DEVELOPMENT OF NEW METHODS FOR ACTIVATION OF INERT N–C BONDS

By

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And approved by

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ABSTRACT OF THE DISSERTATION

DEVELOPMENT OF NEW METHODS FOR ACTIVATION OF INERT N–C BONDS

By

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Dissertation Director:

Professor Michal Szostak

The amide bond is one of the most important functional groups in chemistry and biology. It would be appealing to use amides as N–C(O) electrophiles in transition-metal-catalyzed cross-coupling reactions, however, the high activation energy required for N–C(O) scission, a consequence of amidic resonance (approximately 40% double bond character in planar amides, 15-20 kcal/mol barrier to rotation), makes selective metal insertion into the N–C(O) bond a classic problem in catalysis.

In 2015, our group introduced a new mode for amide bond activation enabled through ground-state-destabilization. Based on this concept, we have successfully developed N-acyl-glutarimide amides as highly effective amide-based electrophiles, in which the amide bond exhibits nearly perpendicular twist ($\tau = 87.8^{\circ}$).

This thesis describes our studies on: 1) the development of novel transition-metal-catalyzed transformations of amides by N–C(O) activation; 2) the development of new amide precursors for cross-coupling reactions; 3) the development of new, general catalytic systems for acyl-cross-coupling reactions. Specifically, the thesis addresses: 1) the development of novel decarbonylative cross-coupling reactions using amides as aryl equivalents, including Ni-catalyzed decarbonylative Suzuki cross-coupling, Pd-catalyzed decarbonylative cyanation, and Pd-catalyzed decarbonylative borylation; 2) the development of a general catalytic system for acyl Negishi cross-coupling reactions of N-acyl-glutarimides, N,N-di-Boc_2 amides and N-acyl-succinimides; 3) the development of Pd-NHC catalytic systems for acyl Suzuki cross-coupling of esters, acyl Buchwald-Hartwig cross-coupling of amides and esters, and acyl Suzuki cross-coupling of triflamides.

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Chapter 1

Introduction

Parts of this section were adapted with permission from the article "Well-Defined Palladium (II)–NHC Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective N–C/O–C Cleavage" (*Acc. Chem. Res.* **2018**, *51*, 2589). Copyright ©2018, American Chemical Society and from the article "Cross-Coupling of Amides by N–C Bond Activation" (*Synlett* **2016**, *27*, 2530). Copyright ©2016, Thieme Gruppe.

1.1 Amides as attractive substrates in catalytic cross-coupling

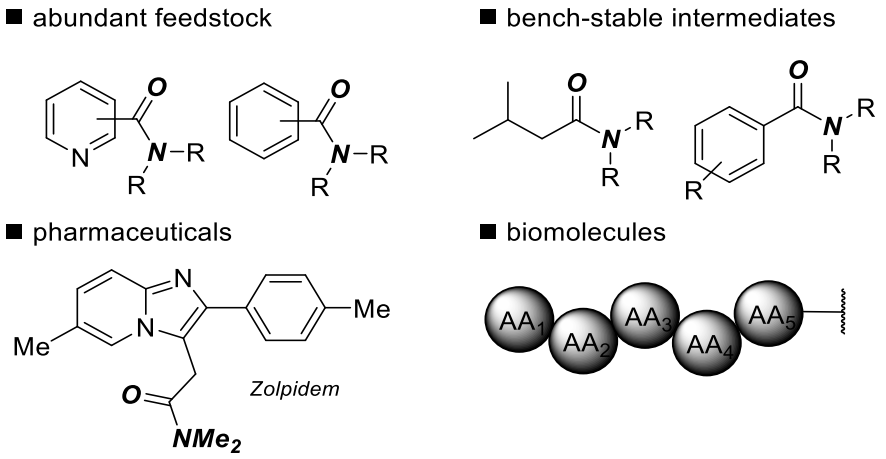

Figure 1.1 The importance of amide bonds.

The amide bond represents one of the most important functional groups in chemistry (Figure 1.1).[1,2] Furthermore, amides are widely present in biologically-active molecules.[3] Given the key role of the amide bond in chemical science,[3–5] new methods that utilize bench-stable amides as synthetic intermediates would provide fundamental tools for molecular assembly in various synthetic contexts. However, the application of amides as

effective N–C(O) electrophiles had not been explored before 2015 due to the challenge arising from amidic resonance. In contrast, other carboxylic acid derivatives, such as acyl halides, anhydrides and thioesters, have long been employed as acyl[6-9] or aryl[10-13] electrophiles in cross-coupling reactions.

1.2 The challenge of using amides as electrophiles in cross-coupling reactions

The major challenge of using amides as electrophilic cross-coupling partners in cross-couplings results from amidic resonance. The resonance structure of the amide bond is a classic effect in organic chemistry, and a typical planar amide bond contains about 40% double-bond character.[14] This n_N to $\pi^*_{C=O}$ conjugation makes the amide bond one of the least reactive functional groups in organic chemistry. The barrier to rotation in planar amides is as high as 15-20 kcal/mol.[15] Collectively, the direct insertion of transition metal into the amide bond is both kinetically and thermodynamically unfavorable.

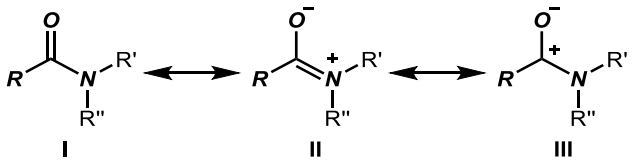

Figure 1.2 Resonance structure of planar amide.

1.3 Amide bond activation via ground-state-destabilization

In 2015, our laboratory introduced a new strategy for activation of amide N–C(O) bonds via ground-state-destabilization (Figure 1.3).[16] This activation method can be used to achieve low-valent metal insertion directly into an otherwise inert amide bond (rotation energy of about 15-20 kcal/mol in planar amides) as a result of disfavoring amidic

resoance by steric and/or electronic effects.[16]

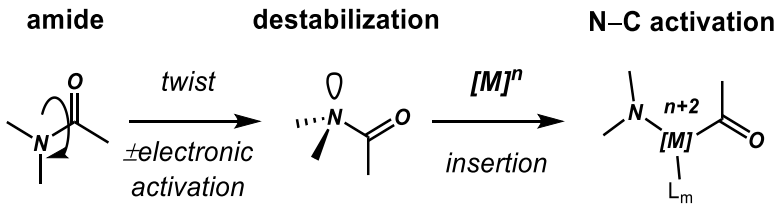

Figure 1.3 Activation of amide N–C(O) bonds by ground-state-destabilization.

When we first introduced this novel mode for amide bond activation,[17] two other groups independently reported new transformations of amides: 1) Garg and co-workers reported the nickel-catalyzed esterification of amides,[18] 2) Zou and co-workers reported the palladium-catalyzed Suzuki-Miyaura cross-coupling of amides (Figure 1.4).[19]

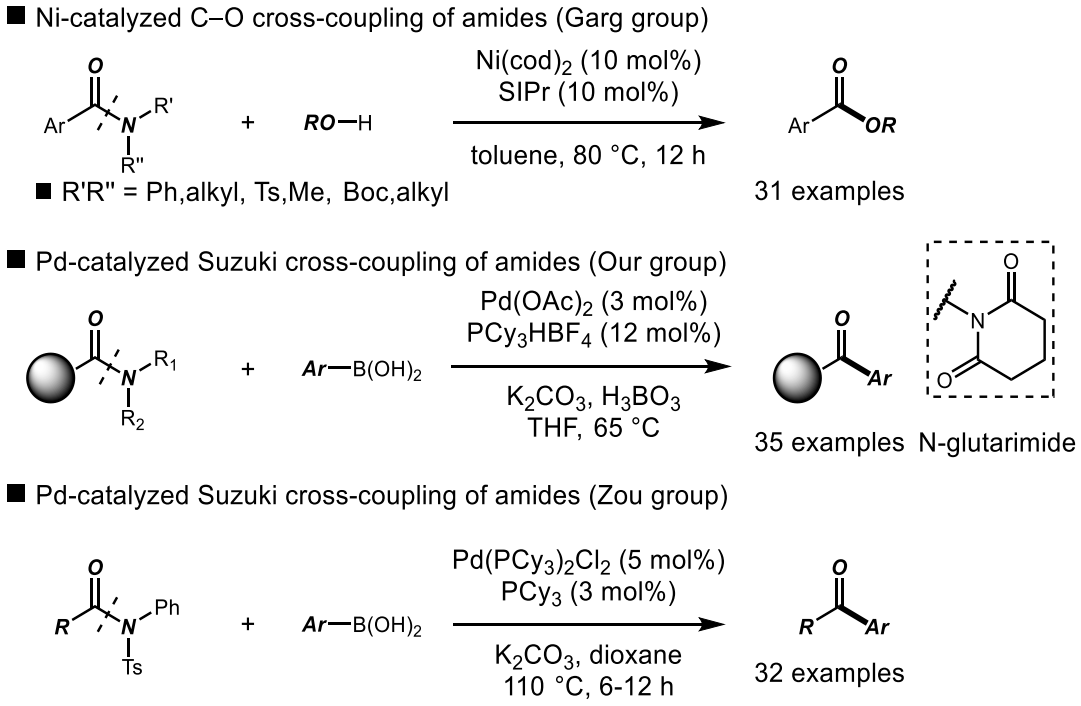

Figure 1.4 Seminal reports on catalytic amide bond activation.

1.4 Acyl cross-coupling and decarbonylative cross-coupling of amides

Mechanistically, the activation of the N–C(O) amide bond is enabled through ground-state-destabilization of the amide bond by steric and/or electronic factors,[20–22] which allows facile insertion of a low valent metal into the N–C(O) bond furnishing acyl-metal intermediate (Figure 1.5). At this stage, two major types of reactions may occur depending on the catalyst, ligand and reaction parameters: (1) decarbonylative cross-coupling, or (2) acyl cross-coupling. Both of these reaction manifolds may proceed with high bond scission selectivity and under mild conditions, thus representing a potentially powerful approach to rapid functionalization of amide bonds by catalytic cross-coupling reactions.

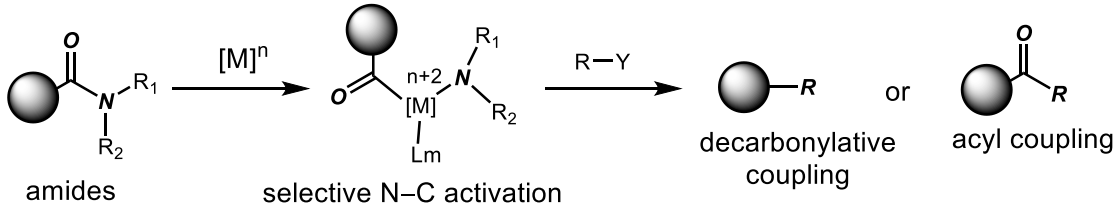

Figure 1.5 Amide bond cross-coupling reactions.

The generalized catalytic cycle for metal catalyzed cross-coupling of amides is shown in Figure 1.6. The key step for both mechanisms involves a selective metal insertion into the N–C(O) amide bond. As implied in Figure 1.6A, the use of amides as aryl electrophiles in decarbonylative cross-couplings is significantly more challenging than in acyl-cross-couplings[10,11] as the success must accommodate two finely-tuned elementary steps: 1) selective metal insertion into the N–C(O) bond, and 2) controlled decarbonylation.

As shown in Figure 1.6B, amides may also serve as acyl electrophiles after selective

metal insertion into the N–C(O) bond and direct reductive elimination.[23,24]

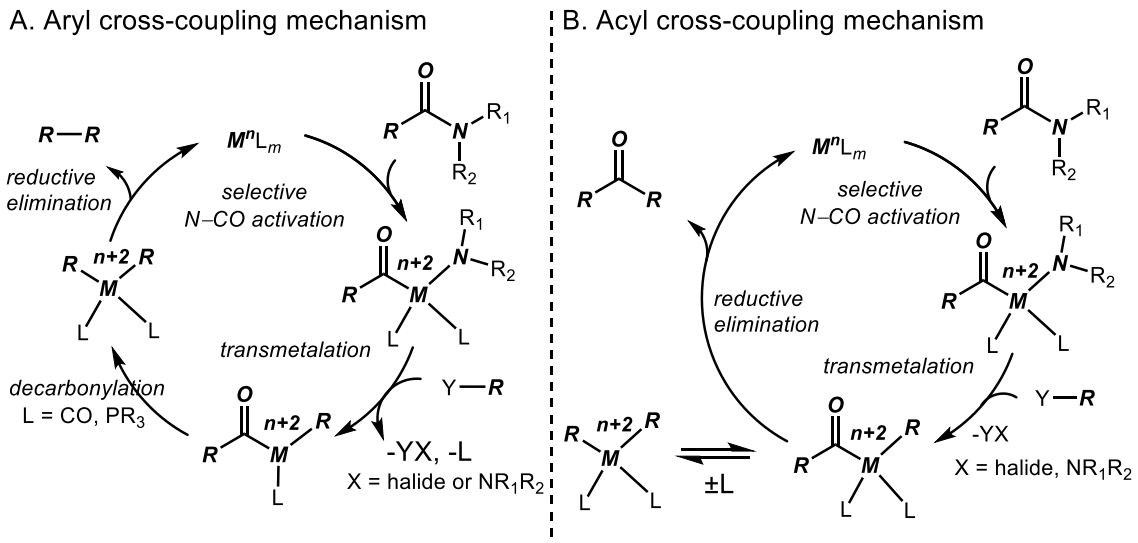

Figure 1.6 Generalized mechanisms for tranition-metal-catalyzed cross-coupling of amides.

1.5 Pd(II)–NHC precatalysts in acyl cross-coupling

Developing robust catalytic system for cross-coupling reactions has been a long-term goal in catalysis.[25,26] Over the past decade, well-defined Pd(II)–NHC precatalysts (NHC = N-heterocyclic carbene) have become attractive alternatives to Pd/phosphine catalysts owing to several major advantages: (1) Pd(II)–NHC complexes are air- and moisture-stable, which makes their handling operationally-convenient; (2) NHC ligands oftentimes show better catalytic activity than electron-rich phosphines due to strong σ-donating properties; (3) many of the Pd(II)–NHC complexes are commercially available, which facilitates ligand screening and reaction optimization; (4) well-defined Pd(II)–NHC precatalysts feature 1:1 Pd:NHC ratio. This avoids using excess of expensive ligand and is optimal for the formation of catalytically-active monoligated Pd(0) species.[25-31]

The successful use of well-defined Pd(II)–NHC precatalysts in challenging cross-couplings[32-37] prompted us to study these catalysts in acyl cross-coupling of amides. Our group was first to introduce a general Pd-NHC catalytic system for acyl Suzuki cross-coupling of amides (Figure 1.7).[38]

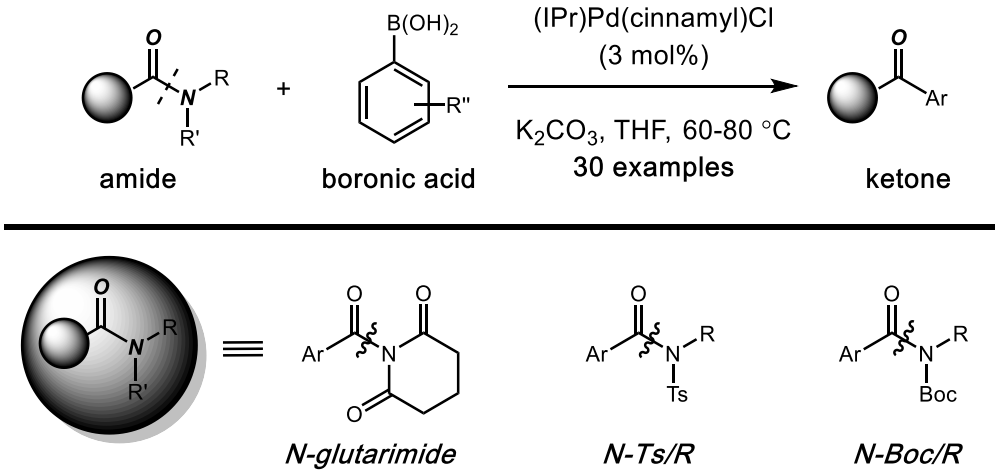

Figure 1.7 Pd(II)-NHCs as general catalysts for Suzuki cross-coupling of amides.

Furthermore, our group has reported the cross-coupling of amides and esters at ambient temperature as well as cross-coupling of more challenging amides with various bench-stable, well-defined Pd(II)–NHC precatalysts (Figure 1.8).[39-44]

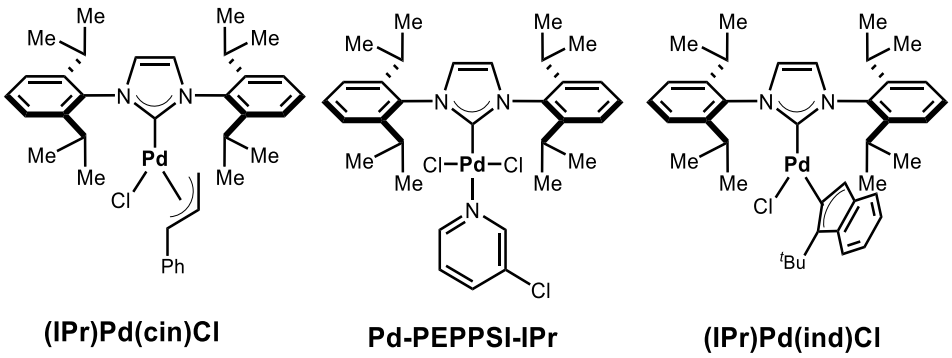

Figure 1.8 Pd(II)–NHC precatalysts employed in acyl cross-coupling of amides.

A general catalytic cycle of NHC-Pd catalyzed cross-couplings is shown in Figure 1.9. Most importantly, the strong σ-donation and flexible steric bulk around palladium in Pd-NHC complexes[31,32,45,46] facilitate oxidative addition and reductive elimination steps, respectively.

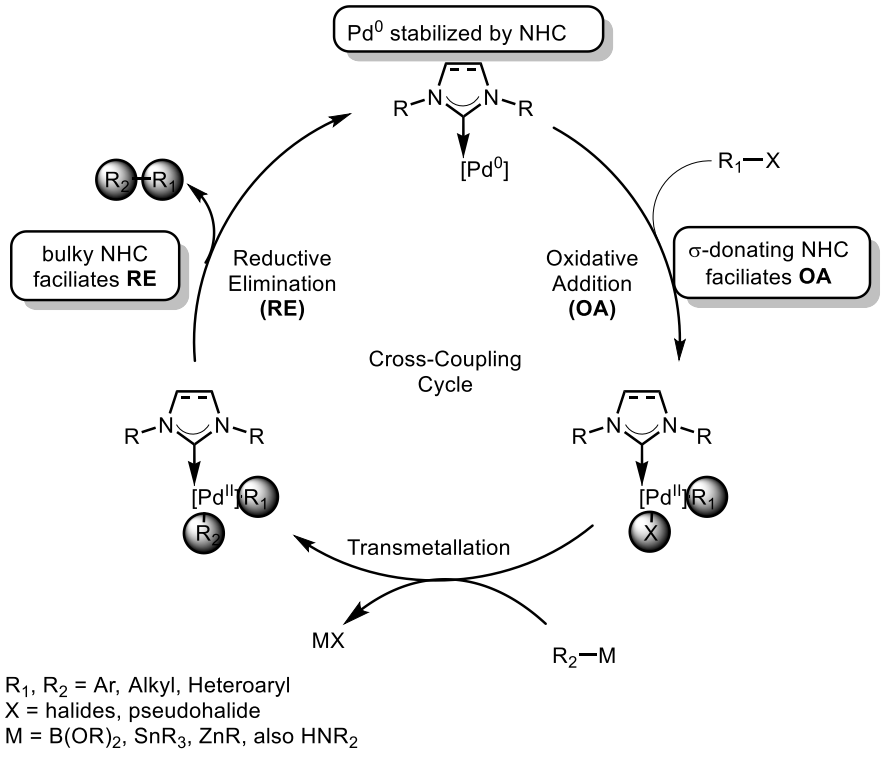

Figure 1.9 Catalyic cycle of Pd-NHC catalyzed cross-coupling reactions.

1.6 Brief summary of the work in this thesis

The research outlined in this thesis has been guided by our concept of amide bond activation enabled through ground-state-destabilization.[17] Our initial results demonstrated amides could serve as acyl and aryl electrophiles for C–C bond formation.[24] The thesis is specifically focused on: 1) the development of novel transition-metal-catalyzed transformations of amides by N–C(O) activation; 2) the development of new amide

precursors for cross-coupling reactions; 3) the development of new, general catalytic systems for acyl-cross-coupling reactions.[23]

After introductory Chapter I, Chapter II will discuss metal-catalyzed decarbonylative cross-coupling amides by N–C(O) bond activation. This chapter will discuss three novel transformations using N-acyl-glutarimides as aryl electrophiles: 1) nickel-catalyzed decarbonylative Suzuki cross-coupling; 2) palladium-catalyzed decarbonylative cyanation; 3) palladium-catalyzed decarbonylative borylation.[47-49] Chapter III will discuss nickel-catalyzed acyl Negishi cross-coupling of amides by N–C bond activation. This chapter will include a detailed study of three types of amide electrophiles: 1) nickel-catalyzed acyl Negishi cross-coupling of N-acyl-glutarimides; 2) nickel-catalyzed acyl Negishi cross-coupling of N,N-di-Boc_2 amides; 3) nickel-catalyzed acyl Negishi cross-coupling of N-acyl-succinimides.[50-52] Chapter IV will discuss the development of Pd(II)-NHC catalyst systems in acyl cross-coupling of amides and esters. This chapter will focus on: 1) the development of Pd(II)-NHC catalysts for acyl Suzuki cross-coupling of esters; 2) the development of Pd(II)-NHC catalysts for acyl Buchwald-Hartwig cross-coupling of amides and esters; 3) the development of Pd(II)-NHC catalysts for cross-coupling of N-triflamides as most reactive amide-based acyl electrophiles.[42-44]

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Chapter 2

Transition-Metal-Catalyzed Decarbonylative Cross-Coupling of Amides

2.1 Nickel-catalyzed decarbonylative Suzuki cross-coupling of amides

Parts of this section were adapted with permission from the article: "Synthesis of Biaryls through Nickel-Catalyzed Suzuki–Miyaura Coupling of Amides by Carbon–Nitrogen Bond Cleavage" (*Angew. Chem. Int. Ed.* **2016**, *55*, 6959). Copyright ©2016, John Wiley and Sons.

2.1.1 Introduction

The Suzuki-Miyaura biaryl coupling reaction represents one of the most powerful carbon-carbon bond-forming reactions for arene functionalization.[1-4] While cross-coupling of classic electrophiles such as aryl halides, triflates, and tosylates have been successfully achieved with Pd catalysts,[5-7] major advances have also been made in the use of new C–O and C–N electrophiles (LG = O, N) as attractive coupling partners using sustainable and more economically viable Ni catalysts.[8] Notable progress has been reported in the cross-coupling of aryl ethers,[10-12] acetates,[13] pivalates,[13,14] carbamates,[15-17] sulfamates[15,16] and ammonium salts.[18] Examples of using aroyl electrophiles in the Suzuki-Miyaura reaction under redox neutral conditions, including anhydrides[19] and esters,[20] with Rh and Ni catalysts have been developed. Furthermore, oxidative cross-coupling of carboxylic acids with boronic acids using Pd has been reported;[22,23] however, this process suffers from limited substrate scope and expensive oxidants. At the time of

this project, despite the notable advances, the Suzuki-Miyaura biaryl coupling of significantly more challenging amides (barrier to N–C resonance of 15-20 kcal/mol, Figure 2.1),[24] after direct oxidative addition into N–C bond, had not been reported, a major deficiency given the pivotal role of amides as key building blocks in peptides and versatile bench-stable intermediates in organic synthesis.[25]

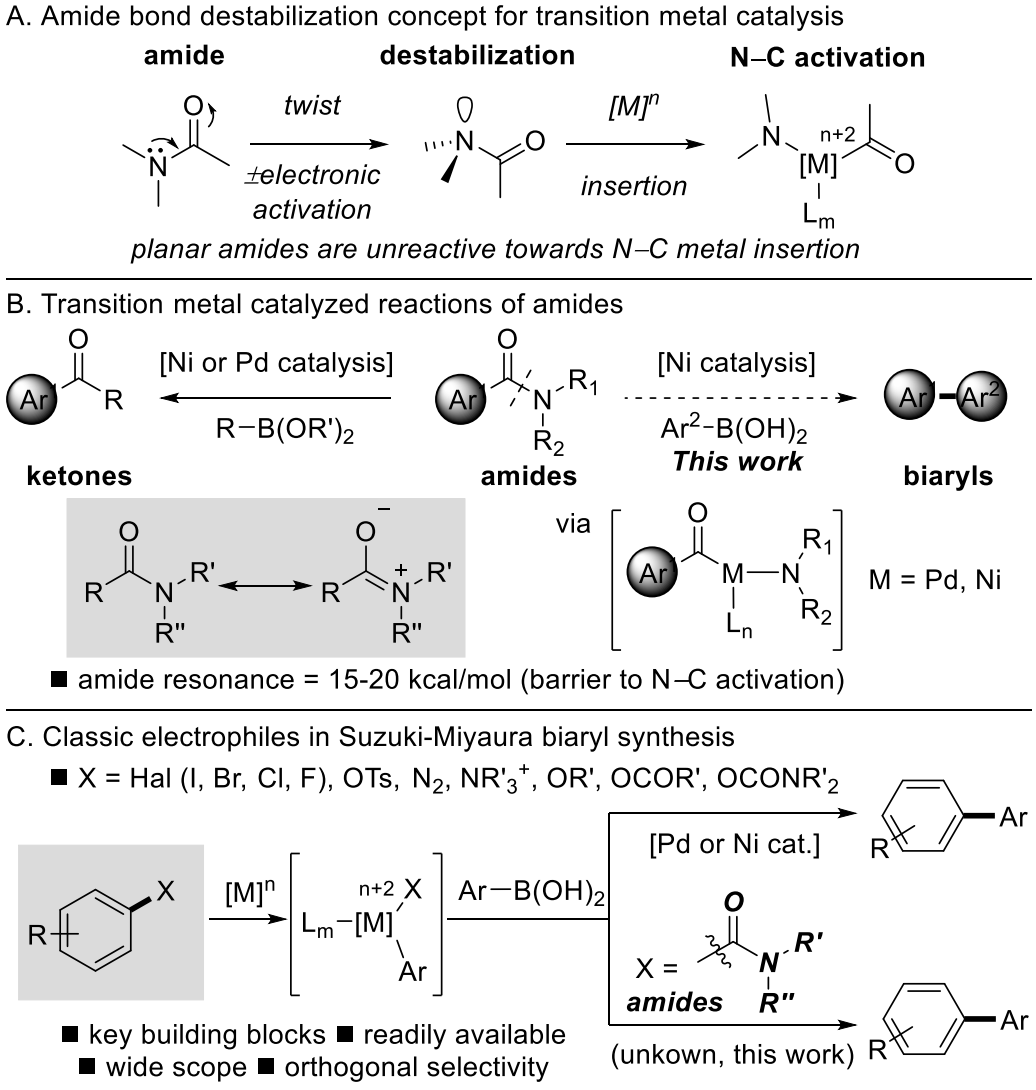


Figure 2.1 Cross-coupling of amides via aryl-metal intermediates.

Biaryls are key structural motifs in numerous bioactive medicinal agents, natural products and polymers.[26] We realized that the development of biaryl synthesis via cross-coupling of readily accessible, bench-stable amide precursors would significantly extend the pool of electrophiles available for the cross-coupling given that (1) amides are traditionally derived from different precursors than halides, phenols and anilines,[27,28] (2) amides are easy to prepare,[29,30] and (3) are typically inert to a variety of reaction conditions allowing for ring prefunctionalization.[29,30] However, the major challenge in using amides as arylation precursors was the low reactivity of the N–C(O) bond for direct oxidative addition and control of the decarbonylation of the acyl-metal intermediate.[31a]

With these considerations in mind, we developed the first Suzuki-Miyaura biaryl coupling reaction of amides by N–C cleavage.[31b] This new Suzuki-Miyaura cross-coupling variant could be accomplished in high yields with a broad range of amide and boronic acid substrates. The reaction employed air-stable, inexpensive Ni catalysts, which are economically advantageous over Pd. Furthermore, the reaction proceeded with full selectivity for Ni-insertion into the N–C(O) amide bond, representing a general method for the synthesis of aryl electrophiles from amides under Ni catalysis. In light of the importance of amides and the advantages offered by nickel catalysis, this concept contributed to providing a modular strategy for the application of ubiquitous amides as unconventional aryl electrophiles in cross-coupling manifolds.

As outlined in the introduction, our laboratory introduced a new mode of activation of amide bonds in transition metal catalysis by geometric distortion (Figure 2.1A).[32] We have established that twisted amides serve as robust and versatile precursors in catalytic

transformations of amide bonds for C–C bond construction by N–C(O) activation under Pd catalysis.[33,34] Independently, Garg[35] and Zou[36] reported the use of twisted imides[14] for the synthesis of ketones under Ni[35] and Pd[36] catalysis. Central to this ground-state-destabilization strategy is ligand coordination to the amide bond to disrupt $n_N \rightarrow \pi^*_{CO}$ conjugation and facilitate oxidative addition.[41-45] Ground state distortion and electronic activation contribute to the observed reactivity. In all cases, amides are readily available from carboxylic acid precursors by standard methods.[29,30] From a synthetic standpoint, the ability to promote previously-elusive transformations of amides via generic metal catalyzed activation modes with high functional group compatibility allows for implementing neutral, bench-stable, readily accessible amides as precursors in cross-couplings.[46,47]

We proposed that under appropriate conditions, the acylmetal intermediate resulting from metal insertion into the inert amide N–C bond would undergo transmetallation with aryl boronic acids and decarbonylation, generating organometal electrophile. Ni catalysts have been successfully utilized in Suzuki-Miyaura reactions of unconventional electrophiles (LG = O, N).[8,10-18] Studies by Yamamoto on C(O)–Ni–O decarbonylation[48] and progress in related cross-couplings provided precedents that decarbonylation of acylnickel complexes could proceed with high selectivity.[49,50] However, at the start of this project it was unclear whether such a pathway using significantly more challenging amides would be feasible given the inert nature of amide N–C(O) bonds,[29,30] reversibility of insertion/decarbonylation[48-50] and the lack of precedents for aryl-aryl bond formation via amide bond cleavage.[31]

2.1.2 Reaction optimization

We began our investigations by evaluating the coupling of amides with 2-naphthyl boronic acid as a standard nucleophile (Table 2.1). We focused on the challenging electron neutral, unconjugated aryl amide electrophiles with the aim of developing a generally applicable method with wide substrate scope. Ni-catalyzed coupling of unconventional electrophiles is typically facilitated using conjugated aromatics, limiting the preparative scope of the chemistry.[11,12] Although desired biaryl products were not detected using Pd catalysts, we found that the proposed Suzuki-Miyaura coupling of amides was indeed feasible using the sterically-distorted N-acyl-glutarimide and a Ni(0)/PCy_3 catalyst system (Figure 2.2). Using the less distorted anilides,[32] only a trace quantity of the cross-coupled product was formed, consistent with metal insertion into the neutral amide N–C(O) bond.[31] Significantly less distorted N-acyl-succinimide[32] resulted in a promising yield of the biaryl product, demonstrating high activity of the catalyst system. In all cases examined, negligible formation of ketone products was detected in crude reaction mixtures, consistent with the high capability of Ni catalyst to facilitate decarbonylation.[48-50] The insertion occurred selectively at the N–C(O) bond, with cleavage of the alternative N–C bond not observed.[46,47]

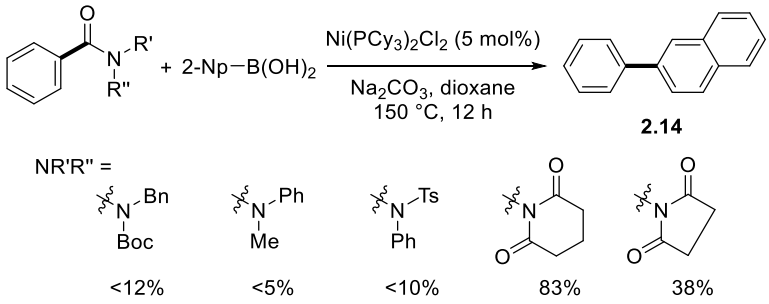
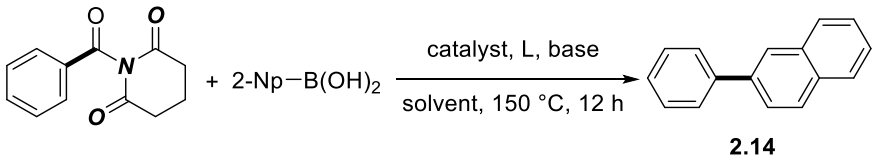


Figure 2.2 The effect of different N-substituents.

Key optimization results are shown in Table 2.1. Various catalysts were tested, and $Ni(PCy_3)_2Cl_2$ showed the best activity. Control experiments in the absence of catalyst resulted in recovery of amide starting material. $Ni(cod)_2$ precatalyst with the addition of bulky, electron-rich phosphane ligands gave low yields of the biaryl product.[10–20] Bidentate phosphanes resulted in markedly poor coupling.[50] $Ni(PPh_3)_2Cl_2$ precatalyst gave lower yields than $Ni(PCy_3)_2Cl_2$, consistent with the ease of oxidative addition. Other Ni precatalysts resulted in inefficient conversions. Additional ligands resulted in inferior results, which might indicate saturation of the coordination sphere of Ni. Previous studies suggested that a single phosphane ligand might be required to facilitate metal insertion into a C–X bond (X = N, O).[21,33] π-Deficient ligands had a negative impact on the reaction.[51] Nucleophilic additives had a deleterious effect on the reaction, rendering the nucleophilic catalysis unlikely. Importantly, efficient coupling was observed with only 5 mol% of Ni catalyst, which compared favorably with the related C–X biaryl couplings (X = O, N).[10-18] The reaction was highly practical and tolerated water, in contrast to C–O couplings, in which boronic acid/ester equilibrium complicated the reaction.[13-17] Finally, we noted that the reaction could ensue at temperatures as low as 80 °C.



2.14

entry	catalyst	L	base	Yield (%)[b]
1	$Ni(cod)_2$	PCy_3	Na_2CO_3	11
2	$Ni(cod)_2$	*n*-Bu_3P	Na_2CO_3	22
3	$Ni(cod)_2$	P*t*-Bu_3	Na_2CO_3	28
4	$Ni(cod)_2$	DPPF	Na_2CO_3	18
5	$Ni(cod)_2$	dppe	Na_2CO_3	<2
6	$Ni(cod)_2$	dppp	Na_2CO_3	24
7	$Ni(cod)_2$	dppb	Na_2CO_3	16
8	$Ni(cod)_2$	IMes	Na_2CO_3	<2
9	$Ni(cod)_2$	SPhos	Na_2CO_3	14
10	$Ni(cod)_2$	PPh_3	Na_2CO_3	20
11	$Ni(OAc)_2$	*n*-Bu_3P	Na_2CO_3	20
12	$Ni(PCy_3)_2Cl_2$	*n*-Bu_3P	Na_2CO_3	29
13	$Ni(PCy_3)_2Cl_2$	PCy_3	Na_2CO_3	40
14	$Ni(PCy_3)_2Cl_2$	-	Na_2CO_3	42
15[d]	$Ni(PCy_3)_2Cl_2$	-	Na_2CO_3	68
16[d]	$Ni(PPh_3)_2Cl_2$	-	Na_2CO_3	59
17[d]	$Ni(dppf)_2Cl_2$	-	Na_2CO_3	21
18[d,e]	$Ni(PCy_3)_2Cl_2$	-	Na_2CO_3	76
19[d–f]	$Ni(PCy_3)_2Cl_2$	-	Na_2CO_3	83[c]
20[d–f]	$Ni(PCy_3)_2Cl_2$	-	K_3PO_4	<5
21[d–g]	$Ni(PCy_3)_2Cl_2$	-	Na_2CO_3	77
22[d–h]	$Ni(PCy_3)_2Cl_2$	-	Na_2CO_3	31

[a]Amide (0.1 mmol), R-$B(OH)_2$ (1.5 equiv), catalyst (10 mol%), base (2.0 equiv), ligand (40 mol%), toluene (0.25 M), 150 °C, 12 h. [b]GC/^{1}H NMR yields. [c]Isolated yield. [d]Dioxane. [e]$Ni(PCy_3)_2Cl_2$ (5 mol%). [f]Na_2CO_3 (4.5 equiv). [g]H_2O (5 equiv). [h]80 °C.

Table 2.1 Optimization of Ni-catalyzed Suzuki biaryl synthesis.[a]

2.1.3 Scope of the reaction

With the optimized conditions in hand, we explored the preparative scope of the biaryl coupling of amides. The scope of the reaction was very broad and tolerated the coupling of electron-neutral, electron-withdrawing and electron-rich substrates. The generality of the amide component was investigated using 4-trifluoromethylphenyl boronic acid to facilitate isolation (Figure 2.3).[17]

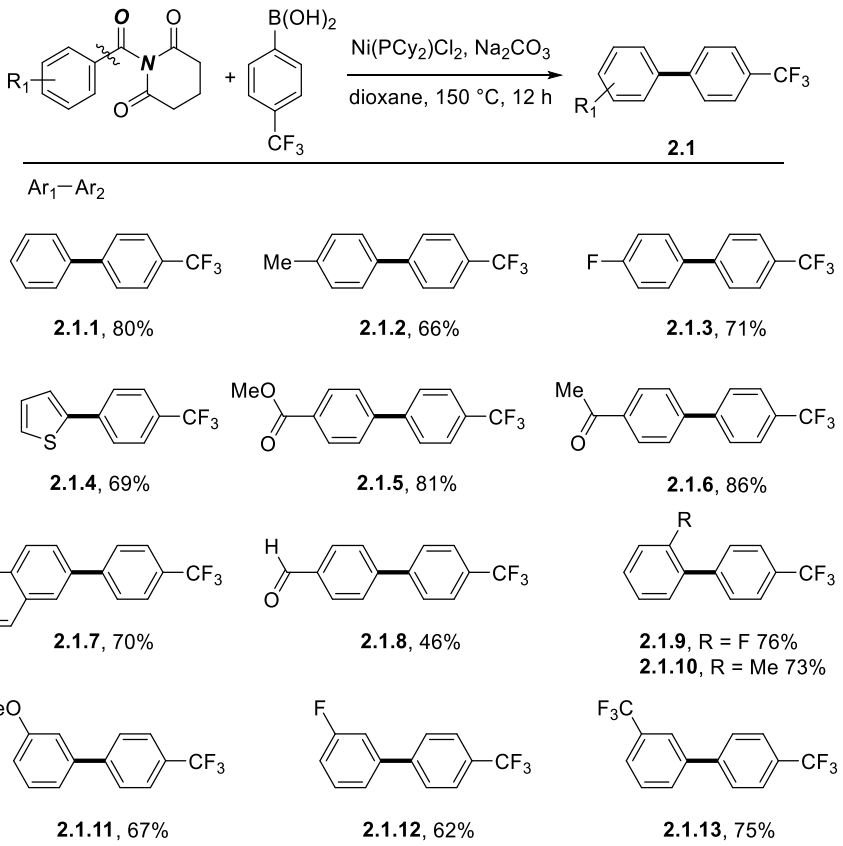


Figure 2.3 Ni-catalyzed Suzuki biaryl synthesis: amide scope.

The prototype phenyl substrate underwent coupling in high yield (entry 1). The reaction tolerated coupling of electron-donating, electron-withdrawing and heterocyclic amide substrates (entries 2-4). Importantly, the coupling proceeded in high yields in the

presence of carbonyl derivatives such as esters and ketones (entries 5-6). Naphthyl is well-tolerated (entry 7). Remarkably, the reaction tolerated even an unprotected aldehyde (entry 8), albeit in lower yield. Aldehydes are not tolerated in related C–O couplings,[13-18] clearly showing the advantage of amide electrophiles in coupling manifolds. Also, ketone-containing substrates were not reported in C–O ester couplings.[20,21] Sterically-hindered substrates showed good reactivity (entries 9-10), consistent with decarbonylation. Other electron-donating and electron-deficient substituents were also compatible with this reaction (entries 11-13).

The scope of boronic acid component was investigated using 4-trifluoromethylphenyl amide as a standard substrate (Figure 2.4). The generality was further demonstrated in additional examples employing electronically-varied substrates (entries 1-4). Electron-deficient nucleophiles were generally less reactive in transmetallation.[1–18] Fluorine-containing biaryls are of great value in medicinal and materials chemistry.[54] The generality was additionally demonstrated by coupling of electronically-varied substrates with neutral boronic acids (entries 22-24). The coupling with 4-trifluoromethyl boronic acid (entry 11) afforded the symmetrical biaryl. In the absence of amide, trace (<9%) quantities of biaryl were formed. The reaction with 4-*tert*-butylboronic acid (entry 20) demonstrated a gram scale coupling. Medicinally-relevant heterocycles including sensitive pyridine, thiophene and furan rings were well-tolerated (entries 26-28). Notably, the reaction tolerated strongly-electron withdrawing substrates as demonstrated by the synthesis of poly-fluorinated biaryls (entries 20-21),[53] complementing C–O coupling manifolds.[13-17] Deconjugation of the trifluoromethyl group did not affect the coupling efficiency (entry 21). The generality of the boronic acid component was further

demonstrated in the coupling of electronically-diverse amides with electron-neutral boronic acids (entries 22-24).

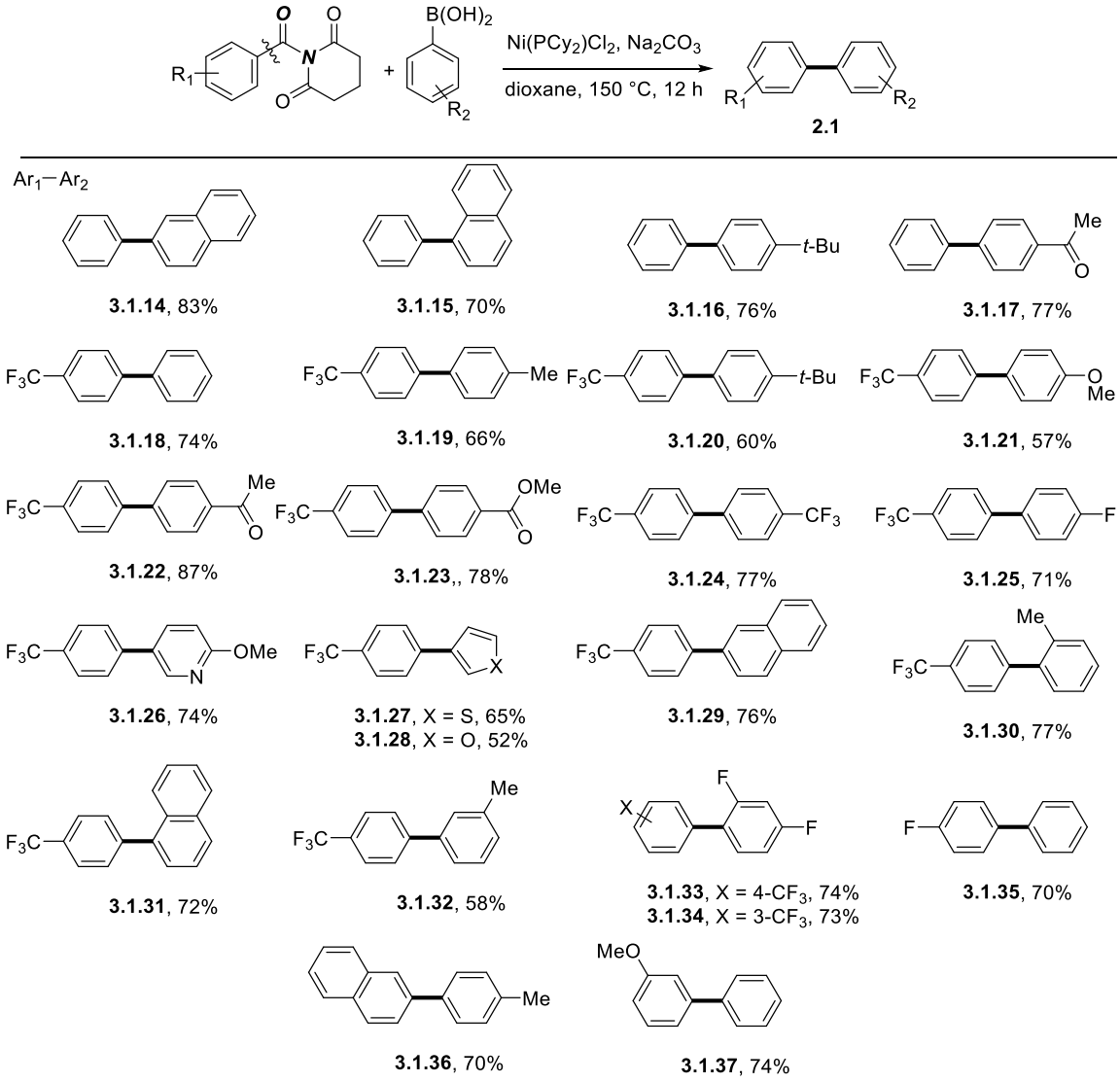


Figure 2.4 Ni-catalyzed Suzuki biaryl synthesis: boronic acid scope.

Overall, the Suzuki-Miyaura biaryl coupling of amides demonstrated a broad reaction scope. Selected examples highlighted complementarity to C–O couplings.[13-16] The major limitation was the presence of C–Cl bonds and the coupling of electron-donating amides

with electron-donating boronic acids; however, the former were also not tolerated in C–O coupling reactions,[5] while the latter was the only combination that results in low efficiency.

2.1.4 Mechanistic Studies

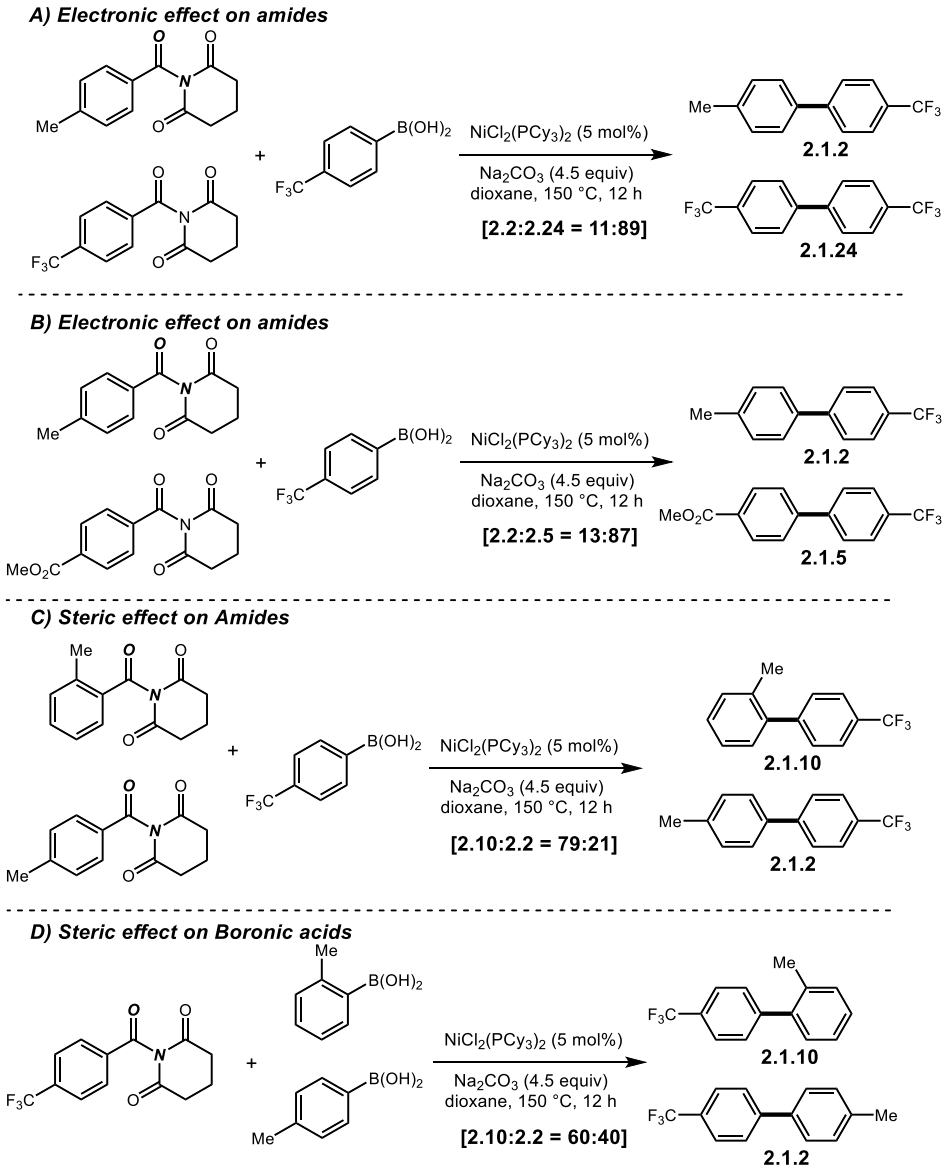


Figure 2.5 Competition experiments to probe electronic and steric effect.

We conducted several mechanistic studies to shed light on the mechanism. Competition experiments were carried out to probe the electronic effect on amide and steric effect on amide and boronic acids (Figure 2.5).

(1) Intermolecular competition experiments revealed that the electronic nature of boronic acid did not affect the reactivity, while electron-poor arenes were more reactive (Figure 2.4.A-B), consistent with facility of metal insertion.[54] (2) Sterically-hindered amides and boronic acids reacted preferentially **(**Figure 2.4.C-D**)**. It is well-established that decarbonylation is favored by steric demand of acylmetal complexes.[48,49]

Stoichiometric ESI-MS measurements indicated the presence of Ni-aryl intermediates, as well as $ArCONiCO_3^{2-}$ cluster complexes,[20] consistent with amide activation by Ni(0) and the key role of the carbonate base. Based on the above studies, we proposed a possible mechanism shown in Figure 2.6.

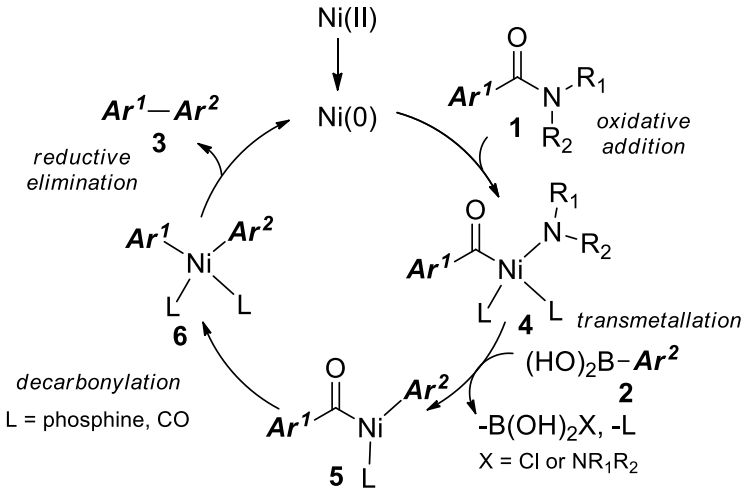


Figure 2.6 Proposed mechanism.

2.1.5 Conclusion

In conclusion, we developed the first example of decarbonylative biaryl Suzuki-Miyaura coupling of amides by N–C(O) bond activation. The reaction was characterized by a broad substrate scope with regard to both the amide and boronic acid components, employed a cost-effective, air-stable $Ni(PCy_3)_2Cl_2$ precatalyst and showed high tolerance towards water. This process advanced the traditional cross-coupling methods to the cross-coupling of amides and opened the door for using Ni-catalysis for the activation of traditionally inert amide bonds by a decarbonylative pathway.

2.1.6 Experimental Section

All experiments involving nickel were performed using standard Schlenk techniques under argon 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 solvents were deoxygenated prior to use. All other 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). All products were identified using ^{1}H NMR analysis and comparison with authentic samples. GC and/or GC/MS analysis was used for volatile products. All yields refer to yields determined by ^{1}H NMR and/or GC or GC/MS using an internal standard (optimization) and isolated yields (preparative runs) unless stated otherwise. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker spectrometers at 500 (^{1}H 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. The injector temperature was 250 °C. The detector temperature was 250 °C. For runs with the initial oven temperature of 50 °C, temperature was increased with a 10 °C/min ramp after 50 °C hold for 3 min to a final temperature of 250 °C, then hold at 250 °C for 15 min (splitless mode of injection, total run time of 35.0 min). High-resolution mass spectra (HRMS) were measured on a 7T Bruker Daltonics FT-MS instrument (for HRMS). Melting point was measured on MeltEMP (laboratory devices). 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. ^1H NMR and ^{13}C NMR data are given for all compounds in the Supporting Experimental for characterization purposes. ^1H NMR, ^{13}C NMR, MS and HRMS data are reported for all new compounds.

General procedure for amide synthesis. An oven-dried round-bottomed flask (100 mL) equipped with a stir bar was charged with amine (8.84 mmol, 1.0 equiv), triethylamine (typically, 2.0 equiv), 4-dimethylaminopyridine (typically, 0.25 equiv) and dichloromethane (typically, 50 mL), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acyl chloride

(typically, 1.1 equiv) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred overnight at room temperature. After the indicated time, the reaction mixture was diluted with Et_2O (20 mL) and filtered. The organic layer was washed with HCl (1.0 *N*, 30 mL), brine (30 mL), dried, and concentrated. Unless stated otherwise, the crude product was purified by recrystallization (toluene) to give analytically pure product.

General procedure for decarbonylative Suzuki-Miyaura cross-coupling. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv), sodium carbonate (4.5 equiv), boronic acid substrate (1.5 equiv) and $Ni(PCy_3)_2Cl_2$ (0.05 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 150 °C, and stirred for the indicated time at 150 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 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 afforded the title product. Caution: Reactions involving high pressure must be carried out in a hood with appropriate pressure vessels, pressure relief equipment and/or blast shields.

2.1.1, 80%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 4 H), 7.61 (d, J = 7.3 Hz, 2 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.42 (t, J = 7.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

144.87, 139.92, 129.48 (q, J^F = 32.5 Hz), 129.13, 128.32, 127.56, 127.42, 125.83 (q, J^F = 3.8 Hz), 124.46 (q, J^F = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.39.

2.1.2, 66%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 4 H), 7.50 (d, J = 7.8 Hz, 2 H), 7.28 (d, J = 7.9 Hz, 2 H), 2.41 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.78, 138.29, 137.01, 129.84, 129.17 (q, J^F = 32.5 Hz), 127.31, 127.25, 125.81 (q, J^F = 3.8 Hz), 124.47 (q, J^F = 270.0 Hz), 21.30. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.37.

2.1.3, 71%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2 H), 7.64 (d, J = 8.2 Hz, 2 H), 7.59-7.54 (m, 2 H), 7.19-7.13 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.95 (d, J^F = 246.2 Hz), 143.73, 135.90, 129.39 (q, J^F = 32.5 Hz), 128.93 (d, J^F = 8.8 Hz), 127.28, 125.78 (q, J^F = 3.8 Hz), 124.25 (q, J^F = 270.0 Hz), 115.95 (d, J^F = 22.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.44, -114.17.

2.1.4, 69%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 2 H), 7.63 (d, J = 8.2 Hz, 2 H), 7.40 (dd, J = 3.6, 1.1 Hz, 1 H), 7.36 (dd, J = 5.1, 1.1 Hz, 1 H), 7.12 (dd, J = 5.1, 3.6 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.76, 137.90, 129.36 (q, J^F = 32.5 Hz), 128.45, 126.36, 126.10, 126.03 (q, J^F = 3.8 Hz), 124.99, 124.29 (q, J^F = 271.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.54.

2.1.5, 81%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.3 Hz, 2 H), 7.72 (s, 4 H), 7.67 (d, J = 8.3 Hz, 2 H), 3.96 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.89, 144.21, 143.67, 130.41, 130.31 (q, J^F = 32.5 Hz), 129.96, 127.76, 127.40, 126.02 (q, J^F = 3.8 Hz), 124.28 (q, J^F = 271.2 Hz), 52.40. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.54.

2.1.6, 86%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2 H), 7.73 (s, 4 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 2.66 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.57, 144.19, 143.41, 136.61, 130.25 (q, J^F = 31.2 Hz), 129.06, 127.62, 127.48, 125.92 (q, J^F = 3.8 Hz), 124.13 (q, J^F = 271.2 Hz), 26.72. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.55.

2.1.7, 70%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.95 (d, *J* = 8.5 Hz, 1 H), 7.94-7.88 (m, 2 H), 7.83 (d, *J* = 8.1 Hz, 2 H), 7.78-7.72 (m, 3 H), 7.54 (ddt, *J* = 11.1, 7.5, 3.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.79, 137.18, 133.69, 133.11, 129.53 (q, J^F = 32.5 Hz), 128.91, 128.45, 127.84, 127.80, 126.74, 126.63, 126.49, 125.97, 125.93 (q, J^F = 3.8 Hz), 125.33, 124.48 (q, J^F = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.35.

2.1.8, 46%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (s, 1 H), 7.99 (d, *J* = 7.8 Hz, 2 H), 7.77 (d, *J* = 7.9 Hz, 2 H), 7.74 (s, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.86, 145.71, 143.39, 136.00, 130.52, 130.51 (q, J^F = 32.5 Hz), 128.08, 127.87, 126.10 (q, J^F = 3.8 Hz), 124.21 (q, J^F = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.59.

2.1.9, 76%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73-7.66 (m, 4 H), 7.45 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.38 (tdd, *J* = 8.0, 5.0, 1.7 Hz, 1 H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.22-7.16 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.85 (d, J^F = 247.5 Hz), 139.55, 130.79, 130.78 (d, J^F = 2.5 Hz), 130.06 (d, J^F = 8.8 Hz), 129.88 (q, J^F = 32.5 Hz), 129.49 (d, J^F = 2.5 Hz), 127.78, 126.11, 125.52 (q, J^F = 3.8 Hz), 124.73 (d, J^F = 3.8 Hz), 124.33 (q, J^F = 270.0 Hz), 116.45 (d, J^F = 22.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.57, -117.85. HRMS calcd for $C_{13}H_8F_4Na$ (M^+ + Na) 263.0454, found 263.0458.

2.1.10, 73%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.9 Hz, 2 H), 7.44 (d, *J* = 7.8 Hz, 2 H), 7.30 (s, 2 H), 7.26 (d, *J* = 5.2 Hz, 1 H), 7.21 (d, *J* = 7.0 Hz, 1 H), 2.27 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.63, 140.51, 135.21, 130.52, 129.58, 129.54, 129.17, 129.04 (q, J^F = 32.5 Hz), 127.95, 125.97, 125.06 (q, J^F = 3.8 Hz), 124.33 (q, J^F = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.38.

2.1.11, 67% yield. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 4 H), 7.39 (t, *J* = 7.9 Hz, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H), 7.13 (t, *J* = 2.1 Hz, 1 H), 6.96 (dd, *J* = 8.2, 2.0 Hz, 1 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.20, 144.74, 141.40, 130.16, 129.61 (q, J^F = 32.5 Hz), 127.66, 125.82 (q, J^F = 3.8 Hz), 124.42 (q, J^F = 270.0 Hz), 119.88, 113.60, 113.27, 55.50. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.42.

2.1.12, 62%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (q, *J* = 8.4 Hz, 4 H), 7.44 (td, *J* = 7.9, 6.0 Hz, 1 H), 7.38 (dt, *J* = 7.7, 1.4 Hz, 1 H), 7.30 (dt, *J* = 10.0, 2.1 Hz, 1 H), 7.14-7.07 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.35 (d, J^F = 247.5 Hz), 143.56, 142.11 (d, J^F = 7.5 Hz), 130.68 (d, J^F = 8.6 Hz), 130.08 (q, J^F = 31.2 Hz) 127.57, 125.99 (q, J^F = 3.8 Hz), 124.31 (q, J^F = 270.0 Hz), 123.08 (d, J^F = 2.5 Hz), 115.18 (d, J^F = 8.8 Hz), 114.38 (d, J^F = 8.8 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.52, -112.51.

2.1.13, 75%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1 H), 7.78 (d, *J* = 7.7 Hz, 1 H), 7.72 (d, *J* = 8.8 Hz, 4 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.61 (t, *J* = 7.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.38, 140.72, 130.62 (q, J^F = 32.5 Hz), 130.71, 130.32 (q, J^F = 32.5 Hz), 129.67, 127.70, 126.11 (q, J^F = 3.8 Hz), 125.01 (q, J^F = 3.8 Hz), 124.26

(q, J^F = 270.0 Hz), 124.24 (q, J^F = 3.8 Hz), 124.16 (q, J^F = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.56, -62.69.

2.1.14, 83%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 7.93 (t, *J* = 8.6 Hz, 2 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 7.79-7.76 (m, 1 H), 7.75 (d, *J* = 7.5 Hz, 2 H), 7.51 (q, *J* = 8.1 Hz, 4 H), 7.40 (t, *J* = 7.4 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.27, 138.70, 133.81, 132.75, 128.99, 128.55, 128.33, 127.78, 127.57, 127.49, 126.42, 126.07, 125.94, 125.73.

2.1.15, 70%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.56-7.49 (m, 6 H), 7.48-7.41 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.90, 140.39, 133.93, 131.75, 130.21, 128.39 (2 x C), 127.76, 127.37, 127.06, 126.16, 126.15, 125.90, 125.51.

2.1.16, 76%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.3 Hz, 2 H), 7.54 (t, *J* = 7.7 Hz, 2 H), 7.48 (d, *J* = 8.6 Hz, 2 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 7.33 (t, *J* = 7.4 Hz, 1 H), 1.38 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.39, 141.21, 138.51, 128.83, 127.16, 127.11, 126.93, 125.85, 34.68, 31.52.

2.1.17, 77%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 7.5 Hz, 2 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.41 (t, *J* = 7.3 Hz, 1 H), 2.64 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.89, 145.92, 140.01, 135.99, 129.09, 129.05, 128.37, 127.41, 127.36, 26.82.

2.1.18, 74%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 4 H), 7.61 (d, *J* = 7.3 Hz, 2 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.42 (t, *J* = 7.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$)

δ 144.87, 139.92, 129.48 (q, J^F = 32.5 Hz), 129.13, 128.32, 127.56, 127.42, 125.83 (q, J^F = 3.8 Hz), 124.46 (q, J^F = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.39.

2.1.19, 66%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 4 H), 7.50 (d, *J* = 7.8 Hz, 2 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 2.41 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.78, 138.29, 137.01, 129.84, 129.17 (q, J^F = 32.5 Hz), 127.31, 127.25, 125.81 (q, J^F = 3.8 Hz), 124.47 (q, J^F = 270.0 Hz), 21.30. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.37.

2.1.20, 60%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 4 H), 7.56 (d, *J* = 8.1 Hz, 2 H), 7.52 (d, *J* = 8.2 Hz, 2 H), 1.39 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.38, 144.57, 136.84, 129.06 (q, J^F = 32.5 Hz), 127.22, 126.94, 125.97, 125.72, 125.67 (q, J^F = 3.8 Hz), 122.22 (q, J^F = 270.0 Hz), 31.34. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.33.

2.1.21, 57%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (q, *J* = 9.0 Hz, 4 H), 7.54 (d, *J* = 9.0 Hz, 2 H), 7.01 (d, *J* = 9.0 Hz, 2 H), 3.87 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.99, 144.43, 132.33, 128.83 (q, J^F = 32.5 Hz), 128.49, 127.01, 125.81 (q, J^F = 3.8 Hz), 122.36 (q, J^F = 270.0 Hz), 55.53. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.32.

2.1.22, 87%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2 H), 7.73 (s, 4 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 2.66 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.57, 144.19, 143.41, 136.61, 130.25 (q, J^F = 31.2 Hz), 129.06, 127.62, 127.48, 125.92 (q, J^F = 3.8 Hz), 124.13 (q, J^F = 271.2 Hz), 26.72. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.55.

2.1.23, 78%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.3 Hz, 2 H), 7.72 (s, 4 H), 7.67 (d, *J* = 8.3 Hz, 2 H), 3.96 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.89,

144.21, 143.67, 130.41, 130.31 (q, J^F = 32.5 Hz), 129.96, 127.76, 127.40, 126.02 (q, J^F = 3.8 Hz), 124.28 (q, J^F = 271.2 Hz), 52.40. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.54.

2.1.24, 77%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 4 H), 7.70 (d, *J* = 8.2 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.25, 130.25 (q, J^F = 32.5 Hz), 127.64, 125.96 (q, J^F = 3.8 Hz), 124.10 (q, J^F = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.57.

2.1.25, 71%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2 H), 7.64 (d, *J* = 8.2 Hz, 2 H), 7.59-7.54 (m, 2 H), 7.19-7.13 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.95 (d, J^F = 246.2 Hz), 143.73, 135.90, 129.39 (q, J^F = 32.5 Hz), 128.93 (d, J^F = 8.8 Hz), 127.28, 125.78 (q, J^F = 3.8 Hz), 124.25 (q, J^F = 270.0 Hz), 115.95 (d, J^F = 22.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.44, -114.17.

2.1.26, 74%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.6 Hz, 1 H), 7.80 (dd, *J* = 8.6, 2.6 Hz, 1 H), 7.70 (d, *J* = 8.2 Hz, 2 H), 7.63 (d, *J* = 8.1 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 1 H), 3.99 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.32, 145.44, 141.62, 137.54, 129.56 (q, J^F = 32.5 Hz), 128.80, 127.02, 126.07 (q, J^F = 3.8 Hz), 124.35 (q, J^F = 270.0 Hz), 111.29, 53.81. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.48. HRMS calcd for $C_{13}H_{10}F_3NONa$ (M^+ + Na) 276.0607, found 276.0633.

2.1.27, 65%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2 H), 7.65 (d, *J* = 8.2 Hz, 2 H), 7.54 (s, 1 H), 7.45-7.39 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.02, 139.31, 129.19 (q, J^F = 32.5 Hz), 126.96, 126.72, 126.29, 125.93 (q, J^F = 3.8 Hz), 124.38 (q, J^F = 270.0 Hz), 121.96. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.44.

2.1.28, 52%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1 H), 7.63 (d, *J* = 8.3 Hz, 2 H), 7.58 (d, *J* = 8.3 Hz, 2 H), 7.51 (t, *J* = 1.6 Hz, 1 H), 6.72 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.27, 139.51, 136.18, 129.09 (q, J^F = 32.5 Hz), 126.10, 125.94 (q, J^F = 3.8 Hz), 125.54, 122.18 (q, J^F = 270.0 Hz), 108.8. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.49.

2.1.29, 76%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.95 (d, *J* = 8.5 Hz, 1 H), 7.94-7.88 (m, 2 H), 7.83 (d, *J* = 8.1 Hz, 2 H), 7.78-7.72 (m, 3 H), 7.54 (ddt, *J* = 11.1, 7.5, 3.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.79, 137.18, 133.69, 133.11, 129.53 (q, J^F = 32.5 Hz), 128.91, 128.45, 127.84, 127.80, 126.74, 126.63, 126.49, 125.97, 125.93 (q, J^F = 3.8 Hz), 125.33, 124.48 (q, J^F = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.35.

2.1.30, 77%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.9 Hz, 2 H), 7.44 (d, *J* = 7.8 Hz, 2 H), 7.30 (s, 2 H), 7.26 (d, *J* = 5.2 Hz, 1 H), 7.21 (d, *J* = 7.0 Hz, 1 H), 2.27 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.63, 140.51, 135.21, 130.52, 129.58, 129.54, 129.17, 129.04 (q, J^F = 32.5 Hz), 127.95, 125.97, 125.06 (q, J^F = 3.8 Hz), 124.33 (q, J^F = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.38.

2.1.31, 72%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 11.8, 8.2 Hz, 2 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.77 (d, *J* = 7.9 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 7.54 (dt, *J* = 12.4, 7.6 Hz, 2 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.42 (d, *J* = 7.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.63, 138.87, 133.92, 131.40, 130.53, 129.63 (q, J^F = 32.5 Hz), 128.57, 128.53, 127.15, 126.58, 126.18, 125.63, 125.48, 125.39 (q, J^F = 3.8 Hz), 124.47 (q, J^F = 270.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.36.

2.1.32 was afforded in 58% yield (13.7 mg). White solid. GC: rt = 12.12 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 4 H), 7.40 (d, *J* = 9.0 Hz, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.23 (d, *J* = 7.2 Hz, 1 H), 2.44 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.00, 139.90, 138.78, 129.10 (q, J^F = 32.5 Hz), 129.05, 129.02, 128.18, 127.55, 125.76 (q, J^F = 32.5 Hz), 124.52, 124.46 (q, J^F = 270.0 Hz), 21.66. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.37.

2.1.33, 74%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.1 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.42 (td, *J* = 8.7, 6.3 Hz, 1 H), 7.02-6.92 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.00 (dd, J^F = 260.0, 11.2 Hz), 159.98 (dd, J^F = 250.0, 11.2 Hz), 138.69, 131.57 (dd, J^F = 10.0, 5.0 Hz), 130.01 (q, J^F = 32.5 Hz), 129.38 (d, J^F = 2.5 Hz), 127.78, 125.62 (q, J^F = 3.8 Hz), 124.26 (q, J^F = 270.0 Hz), 112.05 (dd, J^F = 21.2, 3.8 Hz), 104.62 (t, J^F = 25.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.62, -109.81 (d, *J* = 8.6 Hz), -113.29 (d, *J* = 8.6 Hz). HRMS calcd for $C_{13}H_7F_5Na$ (M^+ + Na) 281.0360, found 281.0342.

2.1.34, 73%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 7.69 (d, *J* = 7.7 Hz, 1 H), 7.64 (d, *J* = 7.8 Hz, 1 H), 7.57 (t, *J* = 7.8 Hz, 1 H), 7.42 (td, *J* = 8.7, 6.3 Hz, 1 H), 7.01-6.97 (m, 1 H), 6.95 (ddd, *J* = 11.0, 8.9, 2.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.78 (dd, J^F = 248.8, 11.2 Hz), 159.79 (dd, J^F = 250.0, 12.5 Hz), 135.72, 132.24, 131.43 (dd, J^F = 10.0, 5.0 Hz), 131.04 (q, J^F = 32.5 Hz), 129.02, 125.68 (q, J^F = 3.8 Hz), 124.50 (q, J^F = 3.8 Hz), 124.02 (q, J^F = 271.2 Hz), 123.93 (dd, J^F = 10.0, 3.8 Hz), 111.90 (dd, J^F = 16.3, 5.0 Hz), 104.62 (t, J^F = 25.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.67, -109.99 (d, *J* = 8.5 Hz), -113.50 (d, *J* = 8.4 Hz). HRMS calcd for $C_{13}H_7F_5Na$ (M^+ + Na) 281.0360, found 281.0357.

2.1.35, 70%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59-7.52 (m, 4 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.13 (t, *J* = 8.7 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.60 (d, J^F = 246.0 Hz), 140.40, 137.48 (d, J^F = 2.5 Hz), 128.96, 128.82 (d, J^F= 8.8 Hz), 127.40, 127.16, 115.74 (d, J^F = 21.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.89.

2.1.36, 70%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1 H), 7.90 (t, *J* = 7.7 Hz, 2 H), 7.87 (d, *J* = 7.8 Hz, 1 H), 7.75 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.64 (d, *J* = 8.1 Hz, 2 H), 7.53-7.45 (m, 2 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 2.43 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.61, 138.36, 137.30, 133.85, 132.63, 129.73, 128.48, 128.27, 127.76, 127.39, 126.36, 125.90, 125.69, 125.56, 21.29.

2.1.37, 74%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 2 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 7.39-7.33 (m, 2 H), 7.19 (d, *J* = 7.1 Hz, 1 H), 7.14 (s, 1 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.06, 142.91, 141.23, 129.87, 128.86, 127.54, 127.33, 119.82, 113.03, 112.81, 55.44.

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2.2 Palladium-catalyzed decarbonylative cyanation of amides

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2.2.1 Introduction

Aromatic nitriles represent useful building blocks in organic synthesis that can be exploited to generate versatile products by standard functional group transformations, including their conversion to benzoic acid derivatives, amines, aldehydes, ketones, imines and heterocycles.[1-3] Furthermore, aryl nitriles represent a common structural motif in a large number of pharmaceuticals, bioactive natural products, agrochemicals, dyes and functional materials (Figure 2.7).[4,5]

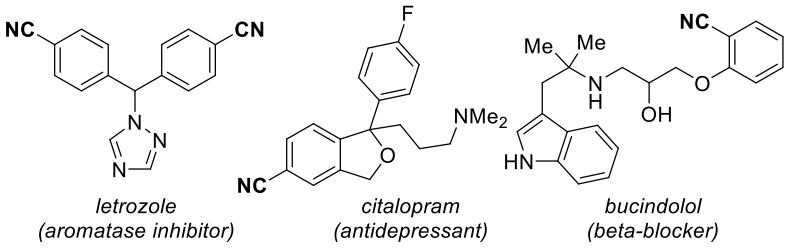


Figure 2.7 Examples of pharmaceutically important benzonitriles.

The synthesis of aryl nitriles has been classically achieved by the Rosenmund–von Braun[6,7] or Sandmeyer reactions[8] of aryl halides or diazonium salts. Significant progress has been made in the development of methods to directly access aryl nitriles by the transition-metal-catalyzed cross-coupling of aryl halides.[9,10] Furthermore, methods for the

chelation-assisted cyanation[11] and electrophilic cyanation of organometal nucleophiles[12-14] have been developed. Direct cyanation of arenes by photoredox mechanism has been disclosed.[15] Progress in the synthesis of alkyl nitriles by transfer hydrocyanation[16] and radical relay[17] mechanisms has been made.[18-24] However, less progress has been made towards the synthesis of aryl nitriles from ubiquitous carboxylic acid derivatives after direct oxidative addition into the acyl bond,[25] a synthetic deficiency given that carboxylic acid derivatives are cheap, readily accessible, and derived from different pool of precursors than halides, phenols, anilines or hydrocarbons.[26,27]

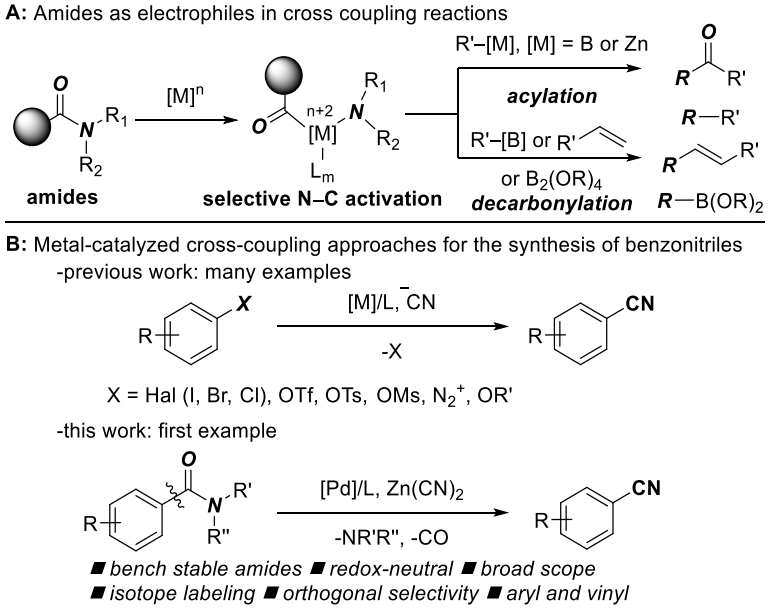


Figure 2.8 (A) Amide bond cross-coupling. (B) Palladium-catalyzed decarbonylative cyanation of amides: a novel strategy for the synthesis of aryl nitriles.

As outlined in the introduction, the development of synthetic methods for the cross-coupling of amide derivatives has been of major synthetic interest (Figure 2.8A).[28-53] Among many advantages of using amides as precursors to acylmetal species is the

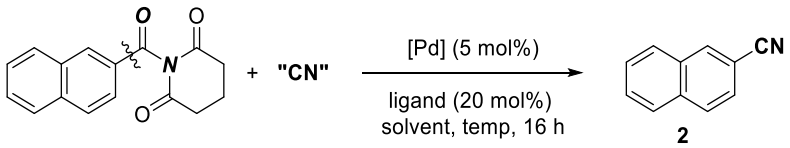
availability of tricoordinate nitrogen geometry that allows controlled access to additional amide geometries by rational variation of the N-substitution that is inaccessible using other bench-stable precursors to generate acylmetals.[54-57] Furthermore, studies to replace common aryl electrophiles with stable carboxylic acid derivatives have been reported.[58-62] Realizing the potential of amides as aryl electrophiles in transition-metal-catalyzed cross-coupling, we developed the first palladium-catalyzed decarbonylative cyanation of amides by carbon–nitrogen bond cleavage for the synthesis of aryl and alkenyl nitriles (Figure 2.8B). At the time of the project, the reaction represented only the second example of a palladium-catalyzed redox-neutral decarbonylative cross-coupling of amide derived electrophiles.[25–30]

We postulated that using amides as aryl electrophiles after selective N–C(O) activation could enable fine-tuning of the acyl bond reactivity for oxidative addition and controlling the relative reactivity of the acyl-metal intermediate towards decarbonylation.[63,64] Since amides play a key role as building blocks in peptides, polymers and pharmaceuticals,[65,66] the development of methods that allow for direct carbon exchange reactions of the amide bond are particularly attractive.

2.2.2 Reaction optimization

At the start of this project, our group had already gained experience in the development of Ni-[40] and Rh-catalyzed[42] decarbonylative reactions of amides. Thus, we questioned whether the amide bond activation might be utilized for the development of redox-neutral decarbonylative cyanation of amides, a reaction that would effectively represent carbon

exchange process of the carbonyl group After a very extensive optimization of various reaction parameters we discovered a catalyst system that promotes the desired cross-coupling (Table 2.2, $Pd(OAc)_2$, 5 mol%; $PCyPh_2$, 20 mol%, $Zn(CN)_2$, 2 equiv, dioxane, 150 °C).[67] Under the optimized conditions the cross-coupling of N-acyl-glutarimide amide afforded the cyanation product in 91% yield. Key optimization results are shown in Table 2.2. Various catalysts were tested, and $Pd(OAc)_2$ showed the best activity. The key optimization result involved identification of $Zn(CN)_2$ as the cyanide source. We hypothesized that low concentration of cyanide ions and faster transmetalation of cyanide to the acylpalladium contributed to its high reactivity.[67] Lower toxicity of zinc cyanide compared with other cyanide sources was also noted.[9,10] Importantly, 71% yield of the coupling product was obtained using only 0.5 equiv of $Zn(CN)_2$, providing an entry point for future studies. Control experiments in the absence of catalyst resulted in recovery of amide. Using the less distorted anilides,[31] N-Boc-carbamates,[54] N-Ts-sufonamides,[54] as well as benzoates[58-61] and thiobenzoates,[62] only a trace quantity of the cross-coupled product was formed, consistent with facility of metal insertion.[55] The insertion occurred selectively at the N–C(O) bond, with cleavage of the alternative σ N–C bond and amide deamidation not observed.[52] To our knowledge, this transformation represented the first example of decarbonylative cyanation of amides. The successful decarbonylative cross-coupling of N-acyl-glutarimide contrasted with the use of other acyl precursors and highlighted the advantageous properties of amide derivatives as active cross-coupling partners in decarbonylative cross-coupling.[28-53]



entry	catalyst	ligand	$M(CN)_x$	Yield (%)[b]
1	$Pd(PPh_3)_4$	-	CuCN	25
2	$Pd(PPh_3)_4$	-	KCN	46
3	$Pd(PPh_3)_4$	-	NaCN	51
4	$Pd(PPh_3)_4$	-	$Zn(CN)_2$	75
5	$Pd(OAc)_2$	PPh_3	$Zn(CN)_2$	21
6	$Pd(OAc)_2$	$P(4\text{-}MeO\text{-}C_6H_4)_3$	$Zn(CN)_2$	81
7	$Pd(OAc)_2$	$P(4\text{-}CF_3\text{-}C_6H_4)_3$	$Zn(CN)_2$	27
8	$Pd(OAc)_2$	dppb	$Zn(CN)_2$	59
9	$Pd(OAc)_2$	dppp	$Zn(CN)_2$	< 2
10	$Pd(OAc)_2$	Sphos	$Zn(CN)_2$	53
11	$Pd(OAc)_2$	Xphos	$Zn(CN)_2$	23
12	$Pd(OAc)_2$	Xanthphos	$Zn(CN)_2$	70
13	$Pd(OAc)_2$	PCy_3HBF_4	$Zn(CN)_2$	12
14	$Pd(OAc)_2$	PCy_2Ph	$Zn(CN)_2$	85
15	$Pd(OAc)_2$	$PCyPh_2$	$Zn(CN)_2$	91[c]
16[d]	$Pd(OAc)_2$	$PCyPh_2$	$Zn(CN)_2$	80
17[e]	$Pd(OAc)_2$	$PCyPh_2$	$Zn(CN)_2$	60
18[f]	$Pd(OAc)_2$	$PCyPh_2$	$Zn(CN)_2$	3
19[g]	$Pd(OAc)_2$	$PCyPh_2$	$Zn(CN)_2$	27
20[h]	$Pd(OAc)_2$	$PCyPh_2$	$Zn(CN)_2$	70
21[i]	$Pd(OAc)_2$	$PCyPh_2$	$Zn(CN)_2$	83
22[j]	$Pd(OAc)_2$	$PCyPh_2$	$Zn(CN)_2$	69
23	$Pd(TFA)_2$	$PCyPh_2$	$Zn(CN)_2$	89
24	$Pd(dba)_2$	$PCyPh_2$	$Zn(CN)_2$	86
25[k]	$Pd(OAc)_2$	$PCyPh_2$	$Zn(CN)_2$	71

[a]Conditions: amide (0.2 mmol), $M(CN)_x$ (2.0 equiv), catalyst (5 mol%), ligand (20 mol%), dioxane (0.25 M), 150 °C, 16 h. [b]GC/^{1}H NMR yields. [c]Isolated yield. [d]$Pd(OAc)_2$ (3 mol%), ligand (12 mol%). [e]$PCyPh_2$ (10 mol%). [f]80 °C. [g]100 °C. [h]130 °C. [i]Toluene. [j]THP. [k]$Zn(OAc)_2$ (0.50 equiv).

Table 2.2 Optimization of Pd-catalyzed decarbonylative cyanation.[a]

2.2.3 Scope of the reaction

With the optimized conditions in hand, we explored the preparative scope of the reaction (Figure 2.9). The scope of the reaction was very broad and tolerated the coupling of electron-neutral (entry 1-4), electron-rich (entry 5-6) and electron-withdrawing (entry 7-8) substrates. Steric hindrance was well-tolerated (entry 2). Importantly, fluoro-substituents that are commonly encountered in medicinal and materials chemistry due to their favorable physicochemical properties were readily accommodated (entry 9-12). Furthermore, saturated oxygen heterocycles that are prone to Ni-catalyzed C–O cleavage (entry 13-14),[68,69] as well as quinoline (entry 15) and thiophene heterocycles (entry 16) provided the corresponding coupling products in moderate to excellent yields. Of particular note, amides containing sensitive aldehyde (entry 17), ketone (entry 18), ester (entry 19) and nitrile (entry 20) groups were tolerated. Aldehydes, ketones and nitriles are not tolerated in related C–O couplings,[58-61] clearly showing the advantage of amide electrophiles in decarbonylative cross-coupling manifolds. In addition, extended naphthalene units (entry 21-22) and conjugated polyarenes (entry 23-24) were well accommodated. Reductive deamidation was not observed in these cases even though this process is facilitated by conjugated aromatics.[52] Finally, the reaction scope could be readily extended to the synthesis of valuable vinyl nitriles (entry 25). Moreover, full selectivity in the amide cross-coupling in the presence of an activated ester that had been reported in Suzuki cross-coupling using Pd-NHC catalysis[70] was observed (entry 26).

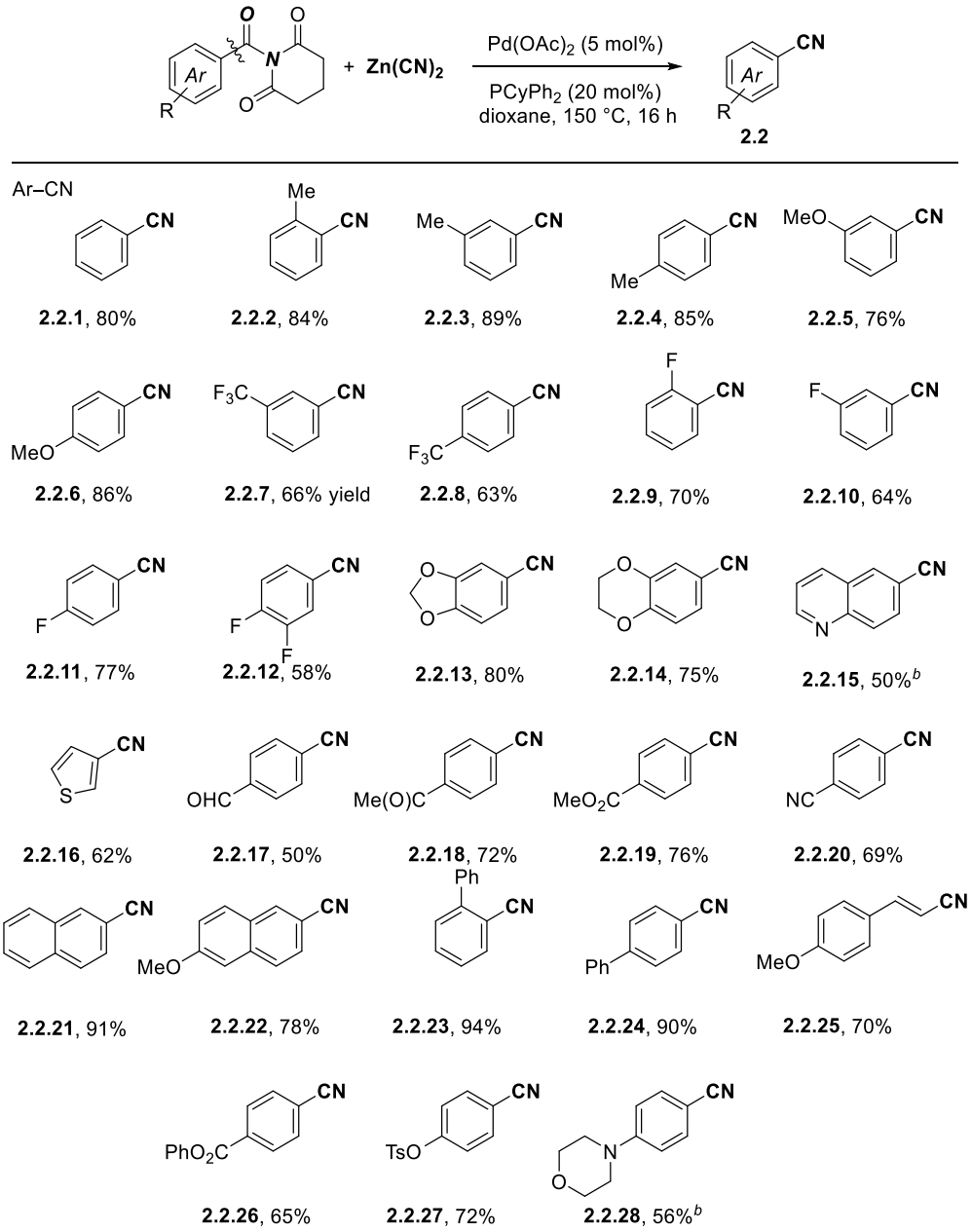


Figure 2.9 Scope of Pd-catalyzed decarbonylative cyanation.

This result highlighted the potential to achieve high cross-coupling selectivity using amide electrophiles under orthogonal cross-coupling conditions. Importantly, amides containing protected alcohols (entry 27) and amines (entry 28) were also competent

substrates for the reaction. The presence of these groups was crucial for further synthetic transformations. For example, benzonitriles react smoothly in Fe-catalyzed sp^3-sp^2 OTs cross-coupling.[71]

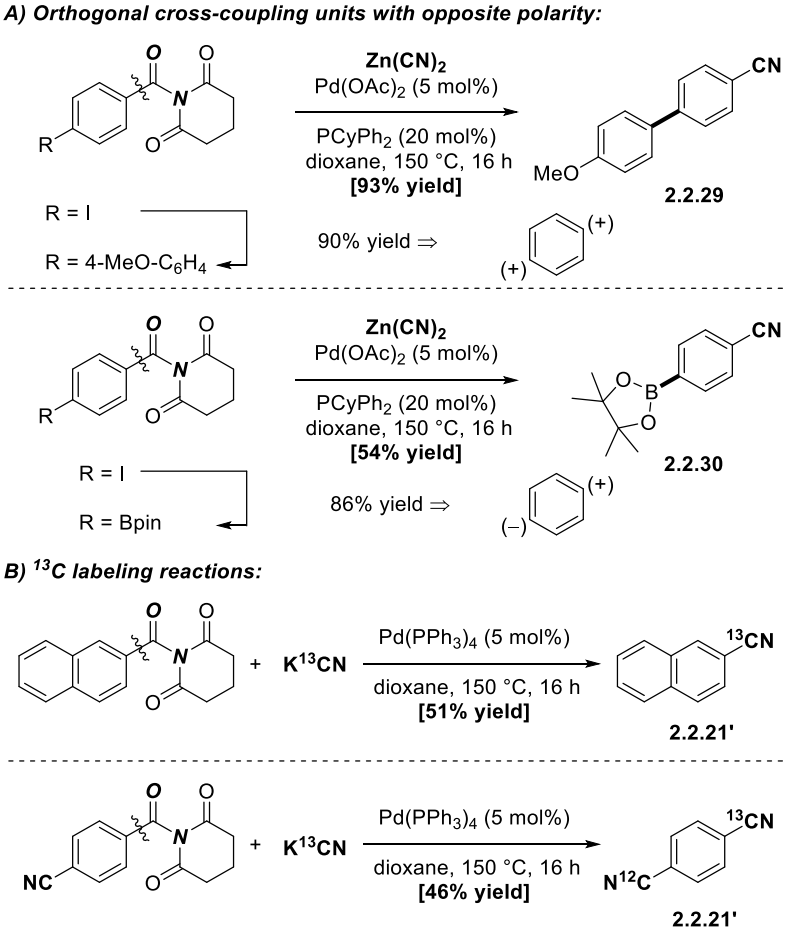


Figure 2.10 Applications of Pd-catalyzed decarbonylative cyanation.

Figure 2.10 highlighted two potential applications of the decarbonylative cyanation. The reaction utility was demonstrated by orthogonal cross-coupling reactions of bench-stable amides to establish cross-coupling synthons with opposite polarity (Figure 2.10A). The amide group was not reactive toward Pd(0)-orthogonal Suzuki-Miyaura and Miyaura

cross-coupling reactions. The utility of this methodology was further demonstrated by the synthesis of isotopically-labeled aryl nitriles by formal carbon exchange in carboxylic acid precursors (Figure 2.10B).[9,10,25-30]

2.2.4 Mechanistic studies

We conducted several studies to gain insight into the reaction mechanism (Figure 2.11). (1) To investigate whether benzoyl cyanide was a possible reaction intermediate, benzoyl cyanide was prepared and subjected to the reaction conditions (Figure 2.11A). Formation of product 2.38 from benzoyl cyanide was observed, suggesting that benzoyl cyanide could be a competent intermediate.[72] (2) Moreover, intermolecular competition experiments revealed that benzoyl cyanide is inherently more reactive than amide (Figure 2.10.B). (3) Cross-over experiments using labeled $K^{13}CN$ revealed only non-cross-over product (Figure 2.11C). The lack of the cross-over product suggests fast insertion/decarbonylation.[73,74] (4) Further intermolecular competition experiments revealed that the electronic nature of amide significantly affected the reactivity in that electron-poor arenes are more reactive (Figure 2.11D), consistent with facility of metal insertion. Moreover, the presence of benzoyl cyanide was not observed during reaction optimization. Recovery of amide starting material was observed in the absence of a Pd-catalyst.

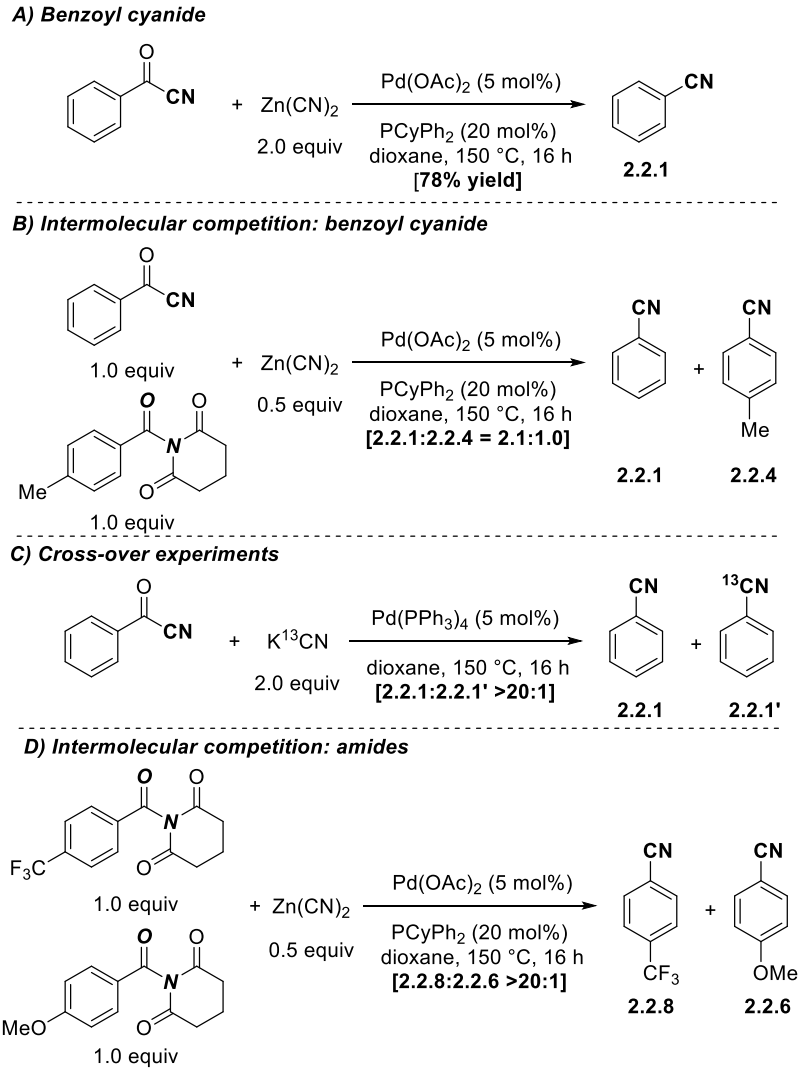


Figure 2.11 Mechanistic studies of Pd-catalyzed decarbonylative cyanation.

A possible mechanism consistent with mechanistic observations is presented in Figure 2.12. We proposed that the key step involved metal insertion into the amide N–C(O) bond and transmetallation. An alternative mechanism involving decarbonylation preceding transmetallation was also possible.

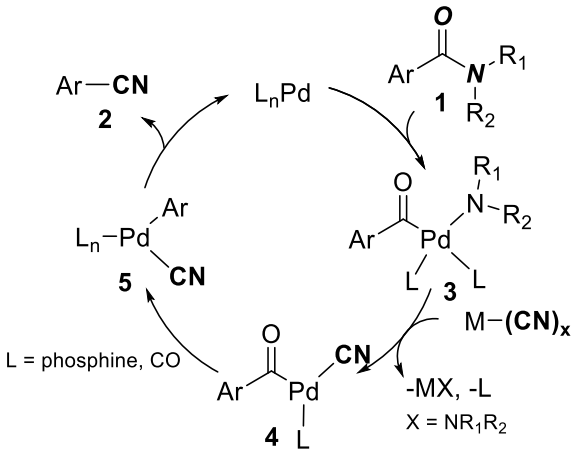


Figure 2.12 Proposed mechanism.

2.2.5 Conclusion

In summary, we developed the first palladium-catalyzed decarbonylative cyanation of amides by carbon–nitrogen bond cleavage for the synthesis of aryl and alkenyl nitriles. The method uses amides as selective acyl precursors for the formation of acylmetal species with high chemoselectivity. The method could be used for the synthesis of functionalized nitriles from amides. Considering the importance of nitriles, the concept of controlled decarbonylation by leveraging stable acyl precursors presents a new opportunity to find broad applications in synthesis.

2.2.6 Experimental Section

General procedure for decarbonylative cyanation. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv), zinc cyanide (2.0 equiv), $PCyPh_2$ (0.20 equiv) and $Pd(OAc)_2$ (0.05 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 150 °C, and stirred for an indicated time at 150 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 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 (EtOAc/hexanes) afforded the title product.

General procedure for decarbonylative cyanation. Variant using $Pd(PPh_3)_4$. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv), sodium cyanide (2.0 equiv) or potassium cyanide (2.0 equiv) and $Pd(PPh_3)_4$ (0.05 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 150 °C, and stirred for an indicated time at 150 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 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 (EtOAc/hexanes) afforded the title product.

2.2.1, 80%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.7 Hz, 2H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.87, 132.24, 129.21, 118.94, 112.54.

2.2.2, 84%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 2.55 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.08, 132.76, 132.65, 130.36, 126.34, 118.28, 112.92, 20.62.

2.2.3, 89%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.44 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.34, 133.75, 132.62, 129.41, 129.10, 119.16, 112.39, 21.29.

2.2.4, 85%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.81, 132.19, 129.96, 119.30, 109.46, 21.99.

2.2.5, 76%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.15-7.11 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.76, 130.45, 124.63, 119.45, 118.88, 116.96, 113.34, 55.67.

2.2.6, 86%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 162.97, 134.14, 119.38, 114.89, 104.15, 55.69.

2.2.7, 66% yield. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.87 (t, J = 7.4 Hz, 2H), 7.66 (t, J = 7.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.30, 132.07 (q, J^F = 21.2 Hz), 129.96, 129.51 (q, J^F = 3.8 Hz), 129.07 (q, J^F = 3.8 Hz), 122.90 (q, J^F = 270.0 Hz), 117.34, 113.52. ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.22.

2.2.8, 62%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.07 (q, J^F = 32.5 Hz), 132.69, 126.21 (q, J^F = 3.8 Hz), 1223.05 (q, J^F = 271.2 Hz), 117.45, 116.08. ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.53.

2.2.9, 70%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.58 (m, 2H), 7.29-7.26 (m, 1H), 7.23 (t, J = 8.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.29 (d, J^F = 255.0 Hz), 135.16 (d, J^F = 7.5 Hz), 133.70, 124.95 (d, J^F = 3.8 Hz), 116.64 (d, J^F = 20.0 Hz), 114.05, 101.75 (d, J^F = 15.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ 106.16.

2.2.10, 58%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.44 (m, 2H), 7.39-7.30 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.30 (d, J^F = 248.8 Hz), 131.27 (d, J^F = 8.8 Hz), 128.34 (d, J^F = 3.8 Hz), 120.67 (d, J^F = 21.2 Hz), 119.33 (d, J^F = 23.8 Hz), 117.66, 114.08 (d, J^F = 10.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ 109.61.

2.2.11, 77%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, J = 7.8, 6.0 Hz, 2H), 7.18 (t, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.19 (d, J^F = 255.0 Hz), 134.83 (d, J^F = 8.8 Hz), 118.17, 117.01 (d, J^F = 22.5 Hz), 108.73 (d, J^F = 3.8 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ 102.39.

2.2.12, 53%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55-7.49 (m, 1H), 7.49-7.44 (m, 1H), 7.30 (q, *J* = 8.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.65 (dd, J^F = 257.5, 11.2 Hz), 150.52 (dd, J^F = 252.5, 12.5 Hz), 129.75 (q, J^F = 3.8 Hz), 121.75 (d, J^F = 20.0 Hz), 118.99 (d, J^F = 18.8 Hz), 116.99, 109.12 (q, J^F = 3.8 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -127.02 (d, *J* = 23.4 Hz), -133.50 (d, *J* = 24.0 Hz).

2.2.13, 80%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.07 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.65, 148.15, 128.35, 119.01, 111.54, 109.26, 105.09, 102.33.

2.2.14, 75%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.11 (m, 2H), 6.91 (d, *J* = 8.1 Hz, 1H), 4.32-4.31 (m, 2H), 4.30-4.26 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.84, 143.91, 126.04, 121.37, 119.01, 118.37, 104.62, 64.71, 64.24.

2.2.15, 50% yield. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.25-8.17 (m, 3H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.54 (dt, *J* = 7.0, 3.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.38, 149.24, 136.48, 134.23, 131.20, 130.24, 127.66, 122.84, 118.60, 110.53.

2.2.16, 62% yield. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.43 (t, *J* = 2.5 Hz, 1H), 7.31 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.49, 128.85, 127.40, 115.24, 110.87.

2.2.17, 50% yield. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.71, 138.88, 133.05, 130.04, 117.85, 117.79.

2.2.18, 72%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 2.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.63, 140.06, 132.66, 128.84, 118.06, 116.58, 26.91.

2.2.19, 76%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 2H), 3.96 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 165.55, 134.05, 132.35, 130.22, 118.08, 116.53, 52.86.

2.2.20, 69%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.91, 117.13, 116.83.

2.2.21, 91% yield. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.91 (t, *J* = 10.1 Hz, 3H), 7.64-7.60 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.78, 134.30, 132.38, 129.34, 129.18, 128.55, 128.19, 127.79, 126.49, 119.40, 109.52.

2.2.22, 78%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.80 (d, *J* = 9.0 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.17 (s, 1H), 3.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.14, 136.54, 133.88, 130.09, 127.92, 127.86, 127.20, 120.80, 119.72, 106.85, 106.01, 55.63.

2.2.23, 94%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.54-7.42 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.59, 138.23, 133.84, 132.91, 130.18, 128.85, 128.83, 128.81, 127.64, 118.82, 111.38.

2.2.24, 90%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.45-7.41 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.76, 139.26, 132.69, 129.21, 128.76, 127.83, 127.32, 119.04, 111.01.

2.2.25, 70%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 16.6 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 2H), 5.71 (d, *J* = 16.6 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.16, 150.14, 129.19, 126.46, 118.82, 114.63, 93.48, 55.57.

2.2.26, 65%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 7.9 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.68, 150.64, 133.53, 132.50, 130.74, 129.76, 126.46, 121.54, 117.96, 117.11.

2.2.27, 72%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.9 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.65, 146.22, 133.99, 131.90, 130.15, 128.55, 123.54, 117.83, 111.29, 21.88.

2.2.28, 62% yield. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 3.85 (t, *J* = 4.5 Hz, 4H), 3.28 (t, *J* = 4.0 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.63, 133.66, 120.00, 114.21, 101.15, 66.60, 47.46.

2.2.29, 62%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR

(125 MHz, $CDCl_3$) δ 160.32, 145.33, 132.69, 131.62, 128.48, 127.22, 119.22, 114.67, 110.22, 55.53.

2.2.30, 54%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 2H), 1.35 (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.23 (2C), 131.27, 119.01, 114.67, 84.63, 25.01.

2.2.19', 52% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 6.0 Hz, 1H), 7.93-7.89 (m, 3H), 7.67-7.60 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.80, 134.31 (d, *J* = 1.2 Hz), 132.40 (d, *J* = 6.2 Hz), 129.34 (d, *J* = 5.0 Hz), 129.18, 128.56, 128.20, 127.80, 126.50 (d, *J* = 2.5 Hz), 119.39, 109.52 (d, *J* = 80.6 Hz). ^{13}C incorporation (>98:2) was determined by ^{13}C NMR ($CDCl_3$, 125 MHz).

2.2.20', 46%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.89, 132.88 (d, *J* = 1.2 Hz), 117.12, 117.03, 116.96 (d, *J* = 8.8 Hz), 116.82 (d, *J* = 1.2 Hz). ^{13}C incorporation (>98:2) was determined by ^{13}C NMR ($CDCl_3$, 125 MHz).

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2.3 Palladium-catalyzed decarbonylative borylation of amides

Parts of this section were adapted with permission from the article: "Sterically-Controlled Pd-Catalyzed Chemoselective Ketone Synthesis via N–C Cleavage in Twisted Amides" (*ACS Omega* **2019**, *4*, 4901).

2.3.1 Introduction

Transition-metal-catalyzed cross-coupling of amides has emerged as a powerful platform for the functionalization of the traditionally inert amide bond ($n_N \rightarrow \pi^*_{C=O}$ donation, barrier to rotation in planar amides of 15-20 kcal/mol).[1–3] The capacity of the amide bond to support selective insertion of a transition-metal into the N–C bond by ground-state destabilization[4] enabled new approaches for the synthesis of important motifs in organic synthesis.[5]

Unfortunately, although great progress has been made in acyl-cross-couplings of the amide bond,[7] the corresponding decarbonylative manifold remained much less developed.[8–15] In particular, palladium-catalyzed decarbonylative cross-couplings have remained a challenging goal, with very few examples of such reactions (cf. Ni) reported.[14] The versatility of Pd catalysis,[16] including broad industrial use of Pd-catalyzed processes,[17] makes the use of Pd attractive in decarbonylative amide bond cross-coupling.

Shi and Rueping group has achieved the Ni-catalyzed decarbonylative borylation of N-Boc activated amides and N-acyl-glutarimides, respectively. However, the use of less nucleophilic Pd (cf. Ni) to promote efficient metal insertion into the amide N–C bond and decarbonylation had not been reported.[6]

Considering that the development of transition-metal-catalyzed borylation reactions is of significant importance for the fields of organic synthesis and medicinal chemistry due to the versatility of organoboron functional groups, we developed the direct Pd-catalyzed decarbonylative borylation of amides by highly selective carbon–nitrogen bond cleavage (Figure 2.13).[18] The method employed the ground-state-destabilization of the amide bond in N-acyl-glutarimides[4] to achieve high selectivity of insertion/decarbonylation. This user-friendly methodology was used for the construction of the organoboron functional group from bench-stable amides using commercially-available and air-stable reagents in the Pd-catalysis manifold akin to the classical Miyaura borylation.[19]

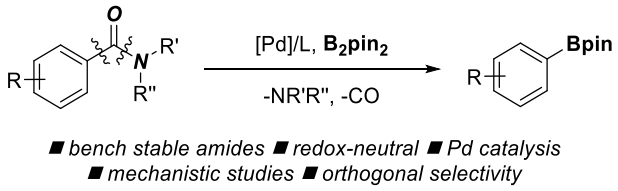


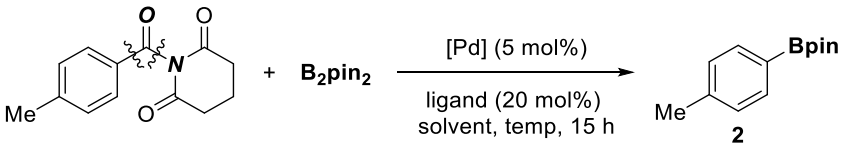
Figure 2.13 Pd-catalyzed decarbonylative borylation of amides.

2.3.2 Reaction optimization

Drawing from our experience in the decarbonylative cross-coupling of amides by N–C(O) activation,[14b,c] we proposed that a Pd-catalyzed decarbonylative borylation of rotationally-inverted N-acyl-glutarimides would be achieved by applying a catalyst system that would favor decarbonylation.

We initiated our studies by investigating the cross-coupling of electronically-unbiased N-acyl-glutarimide amide with bis(pinacolato)diboron as the boron source (Table 2.3).[20]

Table 2.3 Optimization of Pd-catalyzed decarbonylative borylation.[a]



entry	catalyst	Ligand	Base	yield(%)[b]
1	$Pd(OAc)_2$	PPh_3	Na_2CO_3	15
2	$Pd(OAc)_2$	$P(4\text{-}OMe\text{-}C_6H_4)_3$	Na_2CO_3	27
3	$Pd(OAc)_2$	$P(4\text{-}CF_3\text{-}C_6H_4)_3$	Na_2CO_3	12
4	$Pd(OAc)_2$	$PCyPh_2$	Na_2CO_3	24
5	$Pd(OAc)_2$	PCy_2Ph	Na_2CO_3	28
6	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	49
7	$Pd(OAc)_2$	dppb	Na_2CO_3	5
8	$Pd(OAc)_2$	dppp	Na_2CO_3	25
9	$Pd(OAc)_2$	P*n*-Bu_3HBF_4	Na_2CO_3	<5
10	$Pd(OAc)_2$	Xphos	Na_2CO_3	<5
11	$Pd(OAc)_2$	SPhos	Na_2CO_3	<5
12	$Pd(OAc)_2$	PCy_3HBF_4	NaOAc	44
13	$Pd(OAc)_2$	PCy_3HBF_4	KOAc	15
14	$Pd(OAc)_2$	PCy_3HBF_4	K_2CO_3	36
15	$Pd(OAc)_2$	PCy_3HBF_4	K_3PO_4	34
16	$Pd(OAc)_2$	PCy_3HBF_4	Li_2CO_3	20
17	$Pd(OAc)_2$	PCy_3HBF_4	NaO*t*-Bu	16
18	$Pd(CH_3CN)_2Cl_2$	PCy_3HBF_4	Na_2CO_3	55
19	$Pd(PPh_3)_2Cl_2$	PCy_3HBF_4	Na_2CO_3	52
20	$Pd(acac)_2$	PCy_3HBF_4	Na_2CO_3	47
21	$Pd(TFA)_2$	PCy_3HBF_4	Na_2CO_3	64
22	$Pd(dba)_2$	PCy_3HBF_4	Na_2CO_3	58
23	$Pd_2(dba)_3$	PCy_3HBF_4	Na_2CO_3	56
24[c]	$Pd(TFA)_2$	PCy_3HBF_4	Na_2CO_3	58
25[d]	$Pd(TFA)_2$	PCy_3HBF_4	Na_2CO_3	69
26[e]	$Pd(TFA)_2$	PCy_3HBF_4	Na_2CO_3	60

27[φ]	$Pd(TFA)_2$	PCy_3HBF_4	Na_2CO_3	77

[a]Conditions: amide (1.0 equiv), B_2pin_2 (2.0 equiv), [Pd] (5 mol%), ligand (20 mol%),base (2.0 equiv), dioxane(0.25 M), 150 °C, 15 h. [b]GC/^{1}H NMR yields. [c]B_2pin_2 (1.2 equiv). [d]Na_2CO_3 (1.0 equiv). [e]Na_2CO_3 (0.5 equiv). [f]B_2pin_2 (1.2 equiv), Na_2CO_3 (1.0 equiv).

Although initial attempts were unsuccessful, after very extensive survey of the reaction conditions, we identified a catalyst system that provided a significant improvement in the cross-coupling, furnishing the desired decarbonylative borylation product in 77% yield (Table 2.3, entries 1-27). Several optimization results were worth noting. The choice of phosphane ligand had a significant effect on the cross-coupling (entries 1-11). We identified PCy_3 as the preferred ligand for this transformation, presumably due to facile activation of the N–C(O) bond to form the acyl-metal intermediate. In the evaluation of different bases, Na_2CO_3 proved optimal (entries 12-17). Various Pd catalysts were tested, and $Pd(TFA)_2$ showed the best activity (entries 18-24). Further improvement of the reaction efficiency was achieved by careful adjustment of the reagent stoichiometry (entries 25-27), presumably to match decarbonylation with the transmetalation step. Importantly, the reaction proceeded with a complete selectivity for the N–C(O) acyl bond decarbonylation, with products corresponding to the acyl coupling and unselective cleavage of the endocyclic C–O bonds not observed. Furthermore, as an important synthetic advantage, the method utilized commercially-available, bench-stable reagents and did not require preparation of the activated boron source or co-catalytic metal additives.[9b,f]

2.3.3 Scope of the reaction

With the optimal conditions for the cross-coupling, the scope of the reaction was investigated (Figure 2.14). We found that the reaction readily tolerated unbiased neutral, electron-withdrawing and electron-donating arenes, affording the desired organoboranes in 61-71% yields. In contrast, Ni-catalyzed cross-couplings were often limited to the use of conjugated π-systems to favor insertion/decarbonylation.[6b,9c] Electron-donating, oxygen-heterocycles that are important in medicinal chemistry applications such as dioxolane were well-tolerated. Furthermore, amides containing Bpin bonds were also competent substrates, resulting in a formal double borylation by utilizing orthogonal electrophilicity of aryl halide and amide functional groups. Notably, conjugated arenes that are typically prone to reduction under decarbonylative conditions also delivered the corresponding borylated products in good yields. Finally, the method was applied to biaryl amides to generate the desired conjugated adducts, containing synthetically-useful C–B handle for further cross-coupling functionalization.

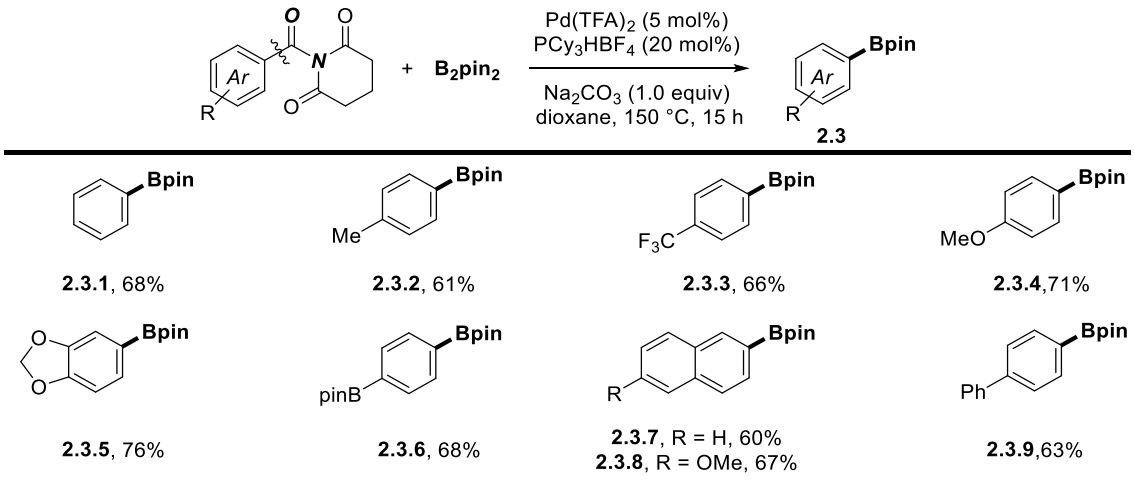


Figure 2.14 Scope of Pd-catalyzed decarbonylative borylation of amides.

We recognized that orthogonal cross-couplings have been an area of significant interest due to permitting versatile disconnections in organic synthesis.[21] An attractive feature of the present methodology was the enabling nature for orthogonal cross-couplings. As shown in Figure 2.15, the amide bond in N-acyl-glutarimides displayed orthogonal electrophilic reactivity to the traditional Pd-catalyzed cross-couplings.[3,19,20] The amide group was not reactive toward Pd(0)-orthogonal Suzuki-Miyaura cross-coupling reactions, highlighting an attractive opportunity for sequential Pd-catalyzed C(sp^2)–C(sp^2) cross-coupling/Pd-catalyzed decarbonylative cross-coupling in organic synthesis.

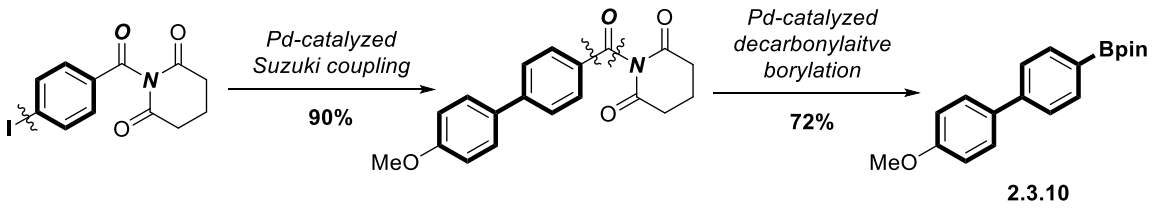


Figure 2.15 Orthogonal cross-coupling/decarbonylative borylation of amides.

2.3.4 Mechanistic studies

To gain insight into the reaction mechanism, intermolecular competition experiments were conducted (Figure 2.16A). To this end, intermolecular competition experiments with 4-substituted amides revealed that electron-deficient amides react preferentially, consistent with facility of metal-insertion (Figure 2.16B).[4] Further competition experiments established that conjugated π-systems such as naphthalenes couple preferentially. Furthermore, competition experiments established that π-conjugated arenes react preferentially over biaryls (Figure 2.16C).[6b]

Overall, the mechanistic studies highlight that (i) electrophilicity of the amide bond, and (ii) capacity of the acyl-metal intermediate to decarbonylate influence the relative reactivity of amides in this decarbonylative (deamidative) cross-coupling.

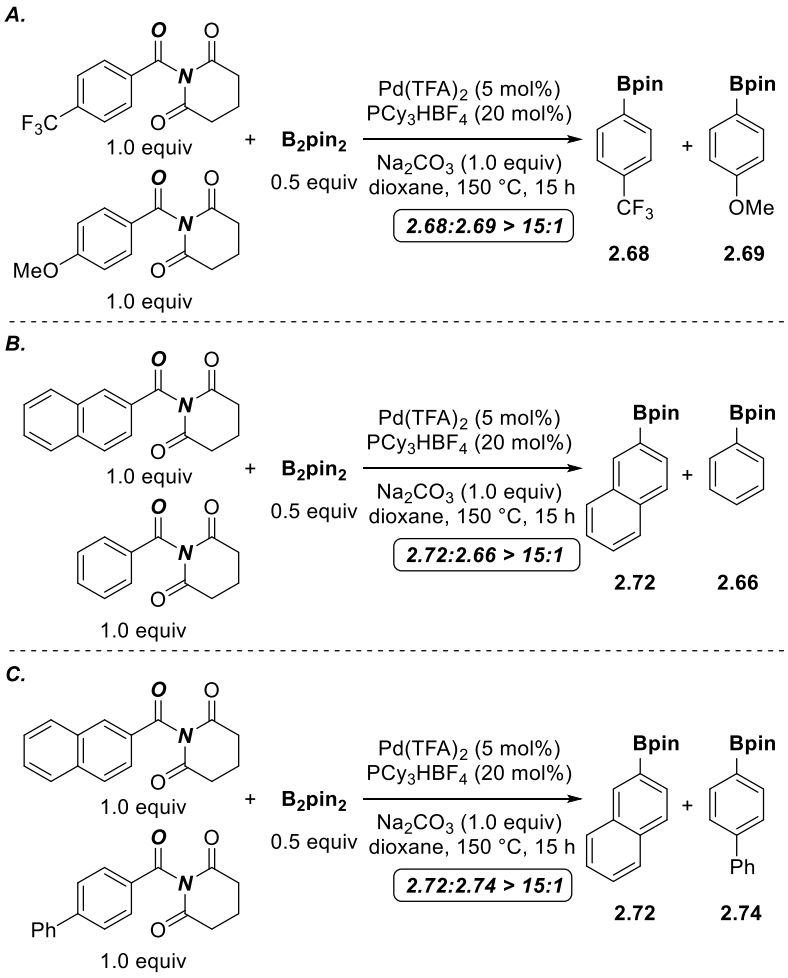


Figure 2.16 Intermolecular competition experiments in decarbonylative borylation.

2.3.5 Conclusion

In summary, we developed the first palladium-catalyzed decarbonylative borylation of amides by selective carbon–nitrogen cleavage for the synthesis of versatile

organoboranes. The method utilized the ground-state-destabilization of the amide bond in N-acyl-glutarimides to achieve Pd-catalyzed insertion into the amide N–C(O) bond and decarbonylation. The method set an important precedent for decarbonylative borylation (i.e. Miyaura coupling) of amides using versatile Pd-catalysis. Moreover, we demonstrated the potential of N–C(O) amide bond disconnection in orthogonal cross-couplings using palladium.

2.3.5 Experimental Section

General procedure for decarbonylative borylation of amides. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv), B_2pin_2 (1.2 equiv), Na_2CO_3 (1.0 equiv), $Pd(TFA)_2$ (5 mol%), PCy_3HBF_4 (20 mol%), 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 150 °C, and stirred for the indicated time at 150 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. A sample was analyzed by ^1H NMR ($CDCl_3$, 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 products.

2.3.1, 68%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J*= 7.5 Hz, 2 H), 7.46 (t, *J* = 7.0 Hz, 1 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 1.35 (s, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.74, 131.26, 127.71, 83.78, 24.89.

2.3.2, 61%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.0 Hz, 2 H), 7.19 (d, *J* = 7.0 Hz, 2 H), 2.37 (s, 3 H), 1.34 (s, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.54, 134.94, 128.66, 83.76, 25.00, 21.87.

2.3.3, 66%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 2 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.14, 132.96 (q, J^F = 32.5 Hz), 124.46 (q, J^F = 3.8 Hz), 124.28 (q, J^F = 271.2 Hz), 84.42, 25.00. ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.04.

2.3.4, 71%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 2 H), 6.90 (d, *J* = 8.5 Hz, 2 H), 3.83 (s, 3 H), 1.34 (s, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.28, 136.64, 113.44, 83.68, 55.23, 25.00.

2.3.5, 76%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.7 Hz, 1 H), 7.24 (s, 1 H), 6.83 (d, *J* = 7.6 Hz, 1 H), 1.33 (s, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.29, 147.32, 129.85, 114.07, 108.42, 100.86, 83.84, 24.97.

2.3.6, 68% yield (44.9 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 4 H), 1.35 (s, 24 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.02, 83.99, 25.02.

2.3.7, 60%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.82-7.79 (m, 3 H), 7.52-7.46 (m, 2 H), 1.39 (s, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.37, 135.14, 132.93, 130.52, 128.75, 127.81, 127.09, 127.08, 125.90, 84.02, 25.03.

2.3.8, 67%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 7.80 (d, *J* = 8.5 Hz, 1 H), 7.78 (d, *J* = 8.5 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.13 (d, *J* = 9.0 Hz, 2 H), 3.93 (s, 3 H), 1.39 (s, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.66, 136.56, 136.12, 131.25, 130.38, 128.51, 126.04, 118.81, 105.75, 83.93, 55.43, 25.07, 25.01.

2.3.9, 63%.White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2 H), 7.65-7.59 (m, 4 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 1.37 (s, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.03, 141.16, 135.39, 128.90, 127.69, 127.37, 126.60, 83.97, 67.24, 25.03.

2.3.10, 72%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 3.0 Hz, 2 H), 7.56 (d, *J* = 4.0 Hz, 2 H), 6.98 (d, *J* = 8.5 Hz, 2 H), 3.85 (s, 3 H), 1.36 (s, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.54, 143.61, 135.39, 133.65, 128.40, 126.13, 114.36, 83.92, 55.51, 25.03.

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Chapter 3

Transition-Metal-Catalyzed Acyl Negishi Cross-Coupling of Amides

3.1 Nickel-catalyzed acyl Negishi cross-coupling of N-acyl-glutarimides

3.1.1 Introduction

Diaryl ketones represent important structural motifs in a wide range of pharmaceuticals, biologically-active natural products and functional organic materials.[1] Moreover, diaryl ketones serve as multifaceted intermediates that can be readily converted into a variety of fundamental diarylmethane building blocks of particular significance in organic synthesis,[2] including bis-benzylic amines, alcohols and heterocycles. Transition-metal-catalyzed acylation of organometallics with acyl electrophiles represents one of the most important methods for the synthesis of diaryl ketones.[3] In 2004, Knochel and co-workers documented the iron-catalyzed arylation of acyl cyanides with functionalized arylmagnesium reagents.[4] While focused on magnesium nucleophiles[5] this study demonstrated that complex diaryl ketones might be efficiently prepared from functionalized organometallic reagents.[5,6]

The Negishi cross-coupling reaction is a powerful transition-metal-catalyzed cross-coupling manifold, wherein the high transmetallation activity and the exceptional functional group tolerance of organozinc reagents provide a direct route to polyfunctionalized products.[6] Recent progress was achieved by Knochel and co-workers through the development of polyfunctionalized organozinc reagents and their application in a wide range of cross-couplings.[7] The development of new catalytic systems by Organ and co-workers[8] and mechanistic studies by the group of Lei are also noteworthy.[9] Examples of the synthesis of biaryl motifs by direct cross-coupling of aryl chlorides,[10a,b] aryl pivalates[10c] and aryl ammonium salts[10d] with organozinc reagents have been reported. Stambuli demonstrated the first diaryl ketone synthesis from less stable thioester electrophiles and organozinc reagents.[11] However, unlike alkylation, diaryl ketone synthesis using organozinc reagents presents a formidable challenge due to incompatibility of oxidative addition/transmetallation steps,[12] which typically results in low yields (Figure 3.1). We realized that despite these significant advances,[6–12] amides had not been employed as electrophilic coupling partners in the Negishi cross-coupling. This was surprising in light of: (1) high bench stability of amides; (2) ease of preparation; (3) the fact that amides are typically inert to the reaction conditions allowing for ring-prefunctionalization; (4) the prevalence of amides in biology (peptides, proteins), as key structural features in pharmaceuticals, drug candidates and agrochemicals, which could allow for a strategic disconnection to access biologically active molecules through using mild and functionalized organozinc reagents.[13]

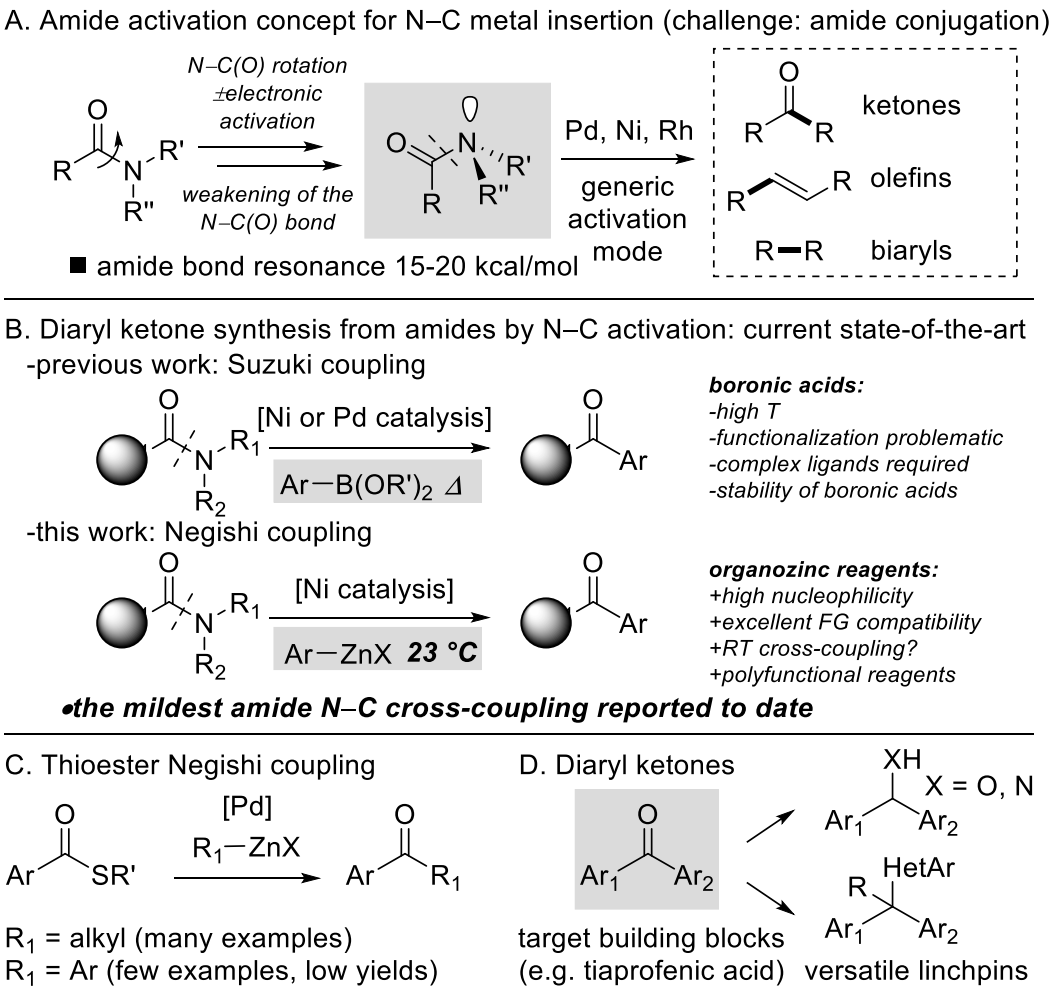


Figure 3.1 A) Amide bond activation concept for metal catalysis. B) Examples of amide N–C bond cross-coupling. C) Classic acyl electrophiles in Negishi reaction. D) Diaryl ketone linchpins.

Although examples of aryl Negishi reactions of aroyl chlorides had been reported,[6,7] at the beginning of this project, the direct metal-catalyzed Negishi arylation of C–N bonds in amides as well as amide arylation at mild room temperature conditions was unknown.[16,17] We realized that a method using organozinc reagents could open the door for functionalization of ubiquitous amide bonds under exceedingly mild conditions (room

temperature, without the requirement for complex ligand, external base, excess of nucleophiles as is the case, for example, with Suzuki couplings).

We recognized that the major challenge in employing amides as electrophilic coupling partners in Negishi cross-coupling by N–C cleavage was the low reactivity for direct oxidative addition[13] (amide bond resonance of 15-20 kcal/mol, $n_N \rightarrow \pi^*_{CO}$ conjugation) and control of the stability of the resulting acyl metal intermediate.[14] As outlined in the introduction, we have introduced a concept of steric-activation of amide bonds to enable C–C bond forming reactions directly from amides, whereby metal insertion into the amide N–C(O) bond proceeds after the amide bond (ca. 40% double-bond character) has been distorted from planarity[15] by steric and/or electronic means.[16a–e] Independently, Garg and Zou reported Ni and Pd-catalyzed Suzuki cross-coupling reactions of acyclic twisted imides.[16f–h] Altogether, these complementary methods demonstrated that typically inert amide bonds can be activated towards unconventional reactivity, thus providing a new catalytic amide bond disconnection approach in organic synthesis.

Continuing our interest in developing new strategies for activation of inert N–C(O) amide bonds,[16a–e] we hypothesized whether amides might be exploited as unique, bench-stable substrates in Negishi cross-coupling to afford diaryl ketones under mild conditions. At the outset, it was unclear whether such scenario would be feasible considering: (1) the high activation barrier for metal insertion into the N–C(O) bond, typically requiring forcing conditions;[16] (2) few precedents for the coupling of aryl (cf. alkyl) zinc reagents

with acyl electrophiles;[12] (3) control of the relative reactivity of acyl- (cf. aryl-) cross-coupling of amide electrophiles.[14]

3.1.2 Reaction optimization

We started our investigations by evaluating the cross-coupling of various amides with arylzinc reagents under a variety of conditions (Figure 3.2).[16] Screening was performed with PhZnCl, and efforts were made to develop operationally-simple reaction conditions. After significant experimentation, we discovered that the proposed Negishi reaction was indeed feasible using the sterically-distorted N-acyl-glutarimide amide and Ni(II)-based precatalyst.[18] Interestingly, using the less distorted amides[15] a promising yield of the diaryl ketone was obtained, demonstrating high reactivity of the catalyst system. Moreover, the marginally less distorted N-acyl-succinimide[15] afforded the desired product in good yield. These initial observations demonstrated viability of the challenging acyl-aryl amide Negishi coupling[11,12] from electronically- and sterically-diverse amides. Importantly, decarbonylation of the acyl-metal intermediate was not observed.[14] The insertion occurred selectively into the amide N–C(O) bond with the scission of the alternative N–C amide bond not observed.[19,20]

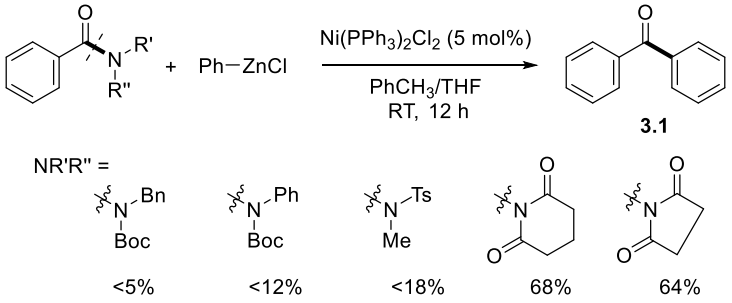
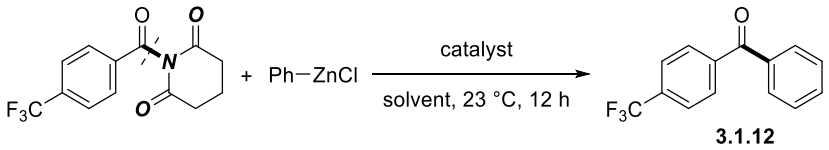


Figure 3.2 The effect of N-substituents.

Table 3.1 summarized key optimization results in the development of amide Negishi cross-coupling reaction. The optimization was performed using 4-trifluoromethyl amide derivative to facilitate analysis. Various catalysts were tested, and $Ni(PPh_3)_2Cl_2$ showed the best catalytic activity (entries 1-17). Interestingly, the nature of the ligand on Ni only moderately affected the yield, with several Ni(II) precatalysts affording the desired product in good yields (entries 12-17). This finding was consistent with the ionic character of the C–Zn bond and high nucleophilicity of organozinc reagents.[6c] Additional ligands had a deleterious effect (entry 18). Moreover, Pd catalysts served as viable promoters for the reaction (entries 1-11). We noted that this result represented the first example of a Pd-catalyzed Negishi coupling of amides,[11,12] thus providing an important entry point for future optimization. Interestingly, polar solvents were not required for the reaction, which represented a significant practical advantage.[21] Various organozinc reagents were tested,[6,7] with ArZnCl providing the best results. Studies by Organ on the salt effect in the transmetallation of zinc reagents highlighted the crucial role of halide salt additives in the coupling of ArZnX reagents in non-polar solvents.[21] Extensive screening of various solvents revealed that the use of diethyl ether gave the best results (entries 19-21). We hypothesized that this cosolvent might be acting to stabilize the putative dihalo-bridged aryl-zinc intermediate.[9b] The finding that the use of diethyl ether facilitates challenging Negishi couplings might be important in other applications of acyl Negishi cross-couplings. Diethyl ether had been rarely used in Negishi couplings.[6,12] Consistent with our hypothesis, the reaction was not observed in the absence of Ni catalysts (entry 22).



3.1.12

Entry	Catalyst	L	Solvent	Yield(%)[b]
1	$Pd(PPh_3)_4$	-	THF	34
2	$Pd(PPh_3)_4$	-	Toluene	62
3	$PdCl_2(PPh_3)_2$	-	Toluene	60
4	$PdCl_2(PPh_3)_2$	-	Dioxane	36
5	$PdCl_2(PPh_3)_2$	DMF[d]	Toluene	54
6	$PdCl_2(PPh_3)_2$	LiCl[e]	Toluene	65
7	$PdCl_2(PPh_3)_2$	CuI[f]	Toluene	<5
8	$Pd(acac)_2$	-	Dioxane	13
9	$Pd_2(dba)_3$	-	Dioxane	23
10	$Pd(OAc)_2$	-	Dioxane	10
11	$PdCl_2(CH_3CN)_2$	-	Toluene	8
12	$NiCl_2(dppe)$	-	Toluene	29
13	$NiCl_2(dppf)_2$	-	Toluene	48
14	$Ni(OAc)_24H_2O$	-	Toluene	56
15	$Ni(PCy_3)_2Cl_2$	-	Toluene	17
16	$Ni(acac)_2$	-	Toluene	62
17	$NiCl_2(PPh_3)_2$	-	Toluene	80
18	$NiCl_2(PPh_3)_2$	PPh_3	Toluene	20
19	$NiCl_2(PPh_3)_2$	-	THF	62
20	$NiCl_2(PPh_3)_2$	-	DMF	48
21	$NiCl_2(PPh_3)_2$	-	Et_2O	92[c]
22	-	-	toluene	<2

[a]Amide (0.1 mmol), Ph-ZnCl (1.5 equiv), catalyst (5 mol%), solvent (0.20 M), 23 °C, 12 h. [b]GC/^{1}H NMR yields. [c]Isolated yield. [d]2 equiv. [e] 5 equiv. [f]1 equiv.

Table 3.1 Optimization of Ni-catalyzed acyl Negishi cross-coupling.[a]

3.1.3 Scope of reaction

With the optimized procedure in hand, the scope of this Negishi cross-coupling was evaluated for amide first (Figure 3.3).

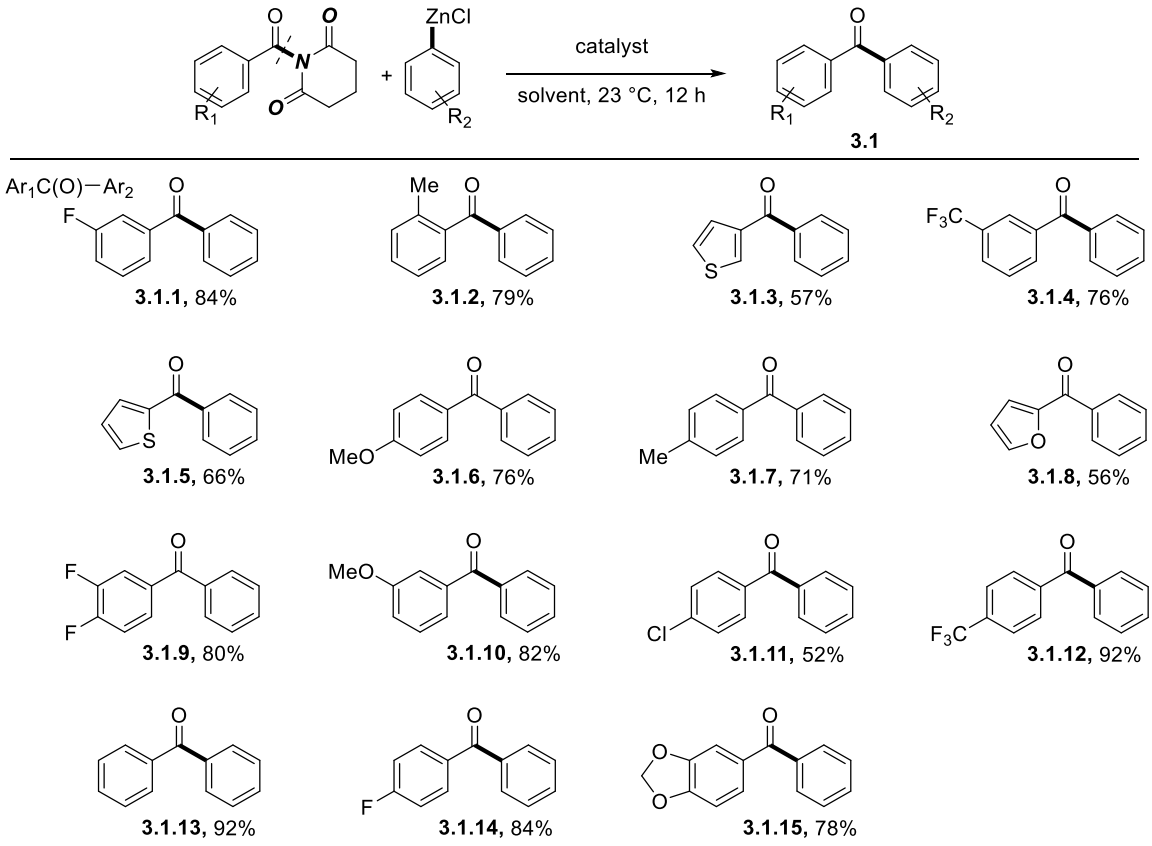


Figure 3.3 Acyl Negishi cross-coupling of N-acyl-glutarimides: amide scope.

A wide variety of functionalized aryl amide electrophiles with a diverse set of substitution could be perfectly accommodated, including 3-fluoro, ortho-methyl, 3-thienyl, 3-trifluoromethyl, 2-thienyl, 4-methoxy, 4-methyl, 4-chloro-, 2-furyl, 3,4-difluoro-, 3-methoxy, and 1,3-dioxolane substituents (**3.1.1-3.1.15**), affording the desired benzophenone products in good to excellent yields. Interestingly, variation of the

electronic nature of the aromatic ring had little impact on the reaction efficiency, with neutral (**3.1.13**), highly electron-withdrawing (**3.1.12**) and electron-donating substituents (**3.1.15**) providing the desired ketone products in uniformly high yields. This reactivity compared very favourably with the related Suzuki coupling by amide N–C cleavage,[16c,f] which tended to be sensitive to electronics of the electrophile.

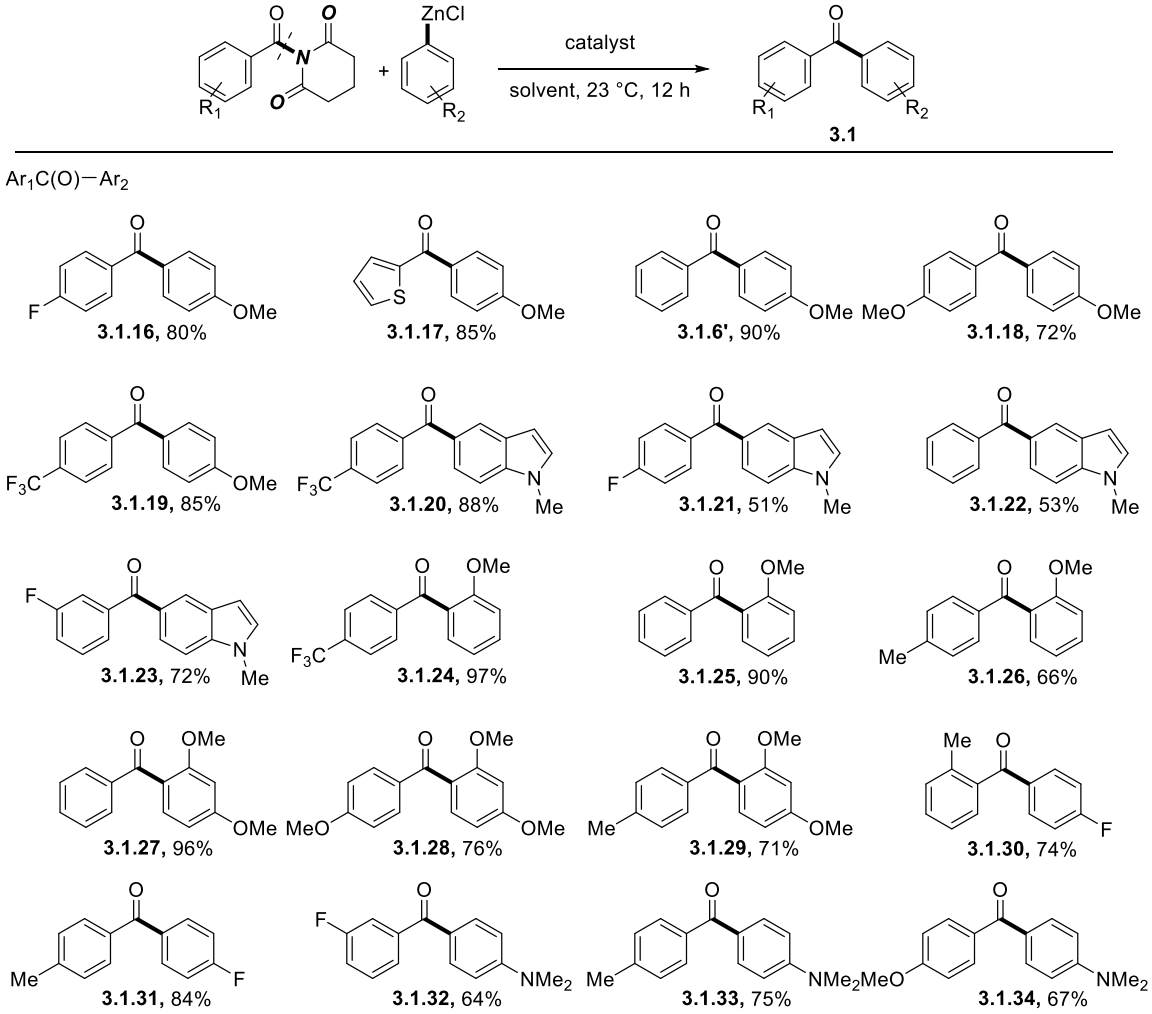


Figure 3.4 Acyl Negishi cross-coupling of N-acyl-glutarimides: organozinc scope.

The reaction could be further extended to the coupling of functionalized aryl zinc nucleophiles (Figure 3.4), affording the desired benzophenones in good to excellent

yields. Of particular note were the cross-couplings of aryl amide electrophiles with indolyl (**3.1.20-3.1.23**), dimethylamino (**3.1.33-3.1.34**) and substituted ortho-methoxy aryl zinc nucleophiles (**3.1.24-3.1.29**). These reactions furnished functionalized indolyl, amino and methoxy-substituted aryl ketones which possessed a wide range of biological activity.[1e–g] These ortho-methoxy-substituted nucleophiles were not tolerated in Suzuki N–C(O) cross-couplings.[16c,f] A limitation was that 4-ethoxycarbonylphenyl- and 4-cyanophenylzinc reagents, readily prepared by direct halide/magnesium exchange,[7] were not tolerated in the reaction; however, the scope of the reaction surpassed the Suzuki cross-coupling of amides. Pharmaceutically-relevant heterocycles, such as thiophene, furane, dioxolane, indole were also perfectly accommodated. The Negishi coupling proceeded under ambient conditions (cf. Suzuki), which was important for practical applications.[22] Importantly, the cross-coupling was carried out on a gram scale in excellent yield (**3.1.19**). Given its user-friendly nature (room temp., bench-top set-up), economically viable profile of components (cf. boronic acids), the method provided an entry point for the utilization of amide Negishi coupling synthetic studies.[22]

3.1.4 Mechanistic studies

A striking feature of this new Negishi cross-coupling reaction was the rate of acyl-aryl coupling that proceeded under exceedingly mild conditions. Monitoring of the reaction profile (**3.1.12**) indicated that the reaction is complete in less than 10 min at room temperature. This marked the fastest N–C(O) amide bond cross-coupling achieved at the time of this project,[16,17] which shows a clear advantage of cross-coupling processes with functionalized organozinc reagents by amide N–C(O) bond activation.

3.1.5 Conclusion

In conclusion, we developed the first diaryl ketone synthesis via Negishi cross-coupling of amides by chemoselective N–C(O) activation. This versatile method was distinguished by broad substrate scope, functional group tolerance, and mild reaction conditions unattainable by the Suzuki cross-couplings with amide electrophiles. Notably, the method represented the mildest conditions for amide N–C activation accomplished. Given the importance of polyfunctional biaryl motifs and high functional group tolerance of organozinc reagents, these studies laid a foundation for further applications of amide Negishi cross-coupling in the synthesis of functionalized ketones.

3.1.6 Experimental Section

Preparation of $ZnCl_2$ solution (1.0 M in THF). A Schlenk flask equipped with a stir bar was flame-dried under vacuum and allowed to cool down to room temperature. Following backfilling/evacuation cycles with argon (3x), $ZnCl_2$ (4.08 g, 30.0 mmol) was added, the flask was placed under vacuum and heated in an oil-bath at 150 °C for 12 h. After the indicated time, the flask was cooled to room temperature, evacuated/backfilled with argon (3x), and THF (anhydrous, 30.0 mL) was added. The mixture was vigorously stirred until all $ZnCl_2$ dissolved.

Preparation of arylzinc reagents. A flame-dried Schlenk flask equipped with a stir bar was charged with a solution of aryl bromide (5.0 mmol) in THF (5.0 mL). The reaction mixture was cooled down to -78 °C and *n*-BuLi (2.2 mL, 5.5 mmol, 1.1 equiv, 2.5 M, hexanes) was added dropwise over 5 min. A precipitate formed immediately, the reaction

mixture was stirred for 60 min at the indicated temperature. After the indicated time, a THF solution of $ZnCl_2$ (5.5 mL, 5.5 mmol, 1.1 equiv) was added dropwise, the reaction mixture was allowed to warm to room temperature, and stirred for an additional 30 min at room temperature. Arylzinc reagents were titrated according to a method reported by Knochel and co-workers.[23] The concentration of arylzinc reagents prepared by this method is from 0.33 M to 0.58 M.

General procedure for Negishi cross-coupling of amides. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv) and $Ni(PPh_3)_2Cl_2$ (0.05 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under vacuum. Diethyl ether (0.20 M) was added with vigorous stirring at room temperature and the reaction was stirred at room temperature for 5 min. A solution of arylzinc reagent (THF solution, 1.5 equiv) was added with vigorous stirring and the reaction mixture was stirred for the indicated time at 23 °C. After the indicated time, the reaction mixture was diluted with HCl (0.1 *N*, 10 mL), the aqueous layer was extracted with EtOAc (3 x 20 mL), organic layers were combined, dried, filtered and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 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 afforded the title product.

3.1.1, 84%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82-7.78 (m, 2 H), 7.64-7.59 (m, 1 H), 7.58 (dt, *J* = 7.7, 1.3 Hz, 1 H), 7.53-7.48 (m, 3 H), 7.48-7.43 (m, 1 H), 7.29 (tdd, *J* = 8.4, 2.7, 1.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 162.6 (d, J^F = 246.3 Hz),

139.8 (d, J = 6.2 Hz), 137.2, 132.9, 130.2, 130.1 (d, J^F = 7.5 Hz), 128.6, 126.0 (d, J^F = 2.5 Hz), 119.6 (q, J^F = 21.2 Hz), 116.9 (q, J^F = 22.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -112.00.

3.1.2, 79%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.78 (m, 2 H), 7.63-7.59 (m, 1 H), 7.48 (t, J = 7.7 Hz, 2 H), 7.42 (td, J = 7.5, 1.5 Hz, 1 H), 7.36-7.30 (m, 2 H), 7.29-7.27 (m, 1 H), 2.36 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.77, 138.74, 137.86, 136.87, 133.25, 131.12, 130.36, 130.26, 128.64, 128.58, 125.32, 20.12.

3.1.3, 57%. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, J = 2.9, 1.4 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 2 H), 7.60 (dd, J = 12.7, 6.3 Hz, 2 H), 7.49 (t, J = 7.4 Hz, 2 H), 7.39 (ddd, J = 4.4, 2.8, 1.1 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.16, 141.45, 138.78, 134.06, 132.45, 129.51, 128.76, 128.52, 126.34.

3.1.4, 76% yield. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.98 (d, J = 7.7 Hz, 1 H), 7.85 (d, J = 7.8 Hz, 1 H), 7.80 (d, J = 7.8 Hz, 2 H), 7.63 (t, J = 7.5 Hz, 2 H), 7.52 (t, J = 7.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.36, 138.41, 136.88, 133.26, 133.16, 133.13 (q, J = 32.5 Hz), 130.16, 129.09, 128.97 (q, J^F = 3.8 Hz), 128.71, 126.84 (q, J^F = 3.8 Hz), 123.82 (q, J^F = 271.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.75.

3.1.5, 66%. Colourless Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 2 H), 7.73 (d, J = 4.8 Hz, 1 H), 7.65 (d, J = 3.2 Hz, 1 H), 7.59 (t, J = 7.4 Hz, 1 H), 7.50 (t, J = 7.4 Hz, 2 H), 7.17 (t, J = 4.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.37, 143.78, 138.29, 134.98, 134.34, 132.40, 129.31, 128.55, 128.09.

3.1.6, 76%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2 H), 7.76 (d, *J* = 7.6 Hz, 2 H), 7.56 (t, *J* = 7.3 Hz, 1 H), 7.47 (t, *J* = 7.4 Hz, 2 H), 6.97 (d, *J* = 8.0 Hz, 2 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.70, 163.35, 138.42, 132.69, 132.02, 130.29, 129.86, 128.32, 113.68, 55.63.

3.1.7, 71% yield. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2 H), 7.73 (d, *J* = 8.2 Hz, 2 H), 7.58 (t, *J* = 7.3 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 2 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 2.44 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.65, 143.37, 138.09, 135.01, 132.29, 130.44, 130.07, 129.11, 128.34, 21.80.

3.1.8, 56% yield. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.2 Hz, 2 H), 7.72 (s, 1 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.24 (d, *J* = 3.5 Hz, 1 H), 6.60 (dd, *J* = 3.5, 1.6 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.72, 152.45, 147.24, 137.42, 132.72, 129.44, 128.57, 120.70, 112.35.

3.1.9, 80%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 2 H), 7.68 (t, *J* = 9.0 Hz, 1 H), 7.60 (t, *J* = 13.0 Hz, 2 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.27 (q, *J* = 8.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.22, 154.42 (dd, J^F = 255.0, 12.5 Hz), 150.33 (dd, J^F = 255.0, 12.5 Hz), 137.01, 134.58 (t, J^F = 3.8 Hz), 132.94, 129.98, 128.63, 127.23 (q, J^F = 3.8 Hz), 119.46 (dd, J^F =17.5, 1.2 Hz), 117.41 (d, J^F = 17.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -130.59 (d, *J* = 21.4 Hz), -136.17 (d, *J* = 21.4 Hz).

3.1.10, 82%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.7 Hz, 2 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.51 (t, *J* = 7.4 Hz, 2 H), 7.39 (p, *J* = 7.5 Hz, 3 H), 7.16 (d, *J* = 8.6

Hz, 1 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.67, 159.71, 139.04, 137.76, 132.56, 130.18, 129.35, 128.40, 123.02, 119.01, 114.45, 55.62.

3.1.11, 52%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (t, *J* = 7.9 Hz, 4 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.55-7.42 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.63, 139.04, 137.41, 136.03, 132.78, 131.60, 130.07, 128.78, 128.55.

3.1.12, 92%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2 H), 7.81 (dd, *J* = 8.3, 1.2 Hz, 2 H), 7.76 (d, *J* = 8.1 Hz, 2 H), 7.66-7.61 (m, 1 H), 7.51 (t, *J* = 7.7 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.68, 140.87, 136.87, 133.87 (q, J^F = 32.5 Hz), 133.24, 130.28, 130.25, 128.68, 125.49 (q, *J* = 3.8 Hz), 123.82 (q, J^F = 271.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.01.

3.1.13, 92%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 2 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.89, 137.73, 132.54, 130.19, 128.41.

3.1.14, 84%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.81 (m, 2 H), 7.77 (d, *J* = 7.7 Hz, 2 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 2 H), 7.16 (t, *J* = 8.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.41, 165.52 (d, J^F = 252.5 Hz), 137.63, 133.94 (d, J^F = 3.8 Hz), 132.80 (d, J^F = 8.8 Hz), 132.61, 130.01, 128.49, 115.68 (d, J^F = 21.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -105.99.

3.1.15, 78%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.7 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 2 H), 7.38 (d, *J* = 9.1 Hz, 2 H), 6.86 (d, *J* = 8.0 Hz, 1

H), 6.07 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.29, 151.66, 148.08, 138.27, 132.13, 132.06, 129.85, 128.35, 127.01, 110.07, 107.84, 101.99.

3.1.16, 80%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.74 (m, 4 H), 7.15 (t, *J* = 8.5 Hz, 2 H), 6.97 (d, *J* = 8.6 Hz, 2 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.23, 165.20 (q, J^F = 252.5 Hz), 163.40, 134.59 (d, J^F = 2.5 Hz), 132.54, 132.42 (d, J^F = 8.8 Hz), 130.18, 115.46 (d, J^F = 22.5 Hz), 113.78, 55.66. ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.94.

3.1.17, 85%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.5 Hz, 2 H), 7.69 (d, *J* = 4.5 Hz, 1 H), 7.67-7.61 (m, 1 H), 7.16 (t, *J* = 4.1 Hz, 1 H), 6.99 (d, *J* = 8.5 Hz, 2 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.99, 163.24, 143.98, 134.12, 133.54, 131.74, 130.84, 127.89, 113.83, 55.64.

3.1.6', 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2 H), 7.76 (d, *J* = 7.6 Hz, 2 H), 7.56 (t, *J* = 7.3 Hz, 1 H), 7.47 (t, *J* = 7.4 Hz, 2 H), 6.97 (d, *J* = 8.0 Hz, 2 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.70, 163.35, 138.42, 132.69, 132.02, 130.29, 129.86, 128.32, 113.68, 55.63.

3.1.18, 72% yield (34.8 mg). White solid. GC: rt = 19.88 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 4 H), 6.96 (d, *J* = 8.4 Hz, 4 H), 3.89 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.60, 162.98, 132.37, 130.93, 113.61, 55.62. MS = 242.1 (EI).

3.1.19, 85%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.79 (m, 4 H), 7.74 (d, *J* = 8.1 Hz, 2 H), 6.98 (d, *J* = 8.9 Hz, 2 H), 3.90 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

194.40, 163.86, 141.65, 133.39 (q, J^F = 32.5 Hz), 132.77, 129.92, 129.49, 125.79 (q, J = 3.8 Hz), 123.87 (q, J^F = 217.3 Hz), 113.95, 55.71. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.94.

3.1.20, 88%. Pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.89 (d, J = 8.0 Hz, 2 H), 7.82 (dd, J = 8.6, 1.7 Hz, 1 H), 7.75 (d, J = 8.1 Hz, 2 H), 7.41 (d, J = 8.7 Hz, 1 H), 7.15 (d, J = 3.2 Hz, 1 H), 6.60 (d, J = 3.1 Hz, 1 H), 3.86 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.07, 142.56, 139.37, 133.05 (q, J^F = 32.5 Hz), 130.83, 130.05, 128.57, 127.91, 125.79, 125.26 (q, J^F = 3.8 Hz), 124.00 (q, J^F = 271.3 Hz), 123.79, 109.50, 103.29, 33.25. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.84.

3.1.21, 51%. Pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.88-7.81 (m, 2 H), 7.79 (d, J = 8.5 Hz, 1 H), 7.40 (d, J = 8.5 Hz, 1 H), 7.21-7.12 (m, 3 H), 6.59 (s, 1 H), 3.86 (s, 3 H). ^{13}C NMR (125 MHz, CDCl3) δ 195.95, 164.04 (d, J^F = 251.2 Hz), 139.1, 135.49 (d, J^F = 3.8 Hz), 132.56 (d, J^F = 8.8 Hz), 130.64, 129.24, 127.83, 125.36, 123.86, 115.31(d, J^F = 22.5 Hz), 109.30, 103.11, 33.25. ^{19}F NMR (471 MHz, $CDCl_3$) δ -107.71.

3.1.22, 53%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1 H), 7.82 (m, 3 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.39 (d, J = 8.6 Hz, 1 H), 7.14 (s, 1 H), 6.59 (s, 1 H), 3.86 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.38, 139.28, 139.12, 131.66, 130.53, 130.03, 129.36, 128.20, 127.80, 125.62, 123.97, 109.22, 103.12, 33.23.

3.1.23, 72%. Pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1 H), 7.81 (d, J = 8.6 Hz, 1 H), 7.58 (d, J = 7.5 Hz, 1 H), 7.50 (d, J = 9.1 Hz, 1 H), 7.46 (q, J = 7.5 Hz, 1 H), 7.40 (d, J = 8.6 Hz, 1 H), 7.29-7.25 (m, 1 H), 7.15 (s, 1 H), 6.60 (s, 1 H), 3.86 (s, 3

H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.84, 162.54 (d, J^F = 248.2 Hz), 141.40 (d, J^F = 6.3 Hz), 139.26, 130.70, 129.86 (d, J^F = 8.8 Hz), 128.80, 127.86, 125.72 (d, J^F = 3.8 Hz), 125.62, 123.86, 118.61 (d, J^F = 21.2 Hz), 116.80 (d, J^F = 22.5 Hz), 109.38, 103.23, 33.25. ^{19}F NMR (471 MHz, $CDCl_3$) δ -112.57.

3.1.24, 97%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 2 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 7.52 (t, *J* = 8.6 Hz, 1 H), 7.42 (d, *J* = 7.5 Hz, 1 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.00 (d, *J* = 8.4 Hz, 1 H), 3.71 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.55, 157.70, 141.06, 133.83 (q, J^F = 32.5 Hz), 132.88, 130.14, 129.98, 127.13, 125.37 (q, *J* = 3.8 Hz), 123.88 (q, J^F = 271.3 Hz), 120.93, 111.66, 55.69. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.99.

3.1.25, 90% yield (38.2 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.8 Hz, 2 H), 7.55 (t, *J* = 7.3 Hz, 1 H), 7.47 (t, *J* = 7.9 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 2 H), 7.36 (d, *J* = 7.4 Hz, 1 H), 7.04 (t, *J* = 7.4 Hz, 1 H), 6.99 (d, *J* = 8.3 Hz, 1 H), 3.72 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.58, 157.48, 137.94, 133.04, 131.99, 129.95, 129.71, 128.99, 128.33, 120.61, 111.58, 55.73.

3.1.26, 66%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.9 Hz, 2 H), 7.45 (t, *J* = 7.9 Hz, 1 H), 7.33 (d, *J* = 7.4 Hz, 1 H), 7.23 (d, *J* = 7.8 Hz, 2 H), 7.03 (t, *J* = 7.4 Hz, 1 H), 6.99 (d, *J* = 8.3 Hz, 1 H), 3.73 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.24, 157.35, 143.93, 135.37, 131.71, 130.18, 129.52, 129.32, 129.09, 120.57, 111.57, 55.77, 21.85.

3.1.27, 96%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.4 Hz, 2 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.41 (t, *J* = 8.2 Hz, 3 H), 6.55 (d, *J* = 8.5 Hz, 1 H), 6.51 (s, 1 H), 3.87 (s, 3 H), 3.70 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.69, 163.48, 159.76, 138.98, 132.46, 132.33, 129.80, 128.14, 121.69, 104.69, 98.96, 55.70, 55.66.

3.1.28, 76%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.54 (d, *J* = 8.4 Hz, 1H), 6.51 (s, 1H), 3.86 (s, 6H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.44, 163.32, 163.01, 159.27, 132.30, 131.69, 131.60, 122.17, 113.42, 104.57, 98.98, 55.75, 55.64, 55.57.

3.1.29, 71%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.6 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 1 H), 7.21 (d, *J* = 7.8 Hz, 2 H), 6.54 (d, *J* = 8.4 Hz, 1 H), 6.51 (s, 1 H), 3.87 (s, 3 H), 3.71 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.40, 162.21, 158.54, 142.29, 135.23, 131.03, 129.08, 127.89, 121.01, 103.57, 97.98, 54.74, 54.65, 20.80.

3.1.30, 74%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ7.85 (dd, *J* = 8.2, 6.0 Hz, 2 H), 7.42 (t, *J* = 7.5 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.29-7.28 (m, 1 H), 7.15 (d, *J* = 8.5 Hz, 2 H), 2.35 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.06, 165.84 (d, J^F = 253.6 Hz), 138.39, 136.62, 134.11 (d, J^F = 3.0 Hz), 131.08, 130.34, 128.28, 125.29, 115.64 (d, J^F = 21.8 Hz), 21.63. ^{19}F NMR (471 MHz, $CDCl_3$) δ -104.94.

3.1.31, 84%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.4, 5.6 Hz, 2 H), 7.71 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 7.15 (t, *J* = 8.5 Hz, 2 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.00, 165.25 (d, J^F = 252.1 Hz), 143.30, 134.82, 134.18

(d, J^F = 3.0 Hz), 132.50 (d, J^F = 9.0 Hz), 130.12, 129.05, 115.32 (d, J^F = 21.7 Hz), 20.80.^{19}F NMR (471 MHz, $CDCl_3$) δ -106.47.

3.1.32, 64%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.9 Hz, 2 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.47-7.38 (m, 2 H), 7.22 (dt, *J* = 8.3, 4.3 Hz, 1 H), 6.68 (d, *J* = 8.9 Hz, 2 H), 3.08 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.64, 163.47 (d, J^F = 241.2 Hz), 153.59, 141.60 (d, J^F = 6.2 Hz), 132.84, 129.77 (d, J^F = 8.8 Hz), 125.23 (d, J^F = 3.0 Hz), 124.28, 118.11 (d, J^F = 21.2 Hz), 116.38 (d, J^F = 22.5 Hz), 110.72, 40.17. ^{19}F NMR (471 MHz, $CDCl_3$) δ -112.73.

3.1.33, 75%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.7 Hz, 2 H), 7.65 (d, *J* = 7.8 Hz, 2 H), 7.25 (d, *J* = 7.5 Hz, 2 H), 6.68 (d, *J* = 8.6 Hz, 2 H), 3.07 (s, 6 H), 2.43 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.08, 153.28, 141.76, 136.59, 132.73, 129.84, 128.80, 125.23, 110.64, 40.19, 21.69.

3.1.34, 67%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (t, *J* = 7.7 Hz, 4 H), 6.95 (d, *J* = 8.2 Hz, 2 H), 6.69 (d, *J* = 8.4 Hz, 2 H), 3.88 (s, 3 H), 3.07 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.28, 162.39, 153.19, 132.62, 132.02, 131.87, 125.52, 113.41, 110.69, 55.57, 40.23.

Determination of the reaction profile. According to the general procedure, a flame-dried Schlenk flask equipped with a stir bar was charged with an amide substrate (0.20 mmol, 1.0 equiv), $Ni(PPh_3)_2Cl_2$ (0.05 equiv) and PhZnCl (1.5 equiv) at room temperature under argon atmosphere. Small aliquots were removed from the reaction mixture at set

time intervals, diluted with diethyl ether (2.0 mL), and analyzed by GC and/or GC-MS to obtain yield and product distribution using internal standard and comparison with authentic samples. Alternatively, the reaction was quenched with HCl (0.1 *N*, 10 mL) at set time intervals and subjected to a standard work-up as described above. The reaction mixture was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain selectivity, conversion and yield using internal standard and comparison with authentic samples. Overall, these findings are consistent with the high nucleophilicity of organozinc reagents in the Ni-catalyzed cleavage of amide N–C bonds and bode well for future application of the method for arylation of amide bonds with functionalized organozinc reagents.

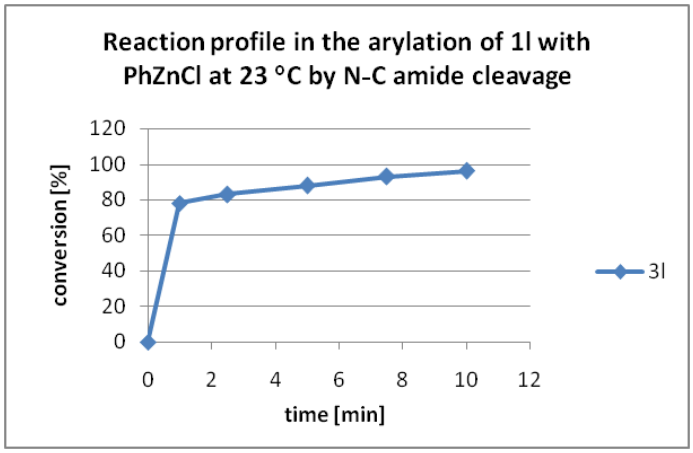


Figure 3.5 Reaction profile in the Negishi cross-coupling using PhZnCl at room temperature. (1l = 4-CF_3-glutarimide, 3l = **3.1.12**)

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3.2 Nickel-catalyzed acyl Negishi cross-coupling of N,N-di-Boc$_2$ amides

Parts of this section were adapted with permission from the article "Nickel-Catalyzed Diaryl Ketone Synthesis by N–C Cleavage: Direct Negishi Cross-Coupling of Primary Amides by Site-Selective N,N-Di-Boc Activation" (*Org. Lett.* **2016**, *18*, 5872).

3.2.1 Introduction

As outlined in previous chapters, the catalytic activation of inert amide N–C(O) bonds represents one of the most challenging transformations in organic synthesis as a consequence of amidic resonance.[1,2] Due to the prevalence of amides in bioactive molecules, synthetic polymers and proteins,[3,4] methods to catalytically engage common amide functional groups in generic transition metal-catalyzed transformations are in great demand.[5] In this context, catalytic cross-coupling reactions by activation of amide N–C bonds have gained significant attention.[6] Following the report by Garg on the Ni-catalyzed esterification of amides,[7] several notoriously challenging transformations by N–C amide cleavage have been developed.[8–10] In particular, the unconventional amide N–C bond disconnection has enabled new strategies for constructing C–C,[8] C–N[9] and C–B[10] bonds using extremely versatile cross-coupling protocols (Figure 3.6A). However, this approach has been largely limited to the use of Boc-activated secondary amides and less common tertiary amides.[7–10] We realized that transformations that allow catalytic functionalization of ubiquitous primary amides[11] in a modular fashion[8l] would hold a particular promise to revolutionize synthetic strategies by the catalytic amide bond

disconnection.[7–10] We developed a new activation method of N–C(O) bonds in primary amides by site-selective N,N-di-Boc$_2$ activation of the amide nitrogen atom and direct nickel insertion into the N–C(O) bond to enable the first functional group tolerant Negishi cross-coupling of primary amides (Figure 3.6B).

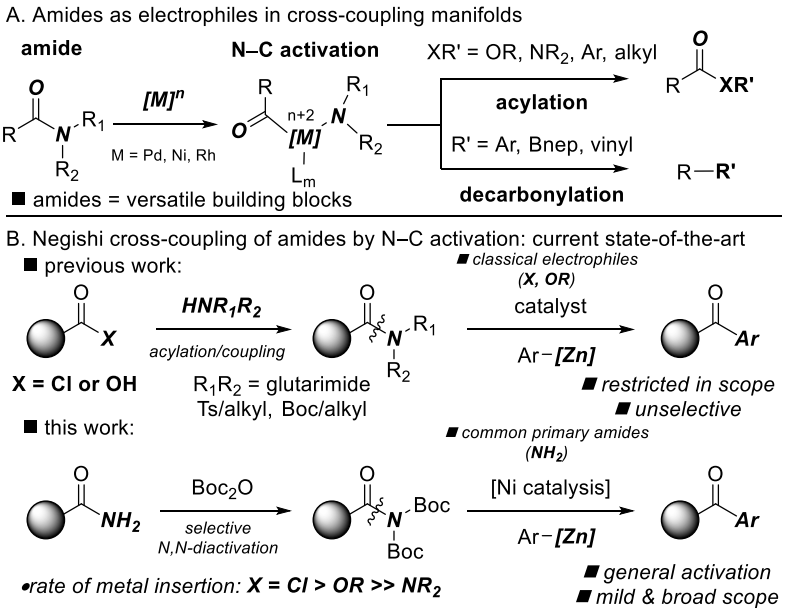


Figure 3.6 N,N-di-Boc$_2$ amides in acyl cross-coupling.

The challenge of cross-coupling of amide N–C(O) bonds arises from structural limitations inherent to the partial double bond character of amides.[1,2] Coordination of electrophiles is electronically biased toward the amide oxygen atom.[12] This O-coordination reinforces the double-bond character of amides, thereby decreasing the susceptibility of N–C(O) amide bonds to direct metal insertion.[13] Although the O-activation has used to generate electrophilic imidoyl cations,[14] this chemistry had been limited to secondary and tertiary amides and reactive organometallic nucleophiles.[15] We proposed that site-selective double N-activation[12] of amides in conjunction with

transition-metal-catalyzed insertion would enable a general method for modular functionalization of primary amides[11] under mild conditions. Specifically, we proposed that the N-functionalization with an electron-withdrawing Boc group[16] would decrease the double-bond character of primary amides (barrier to resonance of 15-20 kcal/mol; acetamide, 18.4 kcal/mol),[17] thus allowing this high-energy precursor to undergo metal insertion into the amidic N–C(O) bond. Importantly, we realized that this reaction design would generate versatile acyl-metal intermediates from primary amides,[11] and thus set the stage for diverse cross-coupling techniques utilizing well-established manifolds of acyl-metals.[18] The proposed approach presented a significant challenge: (1) selective double N-activation of the amide bond must be realized, and the activating group must be stable to the reaction conditions;[19] (2) metal insertion into the N–C(O) bond must be favored over scission of the now weakened σ N–C bond adjacent to N–C(O),[20] which would shut down the desired reaction pathway by reverting to the unreactive precursor; (3) transmetallation must be facile to avoid decomposition of the sensitive acyl-metal intermediate.[18]

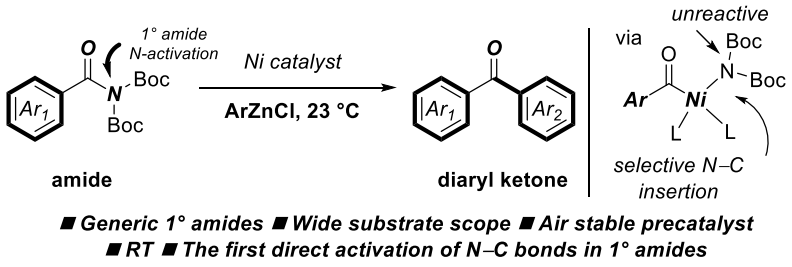
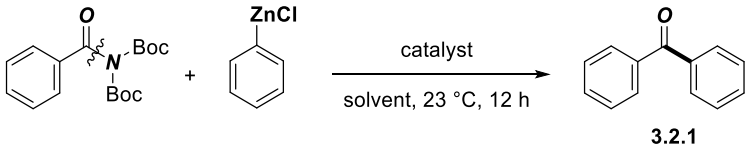


Figure 3.7 Modular acyl Negishi cross-coupling of primary amides.

We described the first modular Negishi cross-coupling of primary amides under exceedingly mild conditions.[21] The method employed cheap and bench-stable Ni-catalysts, which are economically advantageous over Pd-catalysts.[22] We identified N,N-di-Boc_2 amides as readily accessible precursors for highly selective direct Ni insertion into the amide N–C(O) bond (Figure 3.7). The product diaryl ketones are prevalent motifs in biologically-active compounds, agrochemicals, dyes and organic materials.[23] The combination of high transmetallation activity with broad functional group tolerance of organozinc reagents contributed to the widespread industrial and academic application of Negishi coupling manifold.[21a–]We proposed that the overall strategy of activating 1° amide bonds is suitable for a broad range of coupling protocols via acyl-metal intermediates.[5,18]

3.2.2 Reaction optimization

Our study commenced by evaluating the coupling of N,N-di-Boc-benzamide with organozinc reagents under various conditions (Table 3.2). All N,N-di-Boc_2 benzamides were prepared by site-selective double N-acylation of the amide bond in an average yield of 73%, including substrates bearing Lewis basic groups.[16] Traces or low yields of the desired product were detected under conditions for Pd-catalyzed Negishi coupling (entries 1-4). After extensive experimentation, we found that Ni-based catalysts provided the best results. The nature of the ligand had a significant influence of the coupling efficiency (entries 5-10). We established that the inexpensive and bench-stable $NiCl_2(PPh_3)_2$ catalyst afforded the product in good yield and excellent N–C coupling selectivity.



3.2.1

entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$Pd(PPh_3)_4$	-	Et_2O	<5
2	$PdCl_2(PPh_3)_2$	-	toulene	20
3	$PdCl_2(PPh_3)_2$	-	Et_2O	23
4	$PdCl_2(PPh_3)_2$	-	Et_2O	<5
5	$NiCl_2$(dppe)	-	Et_2O	46
6	$NiCl_2$(dppf)	-	Et_2O	43
7	$Ni(OAc)_2$	-	Et_2O	15
8	$NiCl_2(PCy_3)_2$	-	Et_2O	45
9	$Ni(acac)_2$	-	Et_2O	18
10	$NiCl_2(PPh_3)_2$	-	Et_2O	74
11	$NiCl_2(PPh_3)_2$	-	Toluene	64
12	$NiCl_2(PPh_3)_2$	-	THF	62
13	$NiCl_2(PPh_3)_2$	-	DMF	19
14	$NiCl_2(PPh_3)_2$	-	Dioxane	55
15	$NiCl_2(PPh_3)_2$	-	CH_3CN	42
16[c]	$NiCl_2(PPh_3)_2$	-	Et_2O	48
17[d]	$NiCl_2(PPh_3)_2$	Et_3N	Et_2O	42
18[e]	$NiCl_2(PPh_3)_2$	LiCl	Et_2O	69
19[f]	$NiCl_2(PPh_3)_2$	PPh_3	Et_2O	42
20[g]	$NiCl_2(PPh_3)_2$	-	Et_2O	81[h]
21	-	-	Et_2O	<5

[a]Conditions: amide (1.0 equiv), Ph-ZnCl (1.5 equiv), catalyst (5 mol%), solvent (0.20 M), 23 °C, 12 h. [b]GC/^{1}H NMR yields. [c]PhZnCl (3.0 equiv). [d]Et_3N (0.30 equiv). [e]LiCl (1.0 equiv). [f]PPh_3 (0.30 equiv). [g]$Ni(PPh_3)_2Cl_2$ (10 mol%). [h]Isolated yield.

Table 3.2 Optimization of acyl Negishi of N,N-di-Boc$_2$ amides.[a]

Next, extensive evaluation of solvents revealed Et_2O to be the most effective (entries 10-15). Nucleophilic and inorganic additives afforded the product in lower yields (entries 16-19). The optimum results were obtained using $NiCl_2(PPh_3)_2$ (10 mol%) in Et_2O at 23 °C, delivering **3.2.1** in 81% isolated yield (entry 20). Control experiments revealed that the reaction did not proceed without the catalyst (entry 21). Notably, the product was formed with the exclusive C–N(O) acylation selectivity (cf. decarbonylation)[8g–i] with by-products resulting from the σ C–N bond scission not observed.[20] The developed process represented the first example of converting readily available primary amides to diaryl ketones by direct metal insertion.[7–10]

3.2.3 Scope of the reaction

Having identified the optimum conditions for the Negishi acylation of N,N-di-Boc_2 amides, we explored the scope of the reaction with respect to the amide coupling partner. As shown in Figure 3.8, a broad range of simple primary amides underwent efficient coupling upon N,N-di-Boc_2 activation. Diverse functional groups including electronically-diverse (**3.2.1**-**3.2.10**), sterically-hindered (**3.2.2**, **3.2.14**), and various electrophilic functional handles, such as halides (**3.2.5**, **3.2.6**), esters (**3.2.9**), ethers (**3.2.10**), protected alcohols (**3.2.11**), nitriles (**3.2.12**), heterocycles (**3.2.13**) and polyarenes (**3.2.15**) were readily tolerated. Perhaps most notable was the capacity of the reaction to tolerate functional groups that were problematic in the addition to classic Weinreb amides,[15] and employed simple 1° amides as precursors.[1,2,11] The reaction provided a conceptually new method for the synthesis of ketones from primary amides under mild conditions.[7–10] Noteworthy was direct functionalization of 4-

hydroxybenzamide (**3.2.11**, pharmaceutical intermediate) and 2-ethoxybenzamide (**3.2.14**, anti-inflammatory drug), highlighting the potential impact of the method on catalytic cross-coupling.[24]

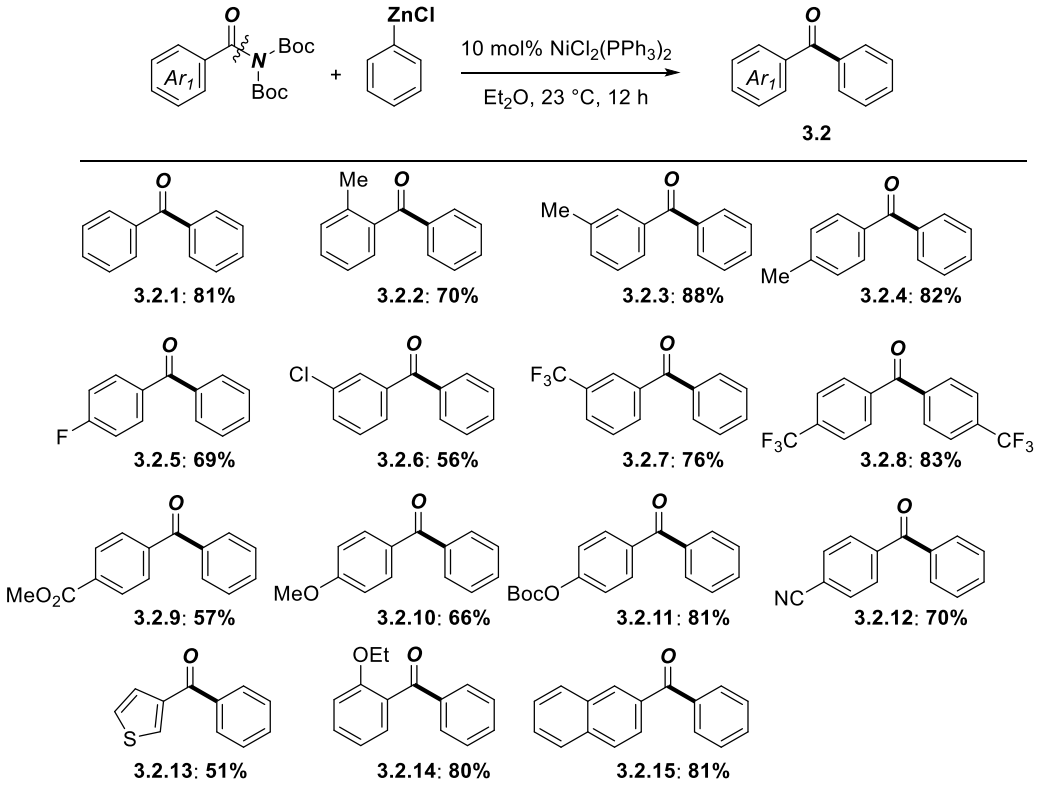


Figure 3.8 Acyl Negishi cross-coupling of N,N-di-Boc$_2$ amides: scope of amides.

Next, we focused on evaluation of the scope of the nucleophilic coupling partner. As shown in Figure 3.9, an array of organozinc reagents performed well in the reaction. Electronically-diverse organozinc reagents readily underwent the coupling (**3.2.10'**-**3.2.5'**). Sterically-hindered nucleophiles were readily tolerated (**3.2.17**, **3.2.2'**). Nucleophiles bearing functional handles for further functionalization by S_NAr (**3.2.5'**) or cross-coupling (**3.2.28**) performed well in the reaction. Furthermore, indole-containing

nucleophiles readily participated in the reaction (**3.2.19**). Importantly, exclusive acylation selectivity was observed using 2-naphthalene-containing electrophiles prone to decarbonylation, attesting to generality of this coupling (**3.2.20**-**3.2.24**).[8g–i]

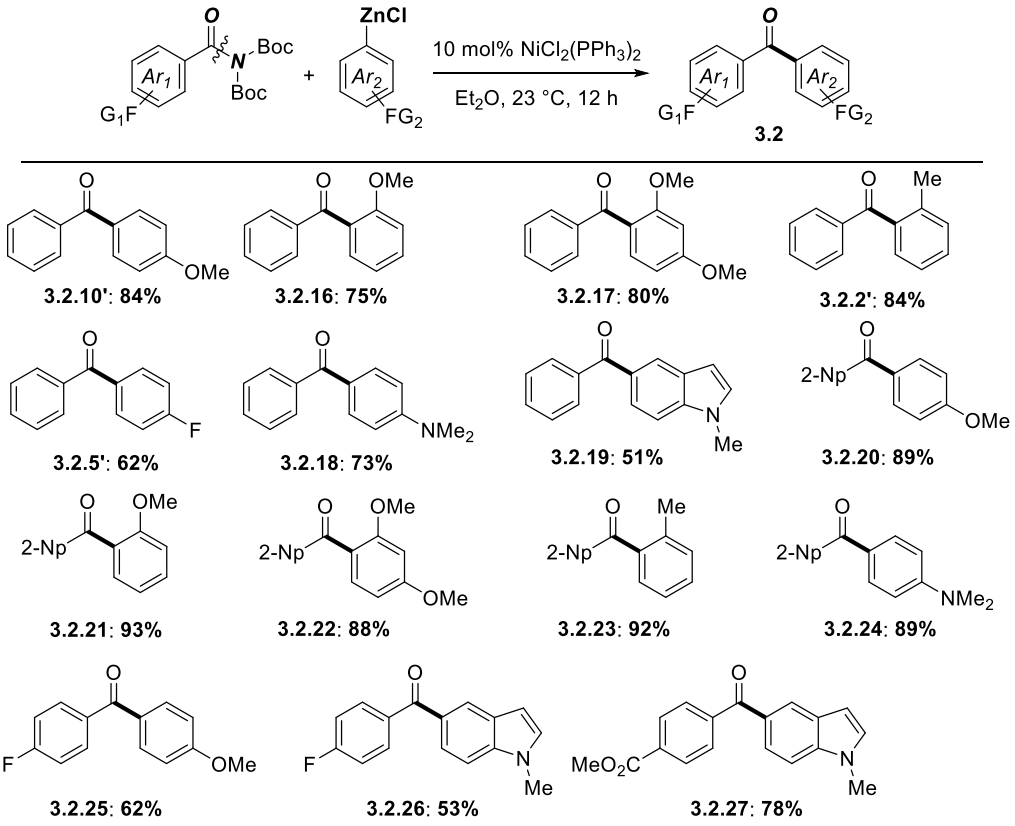


Figure 3.9 Acyl Negishi cross-coupling of N,N-di-Boc$_2$ amides: organozinc reagent scope.

The utility of this method was demonstrated by facile synthesis of functionalized ketones used as precursors to electrochromic materials (**3.2.24**),[23b] agrochemical intermediates (**3.2.25**)[23c] and biological pharmacophores (**3.2.27**),[23d] all directly from 1° amides. The broad functional group tolerance was in line with the well-established mild conditions for

the Negishi cross-coupling[21] and showed a potential for future applications of the methodology.

To assess the scalability of the process, the coupling was performed on a gram scale and gave **3.2.15** in 86% isolated yield (Figure 3.10), attesting to the synthetic utility of the method.

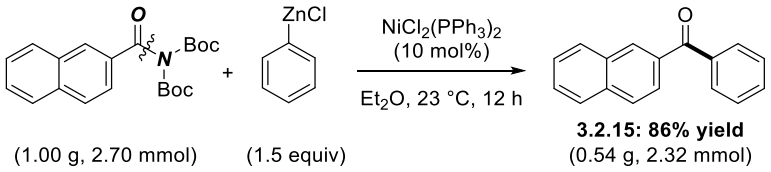


Figure 3.10 A gram-scale acyl Negishi cross-coupling.

3.2.4 Mechanistic studies

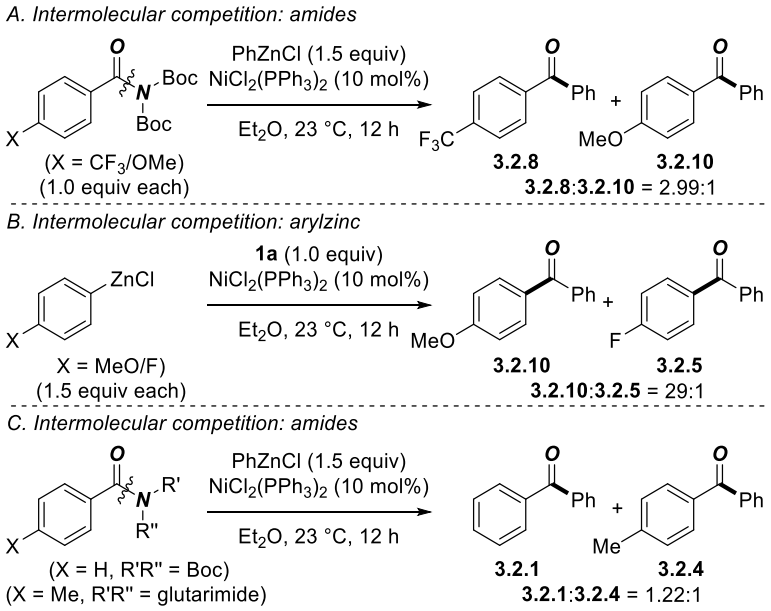


Figure 3.11 Competition studies.

We conducted several studies to gain insight into the reaction mechanism (Figure 3.11).

Intermolecular competition experiments between differently substituted amides revealed that electron-deficient amides were inherently more reactive (Figure 3.8A), consistent with the facility of metal insertion into the N–C(O) bond.[6] Further competition experiments between differently substituted nucleophiles indicated that electron-rich nucleophiles reacted preferentially (Figure 3.11B), consistent with the rate-limiting transmetallation.[25] Intermolecular competition experiments between N,N-di-Boc_2-amides and N-glutarimide amides indicated that the former react preferentially (Figure 3.11C).[8c]

This unexpected observation, in conjunction with the ease of site-selective N,N-di-Boc_2-activation of simple primary amides, clearly demonstrated the synthetic potential of this method. The key step in the proposed mechanism involved direct Ni(0) insertion into the weakened N–C amide bond.[7–10]

3.2.5 Conclusion

In summary, we developed the first Negishi cross-coupling of primary amides enabled by the combined site-selective N,N-di-Boc_2 activation and use of nickel catalysis through direct metal insertion into the N–C(O) bond. The reaction showed excellent functional group tolerance, providing rapid access to functionalized ketones from simple and readily available primary amides, which are among the most commonly utilized amide building blocks in organic chemistry. Given the importance of N–C(O) bond activation manifolds, the site-selective N,N-di-Boc_2 activation/metal insertion strategy is expected to find broad applications in organic synthesis.

3.2.6 Experimental Section

General procedure for Negishi cross-coupling of amides. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv) and $Ni(PPh_3)_2Cl_2$ (0.10 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under vacuum. Diethyl ether (0.20 M) was added with vigorous stirring at room temperature and the reaction was stirred at room temperature for 5 min. A solution of arylzinc reagent (THF solution, 1.5 equiv) was added with vigorous stirring and the reaction mixture was stirred for the indicated time at 23 °C. After the indicated time, the reaction mixture was diluted with HCl (0.1 *N*, 10 mL), the aqueous layer was extracted with EtOAc (3 x 20 mL), organic layers were combined, dried, filtered and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 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.

3.2.1, 81%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.85, 137.78, 132.53, 130.19, 128.41.

3.2.2, 70%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 9.4 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.74, 138.79, 137.92, 136.87, 133.24, 131.12, 130.35, 130.25, 128.64, 128.58, 125.32, 20.10.

3.2.3, 88%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 6.7 Hz, 2H), 7.58 (t, *J* = 6.5 Hz, 1H), 7.45 (t, *J* = 6.7 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 6.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 198.74, 138.79, 137.92, 136.87, 133.24, 131.12, 130.35, 130.25, 128.64, 128.58, 125.32, 20.10.

3.2.4, 82%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.65, 143.37, 138.09, 135.01, 132.29, 130.44, 130.07, 129.11, 128.34, 21.80.

3.2.5, 69%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.81 (m, 2H), 7.77 (d, *J* = 7.9 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.16 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.37, 165.54 (d, J^F = 252.5 Hz), 137.68, 133.97 (d, J^F = 3.8 Hz), 132.80 (d, J^F = 8.8 Hz), 132.59, 130.00, 128.49, 115.59 (d, J^F = 21.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.03.

3.2.6, 56%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.76 (m, 3H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.42, 139.40, 137.09, 134.71, 132.98, 132.50, 130.17, 130.05, 129.78, 128.60, 128.25.

3.2.7, 76%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.32, 138.45, 136.92, 133.25, 133.14,

133.17 (q, J = 32.5 Hz), 130.16, 129.09, 128.97 (q, J^F = 3.8 Hz), 128.71, 126.84 (q, J^F = 3.8 Hz), 123.82 (q, J^F = 271.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.77.

3.2.8, 83%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2 H), 7.81 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.66-7.63(t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.68, 140.86, 136.86, 133.86 (q, J^F = 32.5 Hz), 133.23, 130.28, 130.24, 128.67, 125.48 (q, J = 3.8 Hz), 123.80 (q, J^F = 271.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.01.

3.2.9, 57%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.18, 166.46, 141.46, 137.09, 133.36, 133.09, 130.25, 129.92, 129.64, 128.61, 52.62.

3.2.10, 66%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.70, 163.35, 138.42, 132.69, 132.02, 130.29, 129.86, 128.31, 113.68, 55.63.

3.2.11, 81%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 7.7 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 1.58 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.60, 154.36, 151.32, 137.66, 135.07, 132.57, 131.76, 130.07, 128.45, 121.23, 84.31, 27.82.

3.2.12, 70%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.80-7.78 (m, 4H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.18, 141.37, 136.47, 133.47, 132.31, 130.38, 130.21, 128.78, 118.15, 115.81.

3.2.13, 51%. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 2.8, 1.1 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.65-7.59 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.41 (dd, *J* = 5.0, 2.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.13, 141.49, 138.82, 134.00, 132.43, 129.51, 128.77, 128.52, 126.32.

3.2.14, 80%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.46-7.40 (m, 4H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 3.95 (q, *J* = 7.0 Hz, 2H), 1.06 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.95, 157.00, 138.46, 132.74, 132.13, 129.87, 129.70, 129.23, 128.19, 120.64, 112.59, 64.15, 14.41.

3.2.15, 81%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.95 (s, 2H), 7.94-7.90 (m, 2H), 7.87 (d, *J* = 7.9 Hz, 2H), 7.62 (q, *J* = 7.9, 7.3 Hz, 2H), 7.57-7.51 (m, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 196.83, 138.06, 135.41, 134.99, 132.48, 132.41, 131.96, 130.21, 129.54, 128.46, 128.42, 127.95, 126.92, 125.91.

3.2.10', 84%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.70, 163.35, 138.42, 132.69, 132.02, 130.29, 129.86, 128.31, 113.68, 55.63.

3.2.16, 75%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.1 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.59, 157.47, 137.94, 133.04, 132.00, 129.95, 129.71, 128.98, 128.34, 120.61, 111.58, 55.73.

3.2.17, 80%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.3 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 3H), 6.57-6.53 (m, 1H), 6.53-6.49 (m, 1H), 3.87 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.69，163.47, 159.75, 138.96, 132.46, 132.33, 129.80, 128.13, 121.67, 104.68, 98.95, 55.70, 55.66.

3.2.2', 84%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 9.4 Hz, 2H), 2.36 (s, 3H).^{13}C NMR(125 MHz, $CDCl_3$) δ 198.74, 138.79, 137.92, 136.87, 133.24, 131.12, 130.35, 130.25, 128.64, 128.58, 125.32, 20.10.

3.2.5', 62%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.81 (m, 2H), 7.77 (d, *J* = 7.9 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.16 (t, *J* = 8.5 Hz, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ 195.37, 165.54 (d, J^F = 252.5 Hz), 137.68, 133.97 (d, J^F = 3.8 Hz), 132.80 (d, J^F = 8.8 Hz), 132.59, 130.00, 128.49, 115.59 (d, J^F = 21.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.03.

3.2.18, 73%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H),

3.07 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.27, 153.40, 139.42, 132.86, 131.22, 129.56, 128.12, 124.87, 110.66, 40.18.

3.2.19, 51%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.87-7.77 (m, 3H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.13 (s, 1H), 6.58 (s, 1H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.38, 139.28, 139.12, 131.66, 130.53, 130.03, 129.36, 128.20, 127.80, 125.62, 123.97, 109.22, 103.12, 33.23.

3.2.20, 89%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.96-7.87 (m, 6H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.91 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.65, 163.36, 135.67, 135.17, 132.71, 131.21, 130.60, 129.39, 128.29, 128.15, 127.94, 126.85, 126.02, 113.76, 55.65, 28.18.

3.2.21, 93%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.90-7.87 (m, 3H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.05 (s, 1H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.52, 157.57, 135.76, 135.38, 132.62, 132.23, 132.00, 129.78, 129.77, 129.20, 128.50, 128.18, 127.89, 126.67, 125.26, 120.68, 111.70, 55.79.

3.2.22, 88%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.94-7.86 (m, 4H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.56 (s, 1H), 3.89 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.63, 163.50, 159.79, 136.34, 135.51, 132.61, 132.31, 131.60, 129.63, 128.19, 127.91, 127.85, 126.56, 125.60, 121.90, 104.80, 99.06, 55.74, 55.67.

3.2.23, 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.94-7.86 (m, 3H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.73, 139.03, 136.89, 135.79, 135.22, 132.76, 132.55, 131.16, 130.35, 129.77, 128.75, 128.65, 128.60, 127.95, 126.90, 125.40, 125.22, 20.12.

3.2.24, 89%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.95-7.89 (m, 3H), 7.87 (d, *J* = 8.7 Hz, 3H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.56-7.51 (m, 1H), 6.71 (d, *J* = 8.5 Hz, 2H), 3.08 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.20, 152.43, 135.68, 133.83, 131.90, 131.50, 129.44, 128.22, 127.02, 126.89, 126.69, 125.63, 125.24, 124.18, 109.74, 39.18.

3.2.25, 62%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.78 (m, 4H), 7.15 (t, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.24, 165.20 (d, J^F = 252.5 Hz), 163.39, 134.58 (d, J^F = 2.5 Hz), 132.54, 132.41 (d, J^F = 8.8 Hz), 130.16, 115.46 (d, J^F = 22.5 Hz), 113.77, 55.66. ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.93.

3.2.26, 53%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.90-7.81 (m, 2H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.23-7.08 (m, 3H), 6.59 (s, 1H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.95, 164.05 (d, J^F = 251.2 Hz), 139.13, 135.40 (d, J^F = 3.8 Hz), 132.56 (d, J^F = 8.8 Hz), 130.64, 129.24, 127.83, 125.36, 123.86, 115.31(d, J^F = 22.5 Hz), 109.30, 103.11, 33.25. ^{19}F NMR (471 MHz, $CDCl_3$) δ -107.70.

3.2.27, 78%. White solid. Mp = 68-70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.8 Hz, 2H), 8.08 (s, 1H), 7.88-7.77 (m, 3H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.15 (s, 1H), 6.59 (s,

1H), 3.97 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.62, 166.69, 143.23, 139.32, 132.58, 130.76, 129.71, 129.48, 128.78, 127.87, 125.80, 123.83, 109.43, 103.27, 52.55, 33.26. HRMS calcd for $C_{36}H_{30}N_2O_6Na$ ($2M^+ + Na$) 609.1996, found 609.2010.

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3.3 Nickel-catalyzed acyl Negishi cross-coupling of N-acyl-succinimides

Parts of this section were also adapted with permission from the article "Nickel-Catalyzed Negishi Cross-Coupling of N-Acylsuccinimides: Stable, Amide-Based, Twist-Controlled Acyl-Transfer Reagents via N–C Activation" (*Synthesis* **2017**, *49*, 3602).

3.3.1 Introduction

As outlined in this thesis, the catalytic functionalization of amide N–C(O) bonds has emerged as a new paradigm in organic synthesis (Figure 3.12A).[1,2] In this reactivity manifold, amides serve as stable acyl or aryl synthetic equivalents under redox neutral reaction conditions. The first esterification study was reported by Garg and co-workers in 2015, and focused on Ni-catalysis under mild conditions.[3] Our group has pioneered decarbonylative cross-couplings of amides.[4] We established the working model for amide bond cross-coupling in that amide bond destabilization (steric or electronic) is required to enable selective metal insertion into the resonance weakened amide bond ($n_N \rightarrow \pi^*_{C=O}$ conjugation, 15-20 kcal/mol in planar amides),[5] and developed a range of amide bond activation methods.[6] Significant progress has been made in the field,[7–9] providing the necessary driving force for advances using amides as N–C(O) electrophiles in generic transition-metal-catalyzed manifolds.[10,11]

Despite the advances, the development of new amide-based reagents for selective N–C(O) functionalization with rational design of the N–C(O) bond cleavage selectivity has remained a challenge in the field.[1b,5] Realizing this classic problem, we established a

room temperature, nickel-catalyzed Negishi cross-coupling of N-acyl-succinimides with aryl zinc reagents via selective N–C(O) bond cleavage enabled by amide bond twist. Notably, this study introduced N-acyl-succinimides as stable, crystalline, electrophilic, cost-effective, benign, amide-based acyl transfer reagents via acyl metal intermediates. The reaction selectivity was governed by half-twist of the amide bond[12] in N-acyl-succinimides, and opened the door for applications in metal-catalyzed manifolds via redox-neutral reaction pathways tuneable by amide bond distortion (Figure 3.12B-C).

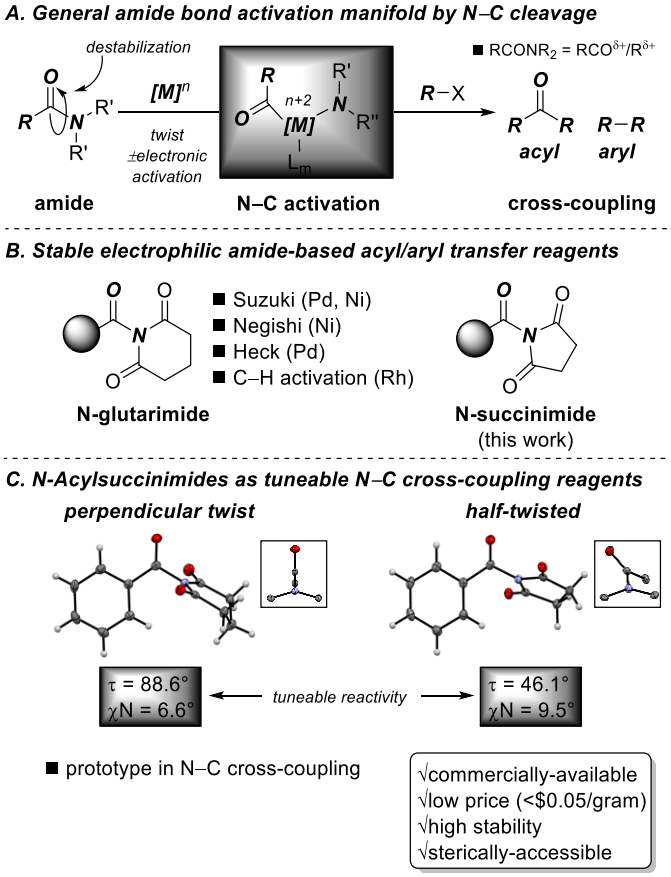


Figure 3.12 N-acyl-succinimides as acyl transfer reagents.

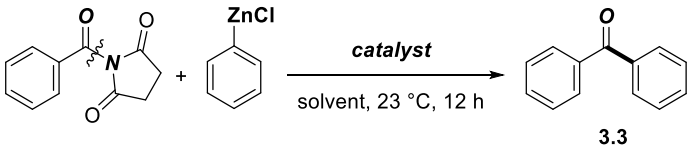
The use of amide derivatives in cross-coupling is of broad potential impact because (1) generic acyl-metal intermediates are generated under mild, chemoselective conditions by tuning amidic resonance; (2) halide waste is not generated during the transition-metal-catalyzed protocols, avoiding the handling of moisture sensitive and corrosive acyl halides; (3) the amide bond activation manifold can be employed in molecular biology and medicinal chemistry in late-stage derivatization.

Studies showed that N-acyl-glutarimide amides introduced by us represent the most reactive amide derivatives reported in N–C cross-coupling.[1,4–6,8g,h] Mechanistically, the high reactivity of N-acyl-glutarimides results from perpendicular amide bond twist, irrespective of the R substitution (Figure 3.12).[5e] To further advance the concept, we considered the use of N-succinimides as attractive precursors for selective acyl-transfer by N–C bond cleavage. On the basis of structural studies, the amide bond in N-succinimide amides is half-twisted (cf. fully perpendicular as in N-glutarimides),[5e] offering a strategic advantage of tuneable N–C(O) insertion reactivity controlled by non-planar geometry of the amide bond. N-acyl-succinimides offer several additional major advantages in amide bond cross-coupling: (1) succinimide is a cheap, widely-available chemical, with a price of <$0.05/gram);[13] (2) the parent N-benzoylsuccinimide is commercially available; (3) N-acyl-succinimides are bench-stable, easily purified crystalline solids; (4) lower bond twist corresponds to higher stability of the amide N–acyl bond in acyl-succinimides (cf. N-acyl-glutarimide amides); (5) the compact five-membered ring is more sterically-accessible for metal insertion (cf. N-acyl-glutarimide

amides); (6) cyclic activating ring prevents undesired cleavage of the σ N–C bond adjacent to the amide bond (cf. saccharins or acyclic amides).[1,3–9,14]

3.3.2 Reaction optimization

We selected Ni-catalyzed Negishi cross-coupling to demonstrate the concept because of the importance of Negishi cross-coupling,[15] advantages of Ni-catalysis,[16] and potentially mild reaction conditions for the coupling.[17] Our investigations commenced with an evaluation of the coupling of N-benzoylsuccinimide with aryl zinc chloride in the presence of various Ni catalysts (Table 3.3). Various nickel catalysts were tested (entries 1-5) and $NiCl_2(PPh_3)_2$ proved the most effective, delivering the cross-coupling product in excellent yield (entry 5). Importantly, other Ni(II) precatalysts such as $NiCl_2$(dppe), $NiCl_2$(dppf), $NiCl_2(PCy_3)_2$, $Ni(acac)_2$ also showed good to high reactivity (entries 1-4), suggesting superior reactivity of N-acyl-succinimide amides vs. N-acyl-glutarimides. A brief solvent screen demonstrated that although Et_2O was the preferred solvent for the coupling (entry 5), good to high yields were obtained with dioxane, THF, CH_3CN and toluene (entries 6-9), indicating high reactivity and/or stability of N-benzoylsuccinimides. Finally, the use of $PdCl_2(PPh_3)_2$ clearly indicated that nickel is the preferred catalyst for the Negishi coupling of amides via N–C(O) activation (entry 10). Importantly, the developed reaction proceeded with a commercially-available, air-stable Ni(II) precatalyst in the absence of additives under exceedingly mild room temperature conditions.



Entry	Catalyst	Solvent	Yield (%)[b]
1	$Ni(dppe)Cl_2$	Et_2O	42
2	$Ni(dppf)Cl_2$	Et_2O	40
3	$Ni(PCy_3)_2Cl_2$	Et_2O	88
4	$Ni(acac)_2$	Et_2O	45
5	$Ni(PPh_3)_2Cl_2$	Et_2O	90[c]
6	$Ni(PPh_3)_2Cl_2$	dioxane	75
7	$Ni(PPh_3)_2Cl_2$	THF	68
8	$Ni(PPh_3)_2Cl_2$	CH_3CN	72
9	$Ni(PPh_3)_2Cl_2$	toluene	59
10	$Pd(PPh_3)_2Cl_2$	Et_2O	<5

[a]Conditions: amide (1.0 equiv), Ph-ZnCl (1.5 equiv), catalyst (5 mol%), solvent (0.20 M), 23 °C, 12 h. [b]GC/^{1}H NMR yields. [c]Isolated yield.

Table 3.3 Optimization of acyl Negishi cross-coupling of N-acyl-succinimides.[a]

3.3.3 Scope of the reaction

With the optimized conditions in hand, the scope of the reaction was next examined (Figure 3.13). We found that the developed coupling is general, providing a versatile platform to generate a range of diaryl ketones.[18] Amide substrates containing neutral (entry 1), electron-donating (entries 2-3) and electron-withdrawing (entry 4) substituents at the 4-position were well-tolerated. Importantly, the cross- coupling of a sterically-demanding ortho-substituted amide afforded the desired product in good yield (entry 5). Both electron-rich (entry 6) and electron-deficient (entry 7) aryl zinc reagents could be employed in this coupling. The higher efficiency using electron-rich nucleophiles was consistent with the transmetallation as the slow step in the Negishi coupling.[19] Metal

insertion could be the rate limiting step in the case of less electrophilic amide cross-coupling partners. The reaction could be further extended to the coupling of sterically-demanding amide precursors with electronically-differentiated arylzincs (entries 8-9). Finally, the reaction of electronically-differentiated amides with electron-rich and electron-poor aryl zinc reagents also proceeded smoothly and gave the diaryl ketone products in 70-82% yields (entries 10-12). The mild conditions and operational-simplicity using a single Ni(II) precatalyst in the absence of additives compared favorably with the Suzuki coupling of amides by N–C(O) activation.

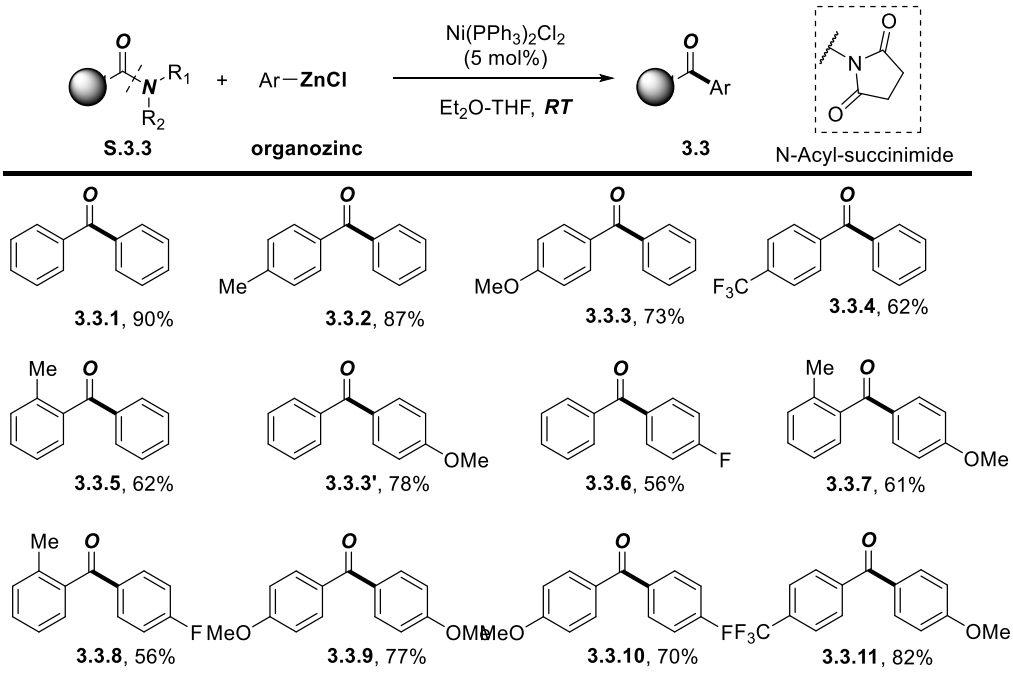


Figure 3.13 Scope of acyl Negishi cross-coupling of N-acyl-succinimides.

3.3.4 Mechanistic studies

Remarkably, we found that the reaction was more selective for the cross-coupling of N-acyl-succinimides cf. N-acyl-glutramides (Figure 3.14). We proposed that the higher reactivity of N-acyl-succinimide amides resulted from more sterically-accessible amide bond, and/or higher stability under the reaction conditions. This finding suggested that N-acyl-succinimides are well suited for the development of a range of N–C activation protocols, especially in cases when stability of N-glutarimide amides is problematic.

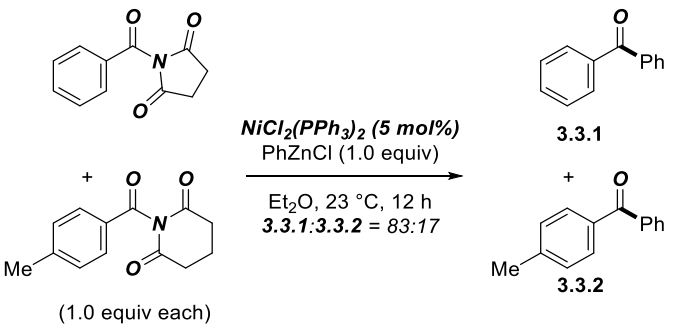


Figure 3.14 Selectivity study: effect of N-substitution.

Furthermore, competition studies demonstrated that electron-deficient amides were inherently more reactive substrates, consistent with the facility of metal insertion (Figure 3.15). This appeared to be a common feature in the amide cross-coupling.[1,2]

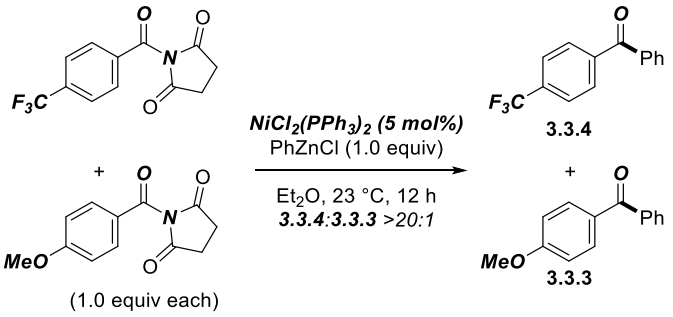


Figure 3.15 Selectivity study: effect of amides.

The potential of using other five-membered N-acyl imides as precursors to afford acyl metal intermediates was briefly evaluated (Figure 3.16A-B). Interestingly, our results demonstrated that N-acyl-saccharins pioneered by our group[6d,4d] and Zeng and co-workers[8b–d] might become suitable cross-coupling partners in the reaction (Scheme 3.16A). However, the capacity for unselective N–C vs. N–SO_2 insertion using Ni was noted.

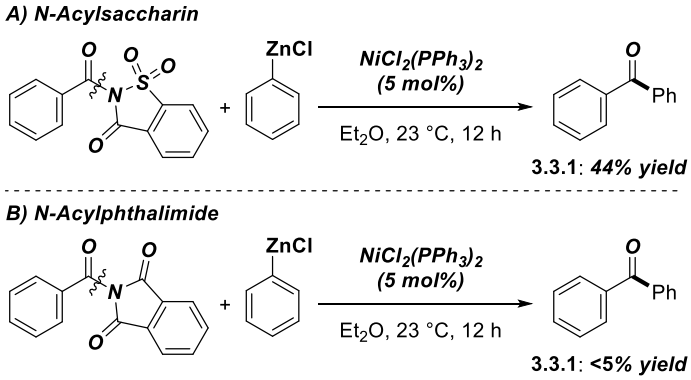


Figure 3.16 Acyl Negishi cross-coupling of N-acyl-saccharins and N-acyl-phthalimides.

In contrast, N-acyl-phthalimides were not suitable amide-based acyl transfer reagents for the cross-coupling under various Ni-conditions (Figure 3.16B). We proposed that the fused benzene ring activated the phthalimide imide bonds towards unselective cleavage. Overall, these results highlighted the beneficial use of N-acyl-succinimide amides as selective acyl-transfer reagents.[20]

3.3.5 Conclusion

In conclusion, we developed N-acyl-succinimides as new, amide-based, electrophilic acyl transfer reagents in which the selectivity of metal insertion was controlled by amide bond

twist. N-acyl-succinimides contain half-twisted amide bonds (cf. fully perpendicular N-glutarimides). This resulted in higher stability under the reaction conditions, while preserving the beneficial features of the imide activating group. Notably, these reagents were considerably cheaper than other amide-based electrophiles. The high selectivity for metal insertion, tuneable twist, ease of purification and high bench-stability are other synthetically appealing features of N-acyl-succinimides. In a broader context, the use of cheap and readily available carboxylic acid amides represents a valuable strategy for the selective formation of acyl-metal intermediates.[10]

3.3.6 Experiment Section

General procedure for Ni-catalyzed Negishi cross-coupling. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv) and $Ni(PPh_3)_2Cl_2$ (0.05 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under vacuum. Diethyl ether (0.20 M) was added with vigorous stirring at room temperature and the reaction was stirred at room temperature for 5 min. A solution of arylzinc reagent (THF solution, 1.5 equiv) was added with vigorous stirring and the reaction mixture was stirred for the indicated time at 23 °C. After the indicated time, the reaction mixture was diluted with HCl (0.1 *N*, 10 mL), the aqueous layer was extracted with EtOAc (3 x 20 mL), organic layers were combined, dried, filtered and concentrated. Purification by chromatography on silica gel afforded the title product.

3.3.1, 90%. White solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.89, 137.73, 132.54, 130.19, 128.41.

3.3.2, 87%. White solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.65, 143.37, 138.09, 135.01, 132.29, 130.44, 130.07, 129.11, 128.34, 21.80.

3.3.3, 73%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H),

3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.70, 163.35, 138.42, 132.69, 132.02, 130.29, 129.86, 128.32, 113.68, 55.63.

3.3.4, 71%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.81 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.66 – 7.61 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.68, 140.87, 136.87, 133.87 (q, J^F = 32.5 Hz), 133.24, 130.28, 130.25, 128.68, 125.49 (q, *J* = 3.8 Hz), 123.82 (q, J^F = 271.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.01.

3.3.5, 62%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.78 (m, 2H), 7.63-7.59 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.42 (td, *J* = 7.5, 1.5 Hz, 1H), 7.36-7.30 (m, 2H), 7.29-7.27 (m, 1H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.77, 138.74, 137.86, 136.87, 133.25, 131.12, 130.36, 130.26, 128.64, 128.58, 125.32, 20.12.

3.3.6, 56%. White solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.81 (m, 2H), 7.77 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.41, 165.52 (d, J^{C-F} = 252.5 Hz), 137.63, 133.94 (d, J^{C-F} = 3.8 Hz), 132.80 (d, J^{C-F} = 8.8 Hz), 132.61, 130.01, 128.49, 115.68 (d, J^{C-F} = 21.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -105.99.

3.3.7, 61%. White solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 6.1 Hz, 2H), 7.26 – 7.22 (m, 1H), 6.93 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.51, 163.84, 139.34, 136.29, 132.64, 130.95, 130.67, 129.92, 128.06, 125.30, 113.84, 55.65, 19.93.

3.3.8, 56%. White solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.2, 6.0 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.29-7.28 (m, 1H), 7.15 (d, *J* = 8.5 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.06, 165.84 (d, J^{C-F} = 253.6 Hz), 138.39, 136.62, 134.11 (d, J^{C-F} = 3.0 Hz), 131.08, 130.34, 128.28, 125.29, 115.64 (d, J^{C-F} = 21.8 Hz), 21.63.^{19}F NMR (471 MHz, $CDCl_3$) δ -104.94.

3.3.9, 77%. White solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 4H), 6.96 (d, *J* = 8.4 Hz, 4H), 3.89 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.60, 162.98, 132.37, 130.93, 113.61, 55.62.

3.3.10, 70%. White solid.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.74 (m, 4H), 7.15 (t, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.23, 165.20 (q, J^{C-F} = 252.5 Hz), 163.40, 134.59 (d, J^{C-F} = 2.5 Hz), 132.54, 132.42 (d, J^{C-F} = 8.8 Hz), 130.18, 115.46 (d, J^{C-F} = 22.5 Hz), 113.78, 55.66. ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.94.

3.3.11, 82% yield. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.79 (m, 4H), 7.74 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.40, 163.86, 141.65, 133.39 (q, J^{C-F} = 32.5 Hz), 132.77, 129.92, 129.49, 125.79 (q, J^{C-F} = 3.8 Hz), 123.87 (q, J^{C-F} = 217.3 Hz), 113.95, 55.71. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.94.

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[21] N-Acylsuccinimides are crystalline, bench-stable solids, with no decomposition observed when stored on an open bench-top at ambient conditions for periods >12 months.

Chapter 4

Pd-NHC Precatalysts in Acyl Cross-Couplings of Amides and Esters

4.1 Pd-PEPPSI catalyzed acyl Suzuki cross-coupling of esters

Parts of this section were adapted with permission from the article "Pd-PEPPSI: A General Pd-NHC Precatalyst for Suzuki–Miyaura Cross-Coupling of Esters by C–O Cleavage" (*Organometallics* **2017**, *36*, 3784). Copyright ©2016, American Chemical Society.

4.1.1 Introduction

Following our studies on transition-metal-catalyzed activation of amide N–C(O) bonds, we became interested in activation of related O–C(O) bonds in esters through direct oxidative addition. We realized that the oxidative addition of a metal to acyl electrophile represents a fundamental step in catalysis.[1] Historically, the use of aryl esters in the cross-coupling manifolds had been difficult due to low reactivity of the C–O bond towards metal insertion as a result of $n_O \rightarrow \pi^*_{C=O}$ conjugation.[2,3] An advance involved the development of decarbonylative cross-couplings of aryl esters facilitated by the design of new electron-rich, chelating phosphine ligands for Ni and Pd to trigger oxidative addition.[4,5] The ability to promote previously inaccessible catalytic pathways engaging C–O ester bonds offered a unique potential to develop valuable bond forming reactions in chemicals synthesis.

As outlined in previous chapters of this thesis, our laboratory introduced a new amide bond activation manifold that permitted the activation and subsequent cross-coupling of the N–C(O) acyl amide bond via ground-state destabilization.[6–8] Expanding upon this theme, we demonstrated that this amide activation platform could be extended to the cross-coupling of aryl esters.[9] This catalytic manifold hinges on the decreased rotational barrier in aryl esters (E_R = 9.3 kcal/mol) and ground-state-destabilized amides (E_R < 10 kcal/mol)[10] to enable selective metal insertion into the acyl bond using synthetically-attractive bench-stable carboxylic acid derivatives.[11,12] The prevalence of aryl esters in organic synthesis provides new avenues for modular cross-coupling processes of common electrophiles. Acyl Suzuki cross-coupling of esters was reported by our group and Newman and co-workers using Pd-NHC precatalysts under mild conditions.[9,11a]

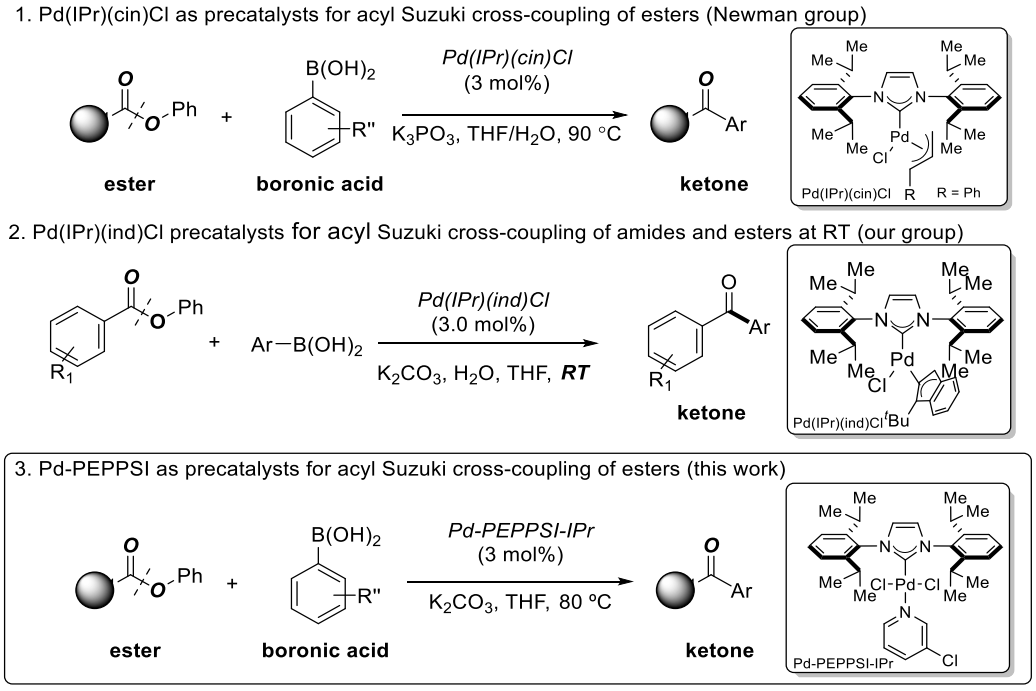


Figure 4.1 Acyl Suzuki cross-coupling of esters.

We hypothesized that to realize the full potential of the acyl cross-coupling manifold of esters it is critical to employ new general catalyst systems that operate under operationally-simple conditions.

We developed versatile, easily prepared, well-defined Pd-PEPPSI type precatalysts[13–15] as highly reactive catalysts for the direct Suzuki-Miyaura cross-coupling[16] of esters. Moreover, we demonstrated that the cross-coupling of aryl esters proceeded with similar rates to the cross-coupling of amides. Considering the modular scaffold of Pd(II)-NHC precatalysts bearing pyridine "throw-away" ligand,[17] the method should advance the development of new catalysts for acyl C–O cleavage reactions.[18]

We proposed that the use of Pd-PEPPSI catalysts in the acyl C–O coupling manifold would involve two immediate advantages: (1) PEPPSI-type complexes are prepared in a single operationally-straightforward step, which is not the case with other Pd-NHC type complexes. This would facilitate a general use of Pd-NHC catalysts in ester C–O cross-couplings. (2) A variety of PEPPSI type complexes could be easily accessed by appending alkyl or halide groups on the NHC scaffold, which could result in the development of even more active catalysts for the acyl C–O cross-coupling. We also found for the first time that, in terms of steric demand, IPr was the preferred NHC scaffold for achieving high efficiency in the acyl cross-coupling, consistent with steric properties of acyl-Pd complexes.[2a]

Our motivation for studying Pd-PEPPSI type precatalysts for the Suzuki-Miyaura cross-coupling of esters originated from their unique catalytic properties; Pd-PEPPSI

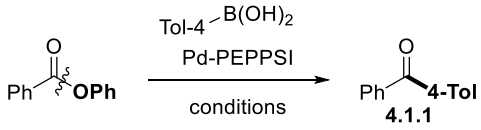
complexes were among the most active catalysts for palladium-catalyzed cross-coupling reactions.[14] PEPPSI-type of Pd-NHC complexes represented a modular class of Pd-NHC catalysts, which is crucial for the rational design of catalysts through changes in the ancillary and throw-away ligand.[18] PEPPSI type complexes were easy and inexpensive to prepare,[14,15] which was the key consideration for the widespread use of acyl cross-couplings in organic synthesis.

4.1.2 Reaction optimization

At the beginning of this project we screened various PEPPSI type catalysts under different conditions for the model reaction between phenyl benzoate and 4-tolylboronic acid (Table 4.1). The optimized catalyst system used Pd-PEPPSI-IPr (3 mol%), 4-Tol-$B(OH)_2$ (3.0 equiv), K_2CO_3 (4.5 equiv), THF, 80 °C, and afforded the desired product in 84% yield. Selected optimization results are summarized in Table 1. THF, toluene and dioxane proved to be the most effective solvents (entries 1-4). The reaction showed strong dependence on the base used with K_2CO_3 and K_3PO_4 providing the best results (entries 5-8). The reaction showed good efficiency at temperatures as low as 40 °C (entries 9-10). Increasing the temperature to 110 °C did not significantly affect the reaction (entry 11). The reaction was inefficient at room temperature. As anticipated, the reaction showed a profound dependence on the PEPPSI-type scaffold (entries 11-14). The pyridine "throw-away" ligand (**4b**) cleanly produced the coupling product (entry 11). 1-Methylimidazole ligand (**4c**) at the palladium also resulted in the efficient cross-coupling (entry 12), with no observable side-products. Intriguingly, the use of more bulky PEPPSI-

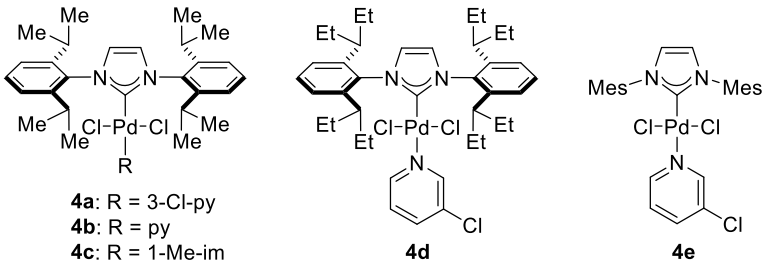
IPent (**4d**)[14b] and less sterically-demanding PEPPSI-IMes (**4e**) gave inferior results (entries 13-14).

Table 4.1 Optimization of ester acyl Suzuki.[a]



entry	catalyst	base	solvent	*T* (°C)	yield (%)[b]
1	**4a**	K_2CO_3	THF	80	84
2	**4a**	K_2CO_3	toluene	80	80
3	**4a**	K_2CO_3	dioxane	80	83
4	**4a**	K_2CO_3	DME	80	48
5	**4a**	K_3PO_4	THF	80	69
6	**4a**	KOH	THF	80	32
7	**4a**	Cs_2CO_3	THF	80	13
8	**4a**	Na_2CO_3	THF	80	<5
9	**4a**	K_2CO_3	THF	60	76
10	**4a**	K_2CO_3	THF	40	39
11	**4a**	K_2CO_3	THF	110	88
12	**4b**	K_2CO_3	THF	80	75
13	**4c**	K_2CO_3	THF	80	53
14	**4d**	K_2CO_3	THF	80	42
15	**4e**	K_2CO_3	THF	80	45
16[c]	**4a**	K_2CO_3	THF	80	72
17[d]	**4a**	K_2CO_3	THF	80	75
18[e]	**4a**	K_2CO_3	THF	80	71

[a]Ester (1.0 equiv), R-$B(OH)_2$ (3.0 equiv), [Pd] (3 mol %), K_2CO_3 (4.5 equiv), THF (0.80 mL), *T*, 16 h. [b]GC/^{1}H NMR yields. [c]K_2CO_3 (1.0 equiv). [d]R-$B(OH)_2$ (1.2 equiv). [e]K_2CO_3 (1.0 equiv), R-$B(OH)_2$ (1.2 equiv).



Finally, the use of close to stoichiometric amount of base and boronic acid leads to efficient coupling, providing an entry point for further development (entries 15-18). Overall, our findings suggested that PEPPSI-IPr might serve as the privileged NHC scaffold for the C–O acyl cross-coupling; and changes in the "throw-away" ligand attached to the palladium center might lead to the development of more active catalysts for the cross-coupling.[18]

4.1.3 Scope of the reaction

The scope of this cross-coupling was next investigated (Figure 4.2). The reaction accommodated a broad range of ester and boronic acid cross-coupling partners. Electronically-diverse ester electrophiles were well-tolerated in this coupling (**4.1.1-4.1.4**), including deactivated electron-rich arenes (**4.1.4**). Sensitive electrophilic functional groups such as esters (**4.1.5**) were readily accommodated. Sterically-demanding esters (**4.1.6**) and even sensitive substrates such as polyfluorinated (**4.1.7**), heterocyclic (**4.1.8**) and aliphatic esters (**4.1.9**) were smoothly converted into the desired products. The scope of the boronic acid component was also quite broad. In general, high to excellent yields of the cross-coupling products were obtained for electron-neutral (**4.1.2'**), electron-rich (**4.1.3'**), electron-deficient (**4.1.10**, **4.1.5'**) and sterically-

demanding (**4.1.6'**, **4.1.12**) arylboronic acids. Moreover, polyaromatic (**4.1.14**) and heterocyclic boronic acids were suitable substrates for this transformation. Turnover number (TON) of 230 was determined for the coupling of esters (Pd-PEPPSI-IPr, 0.10 mol%, 110 °C). We have not observed side products, such as decarbonylation and unselective cleavage of the O–Ph bond.

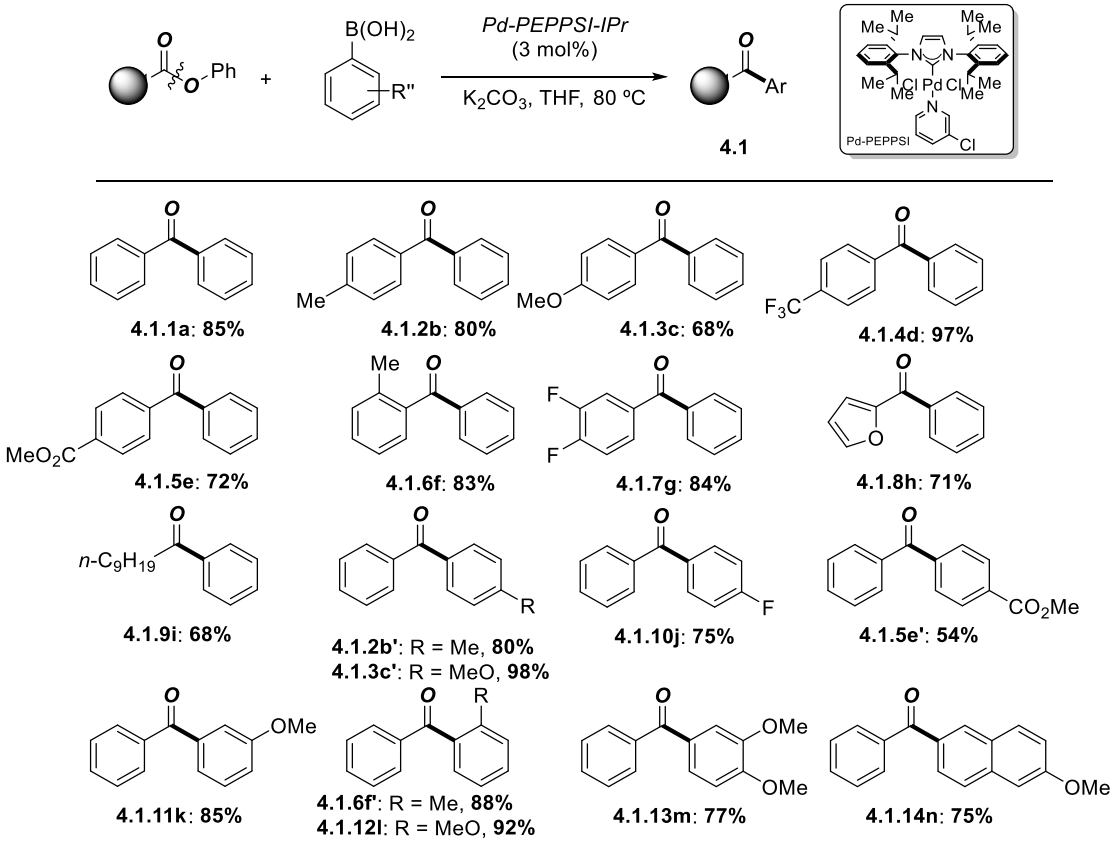


Figure 4.2 Scope of the reaction.

4.1.4 Mechanistic studies

We performed several mechanistic studies to investigate the reaction mechanism. (1) In general, these acyl activation reactions had been subclassified as either C–N or C–O

depending on the bond that undergoes the cross-coupling.[2a] Our study demonstrated that the cross-coupling of aryl esters proceeds with similar rates to the cross-coupling of amides (PhCONBoc/Ph; PhCONTs/Ph).[19]

(2) Studies into the activation of PEPPSI-IPr and (IPr)Pd(cinnamyl)Cl[20] showed more facile activation of PEPPSI-IPr under the developed conditions (PEPPSI: 30 min, 70% yield; 60 min, 77% yield; (IPr)Pd(cinnamyl)Cl: 30 min, 41% yield; 60 min, 48% yield), which suggested a potential for the development of even more active catalysts.

4.1.5 Conclusion

In summary, we developed versatile Pd-PEPPSI type precatalysts as highly reactive catalysts for the direct Suzuki-Miyaura cross-coupling of esters. This reaction featured modular, easily prepared precatalysts, which operate under operationally-convenient conditions. The strong σ-donation of the NHC ligand facilitated oxidative addition, leading to a modular approach to the historically challenging C–O cross-coupling. The generality of this acyl activation platform should enable the productive engagement in modular cross-coupling reactions without restriction to a particular acylmetal precursor.

4.1.6 Experimental Section

General procedure for the Suzuki-Miyaura cross-coupling of esters. An oven-dried vial equipped with a stir bar was charged with an ester substrate (neat, 1.0 equiv), potassium carbonate (typically, 4.5 equiv), boronic acid (typically, 3.0 equiv), PEPPSI-IPr ([1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene](3-chloropyridyl) palladium(II) dichloride, typically, 3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath and stirred for the indicated time. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

4.1.1a, 85%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 4 H), 7.59 (t, *J* = 7.5 Hz, 2 H), 7.49 (t, *J* = 7.6 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.84, 137.77, 132.52, 130.18, 128.40.

4.1.2, 80%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2 H), 7.74 (d, *J* = 8.2 Hz, 2 H), 7.59 (t, *J* = 7.3 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 2.45 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.64, 143.36, 138.08, 135.00, 132.28, 130.43, 130.06, 129.10, 128.33, 21.79.

4.1.3, 68%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 7.6 Hz, 2 H), 7.57 (t, *J* = 7.3 Hz, 1 H), 7.48 (t, *J* = 7.4 Hz, 2 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 3.90 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.69, 163.34, 138.41, 132.68, 132.01, 130.28, 129.85, 128.31, 113.67, 55.62.

4.1.4, 97%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 2 H), 7.82 (dd, *J* = 7.1 Hz, 2 H), 7.77 (d, *J* = 8.1 Hz, 2 H), 7.67-7.62 (m, 1 H), 7.51 (t, *J* = 7.7 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.67, 140.86, 136.86, 133.86 (q, J^F = 32.5 Hz), 133.23, 130.27, 130.24, 128.67, 125.48 (q, *J* = 3.8 Hz), 123.81 (q, J^F = 271.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.02.

4.1.5, 72%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 2 H), 7.85 (d, *J* = 8.0 Hz, 2 H), 7.81 (d, *J* = 8.0 Hz, 2 H), 7.63 (t, *J* = 7.5 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 3.98 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.17, 166.45, 141.45, 137.08, 133.35, 133.08, 130.24, 129.91, 129.63, 128.60, 52.61.

4.1.6, 83%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2 H), 7.64-7.59 (m, 1 H), 7.49 (t, *J* = 7.7 Hz, 2 H), 7.43 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.37-7.31 (m, 2 H), 7.31-7.28 (m, 1 H), 2.37 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.77, 138.75, 137.87, 136.87, 133.25, 131.12, 130.36, 130.25, 128.64, 128.58, 125.32, 20.12.

4.1.7, 84%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2 H), 7.69 (t, *J* = 9.0 Hz, 1 H), 7.61 (t, *J* = 13.2 Hz, 2 H), 7.51 (t, *J* = 8.0 Hz, 2 H), 7.27 (q, *J* = 8.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.21, 154.41 (dd, J^F = 254.8, 12.3 Hz), 150.32 (dd, J^F = 255.0, 12.4 Hz), 137.00, 134.57 (t, J^F = 3.7 Hz), 132.93, 129.97, 128.62, 127.25

(q, J^F = 3.8 Hz), 119.45 (dd, J^F =17.5, 1.3 Hz), 117.40 (d, J^F = 17.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -130.60 (d, *J* = 21.2 Hz), -136.18 (d, *J* = 21.2 Hz).

4.1.8, 71%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) 7.98 (d, *J* = 7.0 Hz, 2 H), 7.73 (s, 1 H), 7.61 (t, *J* = 7.5 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 7.25 (d, *J* = 3.5 Hz, 1 H), 6.61 (dd, *J* = 3.5, 1.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.71, 152.44, 147.23, 137.41, 132.71, 129.43, 128.56, 120.69, 112.34.

4.1.9, 68%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.5 Hz, 2 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.46 (t, *J* = 7.5 Hz, 2 H), 2.96 (t, *J* = 7.0 Hz, 2 H), 1.73 (p, *J* = 7.0, 6.5 Hz, 2 H), 1.40-1.25 (m, 12 H), 0.88 (t, *J* = 6.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.76, 137.25, 132.98, 128.67, 128.19, 38.79, 32.02, 29.63, 29.62, 29.53, 29.43, 24.54, 22.81, 14.25.

4.1.2', 80%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2 H), 7.74 (d, *J* = 8.2 Hz, 2 H), 7.59 (t, *J* = 7.3 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 7.29 (d, *J* = 7.9 Hz, 2 H), 2.45 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.64, 143.36, 138.08, 135.00, 132.28, 130.43, 130.06, 129.10, 128.33, 21.79.

4.1.3', 98%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 7.6 Hz, 2 H), 7.57 (t, *J* = 7.3 Hz, 1 H), 7.48 (t, *J* = 7.4 Hz, 2 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 3.90 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.69, 163.34, 138.41, 132.68, 132.01, 130.28, 129.85, 128.31, 113.67, 55.62.

4.1.10, 75%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.5, 5.5 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 2 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 2 H), 7.16 (t, *J* =

8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.37, 165.54 (d, J^F = 252.5 Hz), 137.68, 133.97 (d, J^F = 3.8 Hz), 132.80 (d, J^F = 8.8 Hz), 132.59, 130.00, 128.49, 115.59 (d, J^F = 21.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.06.

4.1.5', 54%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 2 H), 7.85 (d, *J* = 8.0 Hz, 2 H), 7.81 (d, *J* = 8.0 Hz, 2 H), 7.63 (t, *J* = 7.5 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 3.98 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.17, 166.45, 141.45, 137.08, 133.35, 133.08, 130.24, 129.91, 129.63, 128.60, 52.61.

4.1.11, 85%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.7 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.49 (t, *J* = 7.4 Hz, 2 H), 7.41-7.34 (m, 3 H), 7.14 (d, *J* = 8.6 Hz, 1 H), 3.87 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.66, 159.70, 139.03, 132.55, 130.17, 129.34, 128.39, 123.01, 119.00, 114.44, 55.61.

4.1.6', 88%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2 H), 7.64-7.59 (m, 1 H), 7.49 (t, *J* = 7.7 Hz, 2 H), 7.43 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.37-7.31 (m, 2 H), 7.31-7.28 (m, 1 H), 2.37 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.77, 138.75, 137.87, 136.87, 133.25, 131.12, 130.36, 130.25, 128.64, 128.58, 125.32, 20.12.

4.1.12, 92%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 7.8 Hz, 2 H), 7.56 (t, *J* = 7.1 Hz, 1 H), 7.49 (d, *J* = 7.7 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 7.37 (d, *J* = 7.4 Hz, 1 H), 7.05 (t, *J* = 7.4 Hz, 1 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 3.73 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.58, 157.46, 137.93, 133.03, 131.99, 129.94, 129.70, 128.97, 128.33, 120.60, 111.57, 55.72.

4.1.13, 77%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2 H), 7.57 (t, *J* = 7.0 Hz, 1 H), 7.51-7.44 (m, 3 H), 7.38 (d, *J* = 8.3 Hz, 1 H), 6.89 (d, *J* = 8.3 Hz, 1 H), 3.96 (s, 3 H), 3.95 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.71, 153.13, 149.14, 138.42, 132.01, 130.35, 129.85, 128.30, 125.64, 112.24, 109.85, 56.24, 56.19.

4.1.14, 75%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 1.7 Hz, 1 H), 7.94 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.88-7.79 (m, 4 H), 7.65-7.58 (m, 1 H), 7.51 (dd, *J* = 8.4, 7.0 Hz, 2 H), 7.24-7.17 (m, 2 H), 3.96 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.70, 159.81, 138.33, 137.13, 132.81, 132.24, 132.11, 131.15, 130.10, 128.41, 127.72, 127.13, 126.68, 119.85, 105.88, 55.57.

4.1.15, 81%. Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.86 (d, *J* = 8.3 Hz, 2 H), 7.59 (t, *J* = 7.4 Hz, 1 H), 7.53-7.46 (m, 3 H), 6.91 (d, *J* = 1.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.56, 148.69, 144.09, 138.96, 132.61, 128.96, 128.68, 126.65, 110.35.

Determination of relative reaction rates. An oven-dried vial equipped with a stir bar was charged with an ester substrate (neat, 0.20 mmol, 1.0 equiv), potassium carbonate (3.0 equiv), boronic acid (2.0 equiv) and PEPPSI-IPr (3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 60 °C and stirred at 60 °C for the indicated time. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was

analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and/or GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

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4.2 Pd-PEPPSI-catalyzed acyl Buchwald-Hartwig cross-coupling of esters and amides

Parts of this section were adapted with permission from the article "Pd-PEPPSI: A General Pd-NHC Precatalyst for Buchwald-Hartwig Cross-Coupling of Esters and Amides (Transamidation) under the Same Reaction Conditions" (*Chem. Commun.* **2017**, *53*, 10584).

4.2.1 Introduction

The development of new reactions for the synthesis of amides is an important goal in organic synthesis.[1,2] The ubiquitous presence of amides in pharmaceuticals, polymers and natural products rendered the amide formation as one of the most commonly performed transformations in organic synthesis.[3,4] However, many of the most common amidation methods are either inefficient or suffer from serious drawbacks, such as low atom economy and the use of toxic stoichiometric coupling reagents.[1,2] As a consequence, the development of new methods for the synthesis of amides has been identified as the key green chemistry research area;[5] the discovery of new alternative catalytic methods can have a major impact on chemistry involving organic synthesis, chemical biology and biochemistry.[1–4]

Buchwal-Hartwig cross-couplings represent one of the most efficient methods for the installation of nitrogen atom through C–N bond formation.[6–9] With these Pd-catalyzed cross-coupling reactions, it is possible to rapidly access diverse aromatic amines for various academic and industrial applications. The generality of this

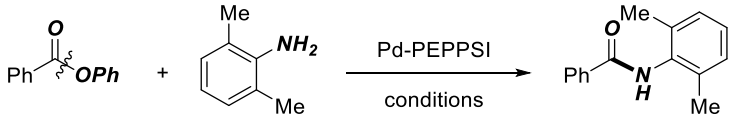
C(sp^2)–amination manifold relies upon identification of suitable supporting ligands and precatalysts to enable broad catalytic activity.[10] However, this pathway has been typically limited to the formation of aryl amines.

We found that the general Buchwald-Hartwig amination manifold of aryl halides could be advanced to both common esters[11] and amides[12] by highly chemoselective C(acyl)–X (X = O, N) cleavage to rapidly access diverse aryl amides by unconventional cross-coupling strategy.[13] This new cross-coupling method employed readily available, unactivated simple esters and amides, non-nucleophilic amines and an air-stable, well-defined precatalyst. Notable features of our study included: (1) robust Pd-catalyzed C(acyl)–amination with non-nucleophilic anilines; (2) for the first time we demonstrated selective C(acyl)–N and C(acyl)–O cleavage/Buchwald-Hartwig amination under the same reaction conditions. This allowed for a streamlined amide synthesis and avoided restriction to a particular acyl metal precursor; (3) in contrast to recently reported transformations, significantly improved access to Pd-precatalysts (synthesis in a single, operationally-trivial step), which is critical for the future identification of ancillary ligands with broad utility. We proposed that there are two major advantages of using PEPPSI-type precatalysts: (1) one-step synthesis in a single operationally-simple step; (2) various PEPPSI complexes are readily accessible by modifications of the NHC scaffold, which would facilitate the development of even more active catalysts.[15]

As outlined in this thesis, the activation of inert acyl C–O and C–N bonds in esters and amides relies on the oxidative addition of a transition metal into the traditionally inert acyl C–X bond (for example, planar amides barrier to rotation 15-20 kcal/mol).[14] Rapid developments in this area involved NHC (N-heterocyclic carbene) ligands[15] that rendered oxidative addition facile owing to much stronger σ-donation than phosphines.[16,17] Furthermore, variable steric bulk around the metal in NHCs facilitated reductive elimination. However, the synthesis of these Pd-NHCs is often challenging, requires multiple steps or strict glovebox techniques. With this in mind, we proposed that Pd-PEPPSI type precatalysts[18] would allow direct access to acyl-Pd intermediates from common esters and amides using simple and readily available reagents and reaction protocols. As a major synthetic advantage, these complexes are easily synthesized on a gram scale in a single, operationally-simple step involving $PdCl_2$, NHC salt, and "throw-away" pyridine ligand.[19] During the cycle, the "throw-away" ligand dissociates to form the active catalyst. Furthermore, in these complexes, Pd and ligand are introduced in the optimal 1:1 ratio, which obviates the use of an excess of the ancillary ligand and significantly simplifies the reaction setup.[10c] Finally, these highly-reactive, air-stable Pd-NHC complexes are modular in nature,[18] which would allow for the rational design of other types of Pd-PEPPSI type complexes bearing diverse pyridine-type "throw-away" ligands.

4.2.2 Reaction optimization

Table 4.2 Optimization of the Pd-catalyzed amination of esters.[a]



4.2

Entry	Catalyst	Base	Solvent	*T* (°C)	Yield (%)[b]
1	**4a**	K_2CO_3	DME	110	>98
2	**4a**	KO*t*-Bu	DME	110	57
3	**4a**	Cs_2CO_3	DME	110	45
4	**4a**	K_3PO_4	DME	110	36
5	**4a**	Na_2CO_3	DME	110	<5
6	**4a**	NaO*t*-Bu	DME	110	<5
7	**4a**	K_2CO_3	THF	110	<5
8	**4a**	K_2CO_3	dioxane	110	<5
9	**4a**	K_2CO_3	toluene	110	<5
10[c]	**4a**	K_2CO_3	DME	110	43
11	**4b**	K_2CO_3	DME	110	96
12	**4c**	K_2CO_3	DME	110	77
13	**4d**	K_2CO_3	DME	110	59
14	**4e**	K_2CO_3	DME	110	26
15[d]	**4a**	K_2CO_3	DME	110	88
16[e]	**4a**	K_2CO_3	DME	110	72

[a]Conditions: ester (1.0 equiv), aniline (2.0 equiv), base (3.0 equiv), [Pd] (3 mol%), solvent (0.25 M), *T*, 16 h. [b]Determined by ^{1}H NMR and GC. [c]H_2O (10 equiv). [d]Aniline (1.2 equiv). [e]Aniline (1.2 equiv), K_2CO_3 (1.2 equiv).

The proposed Buchwald-Hartwig acyl C–O/amination was first optimized in the model reaction between phenyl benzoate and the challenging, extremely sterically-hindered 2,6-dimethylaniline (Table 4.2). We found that the optimized catalyst system using Pd-PEPPSI-IPr (3 mol%), 2,6-dimethylaniline (2.0 equiv), K_2CO_3 (3.0 equiv), DME, 110 °C, affording the desired product in quantitative yield. Importantly, K_2CO_3 proved to be the most efficient base, with Cs_2CO_3 and K_3PO_4 also providing promising results for mildly basic reaction conditions (entries 1-

6).[18] The reaction showed strong dependence on the solvent used with DME providing the best results (entries 7-9). The reaction was sensitive to the presence of excess of water (entry 10).[15e] As anticipated, the reaction showed a strong dependence on the PEPPSI type scaffold (entries 11-14). Interestingly, the pyridine "throw-away" ligand (**4b**) cleanly produced the coupling product (entry 11), while 1-methylimidazole ligand (**4c**) resulted in the less efficient cross-coupling (entry 12). Intriguingly, the use of more bulky PEPPSI-IPent (**4d**)[18c] and less sterically-demanding PEPPSI-IMes (**4e**) gave less efficient coupling (entries 13-14). Finally, we determined that the use of close to stoichiometric amount of base and aniline led to efficient coupling, providing an entry point for future development (entries 15-16). Collectively, these findings suggested that PEPPSI-IPr might serve as the privileged NHC scaffold for the C–O acyl/amination with challenging sterically-hindered anilines; modification of the NHC backbone and "throw-away" ligand within the PEPPSI framework might lead to discovering even more active catalysts.

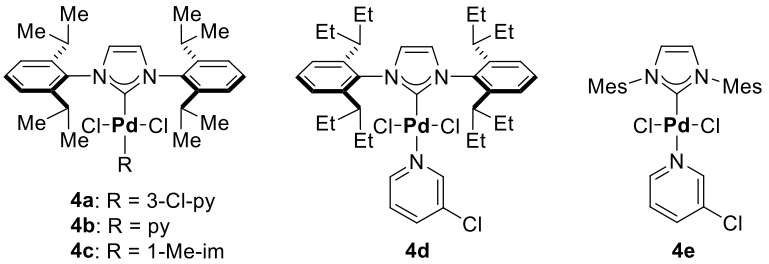


Figure 4.4 Pd-PEPPSI catalysts prepared in a single step.

4.2.3 Scope of the reaction

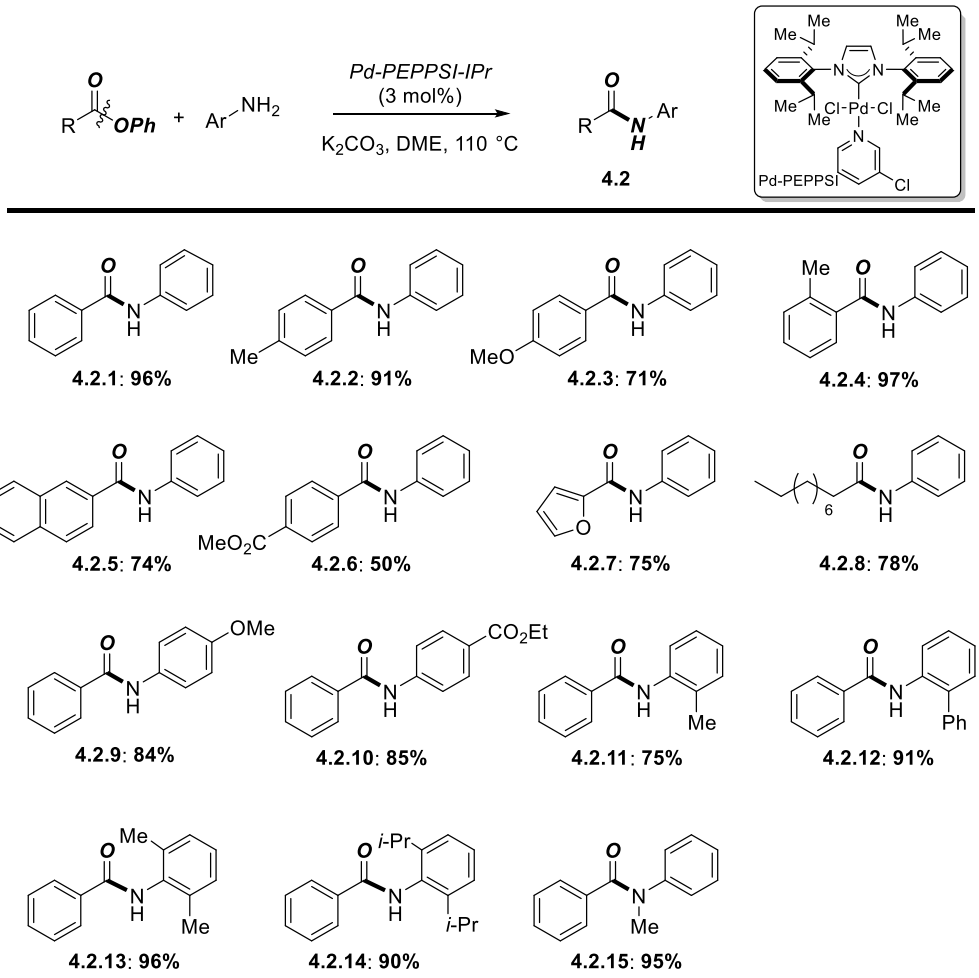


Figure 4.5 Scope of acyl Buchwald-Hartwig cross-coupling of esters.

With the optimized conditions in hand, the generality of the Pd-PEPPSI amination of esters was examined (Figure 4.5). We found that the reaction exhibited broad scope with respect to both the ester and the aryl amine components. Various neutral, electron-rich (**4.2.1**-**4.2.3**), sterically-hindered (**4.2.4**), polyaromatic (**4.2.5**) and electron-withdrawing (**4.2.6**) ester substrates were compatible with this coupling, providing rapid access to diverse amides. Moreover, electron-rich

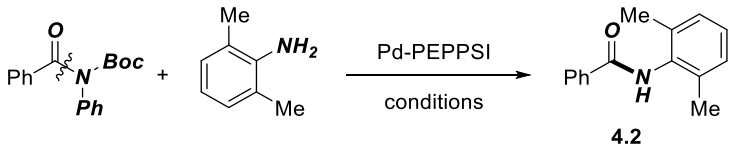
heterocycles conjugated at the deactivating 2-position (**4.2.7**) and aliphatic esters (**4.2.8**) could be selectively cross-coupled. Of particular note was the chemoselectivity for the coupling of phenyl esters in the presence of alkyl counterparts (**4.2.6**, **4.2.10**).

Having developed an efficient protocol for the acyl C–O amination, we then proposed that the high activity of Pd-PEPPSI precatalysts could enable C–N amination of common amides (transamidation) under the same reaction conditions.[2a,b] This process would represent a significant synthetic advantage as it would avoid restriction to a particular acyl metal precursor in the synthesis of aryl amides by a mild cross-coupling approach.[15f] Classic studies by Greenberg demonstrated that rotational barrier in esters is similar to that in resonance destabilized amides (Er = ca. 10 kcal/mol).[20,15f]

We found that Pd-PEPPSI-IPr promoted the desired coupling under the same reaction conditions (Table 4.3), thus providing strong evidence for a common acyl C–X (X = O, N) Buchwald-Hartwig reactivity manifold. Intriguingly, a survey of different PEPPSI-type scaffolds indicated that catalyst (**4b**) bearing pyridine "throw-away" ligand improved the yield (entry 2), which might be due to Pd center being more nucleophilic in this complex to facilitate oxidative addition.[18c] Furthermore, promising results were obtained using 1-methylimidazole-containing catalyst (**4c**) (entry 3) and more bulky PEPPSI-IPent (**4d**) (entry 4), while less sterically-demanding PEPPSI-IMes (**4e**) (entry 5) gave inferior results. Clearly, modifications of the catalyst backbone should result in further enhancement in the

catalytic activity. Note that no reaction was observed using free NHC ligand for both ester and amide (>95% recovery of starting material).

Table 4.3 Optimization of the Pd-catalyzed amination of amides.[a]



4.2

Entry	Catalyst	Base	Solvent	*T* (°C)	Yield (%)[b]
1	**4a**	K_2CO_3	DME	110	71 (>98)
2	**4b**	K_2CO_3	DME	110	82 (96)
3	**4c**	K_2CO_3	DME	110	45 (77)
4	**4d**	K_2CO_3	DME	110	56 (59)
5	**4e**	K_2CO_3	DME	110	21 (26)

[a]Conditions: amide (1.0 equiv), aniline (2.0 equiv), base (3.0 equiv), [Pd] (3 mol%), DME (0.25 M), *T*, 16 h. [b]Determined by ^{1}H NMR and GC. Yield in brackets indicates yield obtained with ester **1a** under identical reaction conditions.

Next, the scope of this coupling was briefly investigated (Figure 4.6A). Importantly, the developed reaction conditions could be directly applied to the coupling of various N-activated amides, including alkyl and aryl N-Boc-carbamates and alkyl and aryl N-sulfonamides (Figure 4.6B). Considering that these N-Boc or N-Ts amides were readily prepared from common secondary amides,[12] this catalytic method complemented classic transamidation techniques of secondary amides, which is traditionally a challenging process on its own.[2a,b]

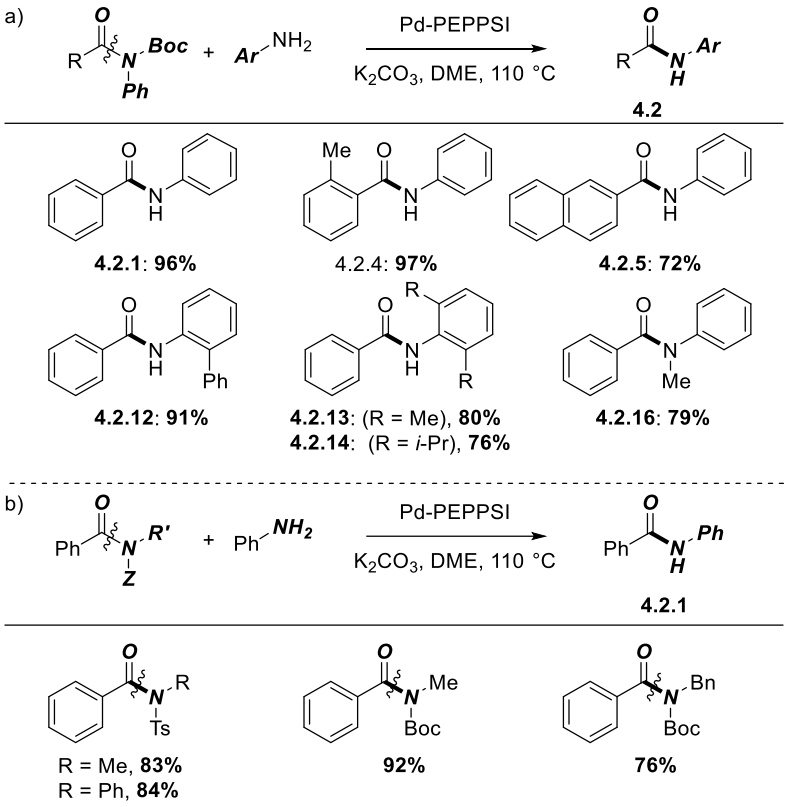


Figure 4.6 Scope of acyl Buchwald-Hartwig cross-coupling of amides.

4.2.4 Mechanistic studies

We conducted several mechanistic studies to gain insight into the reaction mechanism. (1) Kinetic studies showed that reactions using a model ester and amide followed almost identical kinetic profile, consistent with electronic destabilization of the amide and aryl ester bond.[14,15f] (2) A TON of 350 and 320 was obtained in the coupling of esters and amides, respectively, consistent with highly efficient catalysis, and by far exceeding any Pd-phosphine catalyzed acyl-cross-coupling. (3) As expected, an induction period is observed for both ester and amide, consistent with precatalyst activation.[19b] Thus, common acyl cross-coupling

manifold of esters and amides might be much more widely implicated than previously considered in the acyl cross-coupling chemistry.

4.2.5 Conclusion

In summary, we developed the first catalytic Buchwald-Hartwig coupling of both common esters and amides by highly selective C(acyl)-X(X = O, N) cleavage by using well-defined, versatile Pd-PEPPSI precatalysts. This method complemented the classic techniques for amide bond formation and was distinguished by high catalytic reactivity via alternative cross-coupling pathway. Importantly, Pd-PEPPSI precatalysts represented a new general class of catalysts for Buchwald-Hartwig amination of common acyl electrophiles. These well-defined, air- and moisture-stable catalysts were easily prepared in a single, operationally-simple step, providing a modular access to highly reactive catalysts for C–O and C–N acyl amination. Further evaluation of well-defined Pd-NHC precatalysts will lead to general applications of acyl Buchwald-Hartwig cross-coupling in the synthesis of amides.

4.2.6 Experimental Section

General procedure for the Buchwald-Hartwig cross-coupling of esters and amides. An oven-dried vial equipped with a stir bar was charged with an ester or amide substrate (neat, 1.0 equiv), potassium carbonate (typically, 3.0 equiv), amine (typically, 2.0 equiv), PEPPSI-IPr (typically, 3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 1,2-Dimethoxyethane (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath and stirred for an indicated time. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the tile product.

A) Buchwald-Hartwig cross-coupling of esters

4.2.1, 96%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.86 (d, *J* = 7.4 Hz, 2 H), 7.65 (d, *J* = 8.0 Hz, 2 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.35 (t, *J* = 7.9 Hz, 2 H), 7.15 (t, *J* = 7.4 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.97, 138.06, 135.09, 131.91, 129.17, 128.85, 127.16, 124.66, 120.40.

4.2.2, 91%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 8.0 Hz, 2 H), 7.34 (t, *J* = 7.8 Hz, 2 H), 7.24 (d, *J* = 7.8 Hz, 2 H), 7.13 (t,

J = 7.4 Hz, 1 H), 2.41 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.89, 142.39, 138.18, 132.19, 129.47, 129.12, 127.17, 124.49, 120.35, 21.59.

4.2.3, 71%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.7 Hz, 2 H), 7.73 (s, 1 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 7.37 (t, *J* = 7.8 Hz, 2 H), 7.14 (t, *J* = 7.4 Hz, 1 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 3.88 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.64, 138.24, 129.22, 129.01, 124.48, 120.25, 114.14, 55.62.

4.2.4, 97%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 7.43 (d, *J* = 7.2 Hz, 1 H), 7.35 (t, *J* = 7.8 Hz, 3 H), 7.23 (dd, *J* = 16.5, 7.7 Hz, 2 H), 7.15 (t, *J* = 7.4 Hz, 1 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.26, 138.11, 136.51, 136.45, 131.28, 130.30, 129.14, 126.73, 125.93, 124.59, 120.01, 19.88.

4.2.5, 74%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 8.01-7.93 (m, 4 H), 7.91 (d, *J* = 7.8 Hz, 1 H), 7.70 (d, *J* = 7.9 Hz, 2 H), 7.63-7.56 (m, 2 H), 7.41 (t, *J* = 7.9 Hz, 2 H), 7.18 (t, *J* = 7.4 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.90, 138.12, 135.00, 132.75, 129.28, 129.10, 128.92, 128.06, 127.96, 127.65, 127.10, 124.75, 123.67, 120.35.

4.2.6, 50%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.1 Hz, 2 H), 7.93 (d, *J* = 8.1 Hz, 2 H), 7.86 (s, 1 H), 7.65 (d, *J* = 8.0 Hz, 2 H), 7.39 (t, *J* = 7.8 Hz, 2 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 3.96 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.33, 139.00, 137.70, 133.18, 130.19, 129.32, 127.22, 125.08, 125.08, 120.40, 52.6.

4.2.7, 75%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.65 (d, *J* = 7.7 Hz, 2 H), 7.55-7.48 (m, 1 H), 7.37 (t, *J* = 7.9 Hz, 2 H), 7.24 (d, *J* = 3.4 Hz, 1 H), 7.15 (t, *J* =

7.4 Hz, 1 H), 6.56 (dd, *J* = 3.5, 1.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.19, 147.94, 144.29, 137.48, 129.25, 124.66, 120.04, 115.41, 112.77.

4.2.8, 78%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 2 H), 7.31 (t, *J* = 7.9 Hz, 2 H), 7.23 (s, 1 H), 7.09 (t, *J* = 7.4 Hz, 1 H), 2.35 (t, *J* = 7.6 Hz, 2 H), 1.72 (p, *J* = 7.5 Hz, 2 H), 1.38-1.23 (m, 13 H), 0.88 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.60, 138.10, 129.09, 124.27, 119.90, 37.99, 31.99, 29.57, 29.52, 29.40, 25.78, 22.79, 14.24.

4.2.9, 84%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 3 H), 7.55 (t, *J* = 7.2 Hz, 3 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 3.82 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.78, 156.74, 135.15, 131.80, 131.13, 128.85, 127.11, 122.26, 114.35, 55.63.

4.2.10, 85%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 8.02 (d, *J* = 8.3 Hz, 2 H), 7.86 (d, *J* = 7.8 Hz, 2 H), 7.75 (d, *J* = 8.3 Hz, 2 H), 7.54 (t, *J* = 7.2 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 1.38 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.10, 142.28, 134.63, 132.25, 130.90, 128.92, 127.24, 119.36, 61.03, 14.46.

4.2.11, 75%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 1 H), 7.89 (d, *J* = 7.6 Hz, 2 H), 7.68 (s, 1 H), 7.57 (t, *J* = 7.1 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 2 H), 7.28-7.23 (m, 2 H), 7.13 (t, *J* = 7.4 Hz, 1 H), 2.34 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.77, 135.90, 131.98, 130.69, 129.32, 128.97, 127.17, 127.05, 125.49, 123.22, 17.98.

4.2.12, 91%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.2 Hz, 1 H), 8.01 (s, 1 H), 7.61 (d, *J* = 7.9 Hz, 2 H), 7.55-7.51 (m, 2 H), 7.46 (q, *J* = 9.8, 8.4 Hz, 5 H), 7.40 (t,

J = 7.6 Hz, 2 H), 7.32 (d, *J* = 7.4 Hz, 1 H), 7.23 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.08, 138.19, 135.06, 134.92, 132.44, 131.85, 130.12, 129.49, 129.36, 128.87, 128.74, 128.32, 126.93, 124.48, 121.24.

4.2.13, 96%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 2 H), 7.58 (t, *J* = 7.3 Hz, 1 H), 7.50 (t, *J* = 7.4 Hz, 3 H), 7.14 (q, *J* = 5.5 Hz, 3 H), 2.29 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.10, 135.72, 134.58, 133.98, 131.92, 128.88, 128.40, 127.57, 127.33, 18.60.

4.2.14, 90%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.4 Hz, 2 H), 7.59 (t, *J* = 7.3 Hz, 1 H), 7.52 (t, *J* = 7.5 Hz, 2 H), 7.37 (dd, *J* = 13.8, 5.5 Hz, 2 H), 7.24 (d, *J* = 7.7 Hz, 2 H), 3.16 (hept, *J* = 6.7 Hz, 2 H), 1.24 (d, *J* = 6.7 Hz, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.06, 146.51, 134.75, 131.90, 131.27, 128.94, 128.63, 127.31, 123.69, 29.05, 23.79.

4.2.15, 95%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.3, 1.3 Hz, 2 H), 7.26-7.20 (m, 3 H), 7.16 (t, *J* = 6.8 Hz, 2 H), 7.13 (t, *J* = 6.3 Hz, 1 H), 7.04 (d, *J* = 7.5 Hz, 2 H), 3.51 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.75, 145.00, 136.01, 129.66, 129.22, 128.79, 127.80, 126.99, 126.56, 38.48.

B) Buchwald-Hartwig cross-coupling of amides

4.2.1', 96%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.86 (d, *J* = 7.4 Hz, 2 H), 7.65 (d, *J* = 8.0 Hz, 2 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.35 (t,

J = 7.9 Hz, 2 H), 7.15 (t, *J* = 7.4 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.97, 138.06, 135.09, 131.91, 129.17, 128.85, 127.16, 124.66, 120.40.

4.2.4, 97%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 7.43 (d, *J* = 7.2 Hz, 1 H), 7.35 (t, *J* = 7.8 Hz, 3 H), 7.23 (dd, *J* = 16.5, 7.7 Hz, 2 H), 7.15 (t, *J* = 7.4 Hz, 1 H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.26, 138.11, 136.51, 136.45, 131.28, 130.30, 129.14, 126.73, 125.93, 124.59, 120.01, 19.88.

4.2.5, 72%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 8.01-7.93 (m, 4 H), 7.91 (d, *J* = 7.8 Hz, 1 H), 7.70 (d, *J* = 7.9 Hz, 2 H), 7.63-7.56 (m, 2 H), 7.41 (t, *J* = 7.9 Hz, 2 H), 7.18 (t, *J* = 7.4 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.90, 138.12, 135.00, 132.75, 129.28, 129.10, 128.92, 128.06, 127.96, 127.65, 127.10, 124.75, 123.67, 120.35.

4.2.12, 91%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.2 Hz, 1 H), 8.01 (s, 1 H), 7.61 (d, *J* = 7.9 Hz, 2 H), 7.55-7.51 (m, 2 H), 7.46 (q, *J* = 9.8, 8.4 Hz, 5 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.32 (d, *J* = 7.4 Hz, 1 H), 7.23 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.08, 138.19, 135.06, 134.92, 132.44, 131.85, 130.12, 129.49, 129.36, 128.87, 128.74, 128.32, 126.93, 124.48, 121.24.

4.2.13, 80%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 2 H), 7.58 (t, *J* = 7.3 Hz, 1 H), 7.50 (t, *J* = 7.4 Hz, 3 H), 7.14 (q, *J* = 5.5 Hz, 3 H), 2.29 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.10, 135.72, 134.58, 133.98, 131.92, 128.88, 128.40, 127.57, 127.33, 18.60.

4.2.14, 76%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.4 Hz, 2 H), 7.59 (t, *J* = 7.3 Hz, 1 H), 7.52 (t, *J* = 7.5 Hz, 2 H), 7.37 (dd, *J* = 13.8, 5.5 Hz, 2 H), 7.24 (d, *J* =

7.7 Hz, 2 H), 3.16 (hept, *J* = 6.7 Hz, 2 H), 1.24 (d, *J* = 6.7 Hz, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.06, 146.51, 134.75, 131.90, 131.27, 128.94, 128.63, 127.31, 123.69, 29.05, 23.79.

4.2.16, 79%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.3, 1.3 Hz, 2 H), 7.26-7.20 (m, 3 H), 7.16 (t, *J* = 6.8 Hz, 2 H), 7.13 (t, *J* = 6.3 Hz, 1 H), 7.04 (d, *J* = 7.5 Hz, 2 H), 3.51 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.75, 145.00, 136.01, 129.66, 129.22, 128.79, 127.80, 126.99, 126.56, 38.48.

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4.3 Pd-NHC catalyzed acyl Suzuki cross-coupling of triflamides

Parts of this section were adapted with permission from the article: "Triflamides: Highly Reactive, Electronically Activated N-Sulfonyl Amides in Catalytic N–C(O) Amide Cross-Coupling" (*Org. Lett.* **2019**, *21*, 1253). Copyright ©2019, American Chemical Society.

4.3.1 Introduction

As outlined in this thesis, the recent years have witnessed extraordinary progress in metal-catalyzed cross-couplings of amides by selective metal insertion into the inert N–C(O) bond (Figure 4.8A).[1–3] The capacity of the amide bond to control resonance ($n_N \rightarrow \pi^*_{C=O}$ donation, barrier to rotation, planar amides = 15-20 kcal/mol),[4,5] and therefore facility of metal insertion through N-substitution has led to significant interest as a way to develop mild catalytic methods exploiting activation of N–C(O) bonds.[6–13] Given the ubiquity of amide bonds in drugs, polymers and functional materials, new selective methods for functionalization of amides have been shown to offer great opportunities for organic synthesis in both academic and industrial settings.[14]

At the time of this project, most of the successful approaches in cross-coupling of amides utilized N-Ts (Ts = 4-toluenesulfonyl) as an activating group enabling metal insertion into the N–C(O) bond.[2,6–13] Harnessing N-Ts amides has been possible through resonance destabilization of the acyl amide bond (Ar = Ph, R = Ph, RE = 9.7 kcal/mol; τ = 18.8°; χ_N = 18.9°, RE = resonance energy).[5a] In this context, we were attracted by the trifluoromethanesulfonyl group as one of the most powerful electron-withdrawing groups

in organic chemistry.[15] Taking inspiration from our experience in amide bond destabilization,[5] we envisioned that N-Tf (Tf = triflyl) could be employed as a viable activating group for amides, wherein the electron-withdrawing effect would have a two-fold positive effect by (1) facilitating metal insertion,[16] and (2) enhancing the leaving group potential,[15a] thus permitting cross-coupling under mild conditions.

We developed the direct, highly chemoselective Suzuki-Miyaura cross-coupling of trifluoromethanesulfonamides (triflamides) by selective N–C(O) amide bond cleavage (Figure 4.8B). Most importantly, our study introduced triflamides as highly reactive, bench-stable, inexpensive N-sulfonyl amides for catalytic cross-couplings by selective N–C(O) bond activation. Our data strongly suggested that triflamides should be routinely considered as among the most reactive amide bond precursors in the field of amide bond cross-coupling.[2,6–13]

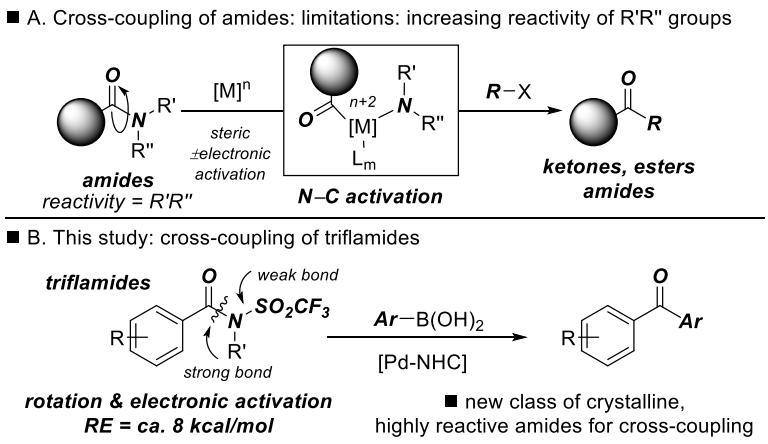

Figure 4.8 (a) Activation of amides and derivatives. (b) Triflamides: new class of highly reactive amides for cross-coupling.

4.3.2 Reaction optimization

Our study began with the examination of the Suzuki-Miyaura cross-coupling of a model N-Tf amide with 4-tolyl boronic acid using various Pd(II)-NHC (NHC = N-heterocyclic carbene) precatalysts (Figure 4.9). There were two main challenges in catalytic activation of amides: (1) selective metal insertion into the N-acyl bond; (2) undesired cleavage of the N-sulfonyl group, deactivating the amide towards insertion.[2a,b] In addition, the stability of acyl-metal intermediate contributed to the efficiency of the cross-coupling. We realized that the use of bench-, air- and moisture-stable strongly σ-donating Pd(II)-NHC precatalysts provided a productive avenue for the synthesis of acyl-metal intermediates from amides.[17] After extensive optimization, we found that the cross-coupling of a model N-Tf amide proceeded under exceedingly mild conditions at 40 °C (eq. 1, [Pd(IPr)(L)Cl] (3 mol%), K_2CO_3 (3 equiv), water (5 equiv), THF, 15 h). Importantly, the high reactivity was observed using Pd-NHC precatalysts bearing various throw-away ligands (Pd-PEPPSI-IPr, 95%; Pd(IPr)(cin)Cl, 94%, Pd(IPr)(1-*t*-Bu-indenyl)Cl, 95%, Figure 4.9),[18] highlighting the aptitude of the N-Tf activating group as the acyl-metal precursor.[16] The observed reactivity of N-Tf amides compared very favorably with the state-of-the-art, namely, the cross-coupling of N-Ts amides, which proceeded at 30% conversion under the same conditions.[6g] Two additional points were noted. (1) The cross-coupling of proceeded in 33%, 38% and 79% yields at 23 °C using Pd-PEPPSI-IPr, Pd(IPr)(cin)Cl, and Pd(IPr)(1-*t*-Bu-indenyl)Cl. (2) Water had only a minor effect on the cross-coupling efficiency (Pd-PEPPSI-IPr, 40 °C, 88% yield),[19] consistent with facile N–C insertion. While all three catalysts (Figure 4.9) served as

excellent throw-away ligands, Pd-PEPPSI was selected for further studies due to ease of synthesis, broad accessibility, low price, and versatility of this class of Pd-NHC precatalysts.[17]

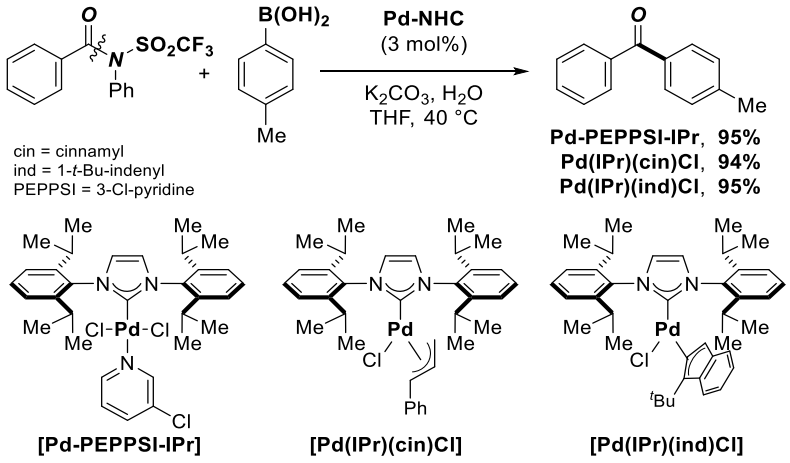

Figure 4.9 Pd-NHCs in acyl Suzuki cross-coupling of triflamides.

4.3.3 Scope of the reaction

Having identified optimal conditions for the cross-coupling of N-Tf amides, we next investigated the scope of this method (Figure 4.10). As shown, a variety of N-Tf amides and aryl boronic acids were successful cross-coupling under exceedingly mild conditions. Neutral- (**4.3.1**-**4.3.2**), sterically-hindered (**4.3.3**), electron-donating (**4.3.4**) and electron-withdrawing (**4.3.5**) groups were well-tolerated on the boronic acid component without any modification of the reaction conditions. The scope of the amide component was equally broad and accommodated electron-neutral (**4.3.2'**), electron-donating (**4.3.4'**), electron-withdrawing (**4.3.6'**) and sterically-hindered (**4.3.3'**) amides, delivering the cross-coupling products in high to excellent yields. Furthermore, this protocol could be

used to readily assemble heterocyclic ketones (**4.3.8**, **4.3.9**, **4.3.11**), albeit in some cases higher temperature was required (**4.3.9**).

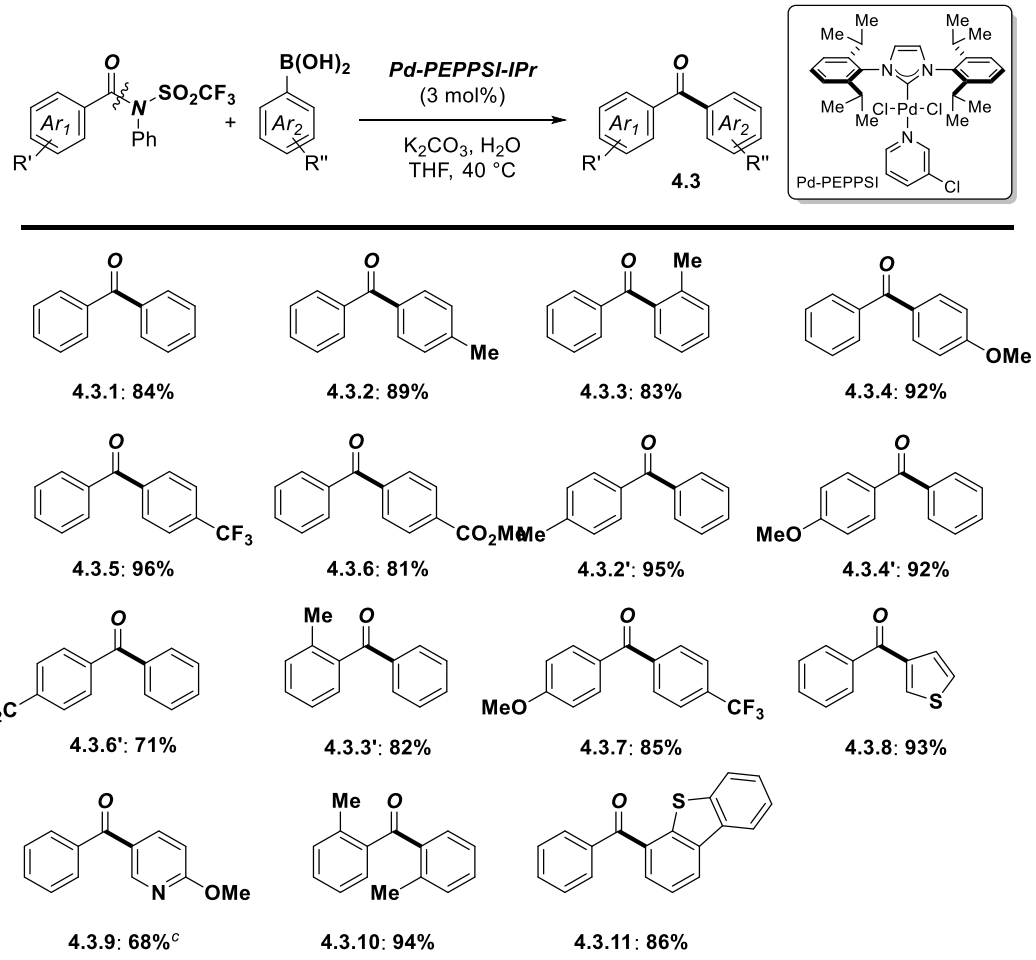

Figure 4.10 Substrate scope.

Nevertheless, we noted that the formation of **4.3.9** failed using N-Ts amide, highlighting the benefits of triflamide activation. As a testament to the high efficiency of N-Tf as the activating group, we demonstrated high facility in the cross-coupling to form a notoriously difficult doubly deactivated ketone **4.3.7**, wherein both the amide electrophile and boronic acid are electronically-disfavored towards the coupling[17] as well as in the

synthesis of bis-sterically-hindered di-*o*-tolylmethanone **4.3.10**. The use of N-Ts amide led to low conversion in both cases. Collectively, the examined examples showed that N-Tf amides permit a broad scope in the direct synthesis of ketones from amides, presenting a powerful alternative to the venerable Weinreb amides[20] with superior functional group tolerance towards electrophilic functional groups.

4.3.4 Additional studies

Given the high catalytic activity of N-Tf amides, we became interested in determining turnover number in the cross-coupling (Figure 4.11).[17] The cross-coupling proceeded with TON of 550-780 at 0.10 mol% loading at 110 °C using Pd-PEPPSI-IPr, Pd(IPr)(cin)Cl, and Pd(IPr)(1-*t*-Bu-indenyl)Cl, respectively. Furthermore, TON of 1150 was observed at 0.05 mol% loading using Pd-PEPPSI-IPr, attesting to the high catalytic efficiency of triflamides as acyl-metal precursors in amide N–C(O) cross-coupling.

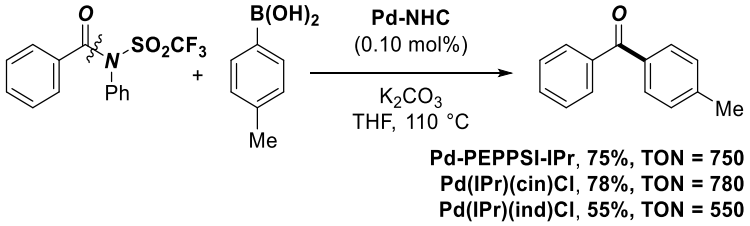

Figure 4.11 Determination of TON in the Cross-Coupling of Triflamides.

Several additional results were obtained: (1) The use of N-Tf activating group could be utilized in the cross-coupling of N-aliphatic amides (Figure 4.12A). (2) We demonstrated that the use of Pd-phosphane catalytic systems was also suitable for the coupling of Pd-N-Tf amides (Figure 4.12B), providing an alternative to Pd-NHC. (3) Perhaps most

interestingly, N-Tf amides served as efficient precursors in both Pd- and Ni-catalyzed Negishi cross-coupling (Figure 4.12C). This was the first example of an acyl-aryl Negishi cross-coupling of simple N-sulfonyl amides. Thus, we concluded that the high reactivity of N-Tf amides might facilitate the development of a range of synthetic methods by selective N–C(O) cleavage that are now unavailable to other amide precursors.

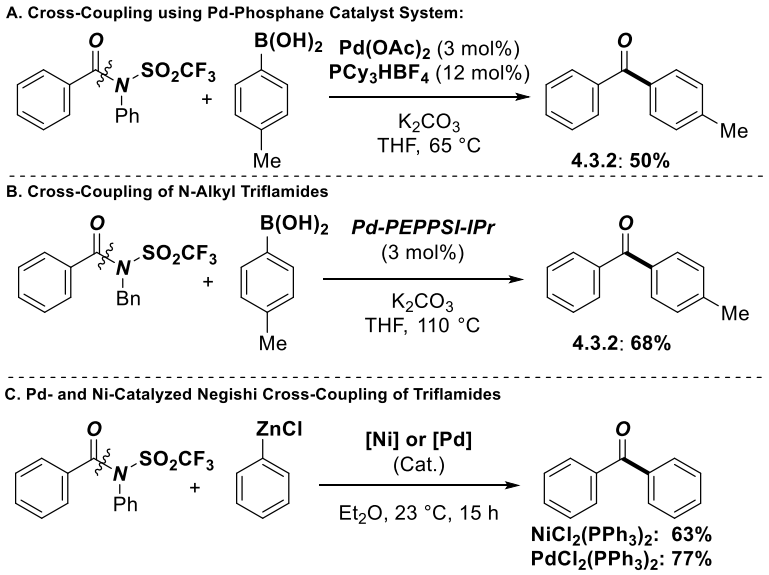

Figure 4.12 Additional studies in cross-coupling of triflamides.

4.3.5 Conclusion

In summary, we developed the first Suzuki-Miyaura cross-coupling of trifluoromethanesulfonamides (triflamides) by highly selective N–C(O) amide bond cleavage. Most crucially, this method introduced N-Tf amides as novel amide bond precursors that favor metal insertion under exceedingly mild conditions. The method enabled the catalytic synthesis of ketones as an attractive alternative to Weinreb amides. We also demonstrated the first example of acyl-aryl Negishi cross-coupling using simple

N-acyclic amides. The key to the high reactivity of N-Tf amides is the powerful electron-withdrawing effect of the triflyl group. Our results strongly suggested that triflamides should be routinely considered as amide bond precursors in the manifold of amide bond cross-coupling.

4.3.6 Experimental Section

General procedure for the Suzuki-Miyaura cross-coupling. An oven-dried vial equipped with a stir bar was charged with a triflamide substrate (neat, 1.0 equiv), potassium carbonate (typically, 3.0 equiv), boronic acid (typically, 2.0 equiv), Pd-NHC precatalyst (typically, 3 mol%) and H_2O (typically, 5.0 equiv), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 40 °C and stirred for the indicated time. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. A sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and/or GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

General procedure for the Ni or Pd-catalyzed Negishi cross-coupling. An oven-dried vial equipped with a stir bar was charged with a triflamide substrate (neat, 1.0 equiv) and $NiCl_2(PPh_3)_2$ (10 mol%) or $PdCl_2(PPh_3)_2$ (5 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Diethyl ether (typically, 0.20 M) was added and the solution was stirred for 5 min, followed by rapid injection of an arylzinc reagent (THF solution, typically, 1.5 equiv) with vigorous stirring and the reaction mixture was stirred for the indicated time at room temperature. After the indicated time, the reaction mixture was quenched with HCl (0.1 *N*, 10 mL), extracted with EtOAc (3 x 20 mL), the organic layers were combined, dried, and

concentrated. A sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and/or GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

4.3.1, 84%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 4 H), 7.59 (t, *J* = 7.5 Hz, 2 H), 7.49 (t, *J* = 7.5 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.85, 137.78, 132.53, 130.19, 128.41.

4.3.2, 89 %. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 2.44 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.65, 143.37, 138.09, 135.01, 132.29, 130.44, 130.07, 129.11, 128.34, 21.80.

4.3.3, 83%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 2 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 7.42 (t, *J* = 7.5 Hz, 1 H), 7.33 (d, *J* = 9.0 Hz, 2 H), 7.28 (d, *J* = 6.5 Hz, 2 H), 2.39 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.77, 138.75, 137.87, 136.87, 133.25, 131.12, 130.36, 130.25, 128.64, 128.58, 125.32, 20.12.

4.3.4, 92%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2 H), 7.76 (d, *J* = 7.5 Hz, 2 H), 7.56 (t, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 2 H), 6.97 (d, *J* = 8.0 Hz, 2 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.70, 163.33, 138.40, 132.67, 132.00, 130.27, 129.84, 128.30, 113.66, 55.61.

4.3.5, 96%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2 H), 7.81 (d, *J* = 7.0 Hz, 2 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.63 (t, *J* = 7.5 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.67, 140.86, 136.86, 133.86 (q, J^F = 32.5 Hz), 133.23, 130.27, 130.24, 128.67, 125.48 (q, J^F = 3.9 Hz), 123.81 (q, J^F = 271.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.04.

4.3.6, 81%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 2 H), 7.84 (d, *J* = 8.0 Hz, 2 H), 7.80 (d, *J* = 8.0 Hz, 2 H), 7.62 (t, *J* = 7.5 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 2 H), 3.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.17, 166.45, 141.45, 137.08, 133.35, 133.08, 130.24, 129.91, 129.63, 128.60, 52.61.

4.3.2b', 95%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 2.44 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.65, 143.37, 138.09, 135.01, 132.29, 130.44, 130.07, 129.11, 128.34, 21.80.

4.3.4', 92%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2 H), 7.76 (d, *J* = 7.5 Hz, 2 H), 7.56 (t, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 2 H), 6.97 (d, *J* = 8.0 Hz, 2 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.70, 163.33, 138.40, 132.67, 132.00, 130.27, 129.84, 128.30, 113.66, 55.61.

4.3.6', 71%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 2 H), 7.85 (d, *J* = 8.0 Hz, 2 H), 7.81 (d, *J* = 8.0 Hz, 2 H), 7.63 (t, *J* = 7.5 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 3.98 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.17, 166.45, 141.45, 137.08, 133.35, 133.08, 130.24, 129.91, 129.63, 128.60, 52.61.

4.3.3c', 82%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 2 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 7.42 (t, *J* = 7.5 Hz, 1 H), 7.33 (d, *J* = 9.0 Hz, 2 H), 7.28 (d, *J* = 6.5 Hz, 2 H), 2.39 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.77, 138.75, 137.87, 136.87, 133.25, 131.12, 130.36, 130.25, 128.64, 128.58, 125.32, 20.12.

4.3.7, 85%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (t, *J* = 9.2 Hz, 4 H), 7.74 (d, *J* = 8.0 Hz, 2 H), 6.98 (d, *J* = 9.0 Hz, 2 H), 3.90 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.39, 163.85, 141.64, 133.38 (q, J^F = 32.5 Hz), 132.76, 129.91, 129.48, 125.78 (q, J^F = 3.8 Hz), 123.86 (q, J^F = 217.5 Hz), 113.94, 55.70. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.96.

4.3.8, 93%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 3.0, 1.1 Hz, 1 H), 7.87 (d, *J* = 8.5 Hz, 2 H), 7.65-7.59 (m, 2 H), 7.52 (t, *J* = 7.5 Hz, 2 H), 7.41 (dd, *J* = 5.0, 3.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.13, 141.49, 138.82, 134.00, 132.43, 129.51, 128.77, 128.52, 126.32.

4.3.9, 68%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1 H), 8.10 (d, *J* = 8.6 Hz, 1 H), 7.78 (d, *J* = 6.7 Hz, 2 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.49 (t, *J* = 7.3 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 1 H), 4.02 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.34, 166.61, 150.96, 140.15, 137.71, 132.63, 129.85, 128.58, 127.09, 111.18, 54.20.

4.3.10, 94%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.5 Hz, 2 H), 7.31 (d, *J* = 7.5 Hz, 2 H), 7.28 (d, *J* = 7.6 Hz, 2 H), 7.20 (t, *J* = 7.5 Hz, 2 H), 2.44 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.91, 139.14, 138.29, 131.55, 131.19, 130.42, 125.54, 20.78.

4.3.11, 86%. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45-8.41 (m, 1 H), 8.24 (dd, *J* = 6.2, 2.3 Hz, 1 H), 7.98 (dd, *J* = 6.2, 2.2 Hz, 1 H), 7.93 (d, *J* = 6.7 Hz, 1 H), 7.82 (d, *J* = 7.1 Hz, 2 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.59-7.50 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.99, 142.01, 141.00, 138.34, 137.58, 134.19, 132.10, 131.79, 130.48, 129.84, 128.51, 127.41, 125.95, 124.72, 123.86, 123.02, 121.61.

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Chapter 5

Conclusion

The main focus of the thesis was on employing amides as electrophiles in metal-catalyzed cross-coupling reactions through selective activation of the amide bond N–C(O) via acyl and decarbonylative mechanism, and the development of new robust catalytic systems for amide N–C(O) and ester O–C(O) bond activation. The main achievements of thesis are summarized below:

(1) Decarbonylative cross-couplings: we developed the first Ni-catalyzed decarbonylative Suzuki cross-coupling of amides using N-acylglutarimides, which we identified as the most reactive amide-based aryl electrophiles. We developed Pd-catalyzed catalyzed decarbonylative cyanation and borylation of amides to give synthetic valuable aryl nitriles and boronic esters.

(2) Acyl Negishi cross-couplings: we developed the first example of Ni-catalyzed acyl–aryl Negishi cross-coupling of amides, which was distinguished by operationally-simple and mild conditions. We demonstrated that primary amides can be used as electrophiles in acyl Negishi cross-coupling after N-selective di-Boc activation. We developed N-acyl-succinimides as highly reactive acyl transfer reagents.

(3) Development of Pd(II)-NHC catalytic systems: we developed general conditions for acyl Suzuki cross-coupling of esters by implementation of well-defined, air- and moisture-stable Pd(II)-NHC precatalysts. We developed general catalytic conditions for acyl Buchwald-Hartwig cross-coupling of esters and amides to synthesize amides by Pd-

catalyzed O–C and N–C disconnection. We developed triflamides as highly reactive N-sulfonyl amides in acyl Suzuki cross-coupling.

Overall, our research on selective N–C(O) activation of the amide bond has contributed to (1) the development of novel transformations of amides as cross-coupling partners, (2) the rational design of novel amide precursors, and (3) the discovery of robust catalytic systems for amide bond activation.