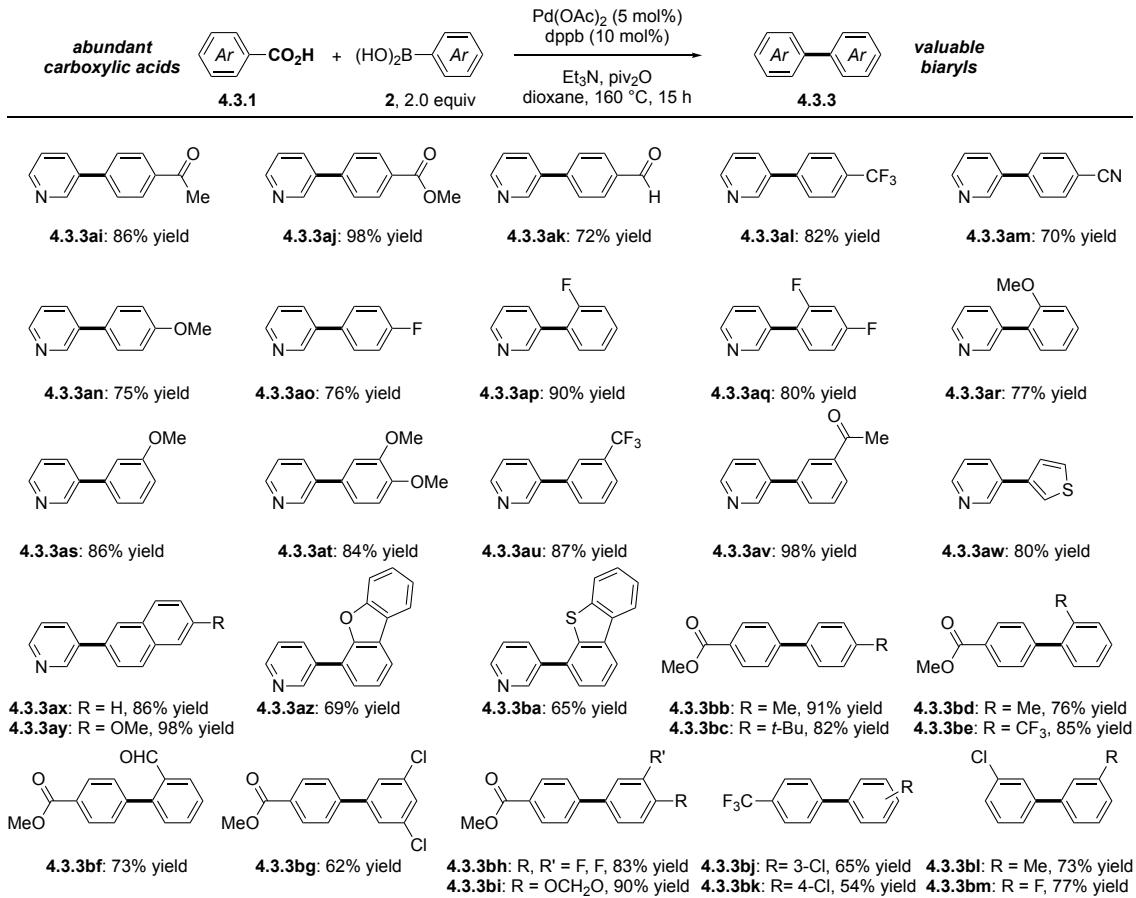
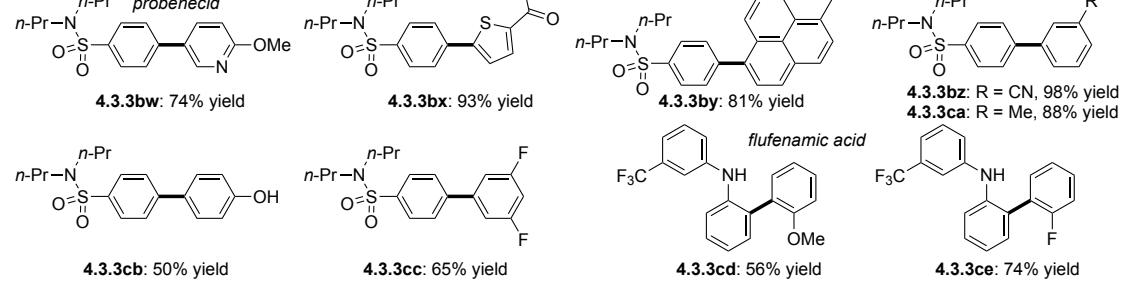
Furthermore, it is worthwhile to note that the vast majority of biaryl products obtained by this method cannot be synthesized using currently available methods engaging ubiquitous carboxylic acids. Typically, only ortho-substituted or electronically biased benzoic acids

were suitable substrates for decarboxylative Suzuki cross-coupling, whereas our method could be employed for any functionalized position on the benzene ring of carboxylic acids as well as for electron-donating, electron-neutral, or electron-withdrawing carboxylic acid substrates.

The absence of an exogenous base also represented a significant advantage because it enabled much broader scope and generality. The use of palladium represented another advantage because it enabled much broader tolerance and more universal applications than nickel. As the final key design strategy, our method involved a one-pot process directly involving ubiquitous carboxylic acids in which all reaction components were combined at the same time, which enabled operational simplicity and rapid screening not available by other methods.

A**B****C [carboxylic acid]**

Scheme 4.3.1 Scope of decarbonylative Suzuki-Miyaura coupling of carboxylic acids.

A**B****C**

Scheme 4.3.2 Scope of decarbonylative Suzuki-Miyaura coupling of carboxylic acids.

4.3.4 Conclusion

In conclusion, we have developed the first general method for the decarbonylative biaryl synthesis from carboxylic acids by Suzuki-Miyaura cross-coupling. The method represented a powerful tool for the synthesis of complex biaryls using ubiquitous and orthogonal carboxylic acid cross-coupling partners. This decarbonylative strategy (loss of carbon monoxide) relied on a complementary approach to the traditional decarboxylation (loss of carbon dioxide). The broad substrate scope, operational simplicity, and the potential to apply in complex molecule synthesis made it evident that decarbonylative cross-couplings³⁸⁻⁴⁰ can have a major impact on organic synthesis.

4.3.5 Experimental section

General Procedure for Suzuki-Miyaura Coupling of Carboxylic Acids. An oven-dried vial equipped with a stir bar was charged with carboxylic acid (neat, 1.0 equiv), boronic acid (neat, 2.0 equiv), Pd(OAc)₂ (typically, 5 mol%), ligand (typically, 10 mol%), triethylamine (typically, 1.5 equiv), boric acid (1.5 equiv) and trimethylacetic anhydride (1.5 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.20 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 160 °C, and stirred for the indicated time at 160 °C.

4.3.3a. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.15-8.13 (d, $J = 8.3$ Hz, 2 H), 7.70-7.68 (d, $J = 8.3$ Hz, 2 H), 7.66-7.65 (d, $J = 7.6$ Hz, 2 H), 7.51-7.48 (t, $J = 7.4$ Hz, 2 H), 7.44-7.41 (t, $J = 7.4$ Hz, 1 H), 3.97 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.02, 145.65, 140.02, 130.13, 128.95, 128.92, 128.17, 127.30, 127.07, 52.15.

4.3.3b. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.07-8.05 (d, $J = 8.2$ Hz, 2 H), 7.72-7.71 (d, $J = 8.3$ Hz, 2 H), 7.66-7.65 (d, $J = 7.8$ Hz, 2 H), 7.52-7.49 (t, $J = 7.4$ Hz, 2 H), 7.44-7.42 (t, $J = 7.4$ Hz, 1 H), 2.67 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.79, 145.81, 139.90, 135.87, 128.98, 128.94, 128.26, 127.30, 127.25, 26.69.

4.3.3c. White solid. ^1H NMR (500 MHz, CDCl_3) δ 10.09 (s, 1 H), 7.99-7.98 (d, $J = 8.2$ Hz, 2 H), 7.79-7.78 (d, $J = 8.1$ Hz, 2 H), 7.67-7.66 (d, $J = 7.4$ Hz, 2 H), 7.53-7.50 (t, $J = 7.4$ Hz, 2 H), 7.46-7.43 (t, $J = 7.2$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 191.98, 147.24, 139.75, 135.22, 130.30, 129.04, 128.50, 127.72, 127.39.

4.3.3d. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.73 (s, 4 H), 7.64-7.63 (d, $J = 7.6$ Hz, 2 H), 7.52-7.49 (t, $J = 7.5$ Hz, 2 H), 7.46-7.43 (t, $J = 7.4$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 144.75, 139.79, 129.36 (q, $J^F = 32.3$ Hz), 129.01, 128.21, 127.44, 127.30, 125.73 (q, $J^F = 3.7$ Hz), 124.34 (q, $J^F = 270.2$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.39.

4.3.3e. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.76 (t, $J = 6.9$ Hz, 4 H), 7.55-7.50 (m, 3 H), 7.47-7.44 (t, $J = 7.5$ Hz, 1 H), 7.39-7.34 (m, 3 H), 7.15-7.13 (d, $J = 8.4$ Hz, 1 H), 7.08-7.06 (d, $J = 8.4$ Hz, 1 H), 2.48 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.02, 140.18, 137.13, 132.74, 131.73, 129.96, 129.79, 128.87, 128.58, 128.25, 127.08, 122.67, 21.74.

4.3.3f. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.76-7.70 (m, 4 H), 7.62-7.61 (d, J = 7.4 Hz, 2 H), 7.53-7.50 (t, J = 7.3 Hz, 2 H), 7.47-7.44 (t, J = 7.2 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.70, 139.20, 132.62, 129.13, 128.68, 127.76, 127.25, 118.97, 110.94.

4.3.3g. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.30-7.26 (m, 6 H), 7.00-6.98 (d, J = 8.6 Hz, 2 H), 3.89 (s, 3 H), 2.31 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.52, 141.56, 135.51, 134.39, 130.31, 130.27, 129.92, 126.99, 125.77, 113.50, 55.30, 20.56.

4.3.3h. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.39-7.33 (m, 3 H), 7.30-7.29 (d, J = 9.5 Hz, 1 H), 7.24-7.20 (m, 2 H), 7.01-6.99 (d, J = 8.6 Hz, 2 H), 3.89 (s, 3 H), 2.40 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.06, 140.56, 137.30, 132.93, 130.47, 130.07, 127.69, 125.09, 124.69, 113.54, 55.28, 16.00.

4.3.3i. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.58-7.57 (d, J = 7.6 Hz, 2 H), 7.47-7.44 (t, J = 7.5 Hz, 2 H), 7.38-7.35 (t, J = 7.1 Hz, 3 H), 7.09-7.06 (t, J = 7.5 Hz, 1 H), 7.04-7.02 (d, J = 8.6 Hz, 1 H), 3.85 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.49, 138.57, 130.92, 130.75, 129.57, 128.64, 128.01, 126.94, 120.85, 111.25, 55.58.

4.3.3j. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.95-7.94 (d, J = 8.6 Hz, 2 H), 7.91-7.89 (d, J = 8.2 Hz, 1 H), 7.58-7.51 (m, 6 H), 7.48-7.45 (m, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 140.79, 140.29, 133.82, 131.64, 130.10, 128.28, 127.65, 127.26, 126.95, 126.05, 126.04, 125.79, 125.40.

4.3.3k. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.02 (s, 1 H), 7.93-7.87 (m, 3 H), 7.76-7.74 (dd, J = 8.5 Hz, 1 H), 7.70-7.69 (d, J = 8.7 Hz, 2 H), 7.54-7.48 (m, 2 H), 7.07-7.05 (d, J = 8.7 Hz, 2 H), 3.91 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.27, 138.17,

133.77, 133.66, 132.33, 128.45, 128.36, 128.07, 127.64, 126.25, 125.66, 125.46, 125.05, 114.34, 55.41.

4.3.3l. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.95-8.95 (d, $J = 2.7$ Hz, 1 H), 8.25-8.20 (m, 2 H), 8.03-8.01 (m, 2 H), 7.76-7.74 (d, $J = 7.5$ Hz, 2 H), 7.55-7.52 (t, $J = 7.5$ Hz, 2 H), 7.47-7.42 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.40, 147.70, 140.35, 139.37, 136.28, 129.92, 129.27, 128.99, 128.49, 127.78, 127.49, 125.51, 121.50.

4.3.3m. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.88 (s, 1 H), 8.63-8.62 (d, $J = 4.5$ Hz, 1 H), 7.91-7.90 (d, $J = 7.9$ Hz, 1 H), 7.62-7.61 (d, $J = 7.5$ Hz, 2 H), 7.53-7.50 (t, $J = 7.5$ Hz, 2 H), 7.45-7.42 (t, $J = 7.4$ Hz, 1 H), 7.41-7.38 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.49, 148.37, 137.87, 136.67, 134.39, 129.10, 128.12, 127.18, 123.56.

4.3.3n. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.68-8.67 (d, $J = 4.5$ Hz, 1 H), 7.99-7.97 (d, $J = 8.7$ Hz, 2 H), 7.75-7.72 (t, $J = 7.8$ Hz, 1 H), 7.70-7.68 (m, 1 H), 7.21-7.18 (t, $J = 6.0$ Hz, 1 H), 7.03-7.02 (d, $J = 8.7$ Hz, 2 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.47, 157.15, 149.56, 136.68, 132.06, 128.18, 121.42, 119.83, 114.13, 55.37.

4.3.3o. White solid. $M_p = 189\text{-}191$ °C. ^1H NMR (500 MHz, CDCl_3) δ 8.04-8.00 (t, $J = 7.9$ Hz, 3 H), 7.98-7.97 (d, $J = 7.5$ Hz, 1 H), 7.77-7.75 (d, $J = 8.2$ Hz, 2 H), 7.69-7.64 (m, 4 H), 7.52-7.46 (m, 2 H), 7.41-7.38 (t, $J = 7.4$ Hz, 1 H), 7.06-7.04 (d, $J = 8.6$ Hz, 2 H), 3.90 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.31, 156.22, 153.44, 140.25, 134.77, 133.35, 129.14, 128.16, 127.25, 126.96, 126.69, 125.56, 124.97, 124.24, 123.26, 122.80, 120.70, 119.63, 114.32, 111.89, 55.39. HRMS calcd for $\text{C}_{25}\text{H}_{18}\text{O}_2\text{Na}$ ($\text{M}^+ + \text{Na}$) 350.1301, found 350.1314.

4.3.3p. White solid. Mp = 198-200 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.24-8.19 (m, 2 H), 7.89-7.87 (m, 1 H), 7.84-7.83 (d, J = 8.1 Hz, 2 H), 7.75-7.73 (d, J = 8.2 Hz, 2 H), 7.66-7.65 (d, J = 8.7 Hz, 2 H), 7.62-7.59 (t, J = 7.5 Hz, 1 H), 7.57-7.55 (m, 1 H), 7.52-7.48 (m, 2 H), 7.06-7.04 (d, J = 8.6 Hz, 2 H), 3.91 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.38, 140.48, 139.63, 138.93, 138.59, 136.73, 136.30, 135.84, 133.22, 128.63, 128.16, 127.05, 126.83, 126.81, 125.14, 124.39, 122.63, 121.75, 120.43, 114.34, 55.38. HRMS calcd for $\text{C}_{25}\text{H}_{18}\text{OSNa} (\text{M}^+ + \text{Na})$ 366.1073, found 366.1065.

4.3.3q. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.78-7.70 (m, 8 H), 7.68-7.66 (d, J = 7.8 Hz, 2 H), 7.51-7.48 (t, J = 7.5 Hz, 2 H), 7.42-7.39 (t, J = 7.4 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 144.23, 141.12, 140.41, 138.60, 129.05 (q, J^F = 56.8 Hz), 128.90, 127.72, 127.65, 127.61, 127.51 (q, J^F = 220.7 Hz), 127.29, 127.09, 125.78 (q, J^F = 4.4 Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.40.

4.3.3r. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.78-7.76 (d, J = 7.4 Hz, 1 H), 7.43-7.33 (m, 9 H), 7.27-7.24 (t, J = 7.4 Hz, 1 H), 7.19-7.16 (d, J = 16.3 Hz, 1 H), 7.09-7.05 (d, J = 16.3 Hz, 1 H), 7.02-7.00 (d, J = 8.6 Hz, 2 H), 3.91 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.85, 140.82, 137.70, 135.48, 133.29, 131.02, 130.29, 129.27, 128.65, 128.07, 127.55, 127.45, 127.25, 126.55, 125.91, 113.59, 55.34.

4.3.3s. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.45-7.43 (m, 4 H), 7.27-7.21 (m, 3 H), 7.19-7.18 (m, 2 H), 7.09-7.08 (d, J = 8.6 Hz, 2 H), 6.79-6.78 (d, J = 8.6 Hz, 2 H), 3.80 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.30, 141.74, 140.49, 140.16, 133.91, 130.94, 130.64, 130.55, 129.89, 127.91, 127.48, 127.14, 126.38, 113.35, 55.18.

4.3.3t. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.59-7.55 (m, 4 H), 7.46-7.43 (t, J = 7.6 Hz, 2 H), 7.34-7.31 (t, J = 7.4 Hz, 1 H), 7.02-7.00 (d, J = 8.7 Hz, 2 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.15, 140.85, 133.80, 128.73, 128.17, 126.76, 126.67, 114.21, 55.37.

4.3.3u. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.49 (t, J = 8.3 Hz, 4 H), 7.41-7.39 (d, J = 8.5 Hz, 2 H), 7.01-6.99 (d, J = 8.7 Hz, 2 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.38, 139.29, 132.69, 132.52, 128.85, 128.03, 127.95, 114.33, 55.39.

4.3.3v. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.31 (s, 1 H), 8.06-8.04 (d, J = 7.8 Hz, 1 H), 7.82-7.81 (d, J = 7.7 Hz, 1 H), 7.66-7.65 (d, J = 7.5 Hz, 2 H), 7.56-7.53 (t, J = 7.7 Hz, 1 H), 7.51-7.48 (t, J = 7.7 Hz, 2 H), 7.42-7.39 (t, J = 7.4 Hz, 1 H), 3.98 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.09, 141.50, 140.14, 131.56, 130.71, 128.91, 128.88, 128.37, 128.30, 127.77, 127.19, 52.23.

4.3.3w. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.21 (s, 1 H), 7.97-7.96 (d, J = 7.7 Hz, 1 H), 7.83-7.81 (d, J = 7.6 Hz, 1 H), 7.66-7.64 (d, J = 7.3 Hz, 2 H), 7.58-7.55 (t, J = 7.7 Hz, 1 H), 7.51-7.48 (t, J = 7.4 Hz, 2 H), 7.43-7.40 (t, J = 7.4 Hz, 1 H), 2.69 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.12, 141.75, 140.21, 137.66, 131.77, 129.07, 128.95, 127.84, 127.22, 127.21, 126.99, 26.79.

4.3.3x. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.60-7.58 (m, 3 H), 7.50-7.46 (m, 3 H), 7.41-7.38 (m, 2 H), 7.35-7.34 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.09, 139.83, 134.66, 130.00, 128.91, 127.88, 127.32, 127.27, 127.13, 125.32.

4.3.3y. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.58-7.57 (d, $J = 8.6$ Hz, 2 H), 7.53-7.51 (d, $J = 8.6$ Hz, 2 H), 7.29-7.28 (d, $J = 8.1$ Hz, 2 H), 7.02-7.00 (d, $J = 8.6$ Hz, 2 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.44, 148.20, 139.64, 132.38, 128.17, 127.97, 121.25, 120.56 (q, $J^F = 255.3$ Hz), 114.34, 55.37. ^{19}F NMR (471 MHz, CDCl_3) δ -57.83.

4.3.3z. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.26-8.25 (d, $J = 7.3$ Hz, 2 H), 7.69-7.66 (t, $J = 7.5$ Hz, 1 H), 7.63-7.61 (d, $J = 8.6$ Hz, 2 H), 7.57-7.54 (m, 4 H), 7.30-7.28 (d, $J = 8.6$ Hz, 2 H), 7.02-7.01 (d, $J = 8.7$ Hz, 2 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.31, 159.22, 149.92, 138.71, 133.63, 133.00, 130.96, 130.22, 128.60, 128.19, 127.80, 121.93, 114.27, 55.38.

4.3.3aa. White solid. $M_p = 50-51$ °C. ^1H NMR (500 MHz, CDCl_3) δ 7.90-7.88 (d, $J = 8.4$ Hz, 2 H), 7.73-7.71 (d, $J = 8.4$ Hz, 2 H), 7.64-7.62 (d, $J = 7.2$ Hz, 2 H), 7.51-7.48 (t, $J = 7.4$ Hz, 2 H), 7.44-7.41 (t, $J = 7.3$ Hz, 1 H), 3.16-3.13 (t, $J = 7.6$ Hz, 4 H), 1.65-1.57 (m, 4 H), 0.93-0.90 (t, $J = 7.4$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.09, 139.38, 138.77, 129.05, 128.41, 127.59, 127.58, 127.29, 50.16, 22.13, 11.24. HRMS calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_2\text{SNa} (\text{M}^+ + \text{Na})$ 340.1342, found 340.1383.

4.3.3ab. Yellow solid. $M_p = 144-145$ °C. ^1H NMR (500 MHz, CDCl_3) δ 7.40-7.29 (m, 6 H), 7.24 (s, 1 H), 7.18-7.08 (m, 3 H), 7.00-6.98 (d, $J = 8.7$ Hz, 2 H), 5.69 (s, 1 H), 3.87 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.17, 144.38, 138.93, 132.53, 131.77 (q, $J^F = 31.8$ Hz), 131.13, 130.38, 129.81, 128.07, 124.10 (q, $J^F = 270.8$ Hz), 122.45, 119.94, 119.07, 118.75, 116.91 (q, $J^F = 3.8$ Hz), 114.38, 113.42 (q, $J^F = 3.9$ Hz), 55.34. ^{19}F NMR

(471 MHz, CDCl₃) δ -62.85. HRMS calcd for C₂₀H₁₆ONF₃Na (M⁺ + Na) 343.1179, found 343.1165.

4.3.3ac. White solid. Mp = 300-302 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.04 (s, 1 H), 7.87-7.85 (d, *J* = 7.1 Hz, 1 H), 7.53-7.48 (m, 4 H), 7.37-7.30 (m, 4 H), 7.17-7.16 (m, 2 H), 7.05-6.99 (m, 4 H), 6.72-6.68 (t, *J* = 9.0 Hz, 1 H), 6.66-6.63 (t, *J* = 7.7 Hz, 1 H), 5.55-5.52 (d, *J* = 14.3 Hz, 1 H), 4.72-4.70 (d, *J* = 14.4 Hz, 1 H), 3.81 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 167.15, 160.02 (q, *J*^F = 268.0 Hz), 159.92 (q, *J*^F = 269.5 Hz), 157.42, 156.45, 153.22, 148.44, 138.78, 138.04, 134.75, 131.91 (q, *J*^F = 32.6 Hz), 131.39 (d, *J*^F = 9.5 Hz), 130.79, 130.07, 130.01, 129.70, 128.75, 128.57, 128.19, 124.65, 121.61 (q, *J*^F = 3.8 Hz), 121.25, 120.88, 118.78, 118.37 (q, *J*^F = 3.8 Hz), 111.33, 104.85 (q, *J*^F = 24.2 Hz), 55.54, 52.32. ¹⁹F NMR (471 MHz, CDCl₃) δ -62.69, -107.80, -113.93. HRMS calcd for C₃₃H₂₃N₂O₃F₅Na (M⁺ + Na) 613.1521, found 613.1527.

4.3.3ad. White solid. Mp = 145-147 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.62-7.57 (m, 6 H), 7.03-7.01 (d, *J* = 8.6 Hz, 2 H), 4.75 (s, 2 H), 3.89 (s, 3 H), 2.64-2.61 (t, *J* = 6.6 Hz, 2 H), 2.27 (s, 3 H), 2.22 (s, 3 H), 2.14 (s, 3 H), 1.89-1.77 (m, 2 H), 1.55-1.53 (m, 3 H), 1.45-1.38 (m, 3 H), 1.35-1.28 (m, 12 H), 1.18-1.14 (m, 3 H), 1.13-1.09 (m, 3 H), 0.90-0.87 (m, 12 H). ¹³C NMR (125 MHz, CDCl₃) δ 159.20, 148.17, 140.39, 136.47, 133.56, 128.16, 127.96, 127.75, 126.82, 125.98, 122.96, 117.62, 114.25, 114.18, 74.85, 74.49, 55.38, 40.11, 39.39, 37.48, 37.44, 37.41, 37.31, 32.82, 32.73, 31.35, 28.00, 24.83, 24.46, 23.92, 22.73, 22.64, 20.71, 19.77, 19.70, 12.91, 12.05, 11.84. HRMS calcd for C₄₃H₆₂O₃Na (M⁺ + Na) 649.4591, found 649.4616.

4.3.3ae. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.39-7.37 (d, $J = 10.6$ Hz, 1 H), 7.34-7.32 (d, $J = 7.7$ Hz, 1 H), 7.25-7.22 (t, $J = 7.3$ Hz, 4 H), 7.16-7.15 (d, $J = 6.7$ Hz, 2 H), 7.08-7.07 (d, $J = 8.4$ Hz, 2 H), 6.78-6.77 (d, $J = 8.3$ Hz, 2 H), 3.80 (s, 3 H), 2.45 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.27, 141.68, 139.98, 137.69, 137.15, 134.03, 131.30, 130.89, 130.58, 129.90, 128.16, 127.85, 126.16, 113.32, 55.17, 21.10.

4.3.3af. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.78 (s, 1 H), 7.59-7.55 (t, $J = 8.1$ Hz, 2 H), 7.52-7.49 (t, $J = 7.5$ Hz, 1 H), 7.42-7.36 (m, 3 H), 7.27-7.25 (d, $J = 7.5$ Hz, 1 H), 7.20 (s, 1 H), 7.10-7.07 (t, $J = 7.3$ Hz, 1 H), 7.05-7.04 (d, $J = 8.1$ Hz, 1 H), 6.94-6.93 (d, $J = 7.8$ Hz, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.94, 156.53, 142.96, 140.89, 139.00, 130.94, 130.59, 129.71, 128.78, 128.70, 128.53, 128.36, 125.85, 120.88, 119.83, 112.98, 112.72, 111.26, 55.61, 55.32. HRMS calcd for $\text{C}_{20}\text{H}_{18}\text{O}_2\text{Na} (\text{M}^+ + \text{Na})$ 313.1199, found 313.1202.

4.3.3ag. Yellow solid. $M_p = 144\text{-}146$ °C. ^1H NMR (500 MHz, CDCl_3) δ 8.97 (s, 1 H), 8.28-8.24 (t, $J = 8.8$ Hz, 2 H), 8.20 (s, 1 H), 8.16 (s, 2 H), 8.01-7.96 (m, 2 H), 7.93-7.89 (m, 2 H), 7.57-7.54 (m, 2 H), 7.49-7.47 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.46, 147.77, 139.25, 137.63, 136.28, 133.71, 132.83, 130.03, 129.41, 128.72, 128.54, 128.30, 127.72, 126.54, 126.39, 126.29, 125.80, 125.55, 121.56. HRMS calcd for $\text{C}_{19}\text{H}_{13}\text{NNa} (\text{M}^+ + \text{Na})$ 278.0940, found 278.0961.

4.3.3ah. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.70-7.66 (m, 6 H), 7.51-7.48 (t, $J = 7.2$ Hz, 2 H), 7.43-7.37 (m, 3 H), 7.11-7.08 (t, $J = 7.3$ Hz, 1 H), 7.06-7.04 (d, $J = 8.2$ Hz, 1 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.58, 141.07, 139.78, 137.57, 130.85, 130.27, 129.95, 128.78, 128.73, 127.21, 127.16, 126.81, 120.93, 111.29, 55.61.

4.3.3ai. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.91 (s, 1 H), 8.68-8.67 (d, $J = 4.0$ Hz, 1 H), 8.11-8.09 (d, $J = 8.2$ Hz, 2 H), 7.95-7.94 (d, $J = 7.9$ Hz, 1 H), 7.72-7.71 (d, $J = 8.3$ Hz, 2 H), 7.45-7.42 (m, 1 H), 2.68 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.59, 149.30, 148.32, 142.35, 136.56, 135.50, 134.56, 129.16, 127.32, 123.73, 26.72.

4.3.3aj. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.90 (s, 1 H), 8.66-8.65 (d, $J = 3.8$ Hz, 1 H), 8.17-8.15 (d, $J = 8.3$ Hz, 2 H), 7.93-7.92 (d, $J = 7.9$ Hz, 1 H), 7.68-7.66 (d, $J = 8.3$ Hz, 2 H), 7.42-7.40 (m, 1 H), 3.96 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.73, 149.26, 148.35, 142.22, 135.56, 134.52, 130.37, 129.76, 127.10, 123.68, 52.26.

4.3.3ak. White solid. ^1H NMR (500 MHz, CDCl_3) δ 10.11 (s, 1 H), 8.93 (s, 1 H), 8.70-8.69 (d, $J = 4.0$ Hz, 1 H), 8.04-8.02 (d, $J = 8.1$ Hz, 2 H), 7.97-7.95 (d, $J = 7.9$ Hz, 1 H), 7.80-7.78 (d, $J = 8.1$ Hz, 2 H), 7.46-7.44 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 191.73, 149.56, 148.40, 143.77, 135.83, 135.36, 134.63, 130.49, 127.79, 123.76.

4.3.3al. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.88 (s, 1 H), 8.68-8.67 (d, $J = 3.8$ Hz, 1 H), 7.92-7.91 (d, $J = 7.9$ Hz, 1 H), 7.77-7.71 (m, 4 H), 7.44-7.42 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.39, 148.36, 141.41, 135.32, 134.54, 130.26 (q, $J^F = 32.6$ Hz), 127.52, 126.07 (q, $J^F = 3.6$ Hz), 124.10 (q, $J^F = 270.4$ Hz), 123.72. ^{19}F NMR (471 MHz, CDCl_3) δ -62.58.

4.3.3am. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.88 (s, 1 H), 8.70-8.69 (d, $J = 4.0$ Hz, 1 H), 7.92-7.91 (d, $J = 7.9$ Hz, 1 H), 7.81-7.79 (d, $J = 8.4$ Hz, 2 H), 7.72-7.71 (d, $J = 8.4$ Hz, 2 H), 7.46-7.44 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.73, 148.22, 142.32, 134.85, 134.56, 132.91, 127.82, 123.85, 118.56, 111.99.

4.3.3an. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.84 (s, 1 H), 8.57-8.56 (d, J = 4.6 Hz, 1 H), 7.86-7.84 (m, 1 H), 7.55-7.53 (d, J = 8.6 Hz, 2 H), 7.37-7.34 (m, 1 H), 7.04-7.03 (d, J = 8.7 Hz, 2 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.78, 148.00, 147.88, 136.27, 133.88, 130.27, 128.24, 123.52, 114.57, 55.40.

4.3.3ao. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.83 (s, 1 H), 8.62-8.61 (d, J = 3.8 Hz, 1 H), 7.86-7.84 (d, J = 7.9 Hz, 1 H), 7.58-7.55 (m, 2 H), 7.40-7.37 (m, 1 H), 7.21-7.18 (t, J = 8.6 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.95 (d, J^F = 246.3 Hz), 148.48, 148.14, 135.78, 134.25, 133.98, 128.86 (d, J^F = 8.1 Hz), 123.61, 116.10 (d, J^F = 21.5 Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -114.19.

4.3.3ap. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.82 (s, 1 H), 8.64-8.64 (d, J = 3.9 Hz, 1 H), 7.91-7.90 (d, J = 7.8 Hz, 1 H), 7.48-7.39 (m, 3 H), 7.30-7.27 (t, J = 6.0 Hz, 1 H), 7.24-7.20 (t, J = 9.0 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.87 (d, J^F = 247.1 Hz), 149.65 (d, J^F = 3.1 Hz), 148.77, 136.37 (d, J^F = 3.3 Hz), 134.10 (d, J^F = 8.5 Hz), 131.68, 130.51 (d, J^F = 3.2 Hz), 129.99 (d, J^F = 8.2 Hz), 124.71 (d, J^F = 3.7 Hz), 123.29, 116.32 (d, J^F = 22.2 Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -117.94.

4.3.3aq. White solid. Mp = 54-56 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.77 (s, 1 H), 8.64-8.64 (d, J = 3.8 Hz, 1 H), 7.86-7.84 (dd, J = 7.8 Hz, 1 H), 7.46-7.39 (m, 2 H), 7.04-6.96 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.88 (dd, J^F = 249.0 Hz), 159.95 (dd, J^F = 249.7 Hz), 149.52 (d, J^F = 2.9 Hz), 148.89, 136.24 (d, J^F = 3.2 Hz), 131.28 (dd, J^F = 9.5 Hz), 130.89, 123.35, 121.93 (dd, J^F = 13.9 Hz), 112.04 (dd, J^F = 21.2 Hz), 104.71 (dd, J^F = 25.5 Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -109.66, -113.37. HRMS calcd for $\text{C}_{11}\text{H}_7\text{NF}_2\text{Na} (\text{M}^+ + \text{Na})$ 214.0439, found 214.0431.

4.3.3ar. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.81 (s, 1 H), 8.60-8.59 (d, J = 3.9 Hz, 1 H), 7.91-7.90 (d, J = 7.9 Hz, 1 H), 7.42-7.34 (m, 3 H), 7.10-7.07 (t, J = 7.5 Hz, 1 H), 7.04-7.03 (d, J = 8.3 Hz, 1 H), 3.85 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.57, 150.20, 147.81, 137.14, 134.42, 130.67, 129.66, 126.87, 123.04, 121.08, 111.30, 55.53.

4.3.3as. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.87 (s, 1 H), 8.62-8.61 (d, J = 4.2 Hz, 1 H), 7.90-7.88 (d, J = 7.9 Hz, 1 H), 7.44-7.37 (m, 2 H), 7.20-7.18 (d, J = 7.4 Hz, 1 H), 7.13 (s, 1 H), 6.99-6.96 (m, 1 H), 3.90 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 160.15, 148.60, 148.35, 139.32, 136.56, 134.45, 130.16, 123.55, 119.62, 113.43, 112.98, 55.38.

4.3.3at. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.85 (s, 1 H), 8.59-8.58 (d, J = 4.0 Hz, 1 H), 7.87-7.86 (d, J = 7.9 Hz, 1 H), 7.38-7.36 (m, 1 H), 7.18-7.16 (m, 1 H), 7.11-7.11 (d, J = 1.8 Hz, 1 H), 7.01-7.00 (d, J = 8.3 Hz, 1 H), 3.99 (s, 3 H), 3.96 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.47, 149.29, 148.07, 148.00, 136.54, 134.07, 130.69, 123.53, 119.63, 111.70, 110.28, 56.04.

4.3.3au. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.92 (s, 1 H), 8.72-8.71 (d, J = 4.1 Hz, 1 H), 7.96-7.95 (d, J = 7.9 Hz, 1 H), 7.85 (s, 1 H), 7.80-7.78 (d, J = 7.7 Hz, 1 H), 7.72-7.70 (d, J = 7.5 Hz, 1 H), 7.66-7.63 (t, J = 7.8 Hz, 1 H), 7.49-7.46 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.69, 147.73, 138.47, 135.63, 134.96, 131.79, 131.53, 130.47, 129.71, 128.08, 124.99 (q, J^F = 3.4 Hz), 124.02 (q, J^F = 3.7 Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.71.

4.3.3av. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.90 (s, 1 H), 8.66-8.66 (d, J = 3.9 Hz, 1 H), 8.20 (s, 1 H), 8.02-8.01 (d, J = 7.7 Hz, 1 H), 7.95-7.93 (d, J = 7.9 Hz, 1 H),

7.82-7.80 (d, $J = 7.7$ Hz, 1 H), 7.63-7.60 (t, $J = 7.8$ Hz, 1 H), 7.44-7.41 (m, 1 H), 2.69 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.78, 149.02, 148.29, 138.43, 137.90, 135.76, 134.52, 131.67, 129.44, 128.05, 126.92, 123.69, 26.77.

4.3.3aw. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.90 (s, 1 H), 8.56-8.55 (d, $J = 4.6$ Hz, 1 H), 7.90-7.88 (d, $J = 7.9$ Hz, 1 H), 7.55-7.55 (d, $J = 1.4$ Hz, 1 H), 7.48-7.46 (m, 1 H), 7.42-7.41 (m, 1 H), 7.36-7.34 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.21, 147.68, 138.80, 133.61, 131.60, 127.02, 125.93, 123.68, 121.48.

4.3.3ax. White solid. ^1H NMR (500 MHz, CDCl_3) δ 9.01 (s, 1 H), 8.66-8.65 (d, $J = 4.1$ Hz, 1 H), 8.08 (s, 1 H), 8.04-8.02 (d, $J = 7.9$ Hz, 1 H), 8.00-7.98 (d, $J = 8.5$ Hz, 1 H), 7.95-7.94 (d, $J = 7.1$ Hz, 1 H), 7.92-7.91 (d, $J = 8.2$ Hz, 1 H), 7.75-7.74 (d, $J = 8.5$ Hz, 1 H), 7.58-7.54 (m, 2 H), 7.45-7.43 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.61, 148.55, 136.63, 135.17, 134.61, 133.61, 132.90, 128.92, 128.26, 127.74, 126.64, 126.48, 126.20, 125.06, 123.64.

4.3.3ay. White solid. ^1H NMR (500 MHz, CDCl_3) δ 9.00 (s, 1 H), 8.64-8.63 (d, $J = 4.0$ Hz, 1 H), 8.03-8.00 (m, 2 H), 7.88-7.83 (m, 2 H), 7.71-7.70 (d, $J = 8.4$ Hz, 1 H), 7.44-7.42 (m, 1 H), 7.23-7.20 (m, 2 H), 3.98 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.16, 148.22, 148.01, 136.81, 134.57, 134.18, 132.83, 129.78, 129.11, 127.73, 126.00, 125.50, 123.69, 119.56, 105.61, 55.39.

4.3.3az. White solid. ^1H NMR (500 MHz, CDCl_3) δ 9.19 (s, 1 H), 8.69-8.69 (d, $J = 3.8$ Hz, 1 H), 8.28-8.26 (d, $J = 7.9$ Hz, 1 H), 8.03-8.00 (m, 2 H), 7.64-7.62 (m, 2 H), 7.53-7.47 (m, 3 H), 7.42-7.39 (t, $J = 7.6$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.17,

153.37, 149.65, 148.82, 135.98, 132.26, 127.54, 126.52, 125.19, 123.98, 123.51, 123.43, 123.03, 122.36, 120.81, 120.62, 111.89.

4.3.3ba. White solid. Mp = 128-129 °C. ^1H NMR (500 MHz, CDCl_3) δ 9.00 (s, 1 H), 8.73-8.72 (d, J = 3.7 Hz, 1 H), 8.24-8.22 (d, J = 7.8 Hz, 2 H), 8.11-8.10 (d, J = 7.8 Hz, 1 H), 7.88-7.86 (m, 1 H), 7.63-7.60 (t, J = 7.5 Hz, 1 H), 7.53-7.47 (m, 4 H). ^{13}C NMR (125 MHz, CDCl_3) δ 149.35, 149.21, 139.30, 138.75, 136.52, 136.31, 135.62, 135.53, 133.40, 127.09, 127.05, 125.29, 124.64, 123.54, 122.73, 121.86, 121.27. HRMS calcd for $\text{C}_{17}\text{H}_{11}\text{NS} (\text{M}^+)$ 261.0607, found 261.0596.

4.3.3bb. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.13-8.11 (d, J = 8.3 Hz, 2 H), 7.68-7.66 (d, J = 8.3 Hz, 2 H), 7.56-7.55 (d, J = 8.0 Hz, 2 H), 7.31-7.29 (d, J = 7.9 Hz, 2 H), 3.96 (s, 3 H), 2.44 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.08, 145.59, 138.13, 137.10, 130.10, 129.67, 128.60, 127.12, 126.81, 52.11, 21.18.

4.3.3bc. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.13-8.12 (d, J = 8.3 Hz, 2 H), 7.70-7.68 (d, J = 8.3 Hz, 2 H), 7.62-7.60 (d, J = 8.3 Hz, 2 H), 7.53-7.51 (d, J = 8.4 Hz, 2 H), 3.97 (s, 3 H), 1.40 (s, 9 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.09, 151.36, 145.49, 137.06, 130.09, 128.63, 126.94, 126.85, 125.92, 52.11, 34.65, 31.34.

4.3.3bd. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.13-8.11 (d, J = 8.0 Hz, 2 H), 7.44-7.42 (d, J = 7.9 Hz, 2 H), 7.31-7.25 (m, 4 H), 3.98 (s, 3 H), 2.30 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.09, 146.78, 140.88, 135.19, 130.51, 129.54, 129.43, 129.29, 128.61, 127.85, 125.92, 52.15, 20.40.

4.3.3be. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.11-8.10 (d, $J = 8.1$ Hz, 2 H), 7.80-7.78 (d, $J = 7.8$ Hz, 1 H), 7.62-7.59 (t, $J = 7.4$ Hz, 1 H), 7.54-7.51 (t, $J = 7.7$ Hz, 1 H), 7.44-7.42 (d, $J = 8.0$ Hz, 2 H), 7.35-7.34 (d, $J = 7.5$ Hz, 1 H), 3.97 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.89, 144.50, 140.31, 131.61, 131.43, 129.50, 129.08, 128.40 (d, $J^F = 30.1$ Hz), 127.88, 126.21 (d, $J^F = 5.2$ Hz), 124.00 (d, $J^F = 272.3$ Hz), 52.19. ^{19}F NMR (471 MHz, CDCl_3) δ -56.81.

4.3.3bf. White solid. ^1H NMR (500 MHz, CDCl_3) δ 9.99 (s, 1 H), 8.18-8.16 (d, $J = 8.2$ Hz, 2 H), 8.08-8.07 (d, $J = 7.7$ Hz, 1 H), 7.71-7.68 (t, $J = 7.1$ Hz, 1 H), 7.59-7.55 (t, $J = 7.6$ Hz, 1 H), 7.50-7.46 (t, $J = 8.4$ Hz, 3 H), 3.99 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 191.79, 166.68, 144.69, 142.48, 133.72, 133.67, 130.63, 130.11, 129.89, 129.67, 128.45, 127.99, 52.33.

4.3.3bg. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.15-8.13 (d, $J = 7.5$ Hz, 2 H), 7.64-7.62 (d, $J = 7.2$ Hz, 2 H), 7.51 (s, 2 H), 7.41 (s, 1 H), 3.97 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.63, 143.00, 142.81, 135.53, 130.32, 128.14, 127.99, 127.07, 125.81, 52.27.

4.3.3bh. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.14-8.12 (d, $J = 7.5$ Hz, 2 H), 7.62-7.61 (d, $J = 7.4$ Hz, 2 H), 7.47-7.43 (t, $J = 8.6$ Hz, 1 H), 7.36 (s, 1 H), 7.30-7.25 (m, 1 H), 3.97 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.75, 151.53 (dd, $J^F = 19.1$ Hz), 149.55 (dd, $J^F = 20.4$ Hz), 143.43, 137.12 (dd, $J^F = 5.6$ Hz), 130.27, 129.49, 126.90, 123.29 (dd, $J^F = 6.2$ Hz), 117.78 (d, $J^F = 17.3$ Hz), 116.26 (d, $J^F = 17.8$ Hz), 52.22. ^{19}F NMR (471 MHz, CDCl_3) δ -137.01, -138.70.

4.3.3bi. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.10-8.09 (d, $J = 7.6$ Hz, 2 H), 7.61-7.59 (d, $J = 7.5$ Hz, 2 H), 7.14-7.12 (m, 2 H), 6.93-6.92 (d, $J = 7.7$ Hz, 1 H), 6.04 (s, 2 H),

3.96 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.99, 148.34, 147.83, 145.30, 134.28, 130.11, 128.54, 126.69, 121.06, 108.72, 107.65, 101.34, 52.10.

4.3.3bj. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.74-7.68 (m, 4 H), 7.61 (s, 1 H), 7.51-7.49 (d, $J = 7.1$ Hz, 1 H), 7.43-7.40 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.31, 141.58, 134.96, 130.24, 129.99 (q, $J^F = 32.4$ Hz), 128.23, 127.45, 127.29, 125.88 (q, $J^F = 3.6$ Hz), 125.45, 124.17 (q, $J^F = 270.4$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.50.

4.3.3bk. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.73-7.67 (m, 4 H), 7.56-7.55 (d, $J = 8.5$ Hz, 2 H), 7.48-7.46 (d, $J = 8.6$ Hz, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.50, 138.20, 134.46, 129.20, 128.65 (d, $J^F = 102.8$ Hz), 128.53, 127.29, 125.86 (d, $J^F = 3.5$ Hz), 124.20 (d, $J^F = 270.3$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.48.

4.3.3bl. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.60 (s, 1 H), 7.50-7.48 (d, $J = 7.6$ Hz, 1 H), 7.41-7.33 (m, 5 H), 7.23-7.21 (d, $J = 7.0$ Hz, 1 H), 2.45 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.23, 139.82, 138.55, 134.60, 129.93, 128.81, 128.62, 127.91, 127.31, 127.17, 125.32, 124.23, 21.52.

4.3.3bm. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.58 (s, 1 H), 7.48-7.36 (m, 5 H), 7.30-7.28 (m, 1 H), 7.11-7.08 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 163.19 (d, $J^F = 244.6$ Hz), 142.06 (d, $J^F = 7.6$ Hz), 141.78 (d, $J^F = 2.1$ Hz), 134.82, 130.41 (d, $J^F = 8.4$ Hz), 130.12, 127.87, 127.29, 125.27, 122.76 (d, $J^F = 2.8$ Hz), 114.71 (d, $J^F = 21.0$ Hz), 114.07 (d, $J^F = 22.1$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -112.71.

4.3.3bn. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.11-8.09 (d, $J = 8.3$ Hz, 2 H), 7.46-7.45 (d, $J = 8.3$ Hz, 2 H), 7.35-7.31 (t, $J = 8.4$ Hz, 1 H), 6.69-6.68 (d, $J = 8.4$ Hz, 2 H),

3.95 (s, 3 H), 3.76 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.27, 157.52, 139.46, 131.11, 129.31, 128.94, 128.38, 118.53, 104.23, 55.91, 52.00.

4.3.3bo. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.03-8.02 (d, $J = 8.2$ Hz, 2 H), 7.49-7.48 (d, $J = 8.1$ Hz, 2 H), 7.35-7.32 (t, $J = 8.4$ Hz, 1 H), 6.70-6.68 (d, $J = 8.4$ Hz, 2 H), 3.77 (s, 6 H), 2.65 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 198.00, 157.51, 139.75, 135.44, 131.30, 129.40, 127.75, 118.37, 104.22, 55.92, 26.62.

4.3.3bp. White solid. ^1H NMR (500 MHz, CDCl_3) δ 10.07 (s, 1 H), 7.95-7.93 (d, $J = 8.0$ Hz, 2 H), 7.56-7.55 (d, $J = 8.0$ Hz, 2 H), 7.37-7.33 (t, $J = 8.4$ Hz, 1 H), 6.71-6.69 (d, $J = 8.4$ Hz, 2 H), 3.77 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 192.26, 157.46, 141.27, 134.82, 131.81, 129.59, 129.09, 118.19, 104.21, 55.90.

4.3.3bq. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.68-7.66 (d, $J = 8.1$ Hz, 2 H), 7.50-7.48 (d, $J = 8.0$ Hz, 2 H), 7.36-7.33 (t, $J = 8.4$ Hz, 1 H), 6.70-6.69 (d, $J = 8.4$ Hz, 2 H), 3.77 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 157.52, 138.10, 131.37, 129.39, 128.67 (q, $J^F = 31.9$ Hz), 124.55 (q, $J^F = 3.8$ Hz), 124.48 (q, $J^F = 270.2$ Hz), 118.09, 104.20, 55.89. ^{19}F NMR (471 MHz, CDCl_3) δ -62.38.

4.3.3br. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.70-7.68 (d, $J = 8.0$ Hz, 2 H), 7.49-7.48 (d, $J = 8.0$ Hz, 2 H), 7.36-7.33 (t, $J = 8.3$ Hz, 1 H), 6.69-6.68 (d, $J = 8.4$ Hz, 2 H), 3.76 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 157.33, 139.54, 131.93, 131.38, 129.80, 119.38, 117.55, 110.29, 104.17, 55.87.

4.3.3bs. White solid. Mp = 146-147 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.81-7.79 (d, $J = 8.1$ Hz, 2 H), 7.36-7.34 (d, $J = 8.1$ Hz, 2 H), 7.29-7.28 (d, $J = 8.4$ Hz, 3 H), 7.04-7.02 (d,

$J = 8.5$ Hz, 2 H), 6.67-6.65 (d, $J = 8.4$ Hz, 2 H), 3.74 (s, 6 H), 2.48 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 157.54, 148.29, 145.12, 133.05, 132.89, 132.28, 129.69, 129.03, 128.57, 121.39, 118.17, 104.26, 55.87, 21.72. HRMS calcd for $\text{C}_{21}\text{H}_{20}\text{O}_5\text{SNa}$ ($\text{M}^+ + \text{Na}$) 407.0924, found 407.0925.

4.3.3bt. White solid. Mp = 104-106 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.93-8.92 (d, $J = 2.9$ Hz, 1 H), 8.19-8.14 (m, 2 H), 7.84 (s, 1 H), 7.75-7.73 (dd, $J = 8.7$ Hz, 1 H), 7.42-7.34 (m, 2 H), 6.74-6.72 (d, $J = 8.4$ Hz, 2 H), 3.77 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 157.77, 150.05, 147.41, 136.27, 133.26, 132.69, 129.59, 129.19, 128.37, 128.10, 120.84, 118.65, 104.29, 55.95. HRMS calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2$ (M^+) 265.1097, found 265.1093.

4.3.3bu. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.91-7.87 (m, 2 H), 7.58-7.55 (m, 1 H), 7.50-7.35 (m, 5 H), 6.76-6.74 (d, $J = 8.4$ Hz, 2 H), 3.66 (s, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 158.50, 133.57, 132.68, 132.59, 129.11, 128.18, 128.05, 127.45, 126.02, 125.47, 125.42, 125.35, 117.73, 104.21, 55.95.

4.3.3bv. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.35 (m, 1 H), 7.28-7.23 (m, 3 H), 7.21-7.20 (d, $J = 7.2$ Hz, 1 H), 7.18-7.16 (dd, $J = 7.4$ Hz, 1 H), 7.05-7.02 (t, $J = 7.4$ Hz, 1 H), 7.00-6.98 (d, $J = 8.3$ Hz, 1 H), 3.79 (s, 3 H), 2.16 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.62, 138.64, 136.83, 131.02, 130.88, 130.01, 129.58, 128.55, 127.29, 125.44, 120.45, 110.68, 55.42, 19.91.

4.3.3bw. White solid. Mp = 108-110 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.44-8.44 (d, $J = 1.7$ Hz, 1 H), 7.90-7.88 (d, $J = 8.2$ Hz, 2 H), 7.84-7.82 (dd, $J = 8.6$ Hz, 1 H), 7.67-7.65 (d, $J = 8.2$ Hz, 2 H), 6.88-6.87 (d, $J = 8.6$ Hz, 1 H), 4.02 (s, 3 H), 3.15-3.12 (t, $J = 7.6$ Hz, 4 H), 1.65-1.57 (m, 4 H), 0.93-0.90 (t, $J = 7.3$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ

164.29, 145.38, 141.83, 138.90, 137.40, 128.34, 127.81, 126.97, 111.19, 53.71, 50.15, 22.13, 11.22. HRMS calcd for $C_{18}H_{24}N_2O_3SNa$ ($M^+ + Na$) 371.1400, found 371.1376.

4.3.3bx. White solid. Mp = 148-150 °C. 1H NMR (500 MHz, $CDCl_3$) δ 7.87-7.85 (d, J = 8.5 Hz, 2 H), 7.78-7.77 (d, J = 8.4 Hz, 2 H), 7.71-7.70 (d, J = 3.9 Hz, 1 H), 7.44-7.43 (d, J = 3.9 Hz, 1 H), 3.14-3.11 (t, J = 7.7 Hz, 4 H), 2.60 (s, 3 H), 1.63-1.55 (m, 4 H), 0.92-0.89 (t, J = 7.4 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.54, 150.09, 144.61, 140.25, 136.95, 133.36, 127.90, 126.57, 125.40, 50.07, 26.67, 22.06, 11.21. HRMS calcd for $C_{18}H_{23}NO_3S_2Na$ ($M^+ + Na$) 388.1012, found 388.1011.

4.3.3by. Orange solid. Mp = 363-365 °C. 1H NMR (500 MHz, $CDCl_3$) δ 8.27-8.25 (m, 2 H), 8.23-8.21 (d, J = 7.5 Hz, 1 H), 8.17-8.12 (m, 2 H), 8.09-8.05 (m, 3 H), 8.04-8.02 (d, J = 8.2 Hz, 2 H), 7.99-7.97 (d, J = 7.9 Hz, 1 H), 7.80-7.78 (d, J = 8.2 Hz, 2 H), 3.26-3.23 (t, J = 7.6 Hz, 4 H), 1.73-1.66 (m, 4 H), 1.00-0.97 (t, J = 7.4 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.44, 139.02, 135.68, 131.45, 131.19, 131.12, 130.87, 128.39, 128.11, 127.96, 127.34, 127.18, 126.26, 125.55, 125.20, 124.96, 124.79, 124.72, 124.49, 50.28, 22.25, 11.29. HRMS calcd for $C_{28}H_{29}NO_2S$ (M^+) 443.1914, found 443.1898.

4.3.3bz. Colorless oil. 1H NMR (500 MHz, $CDCl_3$) δ 7.94-7.91 (t, J = 8.4 Hz, 3 H), 7.86-7.85 (d, J = 7.9 Hz, 1 H), 7.73-7.70 (t, J = 10.0 Hz, 3 H), 7.64-7.61 (t, J = 7.8 Hz, 1 H), 3.16-3.13 (t, J = 7.6 Hz, 4 H), 1.64-1.57 (m, 4 H), 0.93-0.90 (t, J = 7.4 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.62, 140.74, 140.15, 131.73, 131.62, 130.87, 129.95, 127.89, 127.67, 118.46, 113.37, 50.08, 22.07, 11.22. HRMS calcd for $C_{19}H_{22}N_2O_2SNa$ ($M^+ + Na$) 365.1294, found 365.1288.

4.3.3ca. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.89-7.87 (d, $J = 8.4$ Hz, 2 H), 7.72-7.71 (d, $J = 8.3$ Hz, 2 H), 7.44-7.42 (d, $J = 9.4$ Hz, 2 H), 7.40-7.37 (t, $J = 7.5$ Hz, 1 H), 7.26-7.24 (d, $J = 7.3$ Hz, 1 H), 3.14-3.11 (t, $J = 7.6$ Hz, 4 H), 2.60 (s, 3 H), 1.63-1.55 (m, 4 H), 0.92-0.89 (t, $J = 7.4$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.25, 139.41, 138.71, 138.64, 129.13, 128.94, 128.06, 127.58, 127.53, 124.41, 50.12, 22.11, 21.53, 11.23. HRMS calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_2\text{SNa} (\text{M}^+ + \text{Na})$ 354.1498, found 354.1485.

4.3.3cb. White solid. Mp = 82-84 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.35-8.34 (d, $J = 8.4$ Hz, 2 H), 7.98-7.96 (d, $J = 8.4$ Hz, 2 H), 7.49-7.46 (t, $J = 7.8$ Hz, 2 H), 7.25-7.24 (d, $J = 7.8$ Hz, 2 H), 3.17-3.14 (t, $J = 7.7$ Hz, 4 H), 1.63-1.56 (m, 4 H), 0.93-0.90 (t, $J = 7.4$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 163.90, 144.92, 132.88, 130.81, 129.64, 127.19, 126.28, 121.52, 49.96, 21.96, 11.19. HRMS calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_3\text{SNa} (\text{M}^+ + \text{K})$ 372.1030, found 372.1049.

4.3.3cc. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.92-7.90 (d, $J = 8.4$ Hz, 2 H), 7.69-7.67 (d, $J = 8.4$ Hz, 2 H), 7.15-7.14 (d, $J = 6.3$ Hz, 2 H), 6.90-6.85 (m, 1 H), 3.15-3.12 (t, $J = 7.6$ Hz, 4 H), 1.63-1.56 (m, 4 H), 0.93-0.90 (t, $J = 7.4$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 163.41 (dd, $J^F = 247.6$ Hz), 142.60 (d, $J^F = 2.1$ Hz), 140.16, 132.20, 128.00 (d, $J^F = 238.7$ Hz), 127.68 (d, $J^F = 26.1$ Hz), 110.29 (d, $J^F = 26.0$ Hz), 103.64 (dd, $J^F = 25.2$ Hz), 50.09, 22.07, 11.20. ^{19}F NMR (471 MHz, CDCl_3) δ -108.81. HRMS calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_2\text{SF}_2\text{Na} (\text{M}^+ + \text{Na})$ 376.1153, found 376.1148.

4.3.3cd. White solid. Mp = 135-137 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.42-7.39 (t, $J = 7.6$ Hz, 2 H), 7.38-7.27 (m, 4 H), 7.15-7.06 (m, 5 H), 7.02-7.01 (d, $J = 8.2$ Hz, 1 H), 5.98 (s, 1 H), 3.74 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.41, 144.99, 139.95, 131.85,

131.80, 131.57 (q, $J^F = 32.4$ Hz), 130.81, 129.57, 129.32, 128.32, 128.01, 124.17 (q, $J^F = 270.7$ Hz), 122.60, 121.37, 119.53, 119.48, 116.21 (q, $J^F = 3.7$ Hz), 112.94 (q, $J^F = 3.6$ Hz), 111.16, 55.64. ^{19}F NMR (471 MHz, CDCl_3) δ -62.83. HRMS calcd for $\text{C}_{20}\text{H}_{16}\text{NOF}_3$ (M^+) 343.1179, found 343.1165.

4.3.3ce. Orange oil. ^1H NMR (500 MHz, CDCl_3) δ 7.42-7.30 (m, 6 H), 7.25-7.11 (m, 6 H), 5.63 (s, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.87 (d, $J^F = 245.0$ Hz), 144.31, 139.82, 131.91 (d, $J^F = 3.4$ Hz), 131.72, 131.67 (q, $J^F = 31.9$ Hz), 129.79 (d, $J^F = 8.1$ Hz), 129.70, 129.12, 127.43, 126.21 (d, $J^F = 15.9$ Hz), 124.66 (d, $J^F = 3.5$ Hz), 124.08 (q, $J^F = 270.8$ Hz), 122.61, 120.11, 119.48, 116.94 (q, $J^F = 3.7$ Hz), 116.05 (d, $J^F = 22.2$ Hz), 113.63 (q, $J^F = 3.8$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -62.86, -114.15. HRMS calcd for $\text{C}_{19}\text{H}_{13}\text{NF}_4$ (M^+) 331.0979, found 331.0995.

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4.4 Palladium-catalyzed decarbonylative phosphorylation of carboxylic acids

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4.4.1 Introduction

The broad importance of organophosphorus compounds in bioactive products, coordination complexes, synthetic intermediates and functional materials makes the preparation of this class of compounds a critical area of synthetic research.¹⁻³ The C–P bond is typically prepared by a classical nucleophilic addition of Grignard or organolithium reagents to phosphorus halides or by Michaelis-Arbuzov reaction; however, these methods suffer from harsh conditions, toxicity of reagents and major scope limitations.^{4,5} The development of transition-metal-catalyzed C–P bond formation opened up new methods for exploration of organophosphorus compounds (Figure 4.4.1A).^{6,7} This catalytic mechanism is now utilized to access key industrial substrates containing C–P bonds.⁸ A variety of other cross-coupling partners than aryl halides have been successfully employed, including aryl sulfonates,⁹ diazonium salts,¹⁰ boronic acids,¹¹ silanes,¹² organobismuth compounds,¹³ pivalates,¹⁴ and sulfides¹⁵ involving C–X, C–O, C–N, C–B, C–Bi, C–Si and C–S bond activation.⁸⁻¹⁸ In these reactions, the most common mechanism involves oxidative addition of a low-valent metal to the C–X or equivalent bond, followed by ligand exchange with an electron-rich P–H nucleophile;^{5,8} however, oxidative,¹⁷ C–H activation¹⁹ and photoredox²⁰ methods have also emerged. At the same time, challenging C–P bond forming reactions of amide derivatives²¹ and

phenolic esters²² have been achieved. In contrast, at the beginning of this project, no general catalytic method for the formation of organophosphorus compounds directly from ubiquitous carboxylic acids (R-CO₂H to R-P inter-conversion) was available.

Building upon our experience in amide bond activation, we realized that carboxylic acids represent key substrates for chemical synthesis.²⁴ Furthermore, the intrinsic prevalence of carboxylic acids in biologically active molecules offers the unprecedented opportunity to directly synthesize novel motifs by late-stage modification. Carboxylic acids are ubiquitous in every area of chemistry, including agrochemicals, ligands, medicines, bioconjugates, and advanced materials.²⁵ Furthermore, carboxylic acids are cheaper, less toxic and chemically orthogonal to the classical aryl halides.²⁶

In this project, we have developed the first catalytic method for the direct synthesis of organophosphorus compounds from carboxylic acids via redox-neutral decarbonylative palladium catalysis (Figure 4.4.1B).

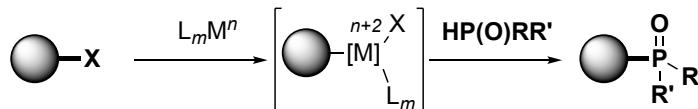
We hypothesized that a critical advantage of the *in situ* activation of the carboxylic acid to form a mixed anhydride (piv = C(O)*t*-Bu) (Figure 4.4.1C) was that (1) carboxylic acids are explored directly without separate preactivation steps using expensive reagents; (2) this mechanistic approach allows to access a range of organophosphorus compounds^{1,3} that would be impossible to synthesize from other derivatives.

We have further realized that decarboxylative strategies (loss of carbon dioxide),^{25,26} are typically limited by specific substitution of the aromatic substrate, require the use of expensive and less practical inorganic oxidants, and suffer from the high energy decarboxylation step.

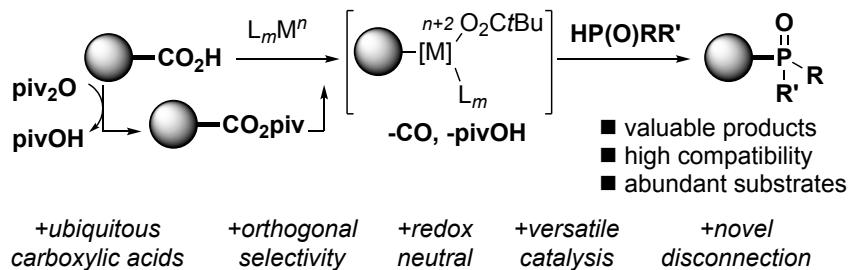
Our strategy was based on selective metal insertion into the C–O acyl bond of the carboxylic acid after in situ activation to afford a mixed anhydride. This process was reminiscent to the classic activation of carboxylic acids for nucleophilic acyl addition reactions.²⁷⁻³¹ In general, this approach makes the decarbonylative mechanism of carboxylic acids a general method to access aryl electrophiles.^{32,33} The method was operationally-simple in that all reactions were performed in a one-pot fashion, while the by-products were a mild organic acid PivOH (pK_a ca. 5) and carbon monoxide.

A Traditional cross-coupling of halides and pseudohalides

■ X = Hal (I, Br, Cl), OR', N₂⁺, NR'₃⁺, OCOR', OCONR'₂



B Redox-neutral decarbonylative cross-coupling of carboxylic acids



C Mechanistic design for decarbonylative phosphorylation

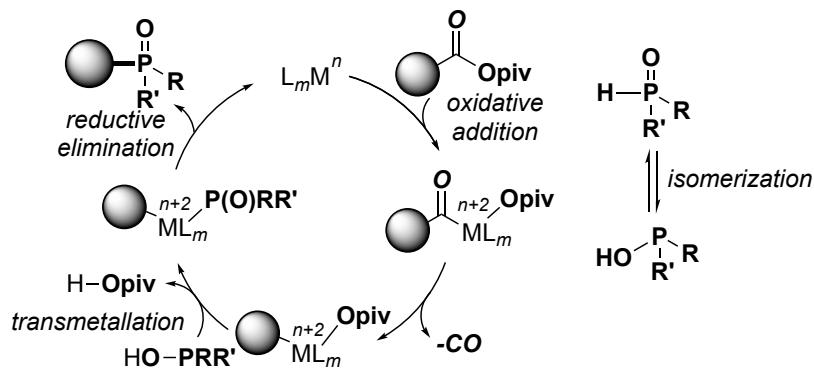
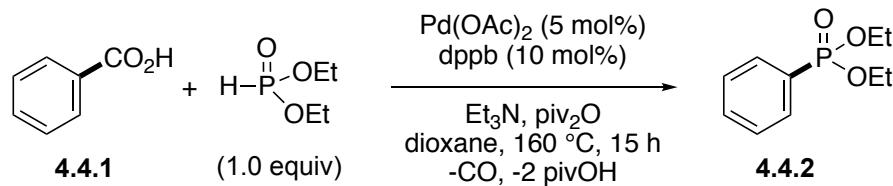


Figure 4.4.1 (a) Conventional synthesis of organophosphorus compounds. (b) Present work. (c) Mechanistic design of decarbonylative phosphorylation.

4.4.2 Reaction optimization

We developed the proposed cross-coupling using benzoic acid and diethyl phosphite as model substrates (Table 4.4.1). After extensive optimization, we were delighted to find that excellent yields could be obtained by reacting benzoic acid (1.0 equiv) with Pd(OAc)₂ (5 mol%) as a catalyst, dppb (10 mol%) as a ligand in the presence of Et₃N (1.0 equiv) and piv₂O (1.0 equiv) additives and equivalent amount of HP(O)(OEt)₂ (1.0 equiv), delivering the desired aryl phosphonate product in 94% yield on a gram scale (Scheme 4.4.1, **4.4.2a**). Control experiments established that all reaction components were required in accord with our design. Notably, the cross-coupling proceeded in the absence of activating groups on the aromatic carboxylic acid cross-coupling partner and utilized cheap and non-toxic organic additives.

Table 4.4.1 Optimization of decarbonylative phosphorylation of carboxylic acids.^a

entry	variation from standard conditions	yield (%) ^a
1	no change	98
2	no piv ₂ O	<2
3	pivCl instead of piv ₂ O	51
4	Boc ₂ O instead of piv ₂ O	17
5	pyridine instead of Et ₃ N	84
6	Na ₂ CO ₃ instead of Et ₃ N	<2
7	PPh ₃ instead of dppb	48
8	dppf instead of dppb	54
9	dppp instead of dppb	83
10	dppPent instead of dppb	63

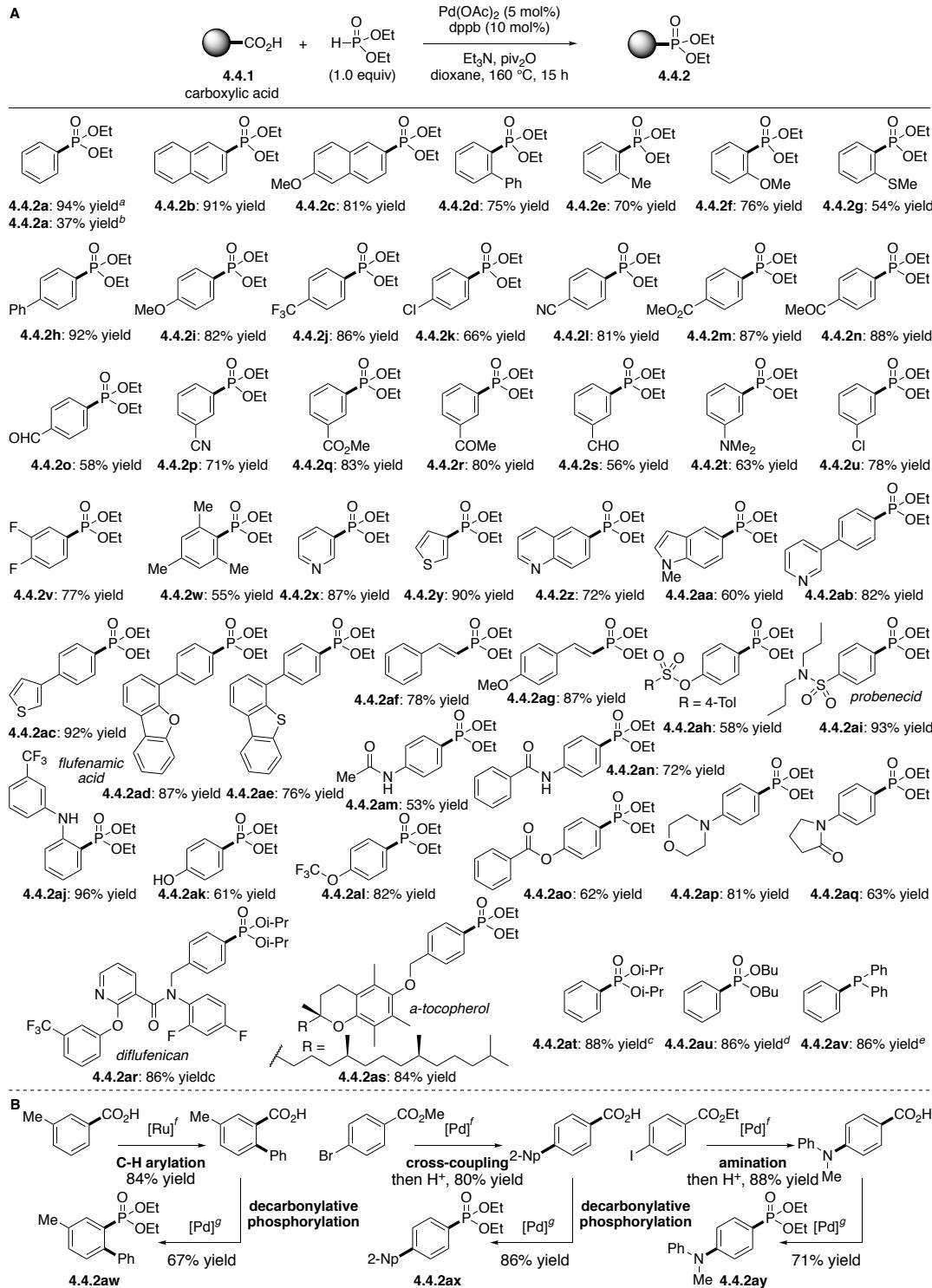
^aStandard conditions: PhCOOH (1.0 equiv), HP(O)(OEt)₂ (1.0 equiv), Pd(OAc)₂ (5 mol%), dppb (10 mol%), Et₃N (1.0 equiv), piv₂O (1.0 equiv), dioxane (0.20 M), 160 °C, 15 h. dppb = 1,4-bis(diphenylphosphino)butane. piv = pivaloyl.

4.4.3 Substrate scope

We next examined the scope of our protocol as outlined in Scheme 4.4.1. We were pleased to find that the reaction exhibited remarkably broad scope, including a vast array of sensitive functional groups that could be utilized for orthogonal cross-coupling strategies or conventional nucleophilic manipulation. The broad potential of our method was highlighted by the fact that simple (**4.4.2a-c**) as well as sterically-demanding carboxylic acids (**4.4.2d-g**, **4.4.2w**) were readily accommodated by this process. Moreover, this transformation appeared to be compatible with substrates bearing diverse electronic substitution, including neutral, electron-donating and electron-withdrawing substituents (**4.4.2c-v**), which is uncommon in decarboxylative manifolds²⁴ and clearly distinguished our mechanism from alternative methods, including Ni-catalysis.³³ Perhaps most notably, a broad range of functional groups was compatible, such as halides (**4.4.2k**, **4.4.2u-v**), nitriles (**4.4.2l**, **4.4.2p**), esters (**4.4.2m**, **4.4.2q**, **4.4.2ao**), ketones (**4.4.2n**, **4.4.2r**), aldehydes (**4.4.2o**, **4.4.2s**), amides (**4.4.2am**, **4.4.2an**), phenols (**4.4.2ak**), anilines (**4.4.2t**, **4.4.2aj**, **4.4.2ap**), nitrogen- (**4.4.2x**, **4.4.2z**, **4.4.2aa**, **4.4.2ab**, **4.4.2ar**), sulfur- (**4.4.2y**, **4.4.2ac**, **4.4.2ae**) and oxygen-heterocycles (**4.4.2ad**, **4.4.2as**), amines (**4.4.2t**, **4.4.2ap**), lactams (**4.4.2aq**), sulfonate esters (**4.4.2ah**), sulfonamides (**4.4.2ai**), trifluoromethyl ethers (**4.4.2al**). The scope of the reaction well superseded other methods for the synthesis of C(sp²)-P bonds by decarbonylative pathway.^{21,22}

Furthermore, this new phosphorylation method could be applied to a direct derivatization of drugs (probenecid, **4.4.2ai**, flufenamic acid, **4.4.2aj**), pesticides (diflufenican, **4.4.2ar**) and natural products (tocopherol, **4.4.2as**), clearly benefiting from the direct use of the ubiquitous carboxylic acid moiety. With respect to the phosphite, sterically-hindered

diisopropylphosphite (**4.4.2at**) and dibutylphosphite (**4.4.2au**) were competent coupling partners for phosphorylation. Notably, this protocol could also be used to form phosphines as indicated in the cross-coupling using diphenylphosphine (**4.4.2av**). To highlight the synthetic utility, we showed that this method could be used to engage carboxylic acids by exploiting orthogonal directing properties of this functional group.²⁴ Thus, C–H arylation³⁴/C–P formation (**4.4.2aw**), Suzuki-Miyaura cross-coupling³⁵/C–P formation (**4.4.2x**) and Buchwald-Hartwig amination³⁶/C–P formation (**4.4.2ay**) demonstrated how this coupling could be used to streamline the synthesis of functionalized organophosphorus compounds.



Conditions: ArCOOH (1.0 equiv), HP(O)(OEt)₂ (1.0 equiv), Pd(OAc)₂ (5 mol%), dppb (10 mol%), Et₃N (1.0 equiv), piv₂O (1.0 equiv), dioxane (0.20 M), 160 °C, 15 h. ^aGram scale. ^bReaction using PhCOCO₂H. ^cHP(O)(O*i*-Pr)₂. ^dHP(O)(OBu)₂. ^eHPPPh₂. ^{f,g}Standard conditions.

Scheme 4.4.1 Scope of decarbonylative phosphorylation of carboxylic acids.

4.4.4 Conclusion

In summary, we have developed the first method for a direct synthesis of organophosphorus compounds from ubiquitous carboxylic acids via redox-neutral decarbonylative palladium catalysis. This versatile C–P bond forming method permitted rapid access to organophosphorus compounds from readily available carboxylic acids, had a very broad scope and tolerated a remarkable range of functional groups. This project further highlighted that the redox-neutral decarbonylative manifold of carboxylic acids represents a unique approach to controlling the cross-coupling reactivity of carboxylic acids and could provide a general cross-coupling platform equivalent to the present use of aryl halides and pseudohalides.

4.4.5 Experimental section

General Procedure for Phosphorylation of Carboxylic Acids. An oven-dried vial equipped with a stir bar was charged with carboxylic acid (neat, 1.0 equiv), phosphite (neat, 1.0 equiv), Pd(OAc)₂ (typically, 5 mol%), ligand (typically, 10 mol%), triethylamine (typically, 1.0 equiv), and pivalic anhydride (typically, 1.0 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (0.20 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 160 °C, and stirred for the indicated time at 160 °C. After the indicated time, the reaction mixture was cooled down to room temperature. Then the sample was analyzed by ¹H NMR (CDCl₃, 500 MHz) and GC-MS to obtain conversion, yield and selectivity using internal standard and comparison with authentic samples. All substrates' yields refer to isolated yields after purification by chromatography on silica gel (ethyl acetate/hexane = 1/5 to 2/1).

4.4.2a. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.86-7.82 (m, 2 H), 7.59-7.56 (t, J = 7.3 Hz, 1 H), 7.51-7.47 (m, 2 H), 4.24-4.07 (m, 4 H), 1.36-1.34 (t, J = 7.0 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 132.39, 132.37, 131.79 (d, J^P = 9.8 Hz), 128.48 (d, J^P = 14.9 Hz), 62.11 (d, J^P = 5.3 Hz), 16.35 (d, J^P = 6.6 Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.81.

4.4.2b. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.48-8.45 (d, J = 15.6 Hz, 1 H), 7.98-7.94 (m, 2 H), 7.92-7.90 (d, J = 8.0 Hz, 1 H), 7.81-7.77 (t, J = 10.5 Hz, 1 H), 7.65-7.58 (m, 2 H), 4.26-4.10 (m, 4 H), 1.38-1.35 (t, J = 6.9 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 135.02 (d, J^P = 2.6 Hz), 134.09 (d, J^P = 10.2 Hz), 132.38 (d, J^P = 16.5 Hz), 128.97, 128.38 (d, J^P = 14.3 Hz), 128.27, 127.84 (d, J^P = 0.6 Hz), 126.90 (d, J^P = 1.1 Hz), 126.48 (d, J^P = 9.8 Hz), 125.45 (d, J^P = 186.7 Hz), 62.19 (d, J^P = 5.2 Hz), 16.39 (d, J^P = 6.4 Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 19.08.

4.4.2c. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.38-8.35 (d, J = 15.3 Hz, 1 H), 7.86-7.81 (m, 2 H), 7.77-7.73 (t, J = 10.6 Hz, 1 H), 7.25-7.23 (d, J = 8.9 Hz, 1 H), 7.18 (s, 1 H), 4.24-4.08 (m, 4 H), 3.97 (s, 3 H), 1.37-1.34 (t, J = 6.9 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.49, 136.65, 133.82, 133.74, 130.51, 127.87 (d, J^P = 17.0 Hz), 127.23 (d, J^P = 6.0 Hz), 127.13 (d, J^P = 10.5 Hz), 119.82, 105.69, 62.08 (d, J^P = 5.1 Hz), 55.43, 16.39 (d, J^P = 6.3 Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 19.72.

4.4.2d. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.09-8.04 (m, 1 H), 7.60-7.57 (t, J = 7.6 Hz, 1 H), 7.48-7.45 (m, 4 H), 7.43-7.38 (m, 3 H), 7.37-7.34 (t, J = 6.4 Hz, 1 H), 3.99-3.91 (m, 2 H), 3.89-3.81 (m, 2 H), 1.16-1.13 (t, J = 7.1 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 146.06 (d, J^P = 9.8 Hz), 141.48 (d, J^P = 4.1 Hz), 133.83 (d, J^P = 9.6 Hz), 131.94 (d, J^P = 2.9 Hz), 131.37 (d, J^P = 14.0 Hz), 130.50 (d, J^P = 23.0 Hz), 129.35, 128.78 (d, J^P

= 10.3 Hz), 127.47 (d, J^P = 6.2 Hz), 126.88 (d, J^P = 14.5 Hz), 61.80 (d, J^P = 6.1 Hz), 16.07 (d, J^P = 6.8 Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.11.

4.4.2e. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.96-7.91 (m, 1 H), 7.46-7.43 (t, J = 7.6 Hz, 1 H), 7.30-7.27 (m, 2 H), 4.22-4.07 (m, 4 H), 2.60 (s, 3 H), 1.37-1.34 (t, J = 7.1 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 141.83 (d, J^P = 10.1 Hz), 133.94 (d, J^P = 10.2 Hz), 132.44 (d, J^P = 3.0 Hz), 131.20 (d, J^P = 14.9 Hz), 126.86 (d, J^P = 182.8 Hz), 125.38 (d, J^P = 14.8 Hz), 61.88 (d, J^P = 5.5 Hz), 21.24 (d, J^P = 3.5 Hz), 16.34 (d, J^P = 6.5 Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 19.47.

4.4.2f. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.83 (m, 1 H), 7.54-7.51 (t, J = 7.4 Hz, 1 H), 7.06-7.02 (m, 1 H), 6.99-6.96 (t, J = 7.4 Hz, 1 H), 4.25-4.11 (m, 4 H), 3.93 (s, 3 H), 1.37-1.35 (t, J = 7.1 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 161.30 (d, J^P = 2.7 Hz), 135.12, 135.07, 134.26 (d, J^P = 2.1 Hz), 120.38 (d, J^P = 14.3 Hz), 111.18 (d, J^P = 9.4 Hz), 62.12 (d, J^P = 5.5 Hz), 55.80, 16.40 (d, J^P = 6.5 Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.18.

4.4.2g. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.98-7.93 (m, 1 H), 7.51-7.49 (t, J = 7.6 Hz, 1 H), 7.34-7.31 (t, J = 6.2 Hz, 1 H), 7.24-7.21 (m, 1 H), 4.26-4.08 (m, 4 H), 2.54 (s, 3 H), 1.40-1.37 (t, J = 7.1 Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.34 (d, J^P = 8.2 Hz), 135.02 (d, J^P = 9.1 Hz), 132.66 (d, J^P = 2.8 Hz), 128.47 (d, J^P = 15.0 Hz), 125.86 (d, J^P = 12.8 Hz), 124.14 (d, J^P = 14.2 Hz), 62.33 (d, J^P = 5.4 Hz), 16.35 (d, J^P = 6.5 Hz), 16.25. ^{31}P NMR (202 MHz, CDCl_3) δ 17.17. HRMS calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3\text{PS}$ ($\text{M}^+ + \text{H}$) 261.0709, found 261.0736.

4.4.2h. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.93-7.89 (m, 2 H), 7.72-7.70 (m, 2 H), 7.64-7.63 (d, $J = 7.4$ Hz, 2 H), 7.51-7.48 (t, $J = 7.3$ Hz, 2 H), 7.44-7.41 (t, $J = 6.8$ Hz, 1 H), 4.26-4.10 (m, 4 H), 1.39-1.36 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.20 (d, $J^P = 3.1$ Hz), 140.01, 132.32 (d, $J^P = 10.1$ Hz), 128.96, 128.17, 127.30, 127.19 (d, $J^P = 15.3$ Hz), 126.19, 62.15 (d, $J^P = 5.5$ Hz), 16.39 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.97.

4.4.2i. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.75 (m, 2 H), 7.00-6.98 (d, $J = 8.6$ Hz, 2 H), 4.18-4.03 (m, 4 H), 3.88 (s, 3 H), 1.35-1.32 (t, $J = 6.8$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 162.85 (d, $J^P = 3.2$ Hz), 133.80 (d, $J^P = 11.3$ Hz), 119.59 (d, $J^P = 193.6$ Hz), 114.02 (d, $J^P = 16.0$ Hz), 61.91 (d, $J^P = 5.3$ Hz), 55.34, 16.35 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 19.72.

4.4.2j. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.99-7.95 (m, 2 H), 7.76-7.74 (m, 2 H), 4.24-4.09 (m, 4 H), 1.38-1.35 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 132.25 (d, $J^P = 10.0$ Hz), 125.40 (q, $J^P = 3.6$ Hz), 125.28 (q, $J^P = 3.8$ Hz), 62.52 (d, $J^P = 5.5$ Hz), 16.35 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.27. ^{19}F NMR (471 MHz, CDCl_3) δ -63.28.

4.4.2k. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.75 (m, 2 H), 7.48-7.46 (m, 2 H), 4.19-4.06 (m, 4 H), 1.36-1.33 (t, $J = 6.8$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 138.97 (d, $J^P = 4.0$ Hz), 133.22 (d, $J^P = 10.6$ Hz), 128.86 (d, $J^P = 15.6$ Hz), 127.80, 62.29 (d, $J^P = 5.4$ Hz), 16.34 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.62.

4.4.2l. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.97-7.93 (m, 2 H), 7.79-7.77 (m, 2 H), 4.25-4.10 (m, 4 H), 1.38-1.35 (t, $J = 6.9$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ

134.00 (d, $J^P = 186.7$ Hz), 132.29 (d, $J^P = 9.8$ Hz), 132.02 (d, $J^P = 14.9$ Hz), 117.88, 116.01, 62.70 (d, $J^P = 5.6$ Hz), 16.36 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 15.34.

4.4.2m. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.15-8.14 (m, 2 H), 7.94-7.90 (m, 2 H), 4.24-4.09 (m, 4 H), 3.97 (s, 3 H), 1.37-1.34 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.27, 133.81 (d, $J^P = 64.0$ Hz), 133.05 (d, $J^P = 118.1$ Hz), 131.81 (d, $J^P = 10.0$ Hz), 129.44 (d, $J^P = 14.9$ Hz), 62.43 (d, $J^P = 5.5$ Hz), 52.49, 16.35 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.01.

4.4.2n. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.06-8.04 (m, 2 H), 7.97-7.93 (m, 2 H), 4.24-4.09 (m, 4 H), 2.67 (s, 3 H), 1.37-1.35 (t, $J = 6.9$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.54, 139.85 (d, $J^P = 3.1$ Hz), 133.43 (d, $J^P = 185.5$ Hz), 132.10 (d, $J^P = 10.0$ Hz), 128.07 (d, $J^P = 15.0$ Hz), 62.45 (d, $J^P = 5.5$ Hz), 26.84, 16.36 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.86.

4.4.2o. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 10.12 (s, 1 H), 8.04-7.98 (m, 4 H), 4.25-4.11 (m, 4 H), 1.38-1.35 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 191.65, 138.76 (d, $J^P = 3.0$ Hz), 134.23, 132.41 (d, $J^P = 9.9$ Hz), 129.38 (d, $J^P = 15.1$ Hz), 62.54 (d, $J^P = 5.6$ Hz), 16.37 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.35.

4.4.2p. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 8.12-8.05 (m, 2 H), 7.86-7.84 (d, $J = 7.8$ Hz, 1 H), 7.65-7.61 (m, 1 H), 4.25-4.11 (m, 4 H), 1.38-1.36 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 135.76, 135.68, 135.46 (d, $J^P = 3.0$ Hz), 135.30 (d, $J^P = 10.7$ Hz), 129.38 (d, $J^P = 14.7$ Hz), 117.82 (d, $J^P = 2.0$ Hz), 113.13 (d, $J^P = 17.3$ Hz), 62.73 (d, $J^P = 5.6$ Hz), 16.36 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 14.99.

4.4.2q. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 8.51-8.48 (d, $J = 13.8$ Hz, 1 H), 8.25-8.24 (d, $J = 7.8$ Hz, 1 H), 8.06-8.01 (m, 1 H), 7.61-7.57 (m, 1 H), 4.24-4.09 (m, 4 H), 3.97 (s, 3 H), 1.37-1.35 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 166.18 (d, $J^P = 2.3$ Hz), 136.02 (d, $J^P = 9.9$ Hz), 133.33 (d, $J^P = 2.9$ Hz), 132.86 (d, $J^P = 10.8$ Hz), 130.55 (d, $J^P = 15.0$ Hz), 130.08, 128.71 (d, $J^P = 14.8$ Hz), 62.39 (d, $J^P = 5.5$ Hz), 52.40, 16.36 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.18.

4.4.2r. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 8.41-8.39 (d, $J = 13.7$ Hz, 1 H), 8.18-8.16 (d, $J = 7.8$ Hz, 1 H), 8.05-8.01 (m, 1 H), 7.63-7.59 (m, 1 H), 4.25-4.10 (m, 4 H), 2.67 (s, 3 H), 1.38-1.35 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 197.18, 137.17 (d, $J^P = 13.8$ Hz), 136.06 (d, $J^P = 9.9$ Hz), 131.85 (d, $J^P = 2.9$ Hz), 131.74 (d, $J^P = 10.5$ Hz), 129.53 (d, $J^P = 188.2$ Hz), 128.96 (d, $J^P = 14.7$ Hz), 62.42 (d, $J^P = 5.6$ Hz), 26.73, 16.37 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.21.

4.4.2s. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 10.10 (s, 1 H), 8.35-8.32 (d, $J = 13.9$ Hz, 1 H), 8.13-8.09 (m, 2 H), 7.70-7.66 (m, 1 H), 4.26-4.11 (m, 4 H), 1.39-1.36 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 191.31, 137.32 (d, $J^P = 10.2$ Hz), 136.39, 136.28, 133.49 (d, $J^P = 10.1$ Hz), 132.60 (d, $J^P = 2.9$ Hz), 129.34 (d, $J^P = 14.5$ Hz), 62.52 (d, $J^P = 5.5$ Hz), 16.38 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.53.

4.4.2t. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.31 (m, 1 H), 7.19-7.16 (d, $J = 15.8$ Hz, 1 H), 7.14-7.10 (m, 1 H), 6.91-6.89 (d, $J = 8.5$ Hz, 1 H), 4.20-4.05 (m, 4 H), 3.01 (s, 6 H), 1.36-1.33 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 150.23 (d, $J^P = 17.3$ Hz), 129.25 (d, $J^P = 17.2$ Hz), 128.55 (d, $J^P = 183.7$ Hz), 119.24 (d, $J^P = 9.1$ Hz),

116.04 (d, $J^P = 3.0$ Hz), 115.28 (d, $J^P = 12.5$ Hz), 62.00 (d, $J^P = 5.2$ Hz), 40.43, 16.36 (d, $J^P = 6.6$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 20.41.

4.4.2u. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.82-7.80 (d, $J = 13.8$ Hz, 1 H), 7.74-7.70 (m, 1 H), 7.55-7.54 (d, $J = 7.9$ Hz, 1 H), 7.46-7.42 (m, 1 H), 4.23-4.08 (m, 4 H), 1.38-1.35 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 134.81 (d, $J^P = 20.2$ Hz), 132.51 (d, $J^P = 2.9$ Hz), 131.68 (d, $J^P = 10.7$ Hz), 130.80 (d, $J^P = 186.8$ Hz), 129.94 (d, $J^P = 16.4$ Hz), 129.82 (d, $J^P = 9.3$ Hz), 62.43 (d, $J^P = 5.5$ Hz), 16.35 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.55.

4.4.2v. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.68-7.58 (m, 2 H), 7.28 (s, 2 H), 4.22-4.07 (m, 4 H), 1.37-1.34 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 128.82, 126.63 (t, $J^P = 3.9$ Hz), 125.10 (t, $J^P = 4.4$ Hz), 121.20 (d, $J^P = 11.5$ Hz), 121.06 (d, $J^P = 11.3$ Hz), 117.92 (t, $J^P = 17.6$ Hz), 62.50 (d, $J^P = 5.5$ Hz), 16.33 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 15.77 (d, $J = 6.6$ Hz). ^{19}F NMR (471 MHz, CDCl_3) δ -130.87 (d, $J = 20.8$ Hz), -136.15 (q, $J = 6.5$ Hz).

4.4.2w. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 6.93-6.92 (d, $J = 4.3$ Hz, 2 H), 4.20-4.01 (m, 4 H), 2.62 (s, 6 H), 2.31 (s, 3 H), 1.35-1.32 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.81 (d, $J^P = 11.8$ Hz), 141.87 (d, $J^P = 3.0$ Hz), 130.37 (d, $J^P = 15.7$ Hz), 122.90 (d, $J^P = 1.2$ Hz), 61.17 (d, $J^P = 5.3$ Hz), 23.16 (d, $J^P = 2.8$ Hz), 21.10 (d, $J^P = 1.4$ Hz), 16.32 (d, $J^P = 6.6$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 20.48.

4.4.2x. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 9.01-9.00 (d, $J = 6.2$ Hz, 1 H), 8.80 (s, 1 H), 8.15-8.11 (m, 1 H), 7.44-7.41 (m, 1 H), 4.26-4.12 (m, 4 H), 1.39-1.36 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 153.00, 152.29 (d, $J^P = 12.0$ Hz), 139.49 (d, J^P

$= 7.9$ Hz), 123.43 (d, $J^P = 1.1$ Hz), 123.34, 62.56 (d, $J^P = 5.6$ Hz), 16.36 (d, $J^P = 6.3$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 15.77.

4.4.2y. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 8.02-8.00 (m, 1 H), 7.46-7.44 (m, 1 H), 7.37-7.35 (m, 1 H), 4.20-4.07 (m, 4 H), 1.36-1.33 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 135.38 (d, $J^P = 17.9$ Hz), 129.54 (d, $J^P = 195.6$ Hz), 129.02 (d, $J^P = 16.6$ Hz), 127.20 (d, $J^P = 19.4$ Hz), 62.18 (d, $J^P = 5.3$ Hz), 16.34 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 13.21.

4.4.2z. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 9.06-9.05 (d, $J = 4.0$ Hz, 1 H), 8.48-8.45 (d, $J = 15.3$ Hz, 1 H), 8.29-8.28 (d, $J = 8.3$ Hz, 1 H), 8.23-8.20 (m, 1 H), 8.05-8.01 (t, $J = 10.0$ Hz, 1 H), 7.54-7.51 (m, 1 H), 4.28-4.12 (m, 4 H), 1.39-1.36 (t, $J = 6.9$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 152.60, 149.76 (d, $J^P = 2.2$ Hz), 136.97, 134.15 (d, $J^P = 10.7$ Hz), 132.20 (d, $J^P = 2.7$ Hz), 130.23 (d, $J^P = 9.5$ Hz), 130.10, 129.99, 122.08 (d, $J^P = 1.1$ Hz), 62.40 (d, $J^P = 5.4$ Hz), 16.39 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.76.

4.4.2aa. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.20-8.18 (d, $J = 14.3$ Hz, 1 H), 7.68-7.64 (m, 1 H), 7.44-7.41 (m, 1 H), 7.16-7.15 (d, $J = 3.1$ Hz, 1 H), 6.61-6.60 (d, $J = 3.1$ Hz, 1 H), 4.20-4.04 (m, 4 H), 3.85 (s, 3 H), 1.35-1.32 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 138.63 (d, $J^P = 1.8$ Hz), 130.15, 130.03, 127.99 (d, $J^P = 38.8$ Hz), 126.43 (d, $J^P = 11.3$ Hz), 124.36 (d, $J^P = 11.9$ Hz), 109.43 (d, $J^P = 16.6$ Hz), 102.22 (d, $J^P = 1.2$ Hz), 61.79 (d, $J^P = 5.0$ Hz), 32.99, 16.38 (d, $J^P = 6.6$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 22.24.

4.4.2ab. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.93-7.82 (m, 3 H), 7.75-7.68 (m, 2 H), 7.59-7.56 (t, $J = 7.5$ Hz, 1 H), 7.51-7.47 (m, 2 H), 4.23-4.07 (m, 4 H), 1.36-1.34 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 132.38 (d, $J^P = 1.8$ Hz), 131.80 (d, $J^P = 9.7$ Hz), 128.96, 128.56, 128.47 (d, $J^P = 14.8$ Hz), 128.17, 127.30, 127.25, 127.13, 62.10 (d, $J^P = 5.6$ Hz), 16.35 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.80. HRMS calcd for $\text{C}_{15}\text{H}_{18}\text{NO}_3\text{P} (\text{M}^+)$ 291.1019, found 291.1058.

4.4.2ac. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.89-7.84 (m, 2 H), 7.73-7.70 (m, 2 H), 7.58 (s, 1 H), 7.45-7.44 (d, $J = 1.9$ Hz, 2 H), 4.23-4.08 (m, 4 H), 1.38-1.35 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 141.17 (d, $J^P = 1.1$ Hz), 139.62 (d, $J^P = 3.1$ Hz), 132.44 (d, $J^P = 10.2$ Hz), 127.45, 126.75, 126.41, 126.23 (d, $J^P = 16.0$ Hz), 121.89, 62.12 (d, $J^P = 5.3$ Hz), 16.37 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.86. HRMS calcd for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{PS} (\text{M}^+ + \text{H})$ 297.0709, found 297.0704.

4.4.2ad. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.07-7.99 (m, 6 H), 7.66-7.63 (t, $J = 7.2$ Hz, 2 H), 7.53-7.47 (m, 2 H), 7.42-7.39 (t, $J = 7.5$ Hz, 1 H), 4.28-4.13 (m, 4 H), 1.40-1.39 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 156.17, 153.32, 140.53, 132.18 (d, $J^P = 10.1$ Hz), 128.79 (d, $J^P = 15.1$ Hz), 128.22, 127.48, 126.89, 126.71, 125.19, 124.64, 124.01, 123.35, 123.00, 120.69 (d, $J^P = 21.7$ Hz), 111.88, 62.19 (d, $J^P = 5.3$ Hz), 16.43 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.78. HRMS calcd for $\text{C}_{22}\text{H}_{22}\text{O}_4\text{P} (\text{M}^+ + \text{H})$ 381.1250, found 381.1238.

4.4.2ae. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.23-8.21 (d, $J = 7.3$ Hz, 2 H), 8.01-7.97 (m, 2 H), 7.89-7.86 (m, 3 H), 7.62-7.59 (t, $J = 7.6$ Hz, 1 H), 7.53-7.50 (m, 3 H), 4.29-4.14 (m, 4 H), 1.43-1.40 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 144.60

(d, $J^P = 3.1$ Hz), 139.40, 138.42, 136.49, 135.82, 135.63, 132.34 (d, $J^P = 10.1$ Hz), 128.68, 128.36 (d, $J^P = 15.1$ Hz), 127.17, 127.04, 125.21, 124.57, 122.66, 121.81, 121.17 62.27 (d, $J^P = 5.4$ Hz), 16.43 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.51. HRMS calcd for $\text{C}_{22}\text{H}_{22}\text{O}_3\text{PS} (\text{M}^+ + \text{H})$ 397.1022, found 397.1025.

4.4.2af. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.57-7.49 (m, 3 H), 7.42-7.40 (m, 3 H), 6.32-6.25 (t, $J = 17.6$ Hz, 1 H), 4.20-4.12 (m, 4 H), 1.39-1.37 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.77 (d, $J^P = 6.5$ Hz), 134.89 (d, $J^P = 23.0$ Hz), 130.25, 128.87, 127.73, 114.00 (d, $J^P = 190.1$ Hz), 61.86 (d, $J^P = 5.4$ Hz), 16.43 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 19.52.

4.4.2ag. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.44 (m, 3 H), 6.93-6.92 (d, $J = 7.7$ Hz, 2 H), 6.15-6.08 (t, $J = 17.6$ Hz, 1 H), 4.18-4.11 (m, 4 H), 3.86 (s, 3 H), 1.39-1.36 (t, $J = 6.8$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.46 (d, $J^P = 7.1$ Hz), 129.35, 127.78, 114.25, 111.67, 110.14, 61.74 (d, $J^P = 5.4$ Hz), 55.40, 16.43 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 20.45.

4.4.2ah. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.79-7.73 (m, 4 H), 7.36-7.34 (d, $J = 8.1$ Hz, 2 H), 7.13-7.11 (m, 2 H), 4.20-4.06 (m, 4 H), 2.48 (s, 3 H), 1.36-1.33 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 152.59, 145.78, 133.53 (d, $J^P = 10.8$ Hz), 132.15, 129.93, 128.50, 128.36, 122.52 (d, $J^P = 15.8$ Hz), 62.36 (d, $J^P = 5.5$ Hz), 21.76, 16.34 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.13.

4.4.2ai. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.98-7.90 (m, 4 H), 4.25-4.11 (m, 4 H), 3.14-3.11 (t, $J = 7.7$ Hz, 4 H), 1.62-1.54 (m, 4 H), 1.38-1.35 (t, $J = 7.1$ Hz, 6 H), 0.91-0.88 (t, $J = 7.4$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.93 (d, $J^P = 3.4$ Hz), 133.81,

132.40 (d, $J^P = 10.2$ Hz), 126.88 (d, $J^P = 15.0$ Hz), 62.60 (d, $J^P = 5.6$ Hz), 50.03, 22.03, 16.36 (d, $J^P = 6.2$ Hz), 11.16. ^{31}P NMR (202 MHz, CDCl_3) δ 16.07. HRMS calcd for $\text{C}_{16}\text{H}_{29}\text{NO}_5\text{PS} (\text{M}^+ + \text{H})$ 378.1499, found 378.1520.

4.4.2aj. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.70 (s, 1 H), 7.63-7.59 (m, 1 H), 7.45-7.40 (m, 3 H), 7.36-7.34 (m, 2 H), 7.26-7.24 (d, $J = 7.5$ Hz, 1 H), 6.95-6.92 (m, 1 H), 4.24-4.08 (m, 4 H), 1.37-1.34 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 147.19 (d, $J^P = 8.0$ Hz), 142.37, 133.84 (d, $J^P = 2.2$ Hz), 133.67 (d, $J^P = 6.6$ Hz), 129.85, 129.57, 124.03 (q, $J^P = 270.8$ Hz), 122.86, 119.62 (d, $J^P = 13.8$ Hz), 119.04, 118.59 (q, $J^P = 3.8$ Hz), 116.23 (q, $J^P = 3.8$ Hz), 115.46 (d, $J^P = 11.8$ Hz), 62.48 (d, $J^P = 5.1$ Hz), 16.27 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 20.21. ^{19}F NMR (471 MHz, CDCl_3) δ -62.77. HRMS calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{NO}_3\text{P} (\text{M}^+)$ 373.1049, found 373.1065.

4.4.2ak. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.88-7.84 (m, 2 H), 7.21-7.19 (m, 2 H), 4.21-4.05 (m, 4 H), 1.36-1.33 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 154.40 (d, $J^P = 3.8$ Hz), 133.40 (d, $J^P = 10.9$ Hz), 126.42, 121.78 (d, $J^P = 15.9$ Hz), 62.19 (d, $J^P = 5.3$ Hz), 16.34 (d, $J^P = 6.6$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.06.

4.4.2al. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.91-7.87 (m, 2 H), 7.33-7.32 (d, $J = 7.7$ Hz, 2 H), 4.23-4.08 (m, 4 H), 1.37-1.34 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 152.23, 133.85 (d, $J^P = 10.9$ Hz), 128.55 (q, $J^P = 147.2$ Hz), 120.49 (d, $J^P = 15.6$ Hz), 120.31 (d, $J^P = 257.1$ Hz), 62.36 (d, $J^P = 5.5$ Hz), 16.35 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.04. ^{19}F NMR (471 MHz, CDCl_3) δ -57.62.

4.4.2am. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.81 (s, 1 H), 7.79-7.74 (m, 2 H), 7.67-7.66 (d, $J = 5.2$ Hz, 2 H), 4.18-4.02 (m, 4 H), 2.23 (s, 3 H), 1.35-1.32 (t, $J = 7.1$ Hz,

6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 168.64, 141.83 (d, $J^P = 3.4$ Hz), 132.97 (d, $J^P = 10.7$ Hz), 130.28 (d, $J^P = 6.5$ Hz), 119.07 (d, $J^P = 15.2$ Hz), 62.12 (d, $J^P = 5.4$ Hz), 24.73, 16.33 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.67.

4.4.2an. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.94 (s, 1 H), 7.92-7.90 (d, $J = 7.6$ Hz, 2 H), 7.88-7.84 (m, 2 H), 7.81-7.79 (m, 2 H), 7.63-7.60 (t, $J = 7.3$ Hz, 1 H), 7.56-7.53 (t, $J = 7.7$ Hz, 2 H), 4.21-4.06 (m, 4 H), 1.37-1.34 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.77, 134.50, 133.16 (d, $J^P = 10.7$ Hz), 132.30, 132.16, 128.97, 127.07, 123.01, 119.44 (d, $J^P = 15.3$ Hz), 62.11 (d, $J^P = 5.3$ Hz), 16.36 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.49. HRMS calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_4\text{P}$ ($\text{M}^+ + \text{H}$) 334.1203, found 334.1237.

4.4.2ao. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.24-8.22 (d, $J = 7.8$ Hz, 1 H), 7.94-7.82 (m, 3 H), 7.70-7.67 (t, $J = 7.7$ Hz, 1 H), 7.59-7.47 (m, 3 H), 7.38-7.36 (m, 1 H), 4.22-4.07 (m, 4 H), 1.39-1.35 (t, $J = 8.5$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 164.68 (d, $J^P = 4.5$ Hz), 154.20 (d, $J^P = 4.2$ Hz), 133.94, 133.52 (d, $J^P = 10.9$ Hz), 131.80 (d, $J^P = 9.7$ Hz), 130.27, 128.70, 128.47 (d, $J^P = 14.9$ Hz), 122.00 (d, $J^P = 15.9$ Hz), 62.10 (d, $J^P = 5.3$ Hz), 16.35 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.81. HRMS calcd for $\text{C}_{17}\text{H}_{20}\text{O}_5\text{P}$ ($\text{M}^+ + \text{H}$) 335.1043, found 335.1034.

4.4.2ap. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.74-7.69 (m, 2 H), 6.95-6.93 (m, 2 H), 4.16-4.04 (m, 4 H), 3.89-3.87 (t, $J = 4.8$ Hz, 4 H), 3.30-3.28 (t, $J = 4.9$ Hz, 4 H), 1.35-1.32 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 151.41 (d, $J^P = 1.5$ Hz), 133.40 (d, $J^P = 11.1$ Hz), 119.44 (d, $J^P = 3.2$ Hz), 113.99 (d, $J^P = 15.4$ Hz), 66.65, 61.79 (d, $J^P =$

5.1 Hz), 47.77, 16.36 (d, $J^P = 6.8$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 20.42. HRMS calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_4\text{P}$ ($\text{M}^+ + \text{H}$) 300.1359, found 300.1363.

4.4.2aq. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.86-7.82 (m, 2 H), 7.79-7.77 (m, 2 H), 4.19-4.04 (m, 4 H), 3.93-3.90 (t, $J = 7.0$ Hz, 2 H), 2.69-2.65 (t, $J = 8.1$ Hz, 2 H), 2.26-2.19 (m, 2 H), 1.35-1.32 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 174.66, 140.91 (d, $J^P = 4.0$ Hz), 132.77 (d, $J^P = 10.6$ Hz), 129.76 (d, $J^P = 1.9$ Hz), 118.96 (d, $J^P = 15.1$ Hz), 62.07 (d, $J^P = 5.4$ Hz), 48.45, 32.86, 17.93, 16.35 (d, $J^P = 6.6$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.64. HRMS calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_4\text{P}$ ($\text{M}^+ + \text{H}$) 298.1203, found 298.1232.

4.4.2ar. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.06-8.04 (m, 1 H), 7.85-7.82 (m, 1 H), 7.77-7.73 (m, 2 H), 7.55-7.47 (m, 3 H), 7.43-7.41 (m, 2 H), 7.16-7.14 (m, 2 H), 7.02-7.00 (m, 1 H), 6.69-6.62 (m, 2 H), 5.42-5.37 (d, $J = 25.6$ Hz, 1 H), 4.82-4.79 (d, $J = 14.6$ Hz, 1 H), 4.73-4.67 (m, 2 H), 1.38-1.37 (d, $J = 6.2$ Hz, 6 H), 1.22-1.21 (d, $J = 6.2$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 167.11 (d, $J^P = 42.2$ Hz), 158.89 (d, $J^P = 4.6$ Hz), 157.43 (d, $J^P = 2.6$ Hz), 153.08, 151.16, 148.66, 147.75, 140.43, 138.77, 137.96, 137.15, 132.09 (d, $J^P = 1.3$ Hz), 132.00, 131.14, 130.11, 128.87 (d, $J^P = 3.2$ Hz), 128.45 (d, $J^P = 15.3$ Hz), 124.68, 121.76 (q, $J^P = 3.2$ Hz), 120.82, 118.80, 111.52 (d, $J^P = 1.7$ Hz), 104.96, 70.82 (d, $J^P = 5.7$ Hz), 52.25, 24.05 (d, $J^P = 4.0$ Hz), 23.78 (d, $J^P = 4.7$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 16.08. ^{19}F NMR (471 MHz, CDCl_3) δ -62.64, -107.19, -115.15. HRMS calcd for $\text{C}_{32}\text{H}_{30}\text{F}_5\text{N}_2\text{O}_5\text{PNa}$ ($\text{M}^+ + \text{Na}$) 671.1705, found 671.1726.

4.4.2as. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.90-7.85 (m, 2 H), 7.64-7.61 (m, 2 H), 4.77 (s, 2 H), 4.23-4.07 (m, 4 H), 2.63-2.60 (t, $J = 6.5$ Hz, 2 H), 2.22 (s, 3 H), 2.17 (s,

3 H), 2.13 (s, 3 H), 1.88-1.77 (m, 2 H), 1.72-1.59 (m, 3 H), 1.55-1.51 (m, 2 H), 1.37-1.34 (t, $J = 7.0$ Hz, 6 H), 1.29-1.27 (m, 19 H), 0.91-0.86 (m, 12 H). ^{13}C NMR (125 MHz, CDCl₃) δ 148.01 (d, $J^P = 26.5$ Hz), 142.78 (d, $J^P = 8.6$ Hz), 134.40, 132.06 (d, $J^P = 10.2$ Hz), 129.31, 127.22 (d, $J^P = 15.2$ Hz), 125.84, 123.39 (d, $J^P = 73.1$ Hz), 122.52, 117.71, 83.98 (d, $J^P = 6.2$ Hz), 74.39 (d, $J^P = 130.5$ Hz), 62.11 (d, $J^P = 5.2$ Hz), 40.06 (d, $J^P = 5.8$ Hz), 39.39, 37.56, 37.43, 37.40, 37.30, 32.80, 31.32, 29.34, 28.00, 24.82, 24.17 (d, $J^P = 70.4$ Hz), 22.70, 22.69 (d, $J^P = 11.6$ Hz), 21.72, 21.05, 20.69 (d, $J^P = 1.4$ Hz), 19.70, 16.37 (d, $J^P = 6.6$ Hz), 12.84, 11.97, 11.83. ^{31}P NMR (202 MHz, CDCl₃) δ 18.79. **HRMS** calcd for C₄₀H₆₅O₅PNa (M⁺ + Na) 679.4462, found 679.4479.

4.4.2at. Colorless oil. ^1H NMR (500 MHz, CDCl₃) δ 7.86-7.82 (m, 2 H), 7.57-7.53 (m, 1 H), 7.49-7.45 (m, 2 H), 4.74-4.68 (m, 2 H), 1.40-1.39 (d, $J = 6.2$ Hz, 6 H), 1.26-1.24 (d, $J = 6.2$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl₃) δ 132.04 (d, $J^P = 3.2$ Hz), 131.79, 131.71, 128.30 (d, $J^P = 14.8$ Hz), 70.70 (d, $J^P = 5.5$ Hz), 24.10 (d, $J^P = 4.0$ Hz), 23.85 (d, $J^P = 4.9$ Hz). ^{31}P NMR (202 MHz, CDCl₃) δ 16.62.

4.4.2au. Colorless oil. ^1H NMR (500 MHz, CDCl₃) δ 7.85-7.81 (m, 2 H), 7.59-7.56 (t, $J = 7.5$ Hz, 1 H), 7.49-7.48 (m, 2 H), 4.13-3.99 (m, 4 H), 1.70-1.65 (m, 4 H), 1.45-1.38 (m, 4 H), 0.94-0.91 (t, $J = 7.4$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl₃) δ 132.33, 132.30, 131.79 (d, $J^P = 9.8$ Hz), 128.44 (d, $J^P = 14.9$ Hz), 65.81 (d, $J^P = 5.7$ Hz), 32.46 (d, $J^P = 6.5$ Hz), 18.75, 13.60. ^{31}P NMR (202 MHz, CDCl₃) δ 18.78.

4.4.2av. White solid. ^1H NMR (500 MHz, CDCl₃) δ 7.38-7.32 (m, 15 H). ^{13}C NMR (125 MHz, CDCl₃) δ 133.76 (d, $J^P = 19.3$ Hz), 128.72, 128.53, 128.48. ^{31}P NMR (202 MHz, CDCl₃) δ -5.40.

4.4.2aw. Colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.92-7.89 (d, $J = 14.6$ Hz, 1 H), 7.44-7.37 (m, 6 H), 7.25-7.23 (t, $J = 6.0$ Hz, 1 H), 3.99-3.81 (m, 4 H), 2.45 (s, 3 H), 1.15-1.12 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 143.13 (d, $J^P = 9.6$ Hz), 141.47 (d, $J^P = 4.1$ Hz), 136.71 (d, $J^P = 14.6$ Hz), 134.50 (d, $J^P = 9.8$ Hz), 132.70 (d, $J^P = 3.1$ Hz), 131.35 (d, $J^P = 14.8$ Hz), 129.44, 127.43, 127.25, 125.80, 61.71 (d, $J^P = 5.9$ Hz), 21.02, 16.06 (d, $J^P = 6.9$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.63. HRMS calcd for $\text{C}_{17}\text{H}_{22}\text{O}_3\text{P}$ ($\text{M}^+ + \text{H}$) 305.1301, found 305.1294.

4.4.2ax. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 8.10 (s, 1 H), 7.98-7.90 (m, 5 H), 7.86-7.84 (m, 2 H), 7.78-7.76 (d, $J = 8.5$ Hz, 1 H), 7.57-7.53 (m, 2 H), 4.26-4.12 (m, 4 H), 1.40-1.37 (t, $J = 7.1$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 145.12 (d, $J^P = 3.2$ Hz), 137.29 (d, $J^P = 1.2$ Hz), 133.57, 133.00, 132.41 (d, $J^P = 10.2$ Hz), 128.73, 128.34, 127.70, 127.50, 127.38, 126.57, 126.46, 126.39, 125.23, 62.18 (d, $J^P = 5.3$ Hz), 16.40 (d, $J^P = 6.5$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 18.96. HRMS calcd for $\text{C}_{20}\text{H}_{22}\text{O}_3\text{P}$ ($\text{M}^+ + \text{H}$) 341.1301, found 341.1288.

4.4.2ay. Yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.65-7.60 (m, 2 H), 7.43-7.40 (t, $J = 7.8$ Hz, 2 H), 7.24-7.22 (m, 3 H), 6.85-6.82 (m, 2 H), 4.15-4.03 (m, 4 H), 3.37 (s, 3 H), 1.34-1.32 (t, $J = 7.0$ Hz, 6 H). ^{13}C NMR (125 MHz, CDCl_3) δ 148.23 (d, $J^P = 2.4$ Hz), 147.48, 133.14 (d, $J^P = 11.2$ Hz), 129.82, 125.83, 125.31, 119.44 (d, $J^P = 9.7$ Hz), 114.20 (d, $J^P = 15.4$ Hz), 61.70 (d, $J^P = 5.1$ Hz), 40.11, 16.37 (d, $J^P = 6.6$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 21.07. HRMS calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 320.1410, found 320.1413.

4.4.2az. Colorless solid. ^1H NMR (500 MHz, CDCl_3) δ 8.44 (d, $J = 15.3$ Hz, 1H), 8.05 – 7.93 (m, 3H), 7.85 – 7.73 (m, 2H), 7.60 (d, $J = 2.4$ Hz, 1H), 7.54 (dd, $J = 8.4, 2.4$ Hz, 1H),

7.00 (d, $J = 8.4$ Hz, 1H), 4.24 – 4.08 (m, 4H), 3.91 (s, 3H), 2.22 – 2.15 (m, 6H), 2.14 – 2.07 (m, 3H), 1.83 – 1.76 (m, 6H), 1.35 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 159.07, 141.55, 139.16, 135.57 (d, $J^P = 2.7$ Hz), 133.96 (d, $J^P = 10.3$ Hz), 132.63, 131.25 (d, $J^P = 16.7$ Hz), 129.42, 128.59 (d, $J^P = 14.2$ Hz), 126.92 (d, $J^P = 9.9$ Hz), 126.84, 125.99 (d, $J^P = 30.0$ Hz), 125.63, 124.89, 124.14, 112.25, 62.32 (d, $J^P = 5.2$ Hz), 55.31, 40.74, 37.26, 29.25, 16.53 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 19.34. HRMS calcd for $\text{C}_{31}\text{H}_{38}\text{O}_4\text{P}$ ($\text{M}^+ + \text{H}$) 505.2508, found 505.2489.

4.4.2ba. White solid. ^1H NMR (500 MHz, CDCl_3) δ 8.73 (s, 1H), 7.97 – 7.93 (m, 2H), 7.81 – 7.74 (m, 2H), 7.64 (s, 1H), 7.56 (d, $J = 8.6$ Hz, 1H), 7.30 (d, $J = 8.5$ Hz, 1H), 4.14 – 4.04 (m, 4H), 1.69 (m, 4H), 1.35 – 1.25 (m, 18H). ^{13}C NMR (125 MHz, CDCl_3) δ 165.23, 145.78, 141.58, 139.36 (d, $J^P = 3.1$ Hz), 135.71, 132.17, 132.11 (d, $J^P = 10.1$ Hz), 130.68, 127.44 (d, $J^P = 15.1$ Hz), 127.26, 118.36 (d, $J^P = 10.8$ Hz), 62.58 (d, $J^P = 5.6$ Hz), 35.20, 34.56, 34.13, 31.97 (d, $J^P = 4.7$ Hz), 16.44 (d, $J^P = 6.4$ Hz). ^{31}P NMR (202 MHz, CDCl_3) δ 17.02. HRMS calcd for $\text{C}_{25}\text{H}_{35}\text{NO}_4\text{P}$ ($\text{M}^+ + \text{H}$) 444.2304, found 444.2284.

4.4.2bb. White solid. ^1H NMR (500 MHz, CDCl_3) δ 7.79 – 7.70 (m, 1H), 7.23 – 7.16 (m, 2H), 7.11 – 7.02 (m, 2H), 6.88 – 6.71 (m, 3H), 5.36 (q, $J = 8.3$ Hz, 1H), 4.20 – 3.95 (m, 6H), 2.96 – 2.89 (m, 2H), 2.66 – 2.57 (m, 2H), 1.72 – 1.69 (m, 2H), 1.61 – 1.47 (m, 6H), 1.39 (t, $J = 6.9$ Hz, 4H), 1.32 (t, $J = 7.1$ Hz, 6H), 0.91 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 168.85, 161.04 (d, $J^P = 3.1$ Hz), 152.65, 142.24 (d, $J^P = 2.4$ Hz), 138.84, 135.73 (d, $J^P = 7.6$ Hz), 128.05, 127.88, 125.21, 122.97, 121.02 (d, $J^P = 14.9$ Hz), 116.31, 114.81, 112.76 (d, $J^P = 9.8$ Hz), 64.27, 62.17 (d, $J^P = 5.6$ Hz), 50.03, 46.81, 44.45, 26.91, 25.48, 24.28, 22.91, 22.67, 16.54 (d, $J^P = 6.6$ Hz), 14.72. ^{31}P NMR (202 MHz, CDCl_3) δ 17.01. HRMS calcd for $\text{C}_{30}\text{H}_{46}\text{N}_2\text{O}_5\text{P}$ ($\text{M}^+ + \text{H}$) 545.3144, found 545.3122.

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Chapter 5

Conclusion

The research outlined in this thesis aimed to develop new catalytic methods for using amides as electrophiles in transition-metal-catalyzed acyl and decarbonylative cross-coupling reactions and to establish carboxylic acids as electrophiles in transition-metal-catalyzed decarbonylative cross-coupling reactions. The main achievements of this work are summarized below:

- (1) Acyl cross-coupling of amides: we have discovered a range of new twisted amides with varying steric and electronic properties and employed them in palladium-catalyzed acyl Suzuki cross-coupling reactions. We have also demonstrated that some of these amides represent the most reactive amides developed thus far in amide bond cross-coupling. We have further established the broadly utilized hypothesis of ground-state destabilization in amide bond cross-coupling.
- (2) Decarbonylative cross-coupling of amides: we have developed the first decarbonylative phosphorylation of amides by palladium and nickel catalysis. This reaction represented the first example of a transition-metal-catalyzed generation of C–P bonds from amides. We have also developed efficient decarbonylative Heck cross-coupling of amides using *N*-acylsaccharins. Furthermore, by exploring related substrates for decarbonylation, we have developed the first intramolecular decarbonylation of thioesters using air- and moisture-stable nickel precatalysts.
- (3) Decarbonylative cross-coupling of carboxylic acids: we have developed the first decarbonylative borylation of carboxylic acids under redox-neutral conditions using well-

defined Pd(0)/(II) catalysis. This strategy has been highlighted in the late-stage derivatization of pharmaceuticals and natural products. Furthermore, we have developed the first step-down reduction of carboxylic acids to aromatic hydrocarbons via palladium catalysis. Subsequently, we have developed the first decarbonylative Suzuki-Miyaura cross-coupling of carboxylic acids. We have demonstrated that this method represents a general strategy for the synthesis of highly useful biaryls, which are key building blocks in many drugs, agrochemicals, and functional materials. Finally, we have developed the first decarbonylative phosphorylation of carboxylic acids by palladium catalysis. The methods represents a straightforward protocol for the synthesis of organophosphorus compounds from ubiquitous carboxylic acids.

For acyl cross-coupling of amides, we suggest to start optimization using *N*-acyl-glutarimides as electrophiles. These amides are in our experience the most reactive amide-based electrophiles. The next step would be to use *N*-acyclic amides as electrophiles, which are more general because these amides can be derived directly from common 1° and 2° amides. For decarbonylative cross-coupling of amides, *N*-acyl-glutarimides are the substrates of choice due to high stability of the *N*-acyl-glutarimide ring under decarbonylative conditions.

We expect that these results will guide the design of new types of reactions of amides and facilitate the development of new strategies for decarbonylative cross-coupling of carboxylic acids as electrophiles.