DEVELOPMENT OF NEW METHODS FOR ACYL C-O AND C-N CROSS-COUPLING

By

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A dissertation submitted to the

Graduate School–Newark

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Doctor of Philosophy

Graduate Program in Chemistry

Written under the direction of

Professor Michal Szostak

And approved by

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Newark, New Jersey

October, 2020

ABSTRACT OF THE DISSERTATION

DEVELOPMENT OF NEW METHODS FOR ACYL C-O AND C-N CROSS-COUPLING

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Dissertation Director:

Professor Michal Szostak

Amide and ester bonds are ubiquitous in organic synthesis, polymers, and drug discovery; therefore the development of catalytic amide and ester bond cross-coupling reactions is of broad interest to selectively functionalize organic molecules. The use of amides and esters as acyl transfer reagents has been a burgeoning area in organic chemistry and the main challenge remains the development of new methods to selectively activate amide and ester bonds.

This thesis describes our studies on: (1) the development of novel transition-metal-catalyzed transformations of amides and esters by X–C(O) (X = NR_2, OR) activation; (2) the development of new amide and ester precursors for cross-coupling reactions; (3) the development of new, robust catalytic systems for acyl-cross-coupling reactions of amides and esters.

Specifically, this thesis addresses the development of pentafluorophenyl esters as highly selective acylating reagents for the Suzuki-Miyaura cross-coupling using Pd-phosphine catalysis. Then, the development of twisted *N*-acyl-phthalimides and electronically-activated *N*-acyl-carbazoles and *N*-acyl-indoles by N_{lp} to Ar delocalization using Pd–NHC catalyst systems for acyl cross-coupling is described. Finally, the development of cross-coupling of various amides using well-defined, air- and moisture-stable Ni–NHC complexes is described.

Acknowledgements

First of all, to my advisor, Dr. Michal Szostak**,** I have gained a lot from his supervision, support, and encouragement during my Ph.D. study. Michal is a great mentor and a brilliant chemist. I have learned not only the skills to perform research efficiently but have now also the tools to evaluate and develop new chemistry. The future achievements of my career will partly be attributed to what he helped me accomplish during my time at Rutgers, thank you very much.

I want to thank Prof. Frieder Jaekle, Prof. Phil Huskey and Prof. Enver Izgu for serving as my committee members.

The help from Dr. Lazaros Kakalis on NMR and the help from Dr. Roman Brukh on GC-MS and HRMS is greatly appreciated. Thanks to Maria and Paul for helping our group maintain all the chemicals and solvents needed for our research. Also, thank you to everyone else in the department that has helped me along the way.

I want to thank all the past and present members of Szostak's group. I was fortunate to be a part of such a talented and hardworking group. Specifically, thank you to Guangrong Meng, Rahman Mahbubur, Shicheng Shi, Chengwei Liu, Guangchen Li, Tongliang Zhou, Pengcheng Gao, Dr. Qun Zhao, Dr. Qinqin Xia, Dr. Jin Zhang. I wish you all the best. Also, Special thanks to Rahman Mahbubur for helping expidite some of the testing.

Finally, thank you to my family. You have shown me to pursue a life well-lived, and I love you for who you are.

List of Tables

Chapter 1

Introduction

Parts of this section were adapted with permission from the article: "Recent Advances in Acyl Suzuki Cross-Coupling" (*Catalysts* **2019**, *9*, 53). Copyright ©2019, MDPI.

1.1. Acyl Suzuki-Miyaura Cross-Coupling

The Suzuki cross-coupling represents the most powerful C–C bond forming reaction in organic synthesis.[1] Traditional Suzuki cross-coupling (also referred to as Suzuki–Miyaura cross-coupling) involves the coupling of an organoboron reagent with an aryl halide or pseudohalide and is most commonly employed for the synthesis of biaryls by a $C(sp^2)$–$C(sp^2)$ disconnection using a palladium or nickel catalyst (Figure 1.1A).[2,3] Since the initial report in 1979, many variants of the Suzuki cross-coupling have been discovered, including acyl cross-couplings.[4] The ability to systematically apply the cross-coupling of organoboron reagents with high predictability, operational-simplicity, and superb functional group tolerance has contributed to the overwhelming success that this reaction enjoys as the key part of the modern chemistry toolbox. The 2010 Nobel Prize in Chemistry is a fitting testament of its impact.[5]

Acyl Suzuki cross-coupling involves the coupling of an organoboron reagent with an acyl electrophile (acyl halide, anhydride, ester, amide) (Figure 1.1B), and in parallel to the biaryl counterpart typically proceeds by a $C(acyl)$–$C(sp^2)$ disconnection (Figure 1.2).[6,7] Since its first discovery in 1999, acylative Suzuki cross-coupling has been established as a new and useful technique for the synthesis of ketones. However, in contrast to the traditional Suzuki cross-coupling, the acylative Suzuki cross-coupling has been much less

developed. While this trend is not surprising given the paucity of methods for the synthesis of biaryls other than cross-couplings,[2,3] the acylative manifold provides a powerful arsenal of catalytic methods for the C–C bond construction at the acyl group with selectivity, precision and functional group tolerance superseding traditional disconnections.

A: *Aryl* Suzuki-Miyaura Cross-Coupling: $C(sp^2)$–$C(sp^2)$ cross-coupling
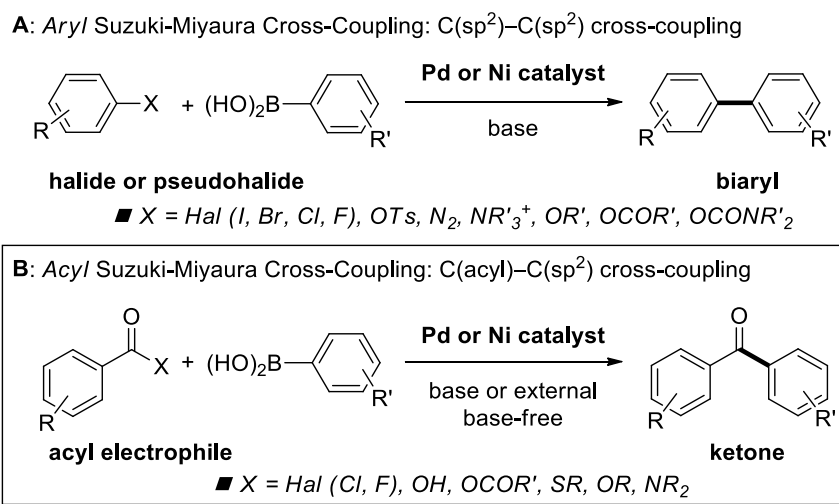
Figure 1.1. Aryl and Acyl Suzuki-Miyaura Cross-Coupling.
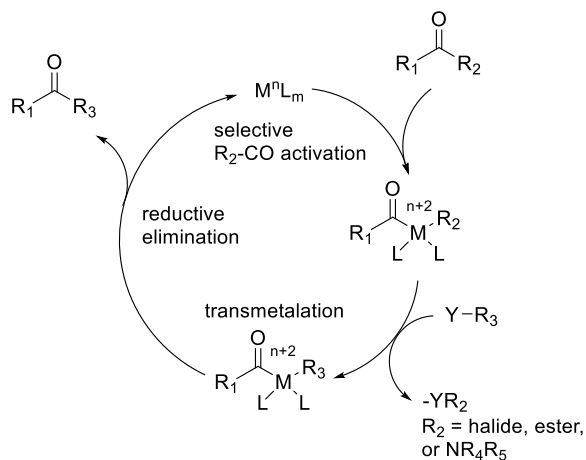
Figure 1.2. Acyl Suzuki-Miyaura Cross-Coupling Mechanism.

This chapter of the thesis provides an introduction to the important advances that have taken place in the acyl Suzuki cross-coupling. Particular emphasis is directed toward the

type of acyl electrophiles, catalyst systems and new cross-coupling partners used. The chapter is organized by a type of electrophile undergoing cross-coupling in the order of their electrophilic reactivity, namely acyl halides, anhydrides, carboxylic acids, esters, and amides.[13]

1.2. Suzuki Cross-Coupling of Acyl Halides

In 1999, Bumagin developed a phosphine-free palladium-catalyzed cross-coupling of boronic acids with acyl chlorides (Scheme 1.1A).[14] The biaryl products were generated in high yields under mild, room temperature conditions using water as the key additive. Independently, also in 1999, Haddach discovered an anhydrous Suzuki cross-coupling of acyl chlorides (Scheme 1.1B).[15] It is important to note that these anhydrous conditions were possible due to the combined use of cesium carbonate and Pd(PPh$_3$)$_4$ in refluxing toluene. Both Bumagin's and Haddach's protocols established important precedents in giving practical alternatives to direct acyl additions of organomagnesium or organolithium reagents or the use of less available organozincs or toxic organostannanes.[9,10]
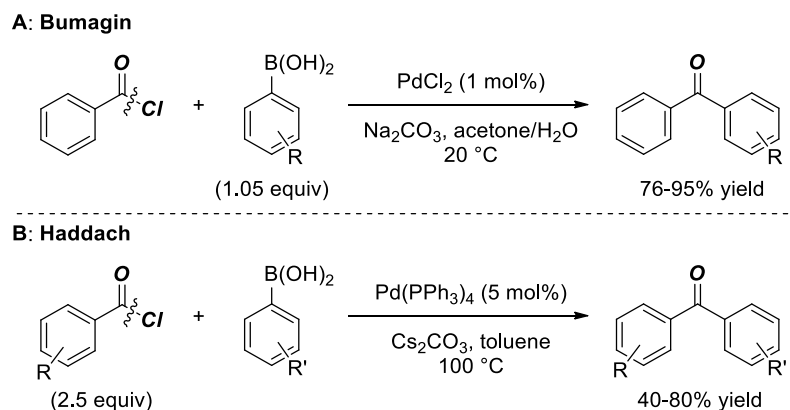
Scheme 1.1. Early Studies in Acyl Suzuki-Miyaura Cross-Coupling: (A) Bumagin; (B) Haddach. For the first cross-coupling of acyl halides with sodium tetrafluoroborates, see, ref.[16]

In an important development, in 2016, Forbes, Magolan and co-workers reported the Suzuki cross-coupling of acyl chlorides using bench-stable organotrifluoroborates (Scheme 1.2A).[17] Organotrifluoroborates offer high functional group tolerance and are moisture-stable making them appealing coupling partners.[18] This coupling offers moderate to excellent yields; however, the reaction appeared to be substrate dependent.

More recently the preparation of ketones using acyl fluorides was reported by Sakai and co-workers (Scheme 1.2B).[19] Compared to typical acyl chloride electrophiles, acid fluorides are more stable towards oxidative addition. The use of acyl fluorides allowed for high functional group tolerance and a wide substrate scope with high yields.

An alternative strategy to the cross-coupling of aroyl halides involves a reversed polarity approach (Scheme 1.3). In 2014, Lee and co-workers developed the cross-coupling of acylindium reagents prepared in situ from aroyl chlorides and indium (Scheme 1.3A).[20] This reaction works well using very mild conditions at 25°C. The tolerance of ketones, esters, and nitriles is advantageous for further functionalization. Krska and co-workers developed a reverse polarity method for the synthesis of biaryl ketones via a Pd-catalyzed cross-coupling between aryl halides and acylsilanes (Scheme 1.3B).[21] The use of a bulky phospha-adamantane was identified as an optimal ligand for the reaction.

A: **Forbes**
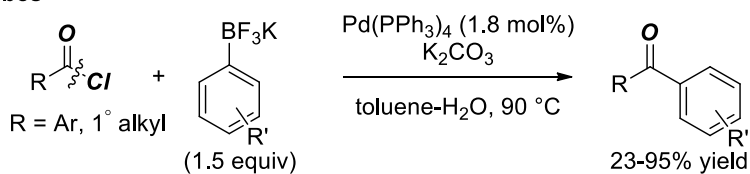
B: **Sakai**
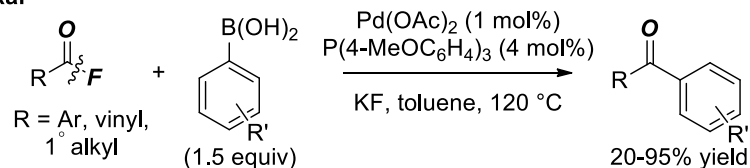
Scheme 1.2. (A) Synthesis of Ketones from Acyl Chlorides using Organotrifluoroborates; (B) Cross-Coupling of Acyl Fluorides.

A: **Lee**
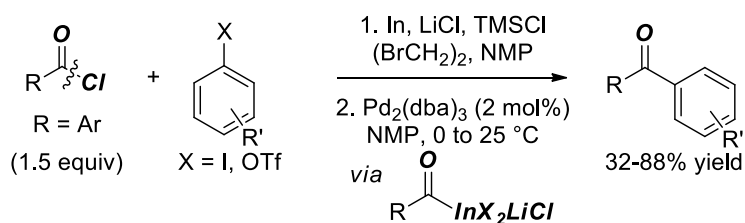
B: **Krska**
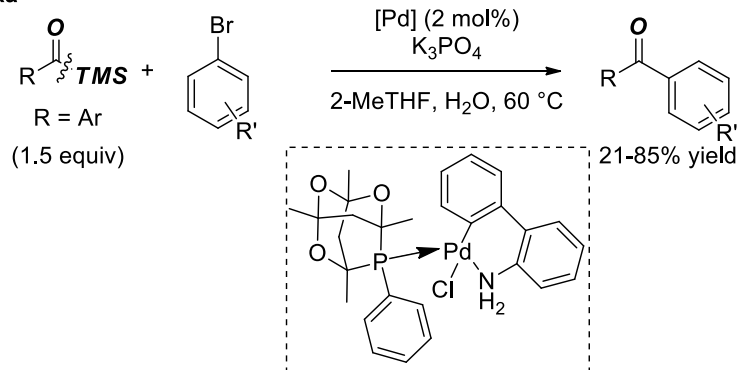
Scheme 1.3. Synthesis of Biaryl Ketones by Polarity Inversion: (A) Acyl Indiums; (B) Acyl Silanes.

1.3. Suzuki Cross-Coupling of Anhydrides

In 2001, Gooßen reported the successful use of anhydrides in acyl Suzuki cross-coupling (Scheme 1.4A).[22] This reaction provides a general route to ketones from carboxylic acids using alternative activating reagents to the synthesis from acyl halides. It is important to

note that this reaction was not able to support the use of pivalic anhydride. Based on this mechanistic insight, the authors developed in situ protocols for acyl Suzuki cross-coupling of carboxylic acids (see Section 1.4.).

Independently, Yamamoto developed an acyl cross-coupling of carboxylic acid anhydrides using readily available Pd(PPh$_3$)$_4$ to form diverse ketone products (Scheme 1.4B).[23] This method permitted for high atom economy and required no base.
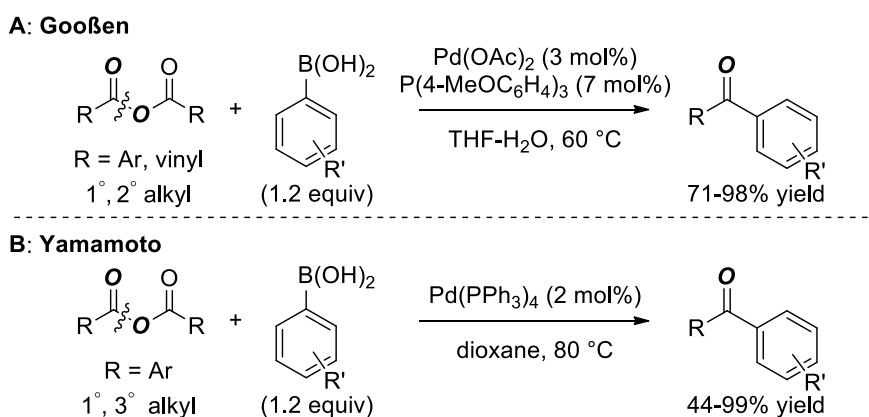
Scheme 1.4. Early Studies in Acyl Suzuki-Miyaura Cross-Coupling of Carboxylic Acid Anhydrides: (A) Gooßen; (B) Yamamoto.

1.4. Suzuki Cross-Coupling of Carboxylic Acids

In 2001, Gooßen reported the direct synthesis of ketones from carboxylic acids by Suzuki cross-coupling via an anhydride intermediate generated in situ (Scheme 1.5A).[22,24] This methodology allowed for the engagement of an array of functionalized aryl and alkyl carboxylic acids, and, as mentioned, relied on the use of an unreactive pivalic anhydride activator.

Independently, Yamamoto developed a related method using dimethyl dicarbonate (DMDC) activator and various carboxylic acids for the synthesis of ketones (Scheme 1.5B).[25] It is important to note that these reactions allow for the direct synthesis of

ketones from ubiquitous carboxylic acids and are easily compatible with meta-substituted benzoic acids which had previously been problematic in the classical Friedel-Crafts acylation.
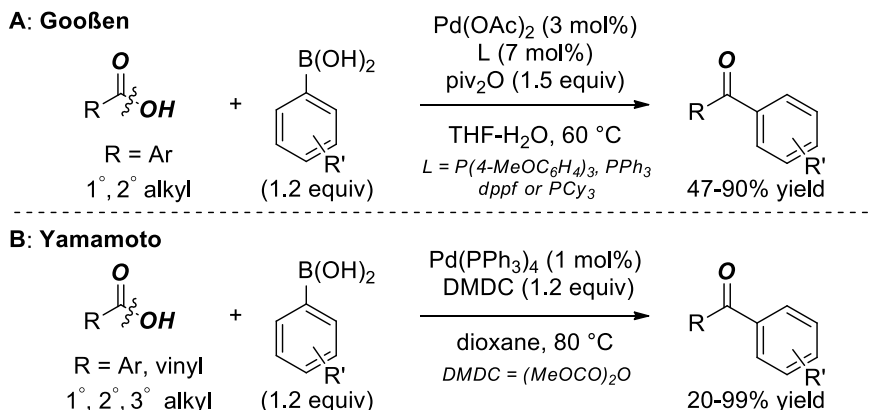
Scheme 1.5. Early Studies in Acyl Suzuki-Miyaura Cross-Coupling of Carboxylic Acids: (A) Gooßen; (B) Yamamoto. DMDC = Dimethyl Dicarbonate. For *N*-Benzoyloxysuccinimide as the Activator, see, ref.[26,27]

In the past decade, significant progress has been achieved in the development of selective activating reagents for acyl Suzuki cross-coupling of carboxylic acids (Schemes 1.6– 1.10). In 2010, Yoon reported the use of EEDQ (*N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline) as an activating reagent in the Suzuki cross-coupling of carboxylic acids with arylboronic acids to make the desired ketone products (Scheme 1.6).[28] EEDQ is a known coupling reagent and serves in this case to make a mixed carboxylic acid anhydride in situ. This simple and efficient method gave diarylketone products in high to excellent yields.

In 2013, Sharma reported DMC (2-chloro-1,3-dimethyl imidazolidinium chloride) as an activating reagent for the synthesis of biaryl ketones via acyl Suzuki cross-coupling of carboxylic acids (Scheme 1.7).[29] This reaction was compatible with electron-donating and

withdrawing substituents on both reaction components; however, aliphatic carboxylic acids were not compatible with the reaction conditions.

More recently, Lindsley reported the use of PyCUI (1-(chloro-1-pyrrolidinylmethylene)-pyrrolidiniumhexafluorophosphate in the synthesis of ketones by acyl Suzuki cross-coupling (Scheme 1.8).[30] This highly reactive in situ activating reagent allows for the transformation of carboxylic acids into unsymmetrical ketones. Furthermore, this one-pot reaction can be conducted at room temperature with reaction times of 2 h or less and gives moderate to high yields.

In 2016, Zeng reported the Suzuki-Miyaura cross-coupling of in situ prepared triazine esters using CMDT (2-chloro-4,6-dimethoxy-1,3,5-triazine) (Scheme 1.9).[31] This process is conducted at low catalyst loading and with short reaction times. Moreover, this one-pot, sequential protocol gave moderate to excellent yields using functionalized and sterically-hindered substrates.

Furthermore, recent progress by Zou in the use of high order aryl boron reagents such as diarylborinic acids and tetra-arylboronates in the acyl Suzuki cross-coupling of carboxylic acids is noteworthy (Scheme 1.10).[32]
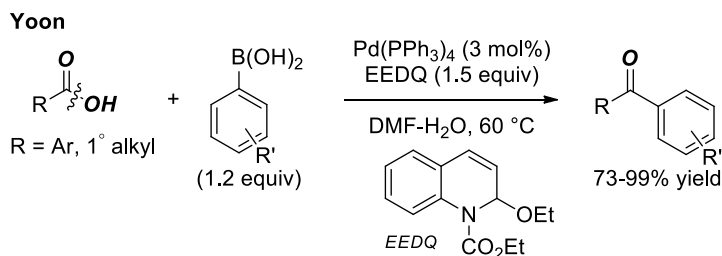
Scheme 1.6. Synthesis of Ketones from Carboxylic Acids using EEDQ. EEDQ = *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline.

Sharma
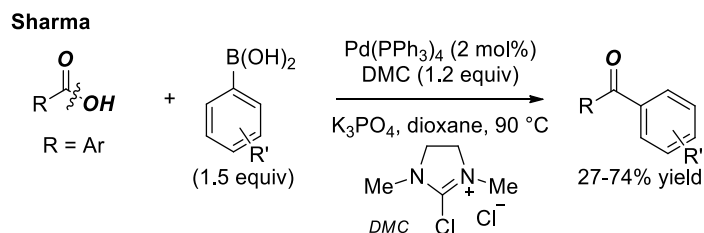
Scheme 1.7. Synthesis of Ketones from Carboxylic Acids using DMC. DMC = 2-Chloro-1,3-dimethylimidazolinium Chloride.

Lindsley
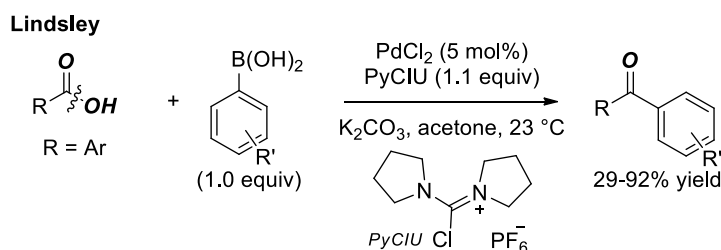
Scheme 1.8. Synthesis of Ketones from Carboxylic Acids using PyClU. PyClU = 1-(Chloro-1-pyrrolidinylmethylene) pyrrolidinium Hexafluorophosphate.

Zeng
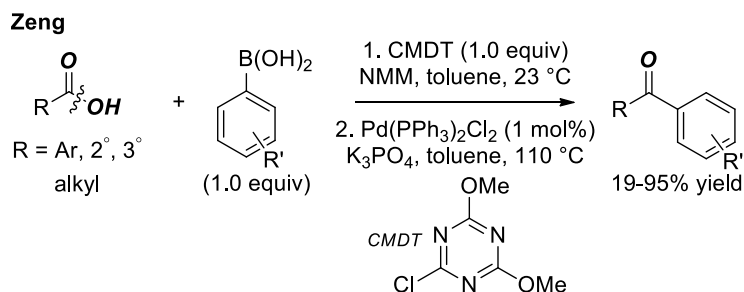
Scheme 1.9. Synthesis of Ketones from Carboxylic Acids using CDMT. CDMT = 2-Chloro-4,6-dimethoxy-1,3,5-triazine. NMM = *N*-Methylmorpholine.

Zou
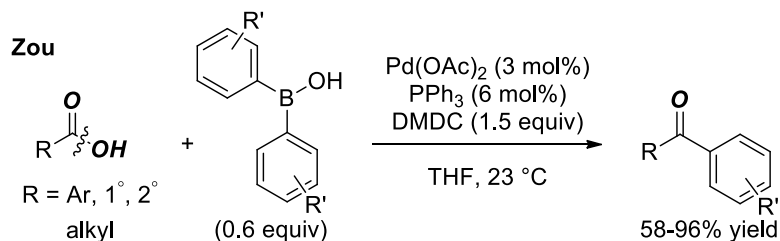
Scheme 1.10. Synthesis of Ketones from Carboxylic Acids and Diarylborinic Acids using DMDC.

These reagents are not only more cost effective than conventional boronic acids but also showed increased reactivity in the cross-coupling using DMDC activator. This acylative Suzuki cross-coupling had a remarkably broad substrate scope, affording products bearing hydroxy, bromo, and carbonyl groups in good to high yields.[32]

1.5. Suzuki Cross-Coupling of Esters

Recently, there have been major developments in the acyl Suzuki cross-coupling of aryl esters (Schemes 1.11–1.13). There are several key advantages of using ester electrophiles in the acyl Suzuki cross-coupling, including (i) high-stability, (ii) prevalence in organic synthesis, (iii) opportunities for orthogonal cross-coupling strategies, (iv) reduction of toxic waste produced in the cross-coupling step.

In 2017, Newman demonstrated the first example of Suzuki cross-coupling of aryl esters (Scheme 1.11).[33] The Pd-NHC catalyst allows for facile insertion into the inactivated C(acyl)–O ester bond, which had proven challenging using Pd-phosphine catalysts. A broad range of phenolic esters and aryl boronic acids were cross-coupled, giving ketones in good to excellent yields.
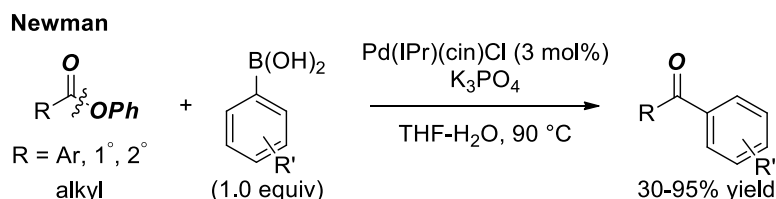
Scheme 1.11. Synthesis of Ketones from Phenolic Esters by Newman and co-workers.

In 2017, our group demonstrated the Suzuki cross-coupling of phenolic esters by selective C(acyl)–O cleavage under very mild conditions (Scheme 1.12A).[34] The use of

bench-stable and commercially-available (η^3-1-t-Bu-indenyl)Pd(IPr)(Cl) precatalyst was critical to achieve high reactivity, affording a wide range of products in good to high yields. Subsequently, our group developed conditions for using practical Pd-PEPPSI precatalysts in the acyl Suzuki cross-coupling of phenolic esters (Scheme 1.12B).[35] The pyridine "throw-away" family of ligands render this class of Pd-NHC precatalysts an attractive method due to simplicity of synthesis and high reactivity in C(acyl)–O insertion. Later, our group demonstrated that the cross-coupling is effectively promoted at remarkably mild room temperature conditions (Scheme 1.12C), while supporting various Pd-NHC precatalysts as well as Pd(II)-NHC hydroxide dimers (Figure 1.3).[36]

The preparation of ketones using (η^3-1-t-Bu-indenyl)Pd(IPr)(Cl) in the presence of a strong base was reported by Hazari (Scheme 1.13).[37] This Pd-NHC effectively coupled esters with aryl boronic acids in good to high yields at room temperature using benign and bench-stable reagents.
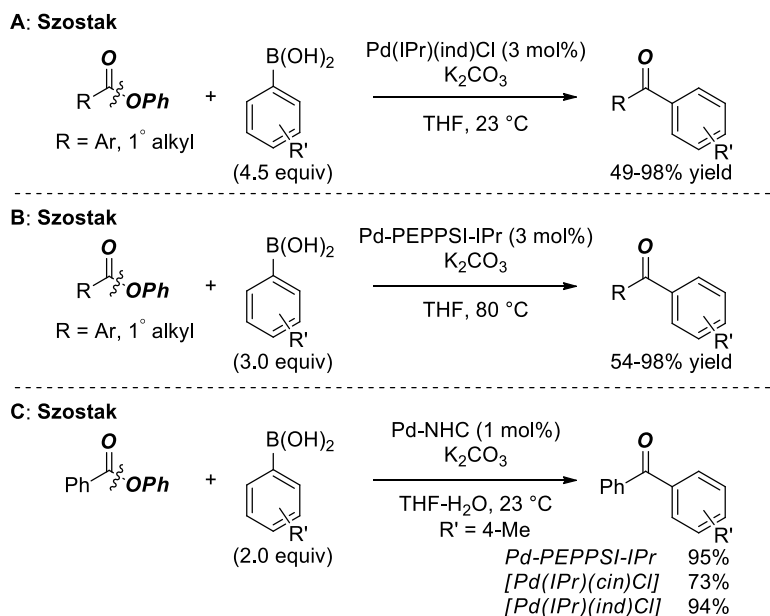
Scheme 1.12. Synthesis of Ketones from Phenolic Esters by Szostak and co-workers.
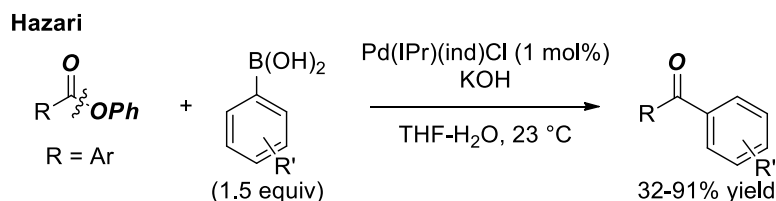
Scheme 1.13. Synthesis of Ketones from Phenolic Esters by Hazari and co-workers.
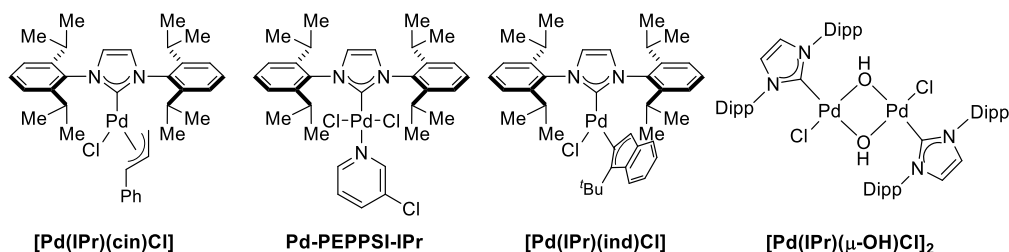
Figure 1.3. Structures of Air-Stable Pd-NHC Precatalysts in Cross-Coupling of Phenolic Esters.

1.6. Suzuki Cross-Coupling of Amides

The ability of transition-metals to catalyze activation of the acyl N–C(O) amide bond was first reported in 2015. Traditionally, the amide bond is the most challenging carboxylic acid derivative to achieve metal insertion due to $n_N \rightarrow \pi^*_{C=O}$ conjugation (15–20 kcal/mol),[38] rendering the typical amide bond approximately 40% double bond in character.

To tackle the challenge of selective metal insertion into the acyl N–C(O) amide bond, our group designed a concept of ground-state-destabilization of the amide bond in transition-metal-catalysis (Scheme 1.14A).[39,40] First, a highly chemoselective, Pd(0)-catalyzed, direct acyl Suzuki cross-coupling between boronic acids and geometrically activated amides was demonstrated. A twisted *N*-acyl-glutarimide diminishes amidic resonance, thus destabilizing the amide ground-state and giving access to versatile ketone products.

Since the initial report, amide ground state destabilization is considered a prevalent theme in amide bond cross-coupling,[41] and all amides thus far have been shown to undergo cross-coupling due to resonance activation.[42–45]

Independently, a new methodology for the synthesis of aryl ketones by acyl Suzuki coupling was developed by Zou, in which amides are used to react with arylboronic acids (Scheme 1.14B).[46] Amide bond activation was achieved by using modifiable activating groups on the nitrogen atom. The reaction gave good to excellent yields and allowed access to sterically-hindered ketones.

At the same time, Garg reported the Ni-catalyzed Suzuki cross-coupling of amide derivatives (Scheme 1.15).[47] This coupling is tolerant to significant changes on both amide and boronate substrates and tolerates both heterocycles and epimerizable stereocenters. The scaffolds produced are diverse and the reaction was applied to the synthesis of bioactive agents.
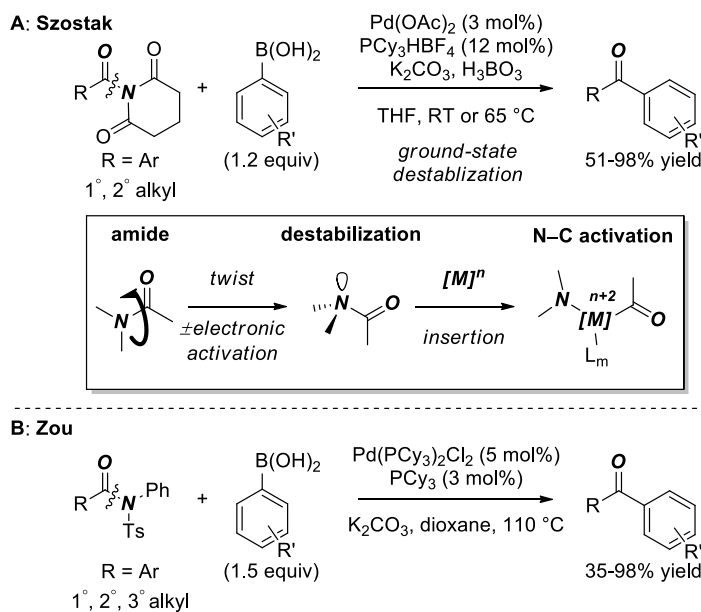
Scheme 1.14. Studies in Suzuki Cross-Coupling of Amides: (a) Szostak; (b) Zou.
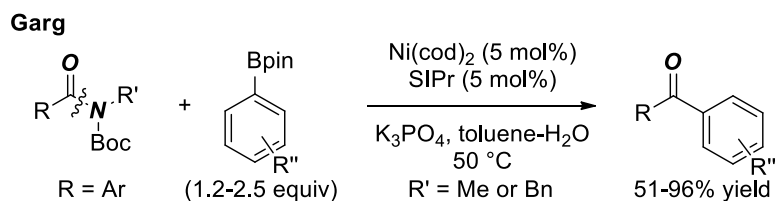
Garg

Scheme 1.15. Studies in Suzuki Cross-Coupling of Amides: Garg. SIPr = 1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine.

Given the indispensable role of the amide bond in chemistry and biology, the amide bond cross-coupling is one of the most rapidly expanding areas of acyl Suzuki coupling.[48–55] The key advances enabling the routine use of this methodology include (1) the development of new amide precursors, (2) the establishment of new catalysts, and (3) the discovery of new types of acyl cross-coupling of amides. These developments are further summarized below.

To enable a better control of the insertion step and participation of common amides, our group has developed a number of activating groups for acyl Suzuki cross-coupling of amides, including saccharin, Ms, Boc$_2$, succinimide, and Ac functional groups (Scheme 1.16A–E).

N-Acyl-saccharins are of interest as bench-stable, highly reactive, and easily prepared amides from low-costing saccharin (Scheme 1.16A).[56] Independently, Zeng and co-workers reported acyl Suzuki cross-coupling of *N*-acyl-saccharins.[57] Our group has also explored the activating effect of the mesyl (Ms) group and found it to be advantageous to the synthesis of biaryl ketones using highly atom-economical sulfonyl activation (Scheme 1.16B).[58] Moreover, *N*,*N*-Boc$_2$-activation was shown to be successful with a combination a Lewis base and palladium catalysis, establishing a new concept for activation of amide

bonds by cooperative catalysis (Scheme 1.16C).[59] Crucially, this method enables the use of primary amides as starting materials. Since primary amides are among the most common amide derivatives in pharmaceuticals and biologically active intermediates, this approach constitutes an attractive method for the synthesis of ketones from common amides.[60]
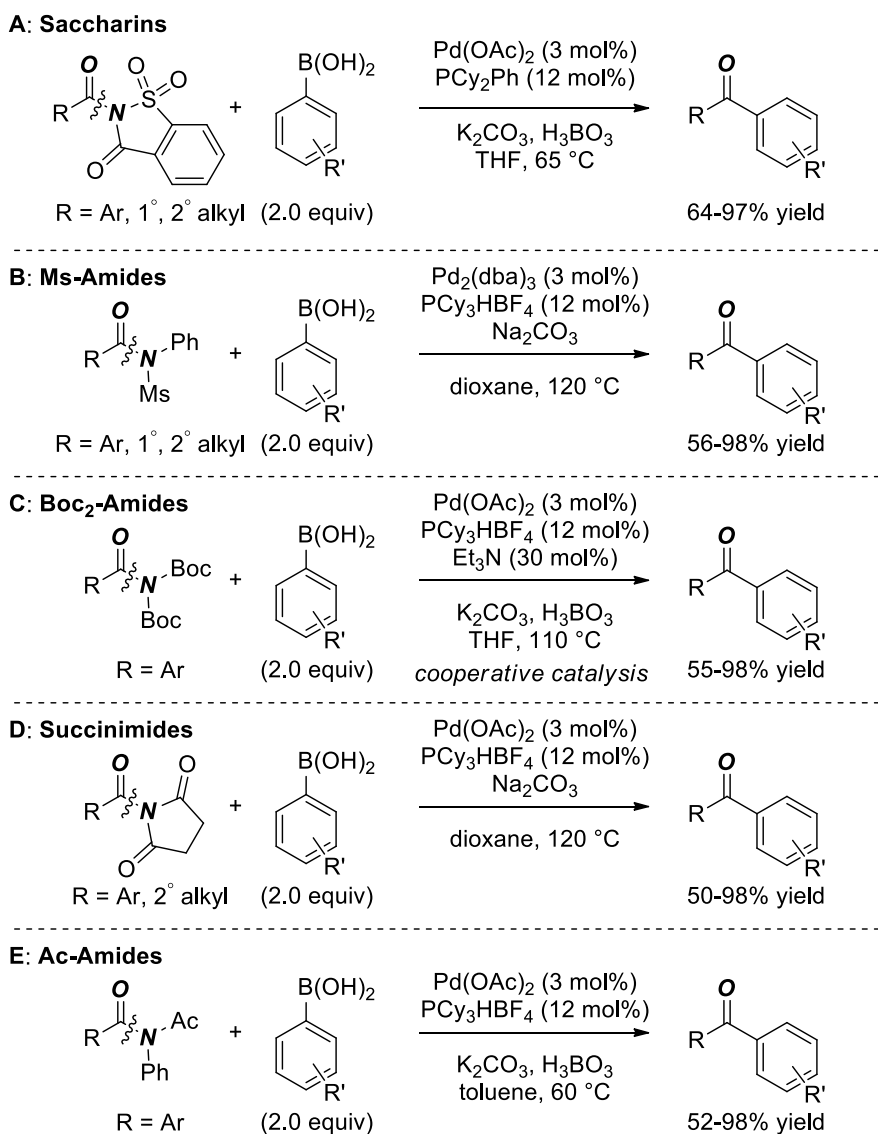
Scheme 1.16. Synthesis of Ketones from Amides using Pd-Phosphine Catalysts: (A) Saccharins; (B) Ms-Amides; (C) Boc2-Amides; (D) Succinimides; (E) Ac-Amides.

"Half-twisted" *N*-acylsuccinimides ($\tau = 46.1°$, τ = twist angle) were also demonstrated as versatile acyl transfer reagents in Suzuki cross-coupling (Scheme 1.16D).[78] This reaction relies on the increase in reactivity of the amide bond due to the half-twist of the amide bond caused by the succinimide moiety (cf. "fully perpendicular" *N*-acylglutarimides, $\tau = 88.6°$), which coupled with high efficiency. Low cost and commercial availability of succinimides make this process a viable candidate for the formation of biaryl ketones. Other catalysts have also been reported for the acyl cross-coupling of *N*-acyl-succinimides.[62,63]

More recently, "mono-twisted" *N*-Ac-amides as highly reactive acyclic amides in acyl Suzuki cross-coupling were reported (Scheme 1.16E).[64] In this work, it was demonstrated that catalyst selection (Pd vs. Ni) dictates an acyl or decarbonylative mechanism. Due to selective mono-twist destabilization mechanism of the amide bond ($\tau = 46.1°$ vs. $\tau = 5.1°$), Ac-amides represent the most reactive acyclic amides developed thus far for amide bond cross-coupling.

Our group reported the structural characterization and acyl Suzuki cross-coupling of the most twisted *N*-acyclic amides prepared to date (Figure 1.4).[65] It was found that a combined *N*-carbamate and *N*-Ts or *N*-Ac activation results in a near perpendicular twist of the amide bond in simple acyclic amides ($\tau = 87.2°$). These amides for the first time matched the distortion achieved in bridged lactams[83] and represent another class of reactive amides for acyl Suzuki cross-coupling.
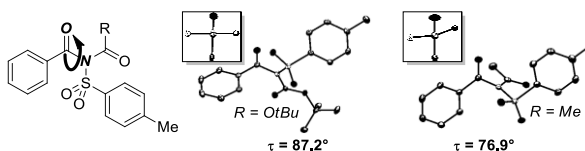
Figure 1.4. Structures of the Most Twisted *N*-Acyclic Amides.
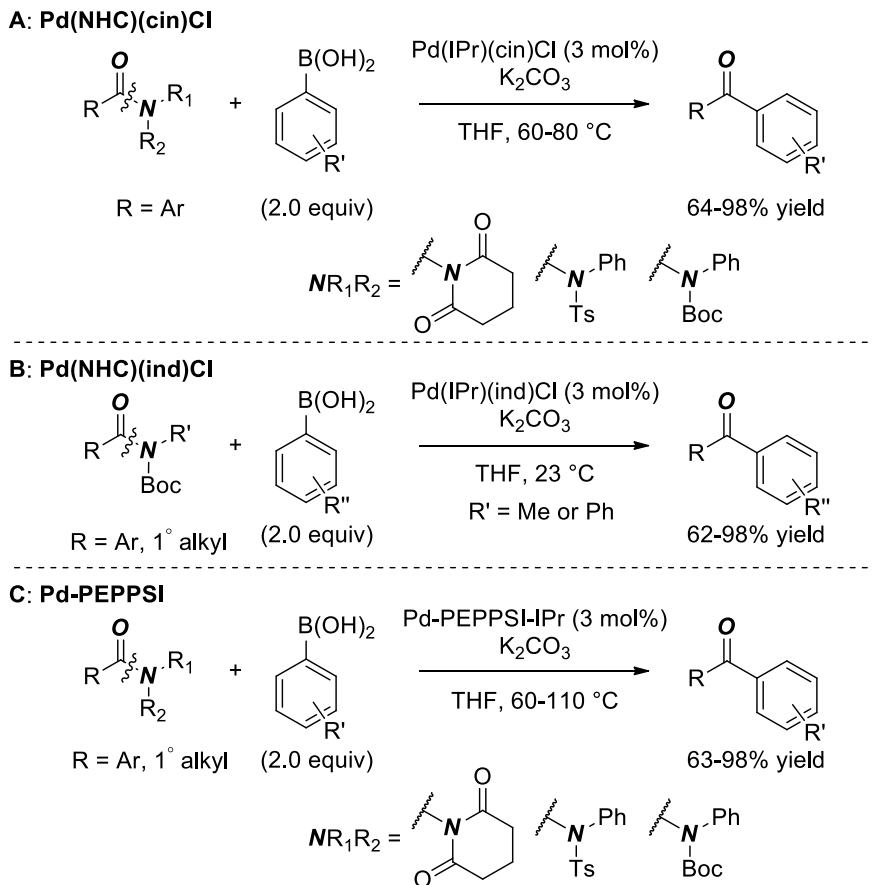
Scheme 1.17. Synthesis of Ketones from Amides using Pd-NHC Catalysts: (A) Pd(NHC)(cin)Cl; (B) Pd(NHC)(ind)Cl; (C) Pd-PEPPSI. For a study using IPr*-type catalysts, see, ref.[68]

A mechanistically distinct approach to improving reactivity of amides in acyl Suzuki cross-coupling involves the development of new catalyst systems (Schemes 1.17–1.21).

Over the past years, our group has made significant contributions to the use of strongly σ-donating Pd-NHCs for ketone synthesis by acyl Suzuki cross-coupling of amides. In 2017, our group has reported (IPr)Pd(cinnamyl)Cl to demonstrate its superior reactivity to all current Pd-phosphine-based catalysts (Scheme 1.17A).[67,68] This catalyst supported a wide range of substrates for ketone synthesis in good to excellent yields. Subsequently, it was found that (IPr)Pd(η^3-1-t-Bu-indenyl)Cl precatalyst not only showed unprecedented reactivity, but it also allowed for very benign reaction conditions (Scheme 1.17B).[34] Of

further significance, Pd-PEPPSI-IPr was used in the acyl Suzuki cross-coupling of an array of amides, showing both excellent catalyst performance and a highly diverse substrate scope (Scheme 1.17C).[69] The ease of synthesis and high air- and moisture-stability of Pd-NHC precatalysts[70–72] are important factors in considering widespread applications in organic synthesis.

In 2017, our group was able to apply (IPr)Pd(cinnamyl)Cl to previously unreactive *N*-acyl-pyrroles and *N*-acyl-pyrazoles (Scheme 1.18A).[73] The cross-coupling of these electronically-activated (RE ca. 10 kcal/mol, RE = resonance energy) planar amides is attributed to the strong σ-donation of the Pd-NHC catalyst platform. Furthermore, this method demonstrates the potential for catalytic cross-coupling of unactivated primary amides.
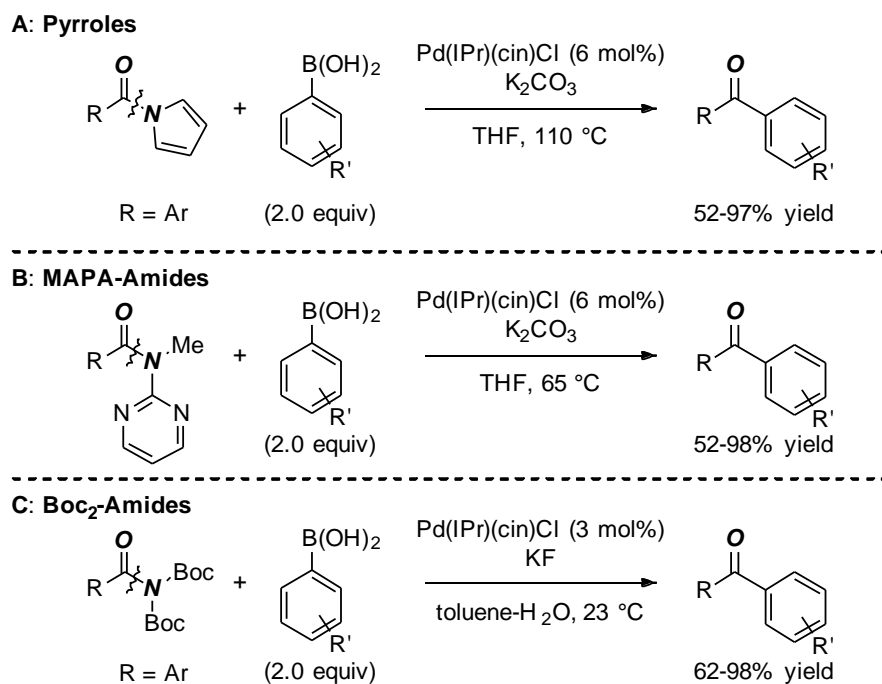
Scheme 1.18. Synthesis of Ketones from Amides using Pd-NHC Catalysts: (A) Pyrroles; (B) MAPA-Amides; (C) Boc2-Amides.

Our group further went on to demonstrate the use of *N*-methylaminopyrimidyl-amides (MAPA) for the acyl Suzuki cross-coupling (Scheme 1.18B).[74] With the use of (IPr)Pd(cinnamyl)Cl precatalyst this reaction occurs with high acyl N–C activation chemoselectivity. Of significance, this work provides MAPA as resonance-controlled (RE = ca. 7 kcal/mol) practical alternative to anilides.

More recently, *N,N*-Boc$_2$ amides also proved to be highly reactive with the application of (IPr)Pd(cinnamyl)Cl (Scheme 1.18C).[75] This reaction demonstrated the synthesis of biaryl ketones under exceedingly mild conditions, achieving a TON of >1,000 for the first time in amide acyl Suzuki cross-coupling.

The acyl Suzuki cross-coupling of higher order aryl boron reagents with amides was reported by Zou (Scheme 1.19).[76] With the use of *N*-mono-3,5(CF$_3$)$_2$C$_6$H$_3$ activating group and Pd(PCy$_3$)$_2$Cl$_2$/PCy$_3$ catalyst system they were able to overcome the electronic and steric factors for the cross-coupling of amides with diarylborinic acids or tetra-arylborates to synthesize ketones (Scheme 1.19A). Later, they reported the use of Pd-PEPPSI-IPr for the cross-coupling of *N*-alkyl-amides with diarylborinic acids (Scheme 1.19B).[77] The method is characterized by a broad substrate scope, affording ketones in good to excellent yields, while it also uses a commercially-available Pd-NHC.

Zeng reported the acyl Suzuki cross-coupling of *N*-acyl-succinimides (Scheme 1.20A, see also Schemes 1.16D and 1.21).[62] This reaction gave moderate to good yields in a short reaction time. More recently, they used structurally-related *N*-acyl-5,5-dimethylhydantoins in the acyl Suzuki cross-coupling with aryl boronic acids (Scheme 1.20B).[78] The use of commercially-available, air- and moisture-stable (IPr)Pd(allyl)Cl precatalyst as well as good tolerance to several functional groups are important features

of this protocol. Our group independently studied the structural features of the amide

bond in *N*-acyl-hydantoins,[79] demonstrating that replacement of the carbon atom in the

succinimide ring with nitrogen to give hydantoin results in a substantial increase of the

amide bond distortion (additive Winkler-Dunitz parameter of 70°).

In 2018, Liu developed the acyl Suzuki cross-coupling of *N*-acyl-succinimides with aryl

boronic acids using benzothiazole-supported Pd-NHC PEPPSI-type precatalyst (Scheme

1.21).[80] This Pd-NHC is easily prepared[81] and provides biaryl ketones in high yields. In

2018, Rhee developed the first example of using *N,N*-bis(methanesulfonyl)amides as

acyl-transfer reagents in Suzuki cross-coupling (Scheme 1.22).[82] In addition to using a

new class of substrates, this reaction works under mild conditions to provide a wide range

of unsymmetrical ketones. Other classes of acyl electrophiles and catalysts continue to be

developed in this cross-coupling manifold.[83]
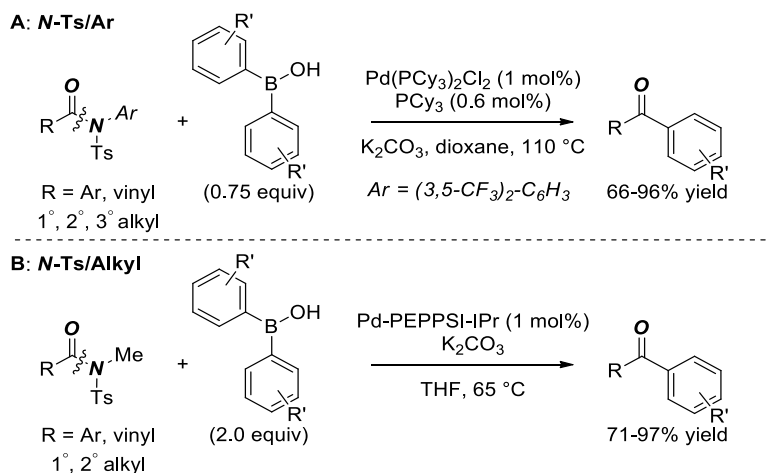
Scheme 1.19. Synthesis of Ketones from Amides using Diarylborinic Acids: (A) *N*-Ts/Ar Amides; (B) *N*-Ts/Alkyl Amides.
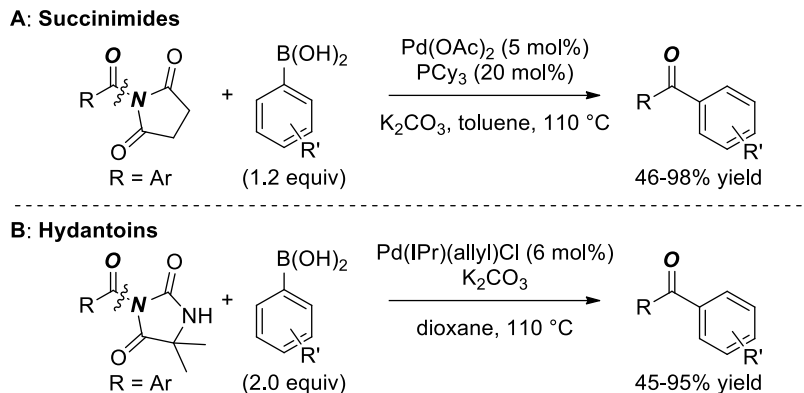
Scheme 1.20. Synthesis of Biaryl Ketones from Amides: (A) Succinimides; (B) Hydantoins.
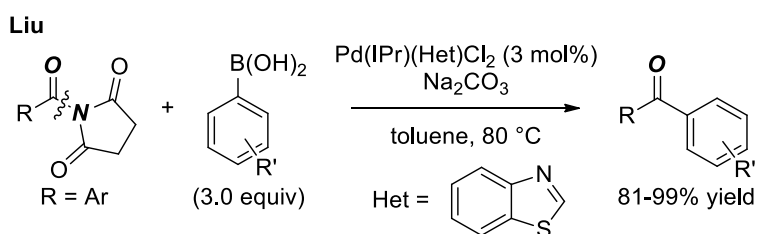
Scheme 1.21. Synthesis of Biaryl Ketones from Amides using Benzothiazole-Supported Pd-NHCs.
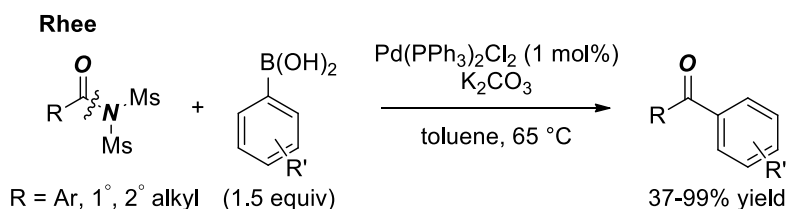
Scheme 1.22. Synthesis of Ketones from Di-Sulfonyl Amides by Rhee and co-workers.

1.7. Brief Summary of the Work in this Thesis

Despite progress in the acyl Suzuki cross-coupling being considerable, as outlined in the previous sections of this chapter, numerous challenges remain. The research outlined in this thesis focuses on several aspects of the acyl Suzuki cross-coupling and explores (1) new substrates, (2) more reactive catalyst systems, and (3) the development of new sustainable protocols for the synthesis of essential ketone products. The work provides

mechanistic studies for a better understanding of the key steps in the acyl Suzuki cross-coupling.

After introductory Chapter I, Chapter II will address the cross-coupling of pentafluorophenyl esters (pentafluorophenyl = pfp) by selective C–O acyl cleavage. This reaction addresses the lack of methods that utilize cheap and readily accessible Pd-phosphine catalysts for the cross-coupling of bench-stable phenolic esters and proceeds efficiently using a $Pd_2(dba)_3/PCy_3$ catalyst system. The unique electronic characteristic of pentafluorophenyl esters is reflected in the fully selective cross-coupling. Of broader interest, our studies established pentafluorophenyl esters as new, highly reactive, bench-stable, ester-based, electrophilic acylative reagents via acyl-metal intermediates. Selectivity studies provided a unified reactivity scale of acyl electrophiles by C(O)–X (X = N, O) activation, wherein the reactivity of pfp esters can be correlated with barriers to rotation around the C(acyl)–X bond.

Chapter III will outline the development of new amide-based precursors for N–C(O) cleavage. First, a general, highly selective method for Suzuki-Miyaura cross-coupling of twisted *N*-acyl-phthalimides by acyl cleavage catalyzed by Pd-PEPPSI type precatalysts will be described. The study introduced *N*-acyl-phthalimides as new, bench-stable, highly reactive, twist-controlled, amide-based precursors to furnish acyl-metal intermediates. Studies demonstrated that cheap, easily prepared and broadly applicable Pd-PEPPSI type precatalysts supported by a sterically-demanding IPr ancillary ligand provide high yields in this reaction. The effect of Pd-NHC complexes with allyl-type throw-away ligands will be described. The second part of Chapter III will focus on the Pd-catalyzed Suzuki–Miyaura cross-coupling of *N*-acyl-carbazoles and *N*-acyl-indoles by a highly selective N–

C(O) amide bond cleavage. The study introduced *N*-acyl-indoles and in particular *N*-acyl-carbazoles as highly effective amide bond electrophiles for selective activation of the N–C(O) bond. In this class of precursors, the key amide bond ground-state-destabilization stems from N_{lp} to Ar conjugation in a flattened carbazole ring and enabled for the first time to achieve reactivity similar to *N*-acyl-sulfonamide and *N*-acyl-carbamate activation in simple anilides. The use of hydrolytically-stable *N*-acyl-carbazoles provides a new approach to the generation of acyl-metals from amides.

Chapter IV will outline the development of Suzuki-Miyaura cross-coupling of amides catalyzed by well-defined, air- and moisture-stable Ni-NHC complexes. The selective amide bond N–C(O) activation was achieved by half-sandwich, cyclopentadienyl complexes, [CpNi(NHC)Cl]. Studies on the effect of NHC ancillary ligand are described. Both the neutral and the cationic complexes were found to be efficient catalysts for the acyl Suzuki-Miyaura cross-coupling of amides. Complete selectivity for the cleavage of N–C(O) acyl bond was observed under the reaction conditions. The study demonstrated for the first time that bench-stable [CpNi(NHC)Cl] complexes can effectively participate in the acyl Suzuki-Miyaura cross-coupling of amide bonds and related bench-stable acyl-electrophiles.

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Chapter 2

Pd-Catalyzed Suzuki–Miyaura Cross-Coupling of Pentafluorophenyl Esters

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2.1. Introduction

The emergence of Suzuki-Miyaura cross-coupling of amide and ester electrophiles by selective C(acyl)–X cleavage represents one of the most promising approaches to functionalization of the traditionally inert amide and ester bonds in organic synthesis.[1-3] Although a broad range of amide precursors have been explored,[4-8] typically benefiting from amide bond twist and electronic activation,[9-13] Pd-catalyzed cross-coupling of esters has received significantly less attention. The study by Newman in 2017 reported the [Pd(NHC)(cin)Cl]-catalyzed cross-coupling of phenolic esters at high temperature.[14] Subsequently, our group reported a general method for the cross-coupling of both esters and amides at room temperature using [Pd(IPr)(1-*t*-Bu-ind)Cl].[15] Further studies established that various Pd(II)–NHC precatalysts are significantly more reactive after optimizing conditions.[16,17] Moreover, Hazari demonstrated the cross-coupling of aryl esters at room temperature conditions using strong bases and [Pd(IPr)(1-*t*-Bu-ind)Cl].[18]

This strategy to develop cross-coupling reactions of aryl esters hinges upon ground-state destabilization of the barrier to rotation around the C(acyl)–O bond.[19] Given the utility of pentafluorophenyl esters as acyl transfer reagents in nucleophilic acyl addition reactions,[20-22] we proposed that the ground-state-destabilization principle would enable

facile cross-coupling of pentafluorophenyl esters under chemoselective conditions that are inaccessible to phenolic esters.[1-3] In 2018 we reported the successful development of this reaction, and reported the first general method for the cross-coupling of pentafluorophenyl esters by selective C–O acyl cleavage.[24] Notable features of our study included: (1) Pd-phosphine-catalyzed Suzuki cross-coupling by C–O activation; (2) high selectivity of the cross-coupling; (3) development of the reactivity scale in the cross-coupling of bench-stable O–C(O) and N–C(O) acyl electrophiles.[23]

More generally, this study established pentafluorophenyl esters as new, highly reactive, bench-stable, ester-based, electrophilic acylative reagents via acyl-metals.[1-3] Considering the versatile role of pfp esters in organic synthesis as acyl transfer reagents,[20-22] we propose that this electronic-activation approach could lead to the development of new cross-coupling reactions of esters by acyl and decarbonylative pathways (Scheme 2.1).[1,2,7,24,25]

A: Previous studies

amides
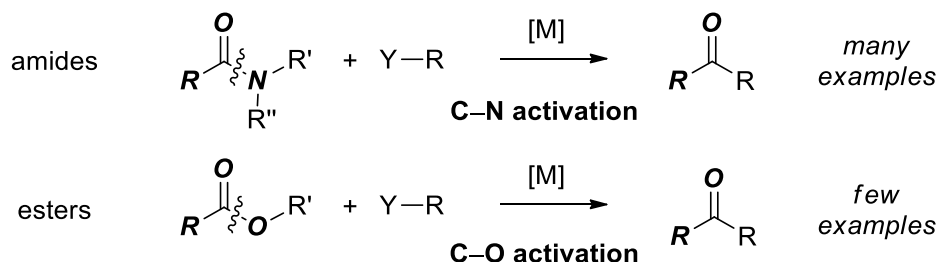
esters

B: This work: the first Suzuki-Miyaura cross-coupling of pfp esters
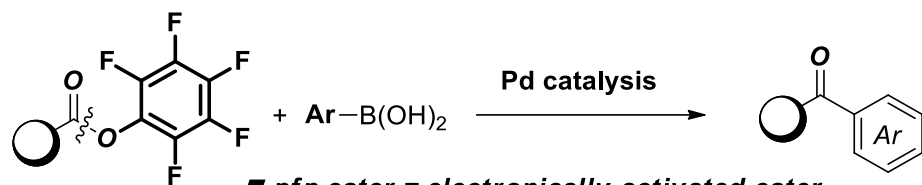
■ *pfp ester = electronically-activated ester*
■ *broad utility in nucleophilic addition*
■ *unexplored in transition-metal-catalysis*
■ *easily-accessible, high stability*
■ *bench-stable, crystalline*
■ *low price, selective C-O activation*

■ *general guidelines for amide and ester coupling:* **barrier to isomerization**

Scheme 2.1. Cross-Coupling of Amides and Esters by C–N and C–O Activation.

2.2. Reaction Optimization

Cross-coupling of pentafluorophenyl benzoate with 4-tolyl boronic acid was selected as our model system (Table 2.1.). From the outset, we sought to develop a catalytic system based on phosphine ligands due to low price, ready availability and orthogonal selectivity compared to the more σ-donating NHCs. Selected optimization results are presented in Table 2.1. As expected, the choice of base (entries 1-6), phosphine ligand (entries 7-12), palladium catalyst (entries 13-15), palladium to ligand ratio (entries 16-18), stoichiometry (entries 19-20) and concentration (entries 21-22) had a major impact on the cross-coupling efficiency. Finally, we established that the optimum conditions involved using

Pd$_2$(dba)$_3$ (3.0 mol%) as a catalyst, PCy$_3$HBF$_4$ (12 mol%) as a ligand, and Na$_2$CO$_3$ (4.5 equiv) as a base in dioxane at 120 °C (entry 20).

Importantly, under the optimized conditions cleavage of the alternative O–C(Ar) bond, nucleophilic addition to the activated pfp group or C–F coupling were not observed. To our knowledge, the reaction represented the first example of a Pd-phosphine-catalyzed Suzuki cross-coupling of a phenolic ester type group by selective C–O cleavage.[1–3,24,25] We also noted that all reaction components in this cross-coupling were easy-to-handle, bench-stable solids, which represented a significant practical advantage over related cross-coupling protocols of ester electrophiles.[1–3,24,25]

Table 2.1. Optimization of the Suzuki-Miyaura Cross-Coupling of Pfp Esters.[a]

Entry	Catalyst	Ligand	Base	[Pd]:L	Yield (%)
1	Pd(OAc)$_2$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	1:4	52
2	Pd(OAc)$_2$	PCy$_3$HBF$_4$	KHCO$_3$	1:4	53
3	Pd(OAc)$_2$	PCy$_3$HBF$_4$	NaHCO$_3$	1:4	30
4	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K$_2$CO$_3$	1:4	12
5	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K$_3$PO$_4$	1:4	47
6	Pd(OAc)$_2$	PCy$_3$HBF$_4$	KF	1:4	56
7	Pd(OAc)$_2$	PPhCy$_2$	Na$_2$CO$_3$	1:4	60
8	Pd(OAc)$_2$	PPh$_2$Cy	Na$_2$CO$_3$	1:4	5
9	Pd(OAc)$_2$	PPh$_3$	Na$_2$CO$_3$	1:4	5
10	Pd(OAc)$_2$	DPPB	Na$_2$CO$_3$	1:4	13
11	Pd(OAc)$_2$	Xantphos	Na$_2$CO$_3$	1:4	<5
12	Pd(OAc)$_2$	P*t*-Bu$_3$HBF$_4$	Na$_2$CO$_3$	1:4	<5
13	Pd(dba)$_2$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	1:4	23
14	PdCl$_2$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	1:4	25
15	Pd$_2$(dba)$_3$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	1:2	74
16[b]	Pd$_2$(dba)$_3$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	1:2	85
17[c]	Pd$_2$(dba)$_3$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	1:1	44
18[d]	Pd$_2$(dba)$_3$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	2:1	30
19[e]	Pd(OAc)$_2$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	1:4	83
20[e]	Pd$_2$(dba)$_3$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	1:2	92
21[f]	Pd$_2$(dba)$_3$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	1:2	75
22[g]	Pd$_2$(dba)$_3$	PCy$_3$HBF$_4$	Na$_2$CO$_3$	1:2	89

[a]Conditions: ester (1.0 equiv), 4-Tol-B(OH)$_2$ (2.0 equiv), base (2.5 equiv), [Pd] (3 mol%), ligand (12 mol%), solvent (0.25 M), 120 °C, 15 h. [b][Pd] (1.5 mol%), ligand (12 mol%), 4-Tol-B(OH)$_2$ (3.0 equiv), base (4.5 equiv). [c][Pd] (3 mol%), ligand (6 mol%), 4-Tol-B(OH)$_2$ (3.0 equiv), base (4.5 equiv). [d][Pd] (3 mol%), ligand (3 mol%), 4-Tol-B(OH)$_2$ (3.0 equiv), base (4.5 equiv). [e]4-Tol-B(OH)$_2$ (3.0 equiv), base (4.5 equiv). [f]Dioxane (0.10 M). [g]Dioxane (0.50 M).

2.3. Scope of the Reaction

With optimized conditions in hand, we examined the scope of the cross-coupling with respect to the boronic acid component (Table 2.2.). We were pleased to find the reaction readily accommodated a range of electronically-diverse boronic acids, including neutral (**2.3a**) electron-rich (**2.3b-c**), electron-deficient bearing electrophilic carbonyl (**2.3d**), sterically-hindered (**2.3e**) as well as fluorinated boronic acids relevant from the medicinal chemistry standpoint (**2.3f-i**).

Table 2.2. Boronic Acid Scope in the Pd-Catalyzed Cross-Coupling of Pfp Esters.[a]
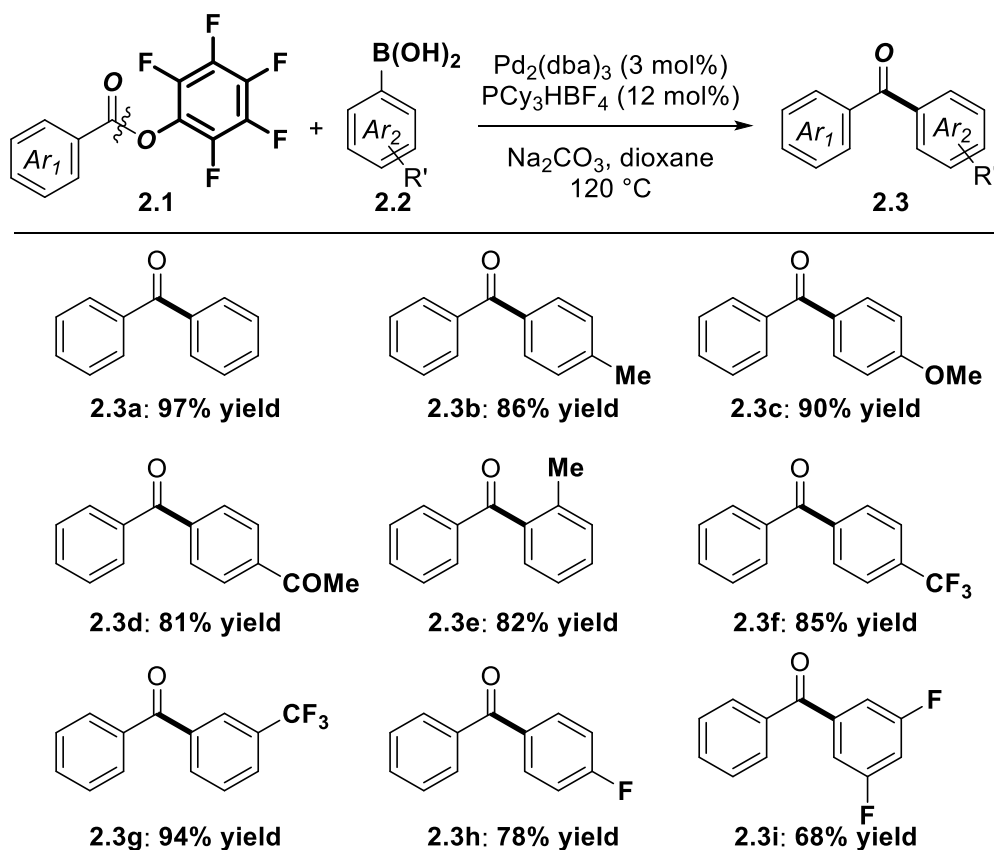
2.3a: 97% yield   **2.3b**: 86% yield   **2.3c**: 90% yield

2.3d: 81% yield   **2.3e**: 82% yield   **2.3f**: 85% yield

2.3g: 94% yield   **2.3h**: 78% yield   **2.3i**: 68% yield

[a]Conditions: ester (1.0 equiv), ArB(OH)$_2$ (3.0 equiv), Na$_2$CO$_3$ (4.5 equiv), Pd$_2$(dba)$_3$ (3 mol%), PCy$_3$HBF$_4$ (12 mol%), dioxane (0.25 M), 120 °C, 15 h.

We next explored the generality of this cross-coupling with respected to the ester electrophile (Table 2.3.). Pleasingly, the reaction tolerated electron-deficient substituents (**2.3f'**, **2.3d'**, **2.3j**), including electrophilic carbonyls (**2.3d'**, **2.3j**), electron-rich deactivating substituents (**2.3c'**), sterically-hindered (**2.3e'**) as well as aliphatic pfp ester precursors (**2.3k**). It is worthwhile to note that the reaction proceeded with full selectivity for the cross-coupling of a pfp ester in the presence of an aliphatic ester (**2.3j**), as expected from the C–O isomerization and our design.[15,19]

Table 2.3. Ester Scope in the Pd-Catalyzed Cross-Coupling of Pfp Esters.[a]
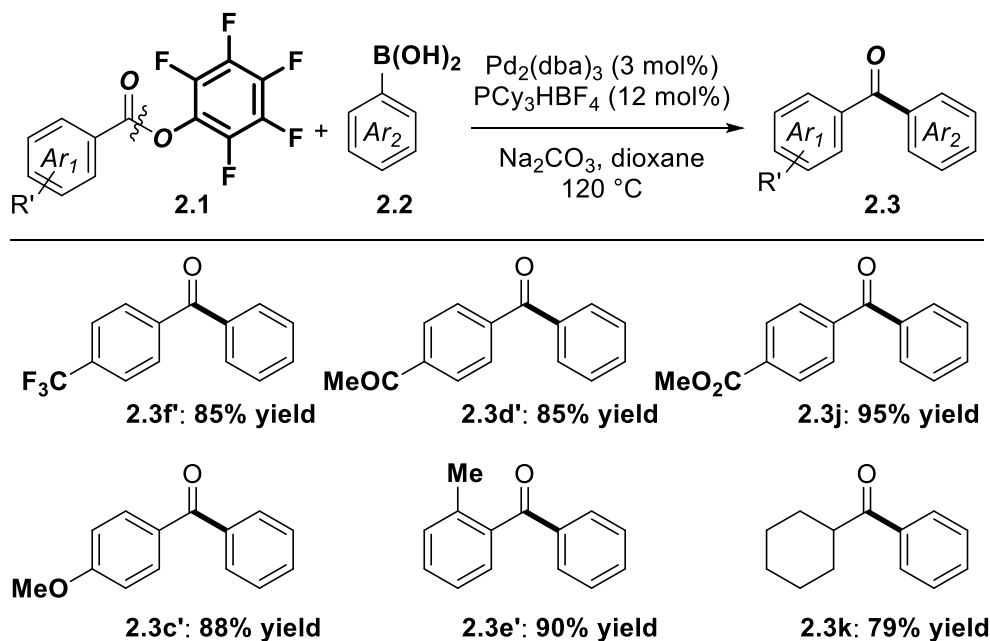
[a]Conditions: ester (1.0 equiv), ArB(OH)$_2$ (3.0 equiv), Na$_2$CO$_3$ (4.5 equiv), Pd$_2$(dba)$_3$ (3 mol%), PCy$_3$HBF$_4$ (12 mol%), dioxane (0.25 M), 120 °C, 15 h.

2.4. Mechanistic Studies

Next, to highlight the synthetic utility of this transformation, we conducted a series of selectivity experiments between pfp esters and ester and amide electrophiles previously established in cross-coupling protocols (Scheme 2.2).[3-8] Most importantly, as expected

from C–O isomerization, the reaction was fully selective for the pfp cross-coupling in the presence of phenolic ester (Scheme 2.2A). Separate experiments using phenyl benzoate under the optimized conditions for the cross-coupling of pfp esters resulted in a quantitative recovery of $PhCO_2Ph$ (not shown).

Furthermore, we found that the reaction was slightly less selective for the cross-coupling of pfp esters vs. *N*-Ts sulfonamides (Scheme 2.2B; Ts/Ph:pfp = 1.3:1), whereas full selectivity was observed in the cross-coupling of *N*-acyl-glutarimides vs. pfp esters (Scheme 2.2C; >20:1), as expected on the basis of amide bond twist and destabilization.[6,11] Overall, the competition experiments demonstrated high chemoselectivity of the cross-coupling of pfp esters, and permitted to establish a reactivity trend in the cross-coupling of ester and amide electrophiles catalyzed by Pd-phosphines (Scheme 2.3).[12]

To gain insight into the reaction mechanism, we conducted additional experiments. (1) Competition experiments with differently substituted pfp esters revealed that electron-deficient arenes are more reactive (4-CF$_3$:4-MeO > 20:1); while (2) differently substituted boronic acids revealed a small preference for electron-rich boronic acids (4-MeO:4-CF$_3$ = 1.1:1) (not shown). Overall, these findings suggested that Pd insertion might be the rate limiting step in this cross-coupling.
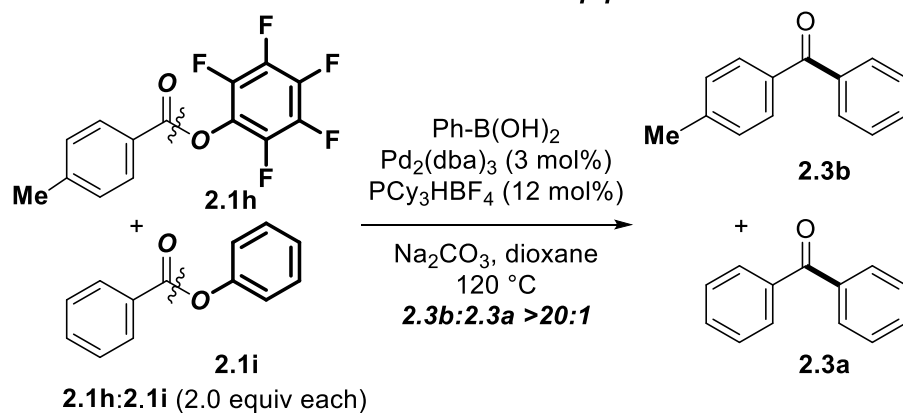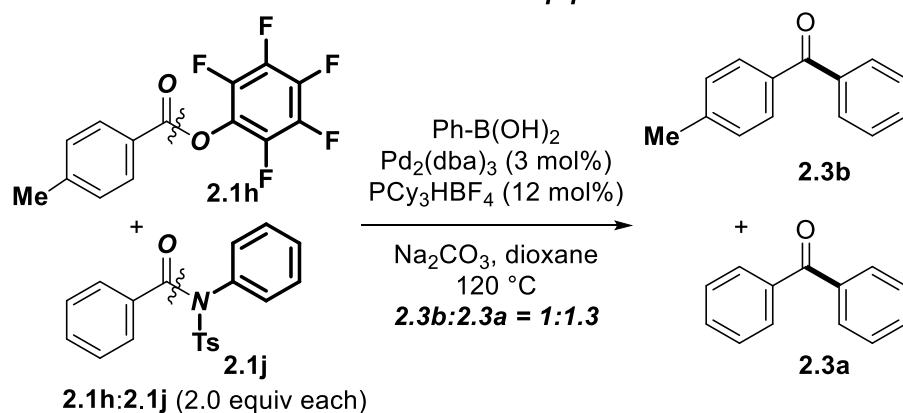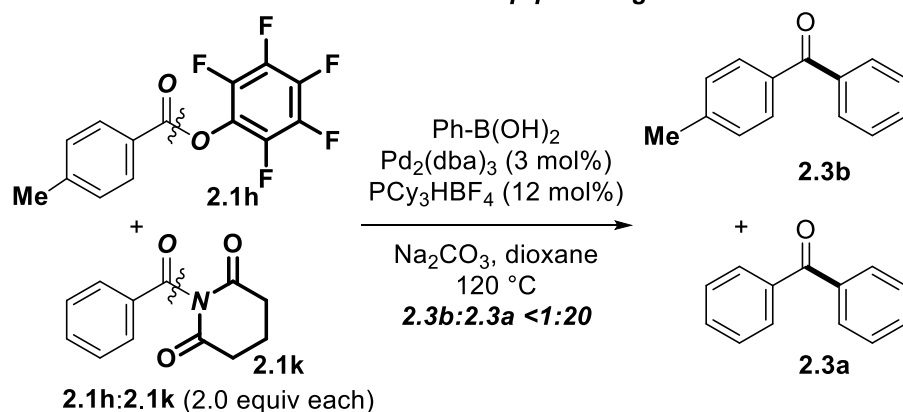
Scheme 2.2. Competition Experiments.
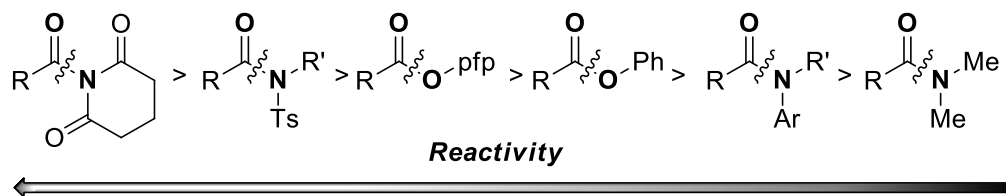
Scheme 2.3. Reactivity Scale in C(acyl)–N and C(acyl)–O Suzuki-Miyaura Cross-Coupling. Note that *N*-acyl-glutarimides, *N*-Ts-sulfonamides and O-pfp esters have been shown to react with Pd-PR₃ catalytic systems, see, ref.[1-3] The reactivity of OPh esters, *N*-Ar amides and *N*-Me amides is based on Pd-NHC catalysts; these substrates are unreactive with Pd-PR₃, see, ref.[1,15]

Finally, we demonstrated that catalytic systems in the Suzuki-Miyaura cross-coupling of pfp esters are not limited to the in situ formed Pd(0)–phosphine catalysts. For example, preformed Pd(II)–phosphine precatalysts[26] as well as Pd(II)–NHCs,[1] such as Pd(PCy₃)₂Cl₂ and Pd–PEPPSI-IPr afforded the coupling product in excellent yields (Scheme 2.4), highlighting the generality and synthetic potential of pentafluorophenyl esters as electrophiles in transition-metal-catalysis.
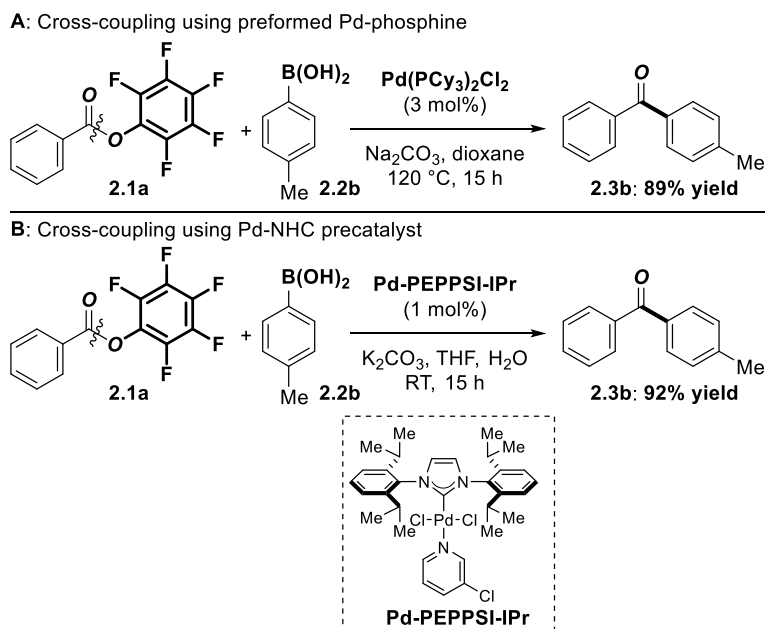
Scheme 2.4. Cross-Coupling using Preformed Pd-Phosphine and Pd(II)-NHC Precatalysts.

2.5. Conclusion

In conclusion, we demonstrated the Suzuki–Miyaura cross-coupling of pentafluorophenyl esters. The reaction was notable for introducing pfp esters as new, ester-based, electrophilic reagents for transition-metal catalyzed cross-coupling reactions. Furthermore, the method reported the use of Pd–phosphine catalysis in chemoselective Suzuki–Miyaura ester coupling by C–O cleavage. Given the broad utility of pfp esters in nucleophilic acyl addition reactions, we proposed that these reagents would find application in the transition-metal-catalyzed cross-coupling. In particular, our study highlighted the utility of ground-state destabilization of acyl electrophiles to achieve chemoselective C–O bond activation. Pentafluorophenyl esters are readily prepared, easy to handle, bench-stable solids, and highly reactive. We believe that future work will focus on expanding the catalyst and reaction portfolio in the cross-coupling of activated esters. With the availability of various catalyst systems, these pfp reagents should expand the future development of C–O cross-coupling in organic synthesis.[14-18]

2.6. Experimental Section

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

General Procedure for Cross-Coupling of Pentafluorophenyl Esters. An oven-dried vial equipped with a stir bar was charged with an ester substrate (neat, 1.0 equiv), boronic acid (typically, 3.0 equiv), sodium carbonate (typically, 4.5 equiv), Pd$_2$(dba)$_3$ (typically, 3 mol%), and PCy$_3$HBF$_4$ (typically, 12 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 120 °C, and stirred for the indicated time at 120 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH$_2$Cl$_2$ (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.

Representative Procedure for Cross-Coupling of Pentafluorophenyl Esters. An oven-dried vial equipped with a stir bar was charged with perfluorophenyl benzoate (neat, 288.2 mg, 1.0 mmol), *p*-tolylboronic acid (408.0 mg, 3.0 mmol, 3.0 equiv), Na_2CO_3 (477.0 mg, 4.5 mmol, 4.5 equiv), $Pd_2(dba)_3$ (27.5 mg, 0.03 mmol, 3 mol%), and PCy_3HBF_4 (44.2 mg, 0.12 mmol, 12 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 120 °C, and stirred for 15 h at 120 °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 ^{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. Yield 86% (168.5 mg). White solid. All other yields represent yields determined by ^{1}H NMR ($CDCl_3$, 500 MHz) analysis.

Characterization Data for Products 2.3a-2.3k.

2.3a. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.9 Hz, 4 H), 7.62 (t, J = 7.4 Hz, 2 H), 7.51 (t, J = 7.6 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.75, 137.61, 132.42, 130.07, 128.28.

2.3b. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.7 Hz, 2 H), 7.75 (d, J = 7.5 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.50 (t, J = 7.2 Hz, 2 H), 7.31 (d, J = 7.7 Hz, 2 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.49, 143.22, 137.98, 134.90, 132.14, 130.31, 129.93, 128.97, 128.20, 21.66.

2.3c. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.86 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 7.6 Hz, 2 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.50 (t, J = 7.4 Hz, 2 H), 6.99 (d, J = 8.0 Hz, 2 H), 3.92 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.56, 163.23, 138.30, 132.57, 131.89, 130.17, 129.74, 128.19, 113.56, 55.51.

2.3d. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (d, J = 8.2 Hz, 2 H), 7.89 (d, J = 8.2 Hz, 2 H), 7.83 (d, J = 7.5 Hz, 2 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.53 (t, J = 7.7 Hz, 2 H), 2.70 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.52, 195.96, 139.57, 136.92, 133.00, 130.11, 130.05, 128.49, 128.17, 26.92.

2.3e. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, J = 7.7 Hz, 2 H), 7.60 (d, J = 6.9 Hz, 1 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.42 (t, J = 7.5 Hz, 1 H), 7.37-7.30 (m, 2 H), 7.30-7.27 (m, 1 H), 2.36 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.64, 138.63, 137.75, 136.75, 133.14, 131.00, 130.24, 130.14, 128.52, 128.46, 125.20, 20.00.

2.3f. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (d, J = 8.0 Hz, 2 H), 7.84 (d, J = 7.7 Hz, 2 H), 7.79 (d, J = 8.0 Hz, 2 H), 7.66 (t, J = 7.4 Hz, 1 H), 7.54 (t, J = 7.6 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.53, 140.74, 136.74, 133.73 (J^F = 32.5 Hz), 133.09, 130.14, 130.11, 128.54, 125.36 (J^F = 7.5 Hz), 123.70 (J^F = 273.0 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -63.41.

2.3g. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.07 (s, 1 H), 7.98 (d, J = 7.8 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.80 (d, J = 7.7 Hz, 2 H), 7.63 (t, J = 7.6 Hz, 2 H), 7.52 (t, J = 7.6 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.32, 138.45, 136.92, 133.25, 133.14, 131.17 (J^F = 32.7 Hz), 130.16, 129.09, 128.97 (J^F = 7.5 Hz), 128.71, 126.84 (J^F = 8.8 Hz), 123.84 (J^F = 272.9 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -62.77.

2.3h. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90-7.84 (m, 2 H), 7.79 (d, J = 7.7 Hz, 2 H), 7.62 (t, J = 6.9 Hz, 1 H), 7.51 (t, J = 7.4 Hz, 2 H), 7.18 (t, J = 8.2 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.26, 165.39 (J^F = 254.1 Hz), 137.51, 133.81 (J^F = 2.5 Hz), 132.67 (J^F = 8.8 Hz), 132.47, 129.88, 128.36, 115.45 (J^F = 21.4 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -105.98.

2.3i. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (dt, J = 40.7, 18.4 Hz, 4 H), 7.03-6.87 (m, 1 H), 6.40 (d, J = 41.0 Hz, 2 H), 6.13 (d, J = 40.9 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 193.95, 162.74 (J^F = 250.3 Hz), 162.65 (J^F = 251.6 Hz), 136.40, 133.16, 129.98, 128.59, 112.96 (J^F = 20.1 Hz), 107.73 (J^F = 25.8 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -108.15.

2.3j. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.17 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H), 7.83 (d, J = 7.5 Hz, 2 H), 7.64 (t, J = 7.4 Hz, 1 H), 7.53 (t, J = 7.6 Hz, 2 H), 3.99 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.03, 166.32, 141.33, 136.96, 133.22, 132.95, 130.11, 129.78, 129.50, 128.47, 52.48.

2.3k. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98-7.96 (d, J = 8.2 Hz, 2 H), 7.58-7.56 (t, J = 7.5 Hz, 1 H), 7.50-7.47 (t, J = 7.7 Hz, 2 H), 3.31-3.27 (t, J = 11.5 Hz, 1 H), 1.93-1.86 (m, 4 H), 1.78-1.75 (d, J = 11.7 Hz, 1 H), 1.54-1.49 (t, J = 13.4 Hz, 2 H), 1.46-1.39 (m, 2 H), 1.34-1.31 (d, J = 12.5 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 203.92, 136.38, 132.73, 128.59, 128.27, 45.65, 29.44, 25.98, 25.88.

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Chapter 3

3. Development of New Acyl Coupling Reagents by N-C Amide Bond Cleavage

3.1 *N*-Acyl-phthalimides: Efficient Acyl Coupling Reagents in Suzuki-Miyaura Cross-Coupling by N–C Cleavage Catalyzed by Pd-PEPPSI Precatalysts

3.1.1. Introduction

The cross-coupling of amides by transition-metal-catalyzed N–C acyl cleavage has emerged as a powerful method for the construction of C–C and C–X bonds, enabling to utilize traditionally-inert amide derivatives in cross-coupling reactions of general synthetic importance.[1-8] The amide bond cross-coupling manifold hinges upon the availability of amide bond precursors to achieve facile metal insertion into the N–C bond under operationally-simple and functional group tolerant reaction conditions.[9-10] The ability to overcome amidic resonance ($n_N \rightarrow \pi^*_{C=O}$ conjugation, 15-20 kcal/mol in planar amides)[11] hinges upon electronic amide bond ground-state-destabilization and amide bond twist, which are well-known to facilitate oxidative addition of the N–C(O) bond.[12]

At the beginning of this project, a wide range of amides and amide-based reagents, including the most reactive *N*-acyl-glutarimides[13] as well as anilides,[14] *N*-Boc-

carbamates,[15] *N*-Ts-sulfonamides[16] *N,N*-di-Boc amides,[17] *N*-acyl-saccharins,[18,19] *N*-Ms-sulfonamides,[20] *N*-acyl-pyrroles,[21] *N*-Me-pyrimidines,[22] *N*-acyl-succinimides[23-25] and *N*-Acyl-amides[26] have been successfully engaged as electrophilic cross-coupling partners by N–C activation. In all examples described, the reactivity has been controlled by a ground-state-destabilization mechanism of the amide bond.[12] However, the widely-used as acylating reagents in organic synthesis *N*-acyl-phthalimides,[27-29] relying on the versatile phthalimide ring typically associated with the classical Gabriel synthesis,[30-32] have not been developed as cross-coupling reagents by N–C(O) bond cleavage.

Our previous structural studies showed high amide bond twist (τ= 55.0°; χ_N= 8.4°, Winkler-Dunitz distortion parameters)[33] and electronically-disconnected amide bond (RE= 0 kcal/mol, RE = resonance energy)[34] in a model benzoyl-phthalimide; note that both of these features are also the controlling amide bond destabilization factors in *N*-acyl-glutarimides, the most reactive amide-based acyl-transfer reagents discovered at this point. However, the major challenge in N–C(O) metal insertion in *N*-acyl-phthalimides are benzylic carbonyls prone to unselective cleavage and/or hydrolysis.

Simultaneously, the development of new catalyst systems resulted in major advancements in acyl cross-coupling of bench-stable amide electrophiles. In particular, Pd-NHC catalysis (NHC = N-heterocyclic carbenes),[35,36] has revolutionized the field and enabled to employ previously unreactive amide precursors under mild and functional group tolerant conditions owing to the strong σ-donating character of NHC ancillary ligands.[37-40]

On the basis of our interest in amide bond cross-coupling and the development of new catalyst systems, we were intrigued to develop the cross-coupling of *N*-acyl-phthalimides

with high N–C(O) insertion selectivity. We have reported a general, highly selective method for Suzuki-Miyaura cross-coupling of *N*-acyl-phthalimides via N–C(O) acyl cleavage catalyzed by Pd-PEPPSI type precatalysts (Scheme 3.3.1.).[41]

The following features of our findings were notable: (1) The method introduced *N*-acyl-phthalimides as new, bench-stable, highly reactive, twist-controlled, amide-based precursors to acyl metal intermediates. (2) The reaction delivered functionalized biaryl ketones by acylative Suzuki-Miyaura cross-coupling with readily available boronic acids. (3) We demonstrated that easily prepared and broadly applicable Pd-PEPPSI type precatalysts supported by a sterically-demanding IPr ancillary ligand provide high yields in this reaction. (4) Selectivity studies and the effect of Pd-NHC complexes with allyl-type throw-away ligands were also studied. Overall, *N*-acyl-phthalimides should find significant use as amide-based acyl coupling reagents and cross-coupling precursors en route to acyl-metal intermediates.

A) Amide bond cross-coupling manifold

amides   selective N–C activation

acyl coupling

decarbonylative coupling

B) Suzuki-Miyaura cross-coupling of N-acyl-phthalimides (this work)

$+ \ Ar-B(OH)_2$ $\xrightarrow{\text{[Pd-NHC]}}$

■ *N-acyl-phthalimides = "half-twisted", electronically-activated amides*

■ *bench-stable, crystalline*
■ *low price, commercially-available*
■ *selective N–C activation*
■ *broad utility in nucleophilic addition*
■ *unexplored in transition-metal-catalysis*
■ *air-stable, practical Pd(II)-NHCs*

twist tunable reactivity $\tau = 55.0°; \ \chi N = 8.4°$

Scheme 3.1.1. (A) Context of this Work; (B) Cross-Coupling of *N*-Acyl-phthalimides by N–C Activation.

3.1.2. Reaction Optimization

At the beginning of this project, the coupling of *N*-benzoyl-phthalimide with 4-tolylboronic acid was selected as the model system. Selected optimization results are shown in Table 3.3.1. *N*-Benzoyl-phthalimide is unreactive under various Pd-phosphine conditions as well as in the more harsh Negishi cross-coupling.[42] From the start, we selected Pd-PEPPSI type precatalysts as our desired precatalysts for this coupling owing to the low price, ease of synthesis and various types of Pd-PEPPSI precatalysts reported to date in diverse cross-couplings.[43-45]

We were delighted to find that the desired cross-coupling proceeded in promising 27% yield using Pd-PEPPSI-IPr (3 mol%), 4-TolB(OH)$_2$ (2.0 equiv) and K$_2$CO$_3$ (3.0 equiv) in

dioxane at 60°C (entry 1). Increasing the reaction temperature had a major effect on the reaction efficiency, affording the product in 80% yield (entry 2). Our further attempts to improve the efficiency by changing the reaction stoichiometry were unsuccessful (entries 3-4). However, we found that by carefully optimizing reaction temperature, the cross-coupling could be achieved in 90% yield (entries 5-6), presumably by improving stability of the acyl-metal intermediate. Interestingly, we found that the solvent choice had a major impact on the reaction (entry 7), while water[46] had a deleterious effect on the cross-coupling (entries 8-9), likely due to hydrolysis.

We gained key insight by evaluating several sterically- and electronically-differentiated Pd-NHC precatalysts (entries 10-12, Figure 3.1.1.). The use of less sterically-demanding IMes ligand significantly decreased the reactivity (entry 10).[47] Similarly, the extremely-sterically-bulky IPr*[48] ligand resulted in a considerable lower yield under the optimized conditions (entry 11). Furthermore, the use of a sterically-demanding aliphatic wingtip, as in IBu^t,[49] resulted in virtually no conversion (entry 12). Generally, IPr is considered as a privileged NHC scaffold in the cross-coupling of aryl electrophiles.[37-40] Our study provided one of the first experimental observations into the ligand effect in the cross-coupling of acyl electrophiles by the Pd-NHC catalysis platform. While further studies will provide additional information about structure-activity relationship, on the basis of our results it appears that IPr should be routinely selected as the first choice in examining the reactivity of amides with Pd-NHC catalysts.

Table 3.1.1. Optimization of the Suzuki-Miyaura Cross-Coupling of *N*-Acyl-phthalimides.[a]
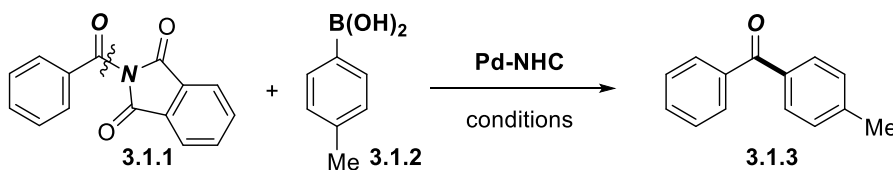
Entry	Catalyst	Ar-B(OH)$_2$ (equiv)	K$_2$CO$_3$ (equiv)	Solvent	T (°C)	Yield (%)
1	Pd-PEPPSI-IPr	2.0	3.0	dioxane	60	27
2	Pd-PEPPSI-IPr	2.0	3.0	dioxane	110	80
3[b]	Pd-PEPPSI-IPr	2.0	3.0	dioxane	110	80
4	Pd-PEPPSI-IPr	3.0	4.5	dioxane	110	50
5	Pd-PEPPSI-IPr	3.0	4.5	dioxane	80	90
6	Pd-PEPPSI-IPr	2.0	3.0	dioxane	80	89
7	Pd-PEPPSI-IPr	2.0	3.0	THF	80	27
8[c]	Pd-PEPPSI-IPr	2.0	3.0	THF	80	32
9[c]	Pd-PEPPSI-IPr	2.0	3.0	dioxane	80	<10
10	Pd-PEPPSI-IMes	2.0	3.0	dioxane	80	30
11	Pd-PEPPSI-IPr*	2.0	3.0	dioxane	80	24
12	Pd-PEPPSI-IBu^t	2.0	3.0	dioxane	80	<5

[a]Conditions: amide (1.0 equiv), 4-Tol-B(OH)$_2$, base, [Pd-NHC] (3 mol%), solvent (0.25 M), *T*, 15 h. [b][Pd-NHC](6 mol%). [c]H$_2$O(5 equiv).
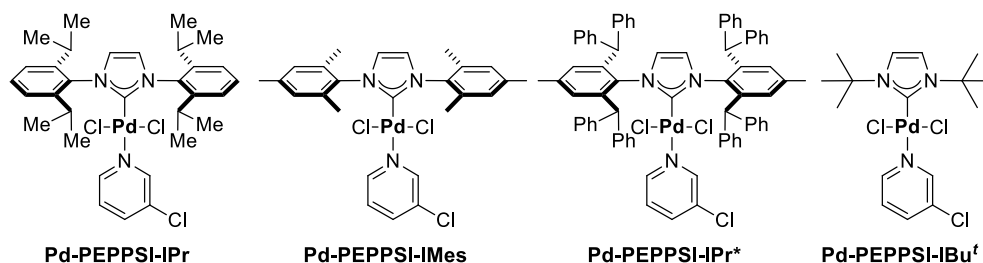
Figure 3.1.1. Structures of Air-Stable Pd-PEPPSI Catalysts in Cross-Coupling of *N*-Acyl-phthalimides.

3.1.3. Scope of the Reaction

With the optimized catalyst system in hand, we next investigated the scope of the reaction with respect to the *N*-acyl-phthalimide component (Scheme 3.1.2.). We were pleased to find that the reaction readily accommodated electronically-diverse substituents (**3.1.3a-3.1.3c**), including deactivating electron-donating groups (**3.1.3b**). Importantly, the reaction was compatible with electrophilic functional groups, such as ketones (**3.1.3d**) and esters (**3.1.3e**). It should be noted that these moieties would not be tolerated in the classic Weinreb amide synthesis.[50] Furthermore, polyfluorinated substrates (**3.1.3f**), biaryl amides (**3.1.3g**) as well as heterocycles important from the medicinal chemistry standpoint (**3.1.3h**) were competent substrates for the cross-coupling. Finally, the reaction conditions were even compatible with the challenging alkyl amides (**3.1.3i**), which often required extensive optimization of the reaction parameters due to less facile metal insertion.[1-8]

Scheme 3.1.2. Amide Scope in Pd-NHC-Catalyzed Cross-Coupling of *N*-Acyl-phthalimides.[a]
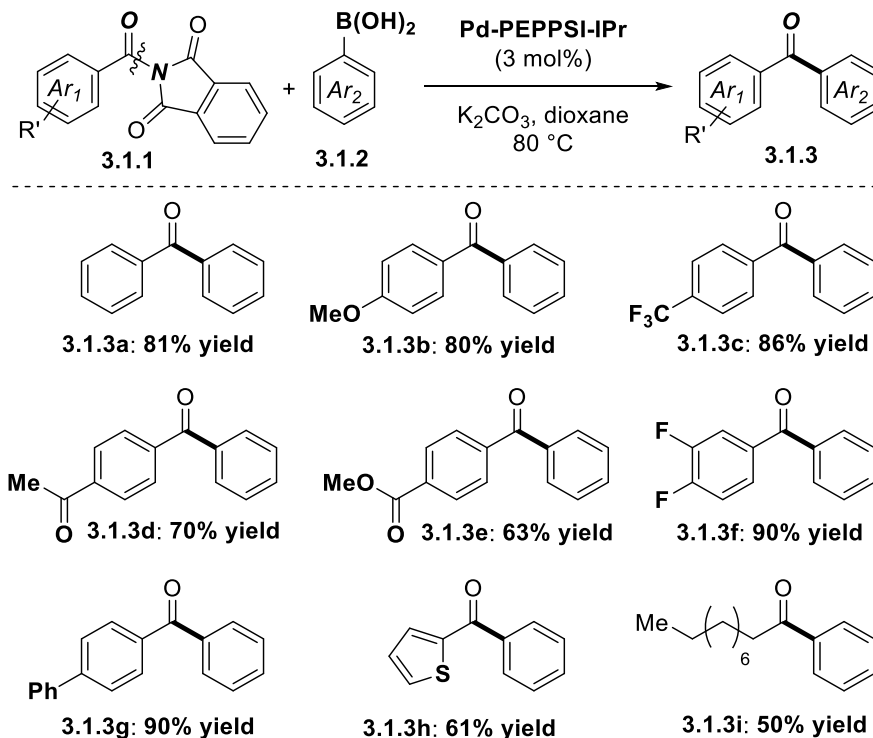
[a]Conditions: amide (1.0 equiv), ArB(OH)$_2$ (2.0 equiv), K$_2$CO$_3$ (3.0 equiv), Pd-PEPPSI-IPr (3 mol%), dioxane (0.25 M), 80 °C, 15 h.

Next, the scope of the reaction with respect to the boronic acid component was examined (Scheme 3.1.3.). Pleasingly, we found this scope to be also broad, including a range of electron-donating (**3.1.3j-3.1.3b'**) and deactivated electron-withdrawing functional groups (**3.1.3c'**). Furthermore, steric hindrance was readily tolerated (**3.1.3k-3.1.3l**). As an important synthetic advantage, the reaction could be used to install electrophilic functional groups that would be problematic in stoichiometric nucleophilic additions, such as aldehydes (**3.1.3m**) and ketones (**3.1.3d'**). Finally, we were pleased to find that heterocyclic boronic acids were also tolerated in this cross-coupling (**3.1.3n**).

Scheme 3.1.3. Boronic Acid Scope in Pd-NHC-Catalyzed Cross-Coupling of *N*-Acyl-Phthalimides.*[a]*
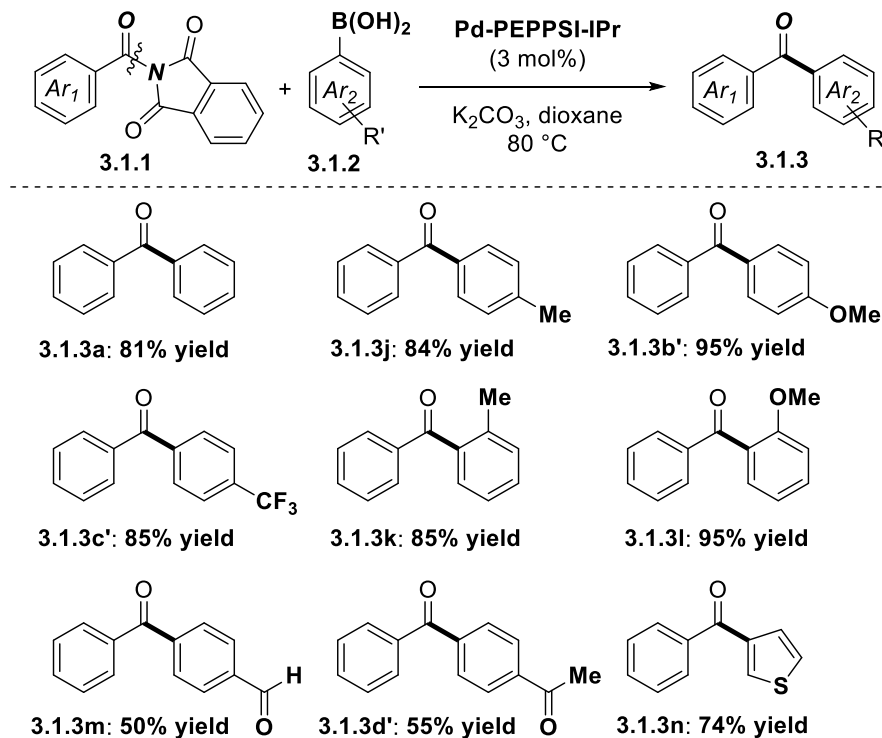
3.1.3a: 81% yield   3.1.3j: 84% yield   3.1.3b': 95% yield

3.1.3c': 85% yield   3.1.3k: 85% yield   3.1.3l: 95% yield

3.1.3m: 50% yield   3.1.3d': 55% yield   3.1.3n: 74% yield

*[a]*Conditions: amide (1.0 equiv), ArB(OH)$_2$ (2.0 equiv), K$_2$CO$_3$ (3.0 equiv), Pd-PEPPSI-IPr (3 mol%), dioxane (0.25 M), 80 °C, 15 h.

3.1.4. Mechanistic Studies

We conducted selectivity studies to gain insight into the reactivity of *N*-acyl-phthalimides in this N–C(O) cleavage reaction (Scheme 3.1.4). *N*-Acyl-phthalimides represent "half-twisted", electronically-activated amides (τ = 55.0°).[33] As expected, these reagents are more selective than "fully-perpendicular" (τ = 88.6°) *N*-acyl-glutarimides (Scheme 3.1.4.A). Importantly, full selectivity in the cross-coupling of *N*-acyl-phthalimides in the presence of electronically-activated pfp esters (pfp = pentafluorophenyl, see Chapter 2) was observed (Scheme 3.1.4.B),[51] thus confirming the unique activation platform of the

amide bond, wherein the selectivity is tuned by both sterics an electronics of N-substituents that is not possible with other acyl electrophiles.
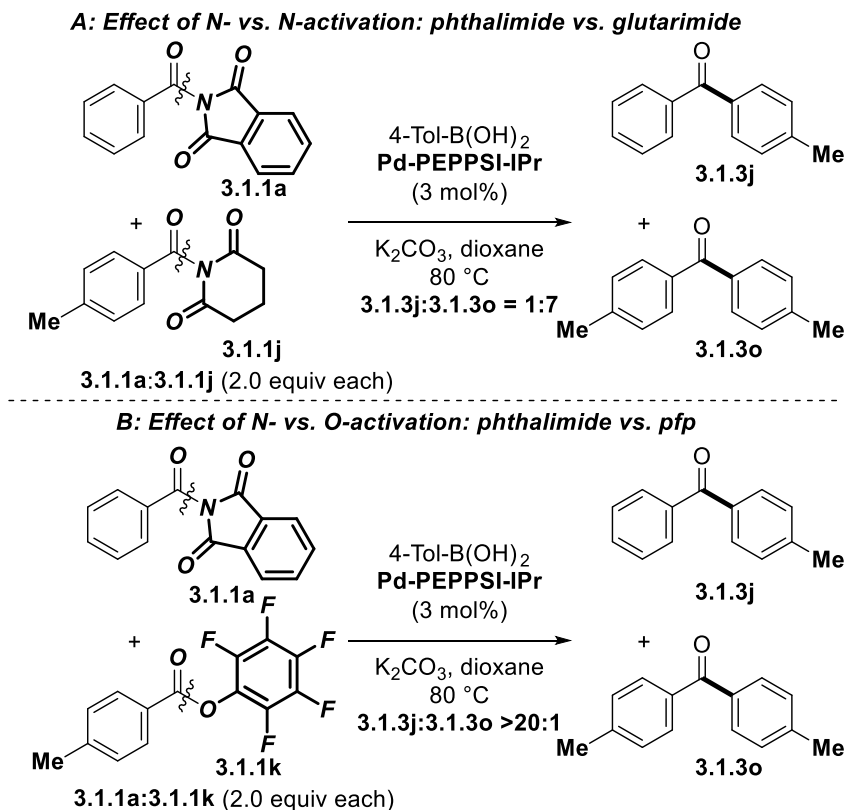
Scheme 3.1.4. Competition Experiments.

Finally, although we were primarily interested in developing a cross-coupling method using readily-available Pd-PEPPSI type precatalysts, we considered it important to compare the reactivity of Pd-NHC precatalysts bearing pyridine throw-away ligands with allyl-type throw-away ligands (Scheme 3.1.5.).[52] Importantly, we found that Pd-NHC precatalysts bearing allyl-type ligands, including (IPr)Pd(allyl)Cl,[53] (IPr)Pd(cinnamyl)Cl[53] and (IPr)Pd(η^3-1-t-Bu-indenyl)Cl[54] all were able to promote the cross-coupling, providing the desired product in high yields. Thus, as an important synthetic point, this cross-coupling is tolerant to the nature of the throw-away ligand.
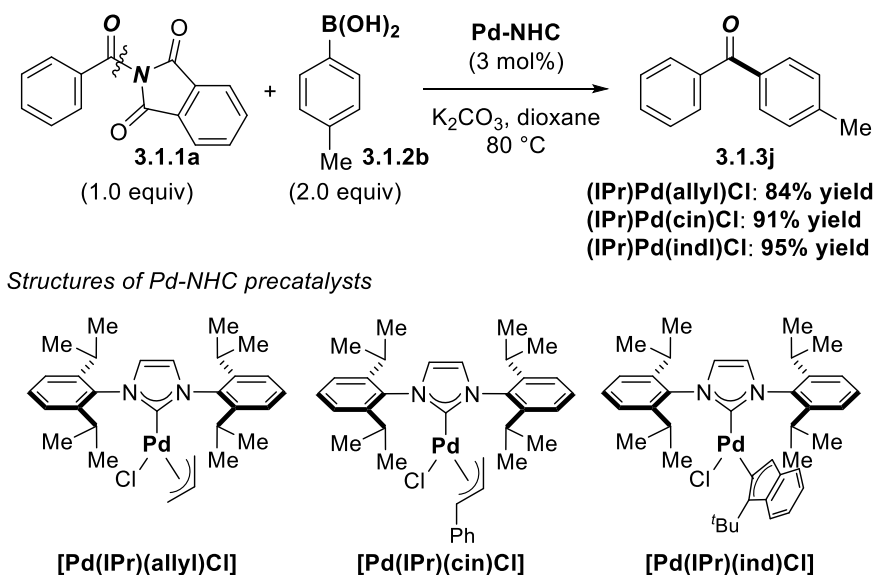
Scheme 3.1.5. Suzuki-Miyaura Cross-Coupling of *N*-Acyl-Phthalimides using Pd-NHC Catalysts with Allyl-Type Throw-Away Ligands.

3.1.5. Conclusion

In conclusion, we have developed a general method for the Suzuki-Miyaura cross-coupling of *N*-acyl-phthalimides using a rational approach to amide bond ground-state-destabilization. Our study markedly highlighted the superb efficiency and selectivity of Pd-NHC precatalysts to achieve cross-coupling of previously incompatible substrates. In a broader context, this work introduced *N*-acyl-phthalimides as new, bench-stable, highly reactive, twist-controlled, amide-based precursors to acyl metal intermediates. Thus, *N*-acyl-phthalimides, classic reagents that rely on the versatile phthalimide ring typically associated with the Gabriel synthesis, are now available for amide bond cross-coupling reactions to afford acyl-metal intermediates. Importantly, this study also provided key insights into the structure-reactivity relationship of Pd-NHC precatalysts in amide bond cross-coupling. Our findings should facilitate a direct use of versatile *N*-acyl-

phthalimides in amide-based cross-coupling reactions that rely on a selective metal insertion into the N–C bond.

3.1.6. Experimental Section

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

General Procedure for Cross-Coupling of *N*-Acyl-Phthalimides. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv), boronic acid (typically, 2.0 equiv), potassium carbonate (typically, 3.0 equiv), Pd-PEPPSI-IPr (typically, 3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dioxane (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 80 °C, and stirred for the indicated time at 80 °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, selectivity and yield using internal standard and comparison with authentic samples.

Representative Procedure for Cross-Coupling of *N*-Acyl-Phthalimides. An oven-dried vial equipped with a stir bar was charged with 2-benzoylisoindoline-1,3-dione (neat, 281.3 mg, 1.0 mmol), 4-tolylboronic acid (272.0 mg, 2.0 mmol, 2.0 equiv), K_2CO_3 (414.6 mg, 3.0 mmol, 3.0 equiv), Pd-PEPPSI-IPr (3 mol%, 20.4 mg), 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 80 °C, and stirred for 15 h at 80 °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 ^{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. Yield 84% (165.0 mg).

White solid. All other yields represent yields determined by ^{1}H NMR (CDCl$_3$, 500 MHz) analysis.

Characterization Data for Products 3.1.3a-3.1.3n.

3.1.3a. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, J = 8.9 Hz, 4 H), 7.62 (t, J = 7.4 Hz, 2 H), 7.51 (t, J = 7.6 Hz, 4 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.75, 137.61, 132.42, 130.07, 128.28.

3.1.3b. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.86 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 7.6 Hz, 2 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.50 (t, J = 7.4 Hz, 2 H), 6.99 (d, J = 8.0 Hz, 2 H), 3.92 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.56, 163.23, 138.30, 132.57, 131.89, 130.17, 129.74, 128.19, 113.56, 55.51.

3.1.3c. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (d, J = 8.0 Hz, 2 H), 7.84 (d, J = 7.7 Hz, 2 H), 7.79 (d, J = 8.0 Hz, 2 H), 7.66 (t, J = 7.4 Hz, 1 H), 7.54 (t, J = 7.6 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.53, 140.74, 136.74, 133.73 (J^F = 32.5 Hz), 133.09, 130.14, 130.11, 128.54, 125.36 (J^F = 7.5 Hz), 123.70 (J^F = 273.0 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -63.41.

3.1.3d. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (d, J = 8.2 Hz, 2 H), 7.89 (d, J = 8.2 Hz, 2 H), 7.83 (d, J = 7.5 Hz, 2 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.53 (t, J = 7.7 Hz, 2 H), 2.70 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.52, 195.96, 139.57, 136.92, 133.00, 130.11, 130.05, 128.49, 128.17, 26.92.

3.1.3e. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.17 (d, J = 8.2 Hz, 2 H), 7.87 (d, J = 8.2 Hz, 2 H), 7.83 (d, J = 7.5 Hz, 2 H), 7.64 (t, J = 7.4 Hz, 1 H), 7.53 (t, J = 7.6 Hz, 2 H),

3.99 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.03, 166.32, 141.33, 136.96, 133.22, 132.95, 130.11, 129.78, 129.50, 128.47, 52.48.

3.1.3f. 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).

3.1.3g. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94-7.92 (d, J = 7.2 Hz, 2 H), 7.88-7.86 (d, J = 7.5 Hz, 2 H), 7.75-7.73 (d, J = 7.3 Hz, 2 H), 7.69-7.68 (d, J = 7.7 Hz, 2 H), 7.65-7.62 (t, J = 7.1 Hz, 1 H), 7.55-7.50 (m, 4 H), 7.45-7.42 (t, J = 6.7 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.38, 145.26, 140.01, 137.79, 136.26, 132.40, 130.75, 130.02, 128.99, 128.33, 128.21, 127.33, 126.99.

3.1.3h. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90-7.89 (d, J = 8.2 Hz, 2 H), 7.76-7.75 (d, J = 4.9 Hz, 1 H), 7.68-7.67 (d, J = 3.7 Hz, 1 H), 7.64-7.61 (t, J = 7.5 Hz, 1 H), 7.54-7.51 (t, J = 7.7 Hz, 2 H), 7.20-7.19 (t, J = 4.8 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 188.26, 143.67, 138.18, 134.86, 134.22, 132.28, 129.20, 128.43, 127.97.

3.1.3i. Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.99-7.98 (d, J = 8.2 Hz, 2 H), 7.59-7.56 (t, J = 7.6 Hz, 1 H), 7.50-7.47 (t, J = 7.7 Hz, 2 H), 3.00-2.97 (t, J = 7.6 Hz, 2 H), 1.79-1.73 (m, 2 H), 1.43-1.29 (m, 12 H), 0.92-0.89 (t, J = 6.1 Hz, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 200.66, 137.12, 132.86, 128.56, 128.07, 38.66, 31.89, 29.50, 29.49, 29.40, 29.30, 24.41, 22.68, 14.12.

3.1.3j. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 (d, J = 7.7 Hz, 2 H), 7.75 (d, J = 7.5 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.50 (t, J = 7.2 Hz, 2 H), 7.31 (d, J = 7.7 Hz, 2 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.49, 143.22, 137.98, 134.90, 132.14, 130.31, 129.93, 128.97, 128.20, 21.66.

3.1.3k. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, J = 7.7 Hz, 2 H), 7.60 (d, J = 6.9 Hz, 1 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.42 (t, J = 7.5 Hz, 1 H), 7.37-7.30 (m, 2 H), 7.30-7.27 (m, 1 H), 2.36 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.64, 138.63, 137.75, 136.75, 133.14, 131.00, 130.24, 130.14, 128.52, 128.46, 125.20, 20.00.

3.1.3l. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85-7.83 (d, J = 7.7 Hz, 2 H), 7.59-7.56 (t, J = 7.5 Hz, 1 H), 7.51-7.48 (t, J = 7.4 Hz, 1 H), 7.47-7.44 (t, J = 7.2 Hz, 2 H), 7.39-7.38 (d, J = 7.7 Hz, 1 H), 7.08-7.05 (t, J = 7.2 Hz, 1 H), 7.03-7.01 (d, J = 7.7 Hz, 1 H), 3.75 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.48, 157.37, 137.83, 132.93, 131.88, 129.85, 129.61, 128.88, 128.22, 120.50, 111.46, 55.62.

3.1.3m. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 10.16 (s, 1 H), 8.04-8.02 (d, J = 8.3 Hz, 2 H), 7.96-7.95 (d, J = 8.2 Hz, 2 H), 7.84-7.83 (d, J = 7.1 Hz, 2 H), 7.68-7.65 (t, J = 7.5 Hz, 1 H), 7.55-7.52 (t, J = 7.9 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.85, 191.65, 142.59, 138.49, 136.76, 133.16, 130.35, 130.14, 129.52, 128.56.

3.1.3n. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (s, 1 H), 7.88-7.87 (d, J = 8.1 Hz, 2 H), 7.64-7.60 (m, 2 H), 7.53-7.50 (t, J = 7.7 Hz, 2 H), 7.42-7.41 (m, 1 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 190.03, 141.33, 138.66, 133.93, 132.32, 129.39, 128.64, 128.40, 126.22.

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3.2 *N*-Acyl-Carbazoles and *N*-Acyl-Indoles: Electronically-Activated Amides for N–C(O) Cross-Coupling by N_{lp} to Ar Conjugation Switch

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3.2.1. Introduction

Activation of amide bonds by selective oxidative insertion into the N–C(O) bond is a particularly attractive strategy for generating acyl-metals from amides.[1,2] Traditionally, the selective activation of N–C(O) amide bonds has been a major challenge due to the classic amidic resonance (nN→π*$_{C=O}$ conjugation, RE, resonance energy, 15-20 kcal/mol in planar amides) (Figure 3.2.1.A-B).[3] In this context, the development of catalytic amide bond cross-couplings is of broad interest to selectively functionalize organic molecules due to the ubiquity of amide bonds in organic synthesis, polymers and drug discovery.[4,5]

Recently, methods for ground-state-destabilization of amide bonds in acyclic amides have been reported.[6–9] The most common is n_N→π*$_{C(O)=O}$ and n_N→π*$_{S=O}$ delocalization in *N*-acyl-carbamates and *N*-acyl-sulfonamides.[7] Alternatively, *N*-acyl-glutarimides[8] and *N*-acyl-mono-amides[9] represent twisted tri- and di-imides that rely on n_N→π*$_{C(R)=O}$ destabilization. This activation concept leads to the twisting of amide bonds out of planarity and enables the catalytic generation of acyl-metals by a combined steric and electronic destabilization.[10–12]

In contrast, at the begining of this project few methods for selective activation of comparatively planar, electronically-activated N-Ar amides have been reported.[13–15] These studies were predominantly limited to *N*-methyl-anilides (RE = 13.5 kcal/mol),[13] which have been successfully utilized in the oxidative addition of N–C(O) bond to Ni; however, were unreactive using other metals. Although *N*-acyl-pyrroles (RE = 9.3 kcal/mol) have been shown to be reactive electrophiles in the oxidative addition of N–C(O) bonds using Pd, these substrates are unsuitable as amides for general cross-coupling reactions due to their well-recognized hydrolytic instability triggered by the release of the azolide ring.[16–18]

On the basis of our research on amide bond activation, we proposed that N_{lp} to Ar conjugation switch in N-Ar amides might be used to effect highly selective oxidative insertion into the amide N–C(O) bond (Figure 3.2.1.C).[19] We reported the palladium-catalyzed Suzuki–Miyaura cross-coupling of *N*-acyl-carbazoles and *N*-acyl-indoles with arylboronic acids by highly selective N–C(O) bond cleavage. The following features of our findings are noteworthy: (1) Our study introduced *N*-acyl-indoles and in particular *N*-acyl-carbazoles as highly effective amide bond electrophiles for selective activation of the N–C(O) bond. (2) The key amide bond ground-state-destabilization stemmed from N_{lp} to Ar conjugation in a flattened carbazole ring; this activation mode is remarkably efficient and enabled for the first time to achieve reactivity similar to *N*-sulfonamide and *N*-carbamate activation in simple anilides. (3) Mechanistic studies provide key insight into bond destabilization of the amide bond. Overall our findings show that bench- and hydrolytically-stable *N*-acyl-azolides that permit facile N–C(O) activation to provide a

very attractive approach to the generation of acyl-metals from amides for a variety of coupling reactions.

■ A. Amide bond resonance (RE = 15-20 kcal/mol, planar amides)
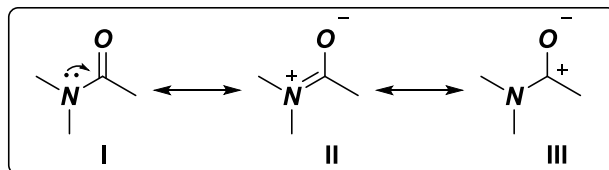
■ B. Cross-coupling of amides. Limitations: increasing reactivity of R'R" groups
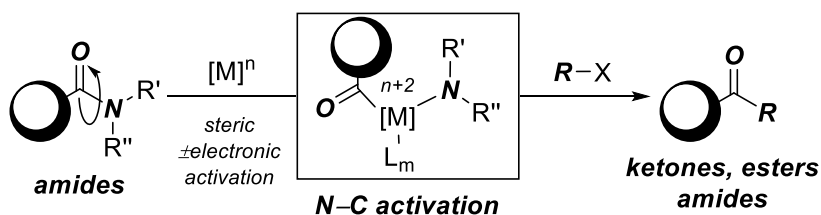
■ anilides: typically unreactive in N−C(O) cross-coupling (RE = 13.5 kcal/mol)

■ C. This study: amide bond destabilization by N_{lp} to Ar switch

■ Cross-coupling of N-acyl-carbazoles and N-acyl-indoles
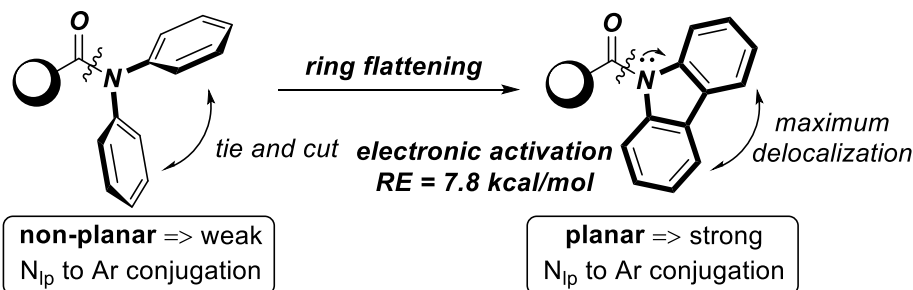
■ Nlp to Ar delocalization switch
■ crystalline, bench-stable solids
■ highly reactive amides for cross-coupling
■ reactivity comparable to N-sulfonamides
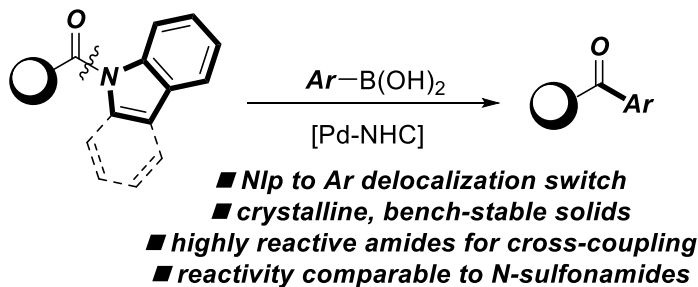
Figure 3.2.1. (A) Amide Bond Resonance. (B) Activation of Amides and Derivatives. (C) This Work: N_{lp} to Ar Conjugation Switch, *N*-Acyl-Carbazoles: New Class of Highly Reactive Amides for N–C(O) Cross-Coupling.

In agreement with our previous studies, we hypothesized that diminution of amidic resonance in anilides might be rendered possible by channeling the $n_N \rightarrow \pi^*_{C=O}$ resonance into another functional group. After significant experimentation, we identified N-acyl-carbazoles as suitable substrates for this process. The amide bond in a model N-benzoyl-carbazole (**3.2.1a**) is relatively planar[16c, d] (τ = 25.1°; χ_N = 3.2°, Winkler-Dunitz parameters, N–C(O) bond length of 1.400 Å, C=O of 1.212 Å), which can be compared with a model predominantly planar N-methyl-anilide (N–C(O) bond length of 1.355 Å, C=O of 1.230 Å).[13]

3.2.2. Reaction Optimization

Selected optimization studies of the Suzuki–Miyaura cross-coupling of N-benzoyl-carbazole (**3.2.1a**) with 4-tolylboronic acid are presented in Table 3.2.1. The optimized conditions utilize Pd–PEPPSI–IPr (3 mol%), K_2CO_3 (4.5 equiv) in THF at 80 °C (Table 3.2.1., entry 1). The use of other bases, including K_3PO_4, Na_2CO_3, Cs_2CO_3 and KOH were less successful (entries 2-5). Several other solvents were examined, such as toluene, dioxane and DCE, and provided inferior results (entries 6-8). Higher temperature was also compatible with this reaction, consistent with the stability of N-acyl-carbazole moiety under these conditions (entry 9). Interestingly, the screen of various Pd(II)–NHC catalysts indicated that catalysts bearing allyl-type throw-away ligands, such as Pd(IPr)(cin)Cl, Pd(IPr)(1-t-Bu-ind)Cl, Pd(IPr)(allyl)Cl are also effective in this reaction, delivering the coupling product in good to high yields (entries 10-12). In contrast, there is a significant impact of the steric demand of the NHC ancillary ligand, with both less-sterically demanding IMes and more-hindered IPent giving low yield of the cross-coupling product (entries 13-14). Finally, we also tested the use of Pd/phosphane

conditions, which resulted in low conversion (entry 15); thus, the high σ-donation of the NHC ligand using bench-stable, well-defined Pd(II)–NHCs is highly beneficial for the coupling.

Table 3.2.1. Optimization of Cross-Coupling of *N*-Acyl-Carbazoles.[a]

entry	Catalyst	base	solvent	yield (%)[b]
1	[Pd–PEPPSI–IPr]	K$_2$CO$_3$	THF	93
2	[Pd–PEPPSI–IPr]	K$_3$PO$_4$	THF	52
3	[Pd–PEPPSI–IPr]	Na$_2$CO$_3$	THF	<5
4	[Pd–PEPPSI–IPr]	Cs$_2$CO$_3$	THF	17
5	[Pd–PEPPSI–IPr]	KOH	THF	13
6	[Pd–PEPPSI–IPr]	K$_2$CO$_3$	toluene	89
7	[Pd–PEPPSI–IPr]	K$_2$CO$_3$	dioxane	51
8	[Pd–PEPPSI–IPr]	K$_2$CO$_3$	DCE	28
9[b]	[Pd–PEPPSI–IPr]	K$_2$CO$_3$	THF	86
10	[Pd(IPr)(cin)Cl]	K$_2$CO$_3$	THF	92
11	[Pd(IPr)(1-*t*-Bu-ind)Cl]	K$_2$CO$_3$	THF	81
12	[Pd(IPr)(allyl)Cl]	K$_2$CO$_3$	THF	71
13	[Pd–PEPPSI–IPent]	K$_2$CO$_3$	THF	50
14	[Pd–PEPPSI–IMes]	K$_2$CO$_3$	THF	15
15[c]	Pd(OAc)$_2$/PCy$_3$HBF$_4$	K$_2$CO$_3$	THF	12

[a]Conditions: amide (1.0 equiv), 4-Tol-B(OH)$_2$ (3.0 equiv), catalyst (3 mol%), base (4.5 equiv), solvent (0.25 M), 80 °C, 15 h. [b]GC/1H NMR yields. [c]120 °C. [d]Pd(OAc)2 (3 mol%), PCy$_3$HBF$_4$ (12 mol%), H$_3$BO$_3$ (2.0 equiv), 80 °C. cin = cinnamyl; ind = indenyl; PEPPSI = 3-Cl-pyridine.

3.2.3. Scope of the Reaction

With the optimized conditions in hand, we examined the scope of this transformation with respect to the amide component (Scheme 3.2.1.). We found that this amide bond activation is well-compatible with neutral (**3.2.3a**), electron-donating (**3.2.3b-3.2.3c**) and electron-withdrawing (**3.2.3d-3.2.3g**) substituents on the amide. It is particularly noteworthy that electrophilic functional groups that would be problematic in classical addition of hard organometallics, such as ketones (**3.2.3f**) and esters (**3.2.3g**) are tolerated under these catalytic conditions. Furthermore, steric-hindrance (**3.2.3h**), aliphatic amides (**3.2.3i**) and heterocyclic amides conjugated at the deactivating, electron-rich position (**3.2.3j-3.2.3k**) were easily tolerated. Next, we examined the scope of the reaction with respect to the boronic acid component (Scheme 3.2.1.). As shown, electron-neutral (**3.2.3b'**), electron-rich (**3.2.3c'**) and electron-deficient (**3.2.3d'**, **2.3.3f'-3.2.3g'**) arylboronic acids were successful substrates, albeit a lower yield using electron-withdrawing groups has been noted. Furthermore, sterically-hindered boronic acids (**3.2.3h'**), polyaromatic boronic acids (**3.2.3l-3.2.3m**) and heterocyclic boronic acids (**3.2.3k'**, **3.2.3n-3.2.3o**) furnished the cross-coupling products in good to high yields.

Encouraged by the success of the Suzuki–Miyaura cross-coupling of *N*-acyl-carbazoles, we investigated the cross-coupling of *N*-acyl-indoles (Scheme 3.2.2). Similar to *N*-acyl-carbazoles, *N*-acyl-indoles are important structural motifs in numerous biologically active compounds and as synthetic intermediates.[16] We were pleased to find that the conditions optimized for the cross-coupling of *N*-acyl-carbazoles are also suitable for the cross-coupling of *N*-acyl-indoles. As shown, electronic- (**3.2.3a**, **3.2.3c**, **3.2.3f**, **3.2.3b'**, **3.2.3c'**,

3.2.3g') and steric variation (**3.2.3h'**) is well-accommodated in the cross-coupling of *N*-acyl-indoles, indicating the generality of the reaction conditions.

Scheme 3.2.1. [Pd–NHC]-Catalyzed Suzuki-Miyaura Cross-Coupling of *N*-Acyl-Carbazoles.[a]

3.2.3a: 93% yield   3.2.3b: 97% yield   3.2.3c: 87% yield

3.2.3d: 95% yield   3.2.3e: 98% yield   3.2.3f: 94% yield

3.2.3g: 98% yield   3.2.3h: 88% yield   3.2.3i: 74% yield

3.2.3j: 96% yield   3.2.3k: 49% yield   3.2.3b': 93% yield

3.2.3c': 98% yield   3.2.3d': 45% yield   3.2.3f': 72% yield

3.2.3g': 78% yield   3.2.3h': 97% yield   3.2.3l: 95% yield

3.2.3m: 94% yield   3.2.3k': 61% yield   3.2.3n: 96% yield (X = O)
                                         3.2.3o: 93% yield (X = S)
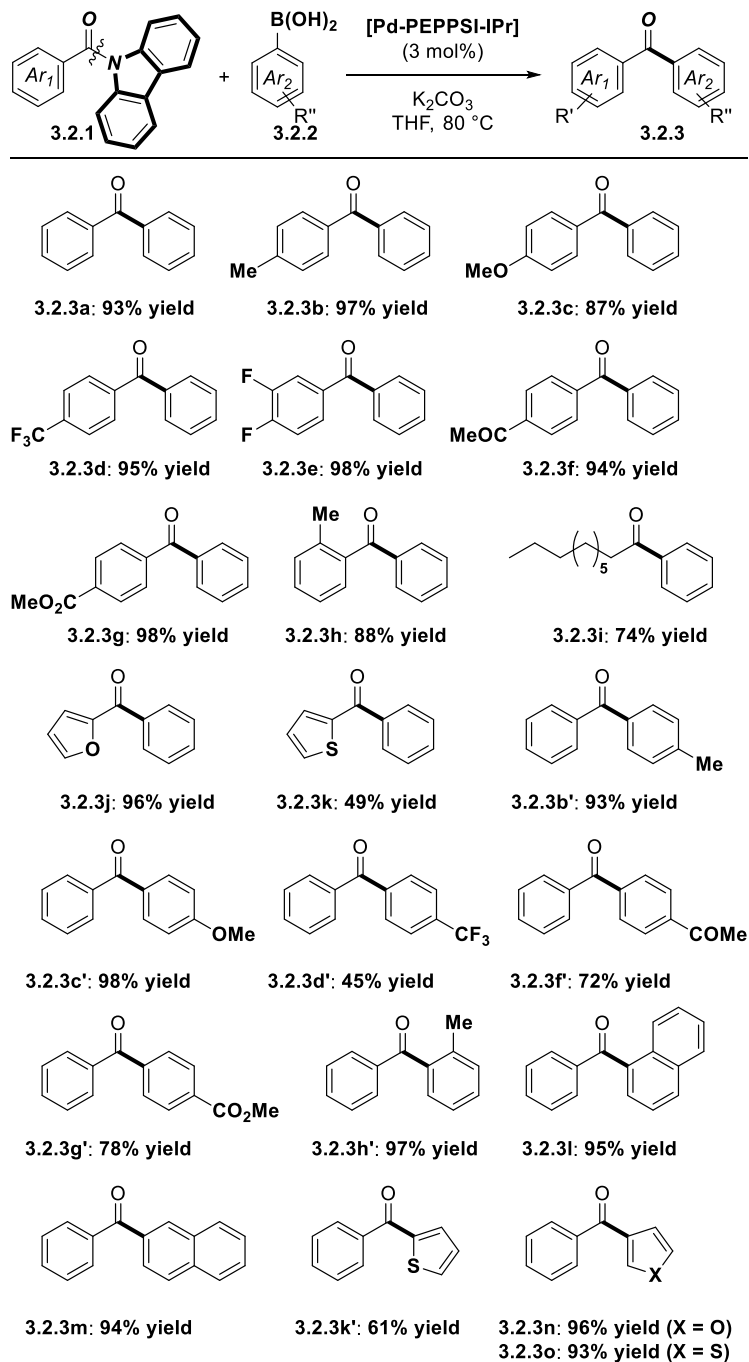
[a]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (3.0 equiv), [Pd] (3 mol%), K$_2$CO$_3$ (4.5 equiv), THF (0.25 M), 80 °C, 15 h.

Scheme 3.2.2. [Pd–NHC]-Catalyzed Suzuki-Miyaura Cross-Coupling of *N*-Acyl-Indoles.[a]

3.2.3a: 91% yield   3.2.3c: 79% yield   3.2.3f: 74% yield

3.2.3b': 91% yield (R = Me)   3.2.3g': 66% yield   3.2.3h': 78% yield
3.2.3c': 98% yield (R = MeO)
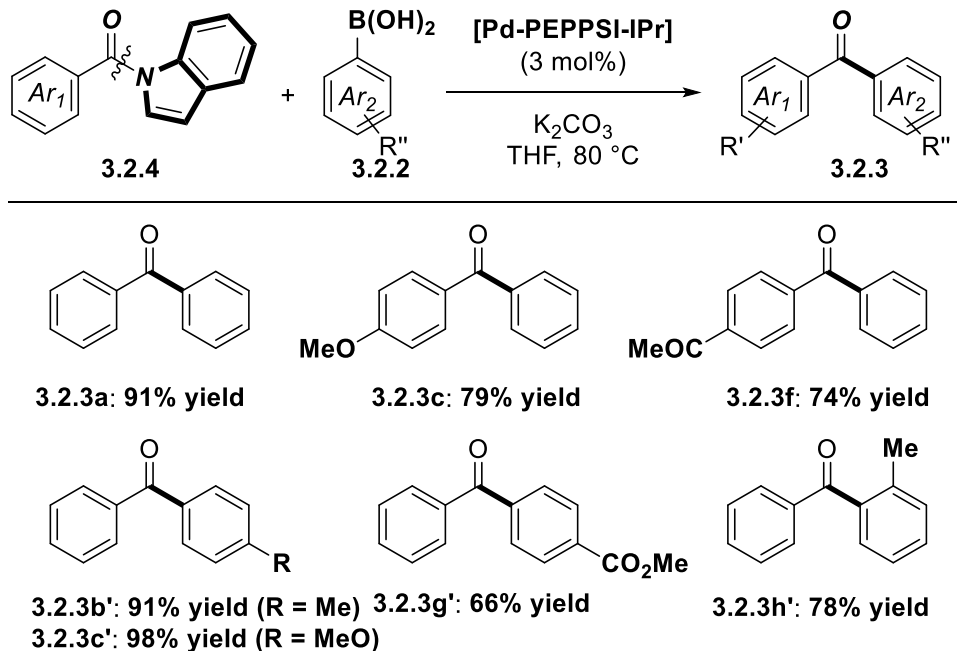
[a]Conditions: see Scheme 3.2.1.

3.2.4. Mechanistic Studies

We were further interested to test *N*-acyl-carbazoles as precursors in acyl-Buchwald-Hartwig-type reactions (Scheme 3.2.3.).[2a] We were pleased to find that a model *N*-benzoyl-carbazole underwent smooth transamidation under Pd–NHC conditions. We expect that this class of reagents will provide an attractive means to trigger various reactions of amides.

Scheme 3.2.3. [Pd–NHC]-Catalyzed Acyl-Buchwald-Hartwig Cross-Coupling of *N*-Acyl-Carbazoles
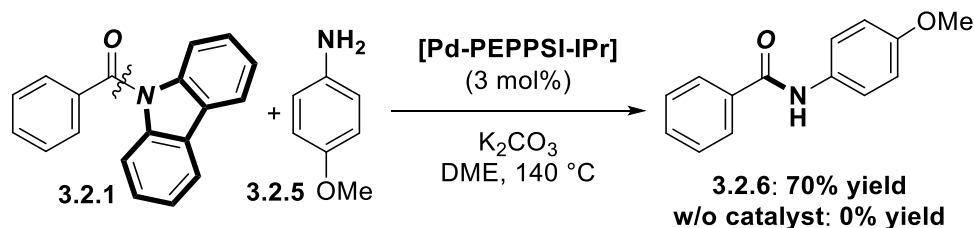
The synthetic advantage of *N*-acyl-carbazoles stems from the well-established stability of the amide bond to hydrolysis conditions, resulting in bench-stable, easily-handled, amide-based acyl-transfer reagents.[16] Furthermore, *N*-acyl-carbazoles are readily prepared from 1° amides by double *N*-arylation or electrophilic cyclization with 2,5-dimethoxytetrahydrofuran (Scheme 3.2.4.).[19] This disconnection permits to generate acyl-metal intermediates from common 1° amides.

Scheme 3.2.4. Synthesis of *N*-Acyl-Carbazoles from 1° Amides
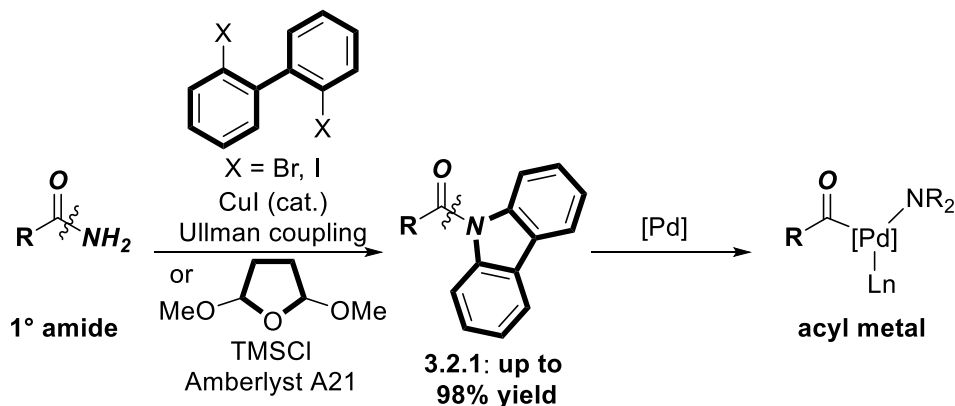
Intrigued by the high reactivity of *N*-acyl-carbazoles in the cross-coupling, we conducted selectivity and kinetic studies (Scheme 3.2.5.). (1) Selectivity experiments demonstrated that *N*-acyl-carbazoles are significantly more reactive than *N*-methyl-anilides (Scheme 3.2.5.A) and *N*-phenyl-anilides (Scheme 3.2.5.B). (2) Intermolecular competition

experiments demonstrated full selectivity for the cross-coupling of *N*-acyl-carbazoles vs.
N-phenyl-anilides (Scheme 3.2.5.C). (3) Most importantly, kinetic studies demonstrated
comparable reactivity of *N*-acyl-carbazoles to *N,N*-Ph/Ts sulfonamide activation (Scheme
3.2.5.D). Thus, *N*-carbazolyl activation permits to achieve reactivity similar to *N*-
sulfonamide activation in simple anilides.[2–18]

Furthermore, intermolecular competition experiments with differently substituted amides
and boronic acids showed that electron-deficient amides are more reactive (4-CF$_3$:4-MeO
= 85:15), while electron-rich boronic acids are more reactive (4-MeO:4-CF$_3$ = 73:27) (not
shown), consistent with metal insertion as the rate limiting step.

Scheme 3.2.5. Selectivity Studies

A. *Effect of electronic activation: N,N-Ph/Me*
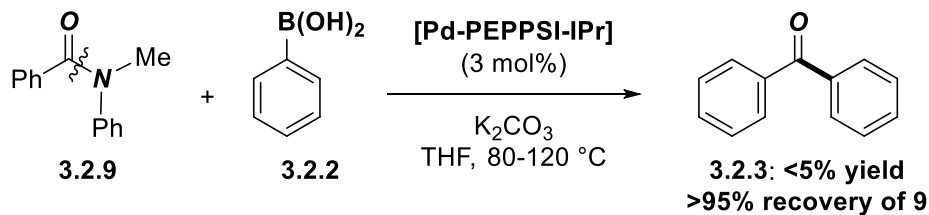
3.2.9 + **3.2.2** → **3.2.3**: **<5% yield**
>95% recovery of 9

B. *Effect of electronic activation: N,N-Ph/Ph*

3.2.8 + **3.2.2** → **3.2.3**: **<20% yield**
>80% recovery of 8

C. *Effect of electronic activation: N-acyl-carbazole vs. N,N-Ph/Ph*

3.2.1b
+
3.2.8
3.2.1b:3.2.8 (2.0 equiv each)

Ph-B(OH)$_2$
[Pd-PEPPSI-IPr]
(3 mol%)

K$_2$CO$_3$, THF
80 °C

3.2.3b:3.2.3a >95:5

3.2.3b
+
3.2.3a
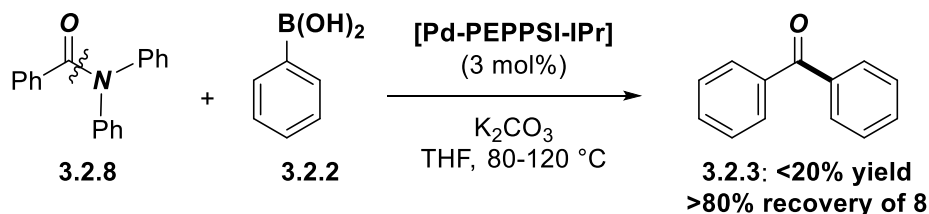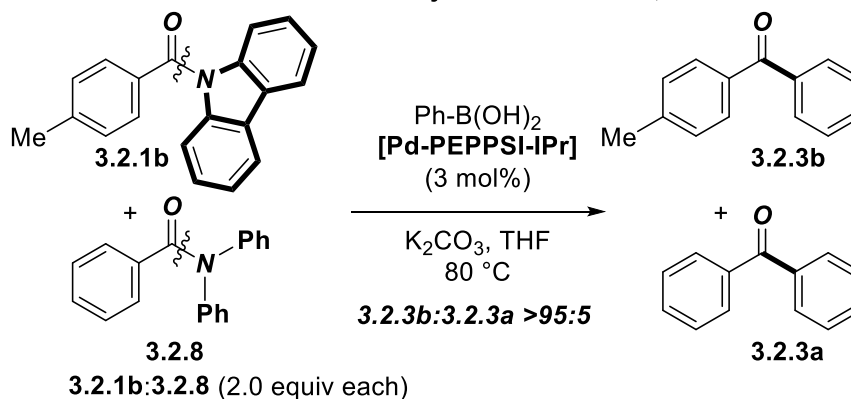
D. *Effect of electronic activation: N-acyl-carbazole vs. N,N-Ts/Ph[a]*

3.2.1a vs. **3.2.10**

Plot of conversion vs. time for **3.2.1a** and **3.2.10**

- (3.2.1a, N-acyl-carbazole)
- (3.2.10, N-acyl-sulfonamide)
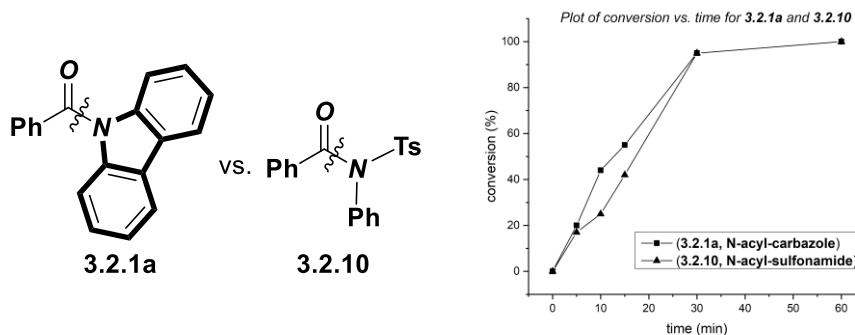
[a]Conditions: amide (1.0 equiv), Ph-B(OH)$_2$ (3.0 equiv) [Pd-PEPPSI-IPr] (3 mol%), K$_2$CO$_3$ (4.5 equiv), THF (0.25 M), 80 °C, 0-60 min.

Destabilization of amidic resonance can be performed by both steric and electronic factors.[2–6] The high feasibility of *N*-acyl-carbazoles in oxidative insertion stems from N_{lp} to Ar conjugation, wherein the presence of carbazole π-system and the planarity of the ring with respect to the amide N_{lp} ensures maximum delocalization switch away from the amide bond.[4,6] We believe that this amide bond delocalization concept is likely to find applications in catalytic reactions of the amide bond[7–18] as well as the design of more active amide bond analogues.[2–6]

3.2.5. Conclusion

In conclusion, we have developed the palladium-catalyzed Suzuki–Miyaura cross-coupling of *N*-acyl-carbazoles and *N*-acyl-indoles with arylboronic acids by highly selective N–C(O) bond cleavage. The reaction was performed using bench-stable and operationally-convenient Pd(II)-NHC precatalysts, and a variety of reaction partners were compatible. This reaction exploited *N*-acyl-indoles and especially *N*-acyl-carbazoles as highly effective amide bond electrophiles for selective oxidative insertion into the N–C(O) bond. Another attractive feature of *N*-acyl-carbazoles was their bench-stability, ease of handling and the potential to generate acyl-metals from 1° amides. Mechanistic studies provided key insight into amide bond ground-state-destabilization and for the first time showed that the reactivity of *N*-acyl-carbazoles is similar to that of N-acyl-sulfonamides. This activation concept of amide bonds by electronic conjugation introduced simple N-Ar amides to be broadly applied in various catalytic processes by N–C(O) bond activation.

3.2.6. Experimental Section

General Methods. All experiments involving transition-metals were performed using Schlenk or glovebox techniques under argon or nitrogen atmosphere unless stated

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

General Procedure for the Suzuki-Miyaura Cross-Coupling. An oven-dried vial equipped with a stir bar was charged with an N-acyl-carbazole or N-acyl-indole substrate (neat, 1.0 equiv), boronic acid (typically, 3.0 equiv), K$_2$CO$_3$ (typically, 4.5 equiv), Pd-NHC precatalyst (3.0 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, and the reaction mixture was placed in

a preheated oil bath at 80 °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 (10mL), 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 (hexanes/ethyl acetate = 10:1) afforded the title product.

Representative Procedure for the Suzuki-Miyaura Cross-Coupling *N*-Acyl-Carbazole. An oven-dried reaction vial equipped with a stir bar was charged with (9*H*-carbazol-9-yl)(phenyl)methanone (1.0 mmol, 271.3 mg, 1.0 equiv), *p*-tolylboronic acid (3.0 mmol, 408.0 mg, 3.0 equiv), K$_2$CO$_3$ (4.5 mmol, 621.9 mg, 4.5 equiv), [Pd-PEPPSI-IPr] (3 mol%, 20.4 mg), 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, and the reaction mixture was placed in a preheated oil bath at 80 °C and stirred for the 15 h. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10mL), filtered and concentrated. A 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 (hexanes/ethyl acetate = 10:1) afforded the title product. Yield 93% (182.0 mg). White solid.

Representative Procedure for the Suzuki-Miyaura Cross-Coupling *N*-Acyl-Indole. An oven-dried reaction vial equipped with a stir bar was charged with (1*H*-indol-1-yl)(phenyl)methanone (1.0 mmol, 221.3 mg, 1.0 equiv), *p*-tolylboronic acid (3.0 mmol, 408.0 mg, 3.0 equiv), K$_2$CO$_3$ (4.5 mmol, 621.9 mg, 4.5 equiv), [Pd-PEPPSI-IPr] (3

mol%, 20.4 mg), 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, and the reaction mixture was placed in a preheated oil bath at 80 °C and stirred for the 15 h. 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 GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate = 10:1) afforded the title product. Yield 91% (178.0 mg). White solid.

General Procedure for the Buchwald-Hartwig Cross-Coupling. An oven-dried reaction vial equipped with a stir bar was charged with an *N*-acyl-carbazole substrate (neat, 1.0 equiv), K_2CO_3 (typically, 3.0 equiv), aniline (typically, 2.0 equiv), Pd-NHC precatalyst (3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Dimethoxyethane (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 140 °C and stirred for the 15 hours. 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 GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (hexanes/ethyl acetate = 4:1) afforded the title product.

Characterization Data

3.2.3a. 93% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.08, 137.96, 132.74, 130.40, 128.61.

3.2.3b. 97% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 – 7.75 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.82, 143.56, 138.31, 135.24, 132.48, 130.64, 130.26, 129.31, 128.54, 21.98.

3.2.3c. 87% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, *J* = 7.9 Hz, 2H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 7.9 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.85, 163.55, 138.62, 132.87, 132.19, 130.49, 130.04, 128.50, 113.88, 55.81.

3.2.3d. 95% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.85 – 7.77 (m, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.65 – 7.60 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.85, 141.08, 137.09, 134.06 (q, J = 132.8 Hz), 133.42, 130.47, 130.44, 128.87, 125.68 (q, *J* = 3.7 Hz), 124.02 (q, *J* = 273.0 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -63.00.

3.2.3e. 98% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.68 (t, *J* = 9.1 Hz, 1H), 7.65 – 7.56 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.24 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.40, 153.58 (J^F = 256.8, 12.9 Hz), 150.50 (J^F = 251.50, 13.0 Hz), 137.24, 134.81 (J^F = 4.1 Hz), 133.13, 130.18, 128.84, 127.43 (J^F = 7.3, 3.7 Hz), 119.66 (J^F = 18.1, 1.5 Hz), 117.61 (J^F = 17.8 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -130.58 (J^F = 20.7 Hz), -136.15 (J^F = 20.7 Hz).

3.2.3f. 94% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.06 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.83 – 7.77 (m, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 2.67 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.83, 196.27, 141.68, 139.91, 137.27, 133.32, 130.43, 130.47, 128.82, 128.50, 27.22.

3.2.3g. 98% yield. 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), 7.81 (d, *J* = 7.9 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.38, 166.67, 141.68, 137.32, 133.58, 133.29, 130.45, 130.12, 129.85, 128.81, 52.81.

3.2.3h. 88% yield. Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 – 7.77 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.40 (td, *J* = 7.5, 1.2 Hz, 1H), 7.31 (dd, *J* = 11.8, 7.6 Hz, 2H), 7.27 – 7.23 (m, 1H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.95, 138.97, 138.09, 137.07, 133.45, 131.32, 130.56, 130.45, 128.83, 128.78, 125.52, 20.30.

3.2.3i. 74% yield. Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.77 – 1.70 (m, 2H), 1.40 – 1.25 (m, 12H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 200.91, 137.46, 133.16, 128.86, 128.38, 38.97, 32.21, 29.82, 29.80, 29.72, 29.62, 24.73, 23.00, 14.43.

3.2.3j. 96% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97 (d, *J* = 7.3 Hz, 2H), 7.71 (s, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 3.4 Hz, 1H), 6.60 (dd, *J* = 3.5, 1.6 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 182.91, 152.66, 147.43, 137.62, 132.91, 129.63, 128.76, 120.88, 112.54.

3.2.3k. 49% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.74 – 7.70 (m, 1H), 7.65 (d, *J* = 3.0 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.17 (dd, *J* = 4.6, 4.1 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 188.56, 144.00, 138.51, 135.16, 134.53, 132.60, 129.51, 128.75, 128.29.

3.2.3b'. 93% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 – 7.75 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.82, 143.56, 138.31, 135.24, 132.48, 130.64, 130.26, 129.31, 128.54, 21.98.

3.2.3c'. 98% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, *J* = 7.9 Hz, 2H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 7.9 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.85, 163.55, 138.62, 132.87, 132.19, 130.49, 130.04, 128.50, 113.88, 55.81.

3.2.3d'. 45% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.85 – 7.77 (m, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.65 – 7.60 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.85, 141.08, 137.09, 134.06 (J^F = 132.8 Hz), 133.42, 130.47, 130.44, 128.87, 125.68 (J^F = 3.7 Hz), 124.02 (J^F = 273.0 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -63.00.

3.2.3f'. 72% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.06 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.83 – 7.77 (m, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 2.67 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.83, 196.27, 141.68, 139.91, 137.27, 133.32, 130.43, 130.47, 128.82, 128.50, 27.22.

3.2.3g'. 78% yield. 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), 7.81 (d, J = 7.9 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.38, 166.67, 141.68, 137.32, 133.58, 133.29, 130.45, 130.12, 129.85, 128.81, 52.81.

3.2.3h'. 97% yield. Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 – 7.77 (m, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.40 (td, J = 7.5, 1.2 Hz, 1H), 7.31 (dd, J = 11.8, 7.6 Hz, 2H), 7.27 – 7.23 (m, 1H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.95, 138.97, 138.09, 137.07, 133.45, 131.32, 130.56, 130.45, 128.83, 128.78, 125.52, 20.30.

3.2.3l. 95% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.10 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.87 (d, J = 7.3 Hz, 2H), 7.63 – 7.57 (m, 2H), 7.57 – 7.49 (m, 3H), 7.47 (t, J = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.34, 138.68, 136.72, 134.07, 133.55, 131.59, 131.31, 130.74, 128.78, 128.74, 128.09, 127.59, 126.79, 126.04, 124.67.

3.2.3m. 94% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.27 (s, 1H), 7.95 (s, 2H), 7.92 (dd, J = 8.2, 2.5 Hz, 2H), 7.87 (d, J = 7.9 Hz, 2H), 7.66 – 7.59 (m, 2H), 7.65 – 7.50 (m, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.09, 138.27, 135.63, 135.19, 132.72, 132.62, 132.21, 130.44, 129.77, 128.69, 128.67, 128.64, 128.17, 127.14, 126.14.

3.2.3k'. 61% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (d, J = 7.2 Hz, 2H), 7.74 – 7.70 (m, 1H), 7.65 (d, J = 3.0 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.17 (dd, J = 4.6, 4.1 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 188.56, 144.00, 138.51, 135.16, 134.53, 132.60, 129.51, 128.75, 128.29.

3.2.3n. 96% yield. Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92 (s, 1H), 7.85 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.52 – 7.46 (m, 3H), 6.91 (d, J = 1.1 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 189.74, 148.88, 144.28, 139.15, 132.79, 129.14, 128.87, 126.84, 110.54.

3.2.3o. 93% yield. Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (dd, J = 2.9, 1.1 Hz, 1H), 7.87 – 7.83 (m, 2H), 7.62 – 7.56 (m, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.38 (dd, J = 5.0, 2.9 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 190.33, 141.65, 138.98, 134.22, 132.63, 129.70, 128.95, 128.71, 126.52.

3.2.3a. 91% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.08, 137.96, 132.74, 130.40, 128.61.

3.2.3c. 79% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, J = 7.9 Hz, 2H), 7.75 (d, J = 7.4 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 6.96 (d, J = 7.9 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.85, 163.55, 138.62, 132.87, 132.19, 130.49, 130.04, 128.50, 113.88, 55.81.

3.2.3f. 74% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.06 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.83 – 7.77 (m, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 2.67 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.83, 196.27, 141.68, 139.91, 137.27, 133.32, 130.43, 130.47, 128.82, 128.50, 27.22.

3.2.3b'. 91% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 – 7.75 (m, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 7.9 Hz,

2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.82, 143.56, 138.31, 135.24, 132.48, 130.64, 130.26, 129.31, 128.54, 21.98.

3.2.3c'. 98% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, *J* = 7.9 Hz, 2H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 6.96 (d, *J* = 7.9 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.85, 163.55, 138.62, 132.87, 132.19, 130.49, 130.04, 128.50, 113.88, 55.81.

3.2.3g'. 66% yield. 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), 7.81 (d, *J* = 7.9 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.38, 166.67, 141.68, 137.32, 133.58, 133.29, 130.45, 130.12, 129.85, 128.81, 52.81.

3.2.3h'. 78% yield. Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 – 7.77 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.40 (td, *J* = 7.5, 1.2 Hz, 1H), 7.31 (dd, *J* = 11.8, 7.6 Hz, 2H), 7.27 – 7.23 (m, 1H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.95, 138.97, 138.09, 137.07, 133.45, 131.32, 130.56, 130.45, 128.83, 128.78, 125.52, 20.30.

3.2.6. 70% yield. White solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.86 (d, *J* = 7.5 Hz, 2H), 7.76 (s, 1H), 7.59 – 7.51 (m, 3H), 7.47 (t, *J* = 7.4 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H).^{13}C NMR (125 MHz, CDCl$_3$) δ 157.00, 135.40, 132.04, 131.35, 129.10, 127.31, 122.43, 114.61, 55.86.

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Chapter 4

Suzuki–Miyaura Cross-Coupling of Amides using Well-Defined, Air- and Moisture-Stable Nickel/NHC (NHC = N-Heterocyclic Carbene) Complexes

Parts of this section were adapted with permission from the article: "Suzuki–Miyaura Cross-Coupling of Amides using Well-Defined, Air- and Moisture-Stable Nickel/NHC (NHC = N-Heterocyclic Carbene) Complexes" (*Catalysts* **2020**, *10*, 372). Copyright ©2020, MDPI.

4.1. Introduction

Nickel catalysis has recently gained significant attention, enabling cleavage of unreactive bonds by this abundant 3d transition metal.[1–3] Simultaneously, major advances have been made in amide cross-coupling, wherein highly selective oxidative addition of the N–C(O) bond enables to use the traditionally unreactive amides as a novel class of acyl and/or aryl electrophiles.[4–10] This unconventional amide bond disconnection is particularly relevant in the view of common presence of amides in natural products, pharmaceuticals and biopolymers, wherein new catalytic methods have a potentially major impact on the way chemists design synthetic routes.

In this context, palladium/NHC (NHC = N-heterocyclic carbene) catalysis using well-defined Pd(II)–NHC precatalysts has been established as the dominant catalytic direction in activating amide N–C(O) bonds for acyl cross-coupling.[4, 11–14] However, at the start of this project, there were no methods for the use of well-defined, air- and moisture-stable nickel/NHC complexes as efficient precatalysts in amide bond activation. In spite of the advances made by *in situ* formed Ni(0) catalysts, such as Ni(cod)$_2$, the lack of air-stability

and difficulty of handling of Ni(cod)$_2$ severely limits the application of Ni catalysis in amide bond cross-coupling.[15–17]

In this context, we were attracted to the advances made in the design of half-sandwich, cyclopentadienyl [CpNi(NHC)X] complexes by Chetcuti and co-workers.[18–24] We have demonstrated that these highly practical [CpNi(NHC)Cl] precatalysts[25–31] are capable of selective activation of amide N–C(O) bonds, and reported the first example of Suzuki–Miyaura cross-coupling of amides catalyzed by well-defined, air- and moisture-stable nickel/NHC (NHC = N-heterocyclic carbene) complexes (Figure 4.1.).[32]

The following features of our study were noteworthy: (1) The reaction represents the first example of acyl-type cross-coupling achieved by half-sandwich [CpNi(NHC)X] complexes. (2) We have showed the following order of reactivity of NHC ligands in amide bond cross-coupling: IPr > IMes >IPaul ≈ IPr*. (3) We have further established that both the neutral and the cationic complexes are efficient catalysts for the Suzuki-Miyaura cross-coupling of amides. (4) Kinetic studies have demonstrated that the reactions reach full conversion in < 1 h at 80 °C. (5) Importantly, we have observed full selectivity in cleavage of the *N*-acyl amide bond. This protocol could open up the application of a wide variety of [CpNi(NHC)X] and related half-sandwich complexes as well-defined, air- and moisture stable precatalysts for cross-coupling of amide N–C bonds.
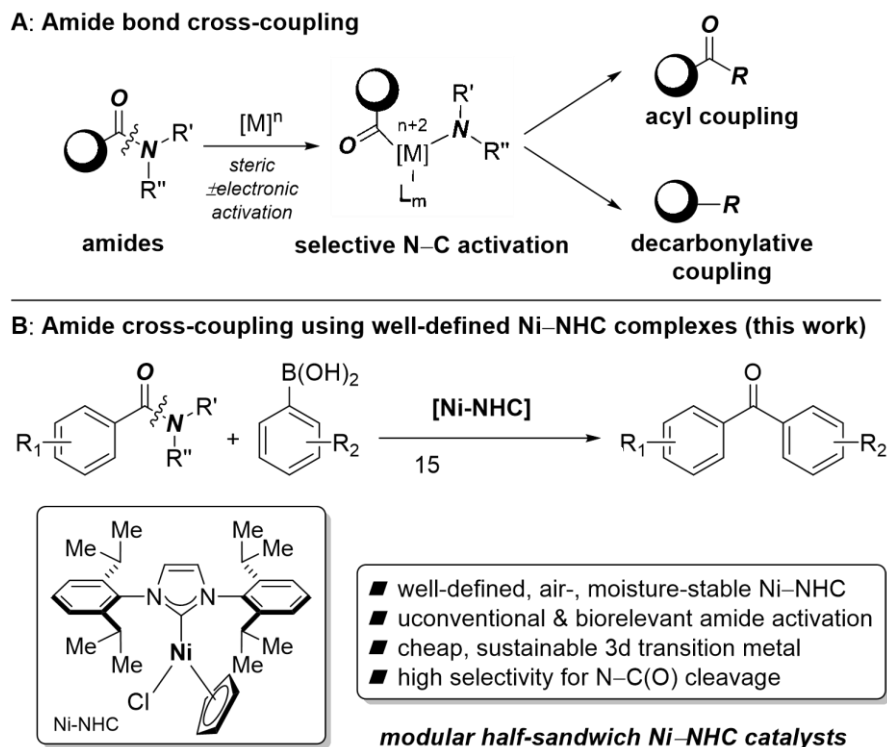
Figure 4.1. (A) Amide Bond Cross-Coupling. (B) Well-Defined, Air- and Moisture-Stable Ni–NHC Complexes in Selective Activation of Amide N–C(O) Bonds (this work).

4.2. Reaction optimization

We first examined the cross-coupling of *N*-acyl-glutarimides as model substrates for the cross-coupling with 4-tolylboronic acid using the readily prepared [CpNi(IPr)Cl] under various conditions (Table 4.1., Figure 4.2.) (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene). Optimization revealed that the desired cross-coupling proceeded in 85% yield in the presence of [CpNi(NHC)Cl] (10 mol%) as catalyst and K_2CO_3 (3.0 equiv) as base in toluene as solvent at 80 °C using 4-Tol-B(OH)$_2$ (3.0 equiv) (Table 4.1., entry 1). Interestingly, increasing the reaction temperature to 120 °C had only a minor effect on the cross-coupling (Table 4.1., entries 2-4). Furthermore, although previous studies suggested the beneficial effect of phosphine ligands on the

Suzuki–Miyaura $C(sp^2)$–$C(sp^2)$ cross-coupling catalyzed by Ni–NHC complexes,[33] in our case the addition of phosphine had an inhibitory effect on the cross-coupling (Table 4.1., entries 5-7). Examination of reaction parameters revealed K_2CO_3 as the optimal base and toluene as the preferred solvent (Table 4.1., entries 8-15). Interestingly, the use of Ni/phosphine catalysts, such as $[Ni(PCy_3)_2Cl_2]$ and $[Ni(PPh_3)_2Cl_2]$ resulted in little or no cross-coupling (Table 4.1., entries 16-19). Likewise, no reaction was observed with nikelocene (Table 4.1., entry 20),[34] supporting the key role of NHC ligand on the cross-coupling. Moreover, the recently studied in cross-coupling of aryl sulfamates $[Ni(dppf)(o\text{-tol})Cl]$[35] was unreactive under our conditions (Table 4.1., entry 21), while the mixed NHC/phosphine Ni(II) complex, $[Ni(IPr)(PPh_3)Cl_2]$,[36] appeared as a promising catalyst, but was less reactive than $[CpNi(IPr)Cl]$ (Table 4.1., entry 22).

Pleasingly, the cationic complex $[CpNi(IPr)(NCMe)](PF_6)$, readily prepared by chloride abstraction with KPF_6 according to the procedure Chetcuti[18] showed promising reactivity (Table 4.1., entries 23-24), indicating potential applications of this class of cationic Ni–NHC catalysts in amide bond cross-coupling in the future.

Further, we were particularly interested in evaluating steric demand of NHC ligands on the performance of $[CpNi(NHC)Cl]$ complexes in amide cross-coupling.[37,38] We found that $[CpNi(IMes)Cl]$ is slightly less reactive than $[CpNi(IPr)Cl]$ (Table 4.1., entries 25-26). Furthermore, examination of the highly attractive class of bulky but flexible NHC ligands, IPaul[38] and IPr*[40] revealed $[CpNi(IPaul)Cl]$ and $[CpNi(IPr*)Cl]$ as promising catalysts for N–C bond activation. Of note, $[CpNi(IPaul)Cl]$ is commercially-available, which should facilitate the development of future cross-couplings of amide bonds mediated by this precatalyst.
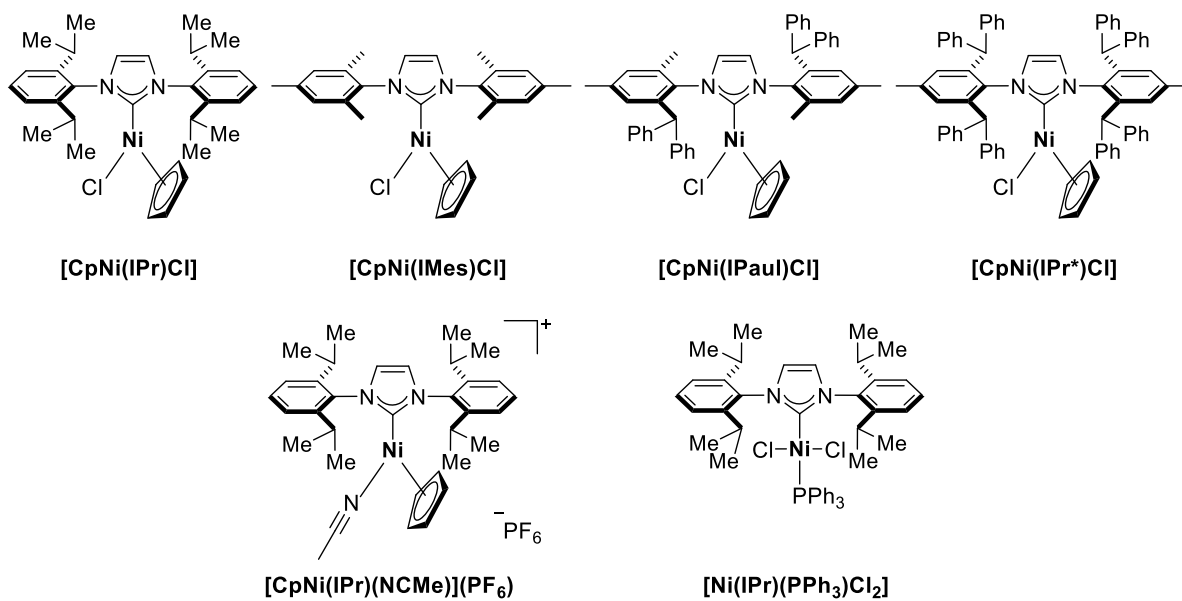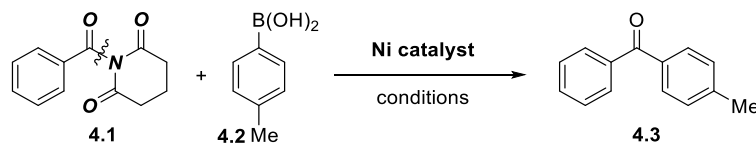
Figure 4.2. Structures of Well-Defined, Air- and Moisture-Stable Ni–NHC Catalysts.

Table 4.1. Optimization of the Suzuki-Miyaura Cross-Coupling of Amides using Ni–NHCs.[a]


Entry	Catalyst	[Ni]	Base	Solvent	T (°C)	Yield
1	[CpNi(IPr)Cl]	10	K_2CO_3	toluene	80	85
2	[CpNi(IPr)Cl]	5	K_2CO_3	toluene	80	42
3	[CpNi(IPr)Cl]	10	K_2CO_3	toluene	120	80
4	[CpNi(IPr)Cl]	5	K_2CO_3	toluene	120	39
5[b]	[CpNi(IPr)Cl]	10	K_2CO_3	toluene	120	40
6[c]	[CpNi(IPr)Cl]	10	K_2CO_3	toluene	120	54
7[c]	[CpNi(IPr)Cl]	10	K_2CO_3	toluene	80	27
8	[CpNi(IPr)Cl]	5	K_2CO_3	dioxane	120	34
9	[CpNi(IPr)Cl]	10	K_2CO_3	dioxane	120	48
10	[CpNi(IPr)Cl]	10	K_2CO_3	THF	80	<10
11	[CpNi(IPr)Cl]	10	Na_2CO_3	THF	80	20
12	[CpNi(IPr)Cl]	10	Na_2CO_3	THF	120	<5
13	[CpNi(IPr)Cl]	10	Na_2CO_3	dioxane	80	<5
14	[CpNi(IPr)Cl]	10	Na_2CO_3	dioxane	120	<5
15	[CpNi(IPr)Cl]	10	K_3PO_4	toluene	80	38
16	[Ni(PCy$_3$)$_2$Cl$_2$]	10	Na_2CO_3	dioxane	80	31
17	[Ni(PCy$_3$)$_2$Cl$_2$]	10	Na_2CO_3	dioxane	120	16
18	[Ni(PPh$_3$)$_2$Cl$_2$]	10	K_2CO_3	toluene	120	<5
19	[Ni(PPh$_3$)$_2$Cl$_2$]	10	Na_2CO_3	dioxane	80	<5
20	[NiCp$_2$]	10	K_2CO_3	toluene	120	<5
21	[Ni(dppf)(o-tol)Cl]	10	K_2CO_3	toluene	120	<5
22	[Ni(IPr)(PPh$_3$)Cl$_2$]	10	K_2CO_3	toluene	120	64
23	[CpNi(IPr)(NCMe)](PF$_6$)	10	K_2CO_3	toluene	80	44
24	[CpNi(IPr)(NCMe)](PF$_6$)	5	K_2CO_3	toluene	80	28
25	[CpNi(IMes)Cl]	10	K_2CO_3	toluene	80	77
26	[CpNi(IMes)Cl]	5	K_2CO_3	toluene	80	40
27	[CpNi(IPaul)Cl]	10	K_2CO_3	toluene	80	68
28	[CpNi(IPaul)Cl]	5	K_2CO_3	toluene	80	39
29	[CpNi(IPr*)Cl]	10	K_2CO_3	toluene	80	63
30	[CpNi(IPr*)Cl]	5	K_2CO_3	toluene	80	42

[a]Conditions: amide (1.0 equiv), 4-Tol-B(OH)$_2$ (3.0 equiv), base (3.0 equiv), [Ni] (5-10 mol%), solvent (0.25 M), T, 15 h. [b]PPh$_3$ (20 mol%). [c]PPh$_3$ (11 mol%).

4.3. Scope of the reaction

With the optimized catalyst system in hand, we examined the scope of this Suzuki–Miyaura cross-coupling catalyzed by well-defined Ni(II)–NHC precatalysts (Tables 4.2. and 4.3.). The reaction was compatible with electron-donating groups on the boronic acid (**4.3a-4.3c**). Steric-hindrance at the ortho-position of the boronic acid was well-tolerated (**4.3d-4.3e**). Furthermore, fluorine functionalized boronic acids, such as 3-fluoro and 3-trifluoromethyl (**4.3f-4.3g**) could be introduced by this Ni-catalyzed approach. We were further pleased that conjugated arenes, such as naphthalene and biphenyl delivered the desired biaryl ketone products in good yields (**4.3h-4.3i**). Only one aliphatic boronic acid was tested, and it was incompatible with the reaction conditions (entry 10). In terms of the amide scope, pleasingly, electron-rich and electron-withdrawing groups were well-tolerated on the amide component (**4.3a**, **4.3c**, **4.3j**), while the electron-deficient amides appeared to be more reactive. Steric hindrance at the ortho-position of the amide was tolerated, albeit it exerted a more pronounced effect than on the boronic acid, consistent with a decreased amide bond twist by ortho-substitution (**4.3d**). Furthermore, fluorine-containing amides and heterocyclic amides provided the desired products in good yields (**4.3k-4.3l**). It is noteworthy that decarbonylation was not observed under the reaction conditions,[41] consistent with the stability of acyl-Ni(NHC) intermediate.

Table 4.2. Scope of the Suzuki-Miyaura Cross-Coupling of Boronic Acids using [CpNi(IPr)Cl].[a]
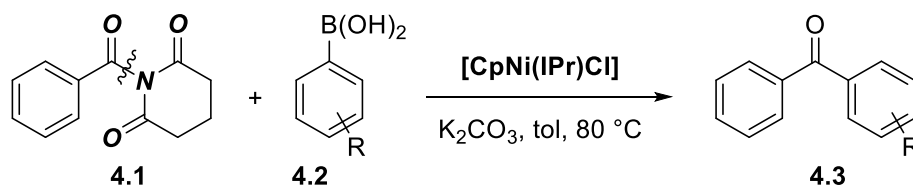
Entry	Amide	Ar-B(OH)$_2$	**4.3**	Yield (%)
1	C$_6$H$_5$	4-Me-C$_6$H$_4$	**4.3a**	85
2	C$_6$H$_5$	4-t-Bu-C$_6$H$_4$	**4.3b**	87
3	C$_6$H$_5$	4-MeO-C$_6$H$_4$	**4.3c**	79
4	C$_6$H$_5$	2-Me-C$_6$H$_4$	**4.3d**	85
5	C$_6$H$_5$	2-MeO-C$_6$H$_4$	**4.3e**	58
6	C$_6$H$_5$	3-F-C$_6$H$_4$	**4.3f**	48
7	C$_6$H$_5$	3-CF$_3$-C$_6$H$_4$	**4.3g**	56
8	C$_6$H$_5$	2-Np	**4.3h**	71
9	C$_6$H$_5$	4-Ph-C$_6$H$_4$	**4.3i**	67
10[b]	C$_6$H$_5$	Cyclopentyl	-	<5

[a]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (3.0 equiv), K$_2$CO$_3$ (3.0 equiv), [CpNi(IPr)Cl] (10 mol%), toluene (0.25 M), 80 °C, 15 h. [b]Cyclopentylboronic acid was used.

Table 4.3. Scope of the Suzuki-Miyaura Cross-Coupling of Amides using [CpNi(IPr)Cl].[a]
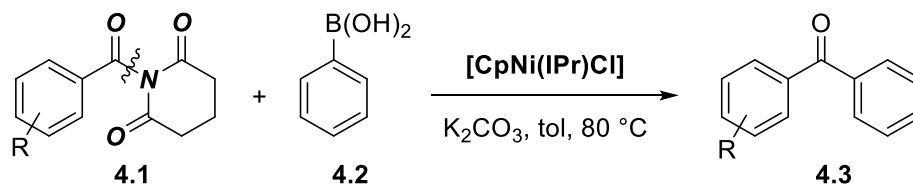

Entry	Amide	Ar-B(OH)$_2$	**4.3**	Yield (%)
1	4-Me-C$_6$H$_4$	C$_6$H$_5$	**4.3a**	70
2	4-MeO-C$_6$H$_4$	C$_6$H$_5$	**4.3c**	67
3	4-CF$_3$-C$_6$H$_4$	C$_6$H$_5$	**4.3j**	96
4	2-Me-C$_6$H$_4$	C$_6$H$_5$	**4.3d**	39
5	3,4-F$_2$-C$_6$H$_3$	C$_6$H$_5$	**4.3k**	70
6	2-thienyl	C$_6$H$_5$	**4.3l**	55

[a]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (3.0 equiv), K$_2$CO$_3$ (3.0 equiv), [CpNi(IPr)Cl] (10 mol%), toluene (0.25 M), 80 °C, 15 h.

4.4. Mechanistic Studies

We conducted intermolecular competition experiments to gain insight into the reaction (Schemes 4.1.-4.2.). As shown, competitions revealed electron-deficient amides to be significantly more reactive than electron-rich amides (Scheme 4.1., CF$_3$:MeO = 93:7). In contrast, a comparable reactivity of electron-rich and electron-deficient boronic acids was observed (Scheme 4.2., MeO:CF$_3$, 58:42). These studies are consistent with oxidative addition of the N–C(O) bond as the rate limiting step of the reaction.[42]
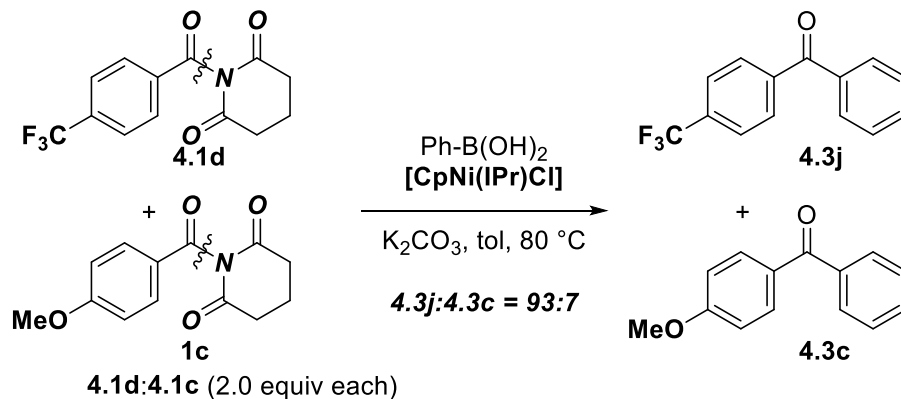
Scheme 4.1. Competition Experiments – Amides.
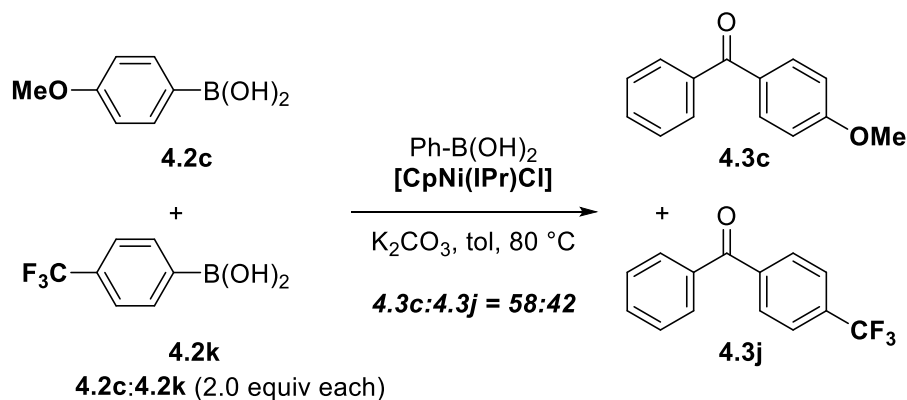
Scheme 4.2. Competition Experiments – Boronic Acids.

We also performed kinetic studies to gain insight into the reaction profile (Figure 4.3.). As shown, the reaction reached 75% conversion after 5 min, while 86% and >95% conversion was observed after 30 and 60 min, respectively, consistent with efficient generation of the reactive Ni(0)–NHC catalyst under the reaction conditions.
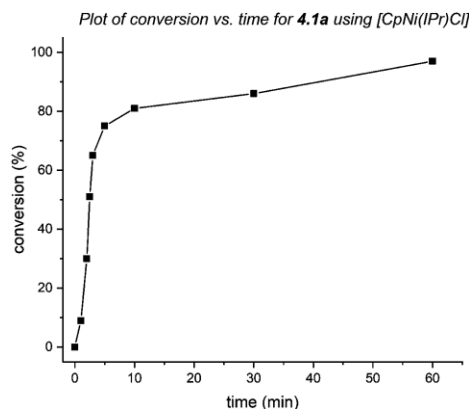
Figure 4.3. Kinetic Profile of **4.1a**. Conditions: **4.1a**, 4-Tol-B(OH)$_2$ (3.0 equiv), [CpNi(IPr)Cl] (10 mol%), K$_2$CO$_3$ (3.0 equiv), toluene (0.25 M), 80 °C, 1-60 min.

Finally, we were interested to probe the effect of different acyl leaving groups on the cross-coupling (Scheme 4.3.).
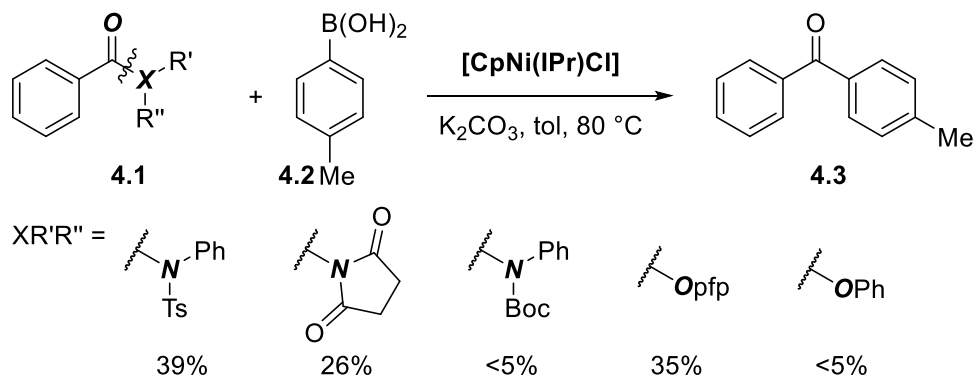
Scheme 4.3. Suzuki-Miyaura Cross-Coupling of Different Amides and Esters using [CpNi(IPr)Cl].

N-Acyl-glutarimides have emerged as the go-to amides to develop new cross-coupling methods by N–C activation.[6,10] Furthermore, this cross-coupling was found to be compatible with *N*-sulfonyl activation in acyclic amides, such as *N,N*-Ph/Ts, and *N*-acyl-succinimides, albeit the cross-coupling product was obtained in lower yield under these conditions (Scheme 4.3.). In contrast, *N*-Boc-carbamates, were recovered unchanged

from the reaction conditions, indicating a potential for chemoselective coupling. Moreover, the C–O cross-coupling was also found to be feasible under these conditions as demonstrated by the cross-coupling of Opfp ester (pfp = pentafluorophenyl, see Chapter 2).[43,44] In contrast, the unactivated phenolic ester was recovered unchanged, consistent with a considerable potential of [CpNi(NHC)Cl] catalysts in chemoselective activation of C(acyl)–O electrophiles.

4.5. Conclusion

In summary, we have developed the first example of Suzuki–Miyaura cross-coupling of amides catalyzed by well-defined, air- and moisture-stable nickel/NHC complexes. The reaction delivered biaryl ketones in good yields using inexpensive nickel catalyst with excellent N–C(O) cleavage selectivity. In a broader context, this report established the capacity of highly attractive half-sandwich [CpNi(NHC)Cl] complexes as catalysts for activation of amide N–C(O) bonds. Furthermore, we have demonstrated the order of reactivity of NHC ligands in [CpNi(NHC)Cl] complexes as IPr > IMes > IPaul ≈ IPr*, and showed that both neutral and cationic complexes serve as efficient catalysts for amide bond cross-coupling. Reaction profile studies demonstrated that these reactions are complete in < 1 h at 80 °C. Considering the utility of nickel catalysis in activation of unreactive bonds, [CpNi(NHC)Cl] complexes should be of interest in activation of bench-stable amide and ester electrophiles.

4.6. Experimental section

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

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

General Procedure for [CpNi(IPr)Cl] Catalyzed Cross-Coupling of Amides. In a typical cross-coupling procedure, an oven-dried vial was charged with an amide substrate (neat, 1.0 equiv), boronic acid (typically, 3.0 equiv), potassium carbonate (typically, 3.0 equiv), [CpNi(NHC)Cl] (typically, 10 mol%), placed under a positive pressure of argon or nitrogen, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (0.25 M) was added at room temperature, the reaction mixture was placed in a preheated oil bath at 80 °C, and stirred at 80 °C. After the indicated time, the reaction

was cooled down, 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, selectivity and yield using internal standard and comparison with authentic samples.

Representative Procedure for [CpNi(IPr)Cl] Catalyzed Cross-Coupling of Amides.

An oven-dried vial was charged with 1-benzoylpiperidine-2,6-dione (neat, 108.6 mg, 0.5 mmol), 4-tolylboronic acid (204.0 mg, 1.5 mmol, 3.0 equiv), K_2CO_3 (207.3 mg, 1.5 mmol, 1.5 equiv), [CpNi(IPr)Cl] (10 mol%, 27.4 mg), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Toluene (0.25 M) was added at room temperature, the reaction mixture was placed in a preheated oil bath at 80 °C, and stirred for 15 h at 80 °C. After the indicated time, the reaction was cooled down, 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 product. Yield 81% (79.5 mg). All other yields represent yields determined by ^1H NMR ($CDCl_3$, 500 MHz) analysis.

Characterization Data for Products 4.3a-4.3l.

4.3a. ^1H NMR (500 MHz, $CDCl_3$) δ 7.82-7.80 (d, J = 8.1 Hz, 2 H), 7.76-7.74 (d, J = 8.0 Hz, 2 H), 7.62-7.59 (t, J = 7.5 Hz, 1 H), 7.51-7.48 (t, J = 7.6 Hz, 2 H), 7.32-7.28 (d, J = 7.9 Hz, 2 H), 2.47 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.53, 143.26, 137.98, 134.90, 132.17, 130.33, 129.95, 128.99, 128.22, 21.68.

4.3b. ^1H NMR (500 MHz, $CDCl_3$) δ 7.84-7.82 (d, J = 7.7 Hz, 2 H), 7.80-7.78 (d, J = 8.3 Hz, 2 H), 7.61-7.58 (t, J = 7.3 Hz, 1 H), 7.53-7.48 (m, 4 H), 1.39 (s, 9 H). ^{13}C NMR (125

MHz, CDCl$_3$) δ 196.45, 156.19, 137.97, 134.85, 132.17, 130.15, 129.98, 128.22, 125.26, 35.13, 31.17.

4.3c. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87-7.85 (d, J = 8.7 Hz, 2 H), 7.79-7.77 (d, J = 8.2 Hz, 2 H), 7.61-7.58 (t, J = 6.8 Hz, 1 H), 7.51-7.48 (t, J = 7.6 Hz, 2 H), 7.00-6.98 (d, J = 8.7 Hz, 2 H), 3.92 (s, 3 H).^{13}C NMR (125 MHz, CDCl$_3$) δ 195.59, 163.24, 138.31, 132.58, 131.90, 130.19, 129.75, 128.20, 113.57, 55.52.

4.3d.^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84-7.82 (d, J = 8.3 Hz, 2 H), 7.62-7.59 (t, J = 7.5 Hz, 1H), 7.50-7.47 (t, J = 7.9 Hz, 2 H), 7.43-7.40 (t, J = 7.5 Hz, 1 H), 7.35-7.31 (t, J = 7.8 Hz, 2 H), 7.29-7.26 (t, J = 7.5 Hz, 1 H), 2.36 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.67, 138.63, 137.76, 136.77, 133.14, 131.01, 130.25, 130.15, 128.53, 128.47, 125.21, 20.00.

4.3e. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85-7.83 (d, J = 7.7 Hz, 2 H), 7.59-7.56 (t, J = 7.5 Hz, 1 H), 7.51-7.48 (t, J = 7.4 Hz, 1 H), 7.47-7.44 (t, J = 7.2 Hz, 2 H), 7.39-7.38 (d, J = 7.7 Hz, 1 H), 7.08-7.05 (t, J = 7.2 Hz, 1 H), 7.03-7.01 (d, J = 7.7 Hz, 1 H), 3.75 (s, 3 H).^{13}C NMR (125 MHz, CDCl$_3$) δ 196.48, 157.37, 137.83, 132.93, 131.88, 129.85, 129.61, 128.88, 128.22, 120.50, 111.46, 55.62.

4.3f. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83-7.82 (d, J = 7.5 Hz, 2 H), 7.65-7.59 (m, 2 H), 7.54-7.47 (m, 4 H), 7.33-7.30 (t, J = 8.3 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 164.59, 162.51 (d, J^F = 246.78 Hz), 137.05, 132.79, 130.03, 130.01, 129.95, 128.44, 125.83 (d, J^F = 2.9 Hz), 119.44 (d, J^F = 21.4 Hz), 116.77 (d, J^F = 22.3 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -111.99.

4.3g. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (s, 1 H), 8.01-7.99 (d, J = 7.7 Hz, 1 H), 7.88-7.86 (d, J = 7.8 Hz, 1 H), 7.83-7.81 (d, J = 7.1 Hz, 2 H), 7.67-7.64 (t, J = 7.6 Hz, 2 H), 7.55-7.52 (t, J = 7.8 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.24, 138.29, 136.76, 133.14, 133.03, 131.01 (q, J^2 = 32.7 Hz), 130.04, 128.97, 128.86 (q, J^F = 3.5 Hz), 128.58, 126.72 (q, J^F = 3.8 Hz), 123.71 (q, J^F = 270.8 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -62.74.

4.3h. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.30 (s, 1 H), 7.98 (s, 2 H), 7.96-7.94 (d, J = 8.0 Hz, 2 H), 7.90-7.89 (d, J = 7.4 Hz, 2 H), 7.65 (s, 2 H), 7.60-7.53 (m, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.78, 137.93, 135.29, 134.85, 132.40, 132.28, 131.89, 130.12, 129.44, 128.36, 128.34, 128.32, 127.84, 126.82, 125.81.

4.3i. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94-7.92 (d, J = 7.2 Hz, 2 H), 7.88-7.86 (d, J = 7.5 Hz, 2 H), 7.75-7.73 (d, J = 7.3 Hz, 2 H), 7.69-7.68 (d, J = 7.7 Hz, 2 H), 7.65-7.62 (t, J = 7.1 Hz, 1 H), 7.55-7.50 (m, 4 H), 7.45-7.42 (t, J = 6.7 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.38, 145.26, 140.01, 137.79, 136.26, 132.40, 130.75, 130.02, 128.99, 128.33, 128.21, 127.33, 126.99.

4.3j. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93-7.91 (d, J = 8.0 Hz, 2 H), 7.84-7.82 (d, J = 8.2 Hz, 2 H), 7.79-7.77 (d, J = 8.1 Hz, 2 H), 7.67-7.64 (t, J= 7.6 Hz, 1 H), 7.55-7.52 (t, J = 7.7 Hz, 2 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.55, 140.74, 136.75, 133.74 (q, J^2 = 32.5 Hz), 133.11, 130.15, 130.12, 128.55, 125.37 (q, J^3 = 3.7 Hz), 123.69 (q, J^1 = 270.9 Hz). ^{19}F NMR (471 MHz, CDCl$_3$) δ -63.00.

4.3k. ^{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).

4.3l. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90-7.89 (d, J = 8.2 Hz, 2 H), 7.76-7.75 (d, J = 4.9 Hz, 1 H), 7.68-7.67 (d, J = 3.7 Hz, 1 H), 7.64-7.61 (t, J = 7.5 Hz, 1 H), 7.54-7.51 (t, J = 7.7 Hz, 2 H), 7.20-7.19 (t, J = 4.8 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 188.26, 143.67, 138.18, 134.86, 134.22, 132.28, 129.20, 128.43, 127.97.

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Chapter 5

Conclusion

The main focus of this thesis was the development of new methods for employing amides and esters as bench-stable X–(O)C (X = OR, NR$_2$) electrophiles in metal-catalyzed cross-coupling reactions through selective activation of the amide and ester bond via acyl-metal intermediates, and the development of new robust catalytic systems for amide N–C(O) and ester O–C(O) bond activation. The main achievements of this thesis are summarized below:

(1) Cross-coupling of pentafluorophenyl esters by selective C–O acyl cleavage: we have demonstrated pentafluorophenyl esters as new, highly reactive, bench-stable, ester-based, acyl cross-coupling reagents. We have developed a new cross-coupling method that utilizes cheap and readily accessible Pd-phosphine catalysts for the selective cross-coupling of bench-stable esters that proceeds efficiently using a Pd$_2$(dba)$_3$/PCy$_3$ catalyst system.

(2) Development of new amide-based precursors for N–C(O) cleavage: we have demonstrated *N*-acyl-phthalimides as new highly reactive, twist-controlled, amide based cross-coupling reagents. We have further demonstrated *N*-acyl-carbazoles and *N*-acyl-indoles as highly reactive amide based cross-coupling precursors, wherein the reactivity is controlled by N$_{lp}$ to Ar delocalization, for the first time matching the reactivity of *N*-acyl-sulfonamides and *N*-acyl-carbamates in simple anilides. We have established Pd-NHC catalysis as a general reactivity manifold in the Suzuki-Miyaura cross-coupling of *N*-acyl-phthalimides, *N*-acyl-indoles and *N*-acyl-carbazoles.

(3) Development of Suzuki-Miyaura cross-coupling of amides catalyzed by well-defined, air- and moisture-stable Ni-NHC complexes: we have developed selective amide bond N–C(O) activation by half-sandwich, cyclopentadienyl complexes, [CpNi(NHC)Cl]. We have established for the first time that bench-stable [CpNi(NHC)Cl] complexes can effectively participate in the acyl Suzuki-Miyaura cross-coupling of amide bonds and related bench-stable acyl-electrophiles.

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

We expect that our research results will guide the design of new types of reactions and the development of new strategies for activation of amide and ester bonds.