Well-Defined Palladium(II)–NHC Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective N–C/O–C Cleavage

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CONSPECTUS: Transition-metal-catalyzed cross-coupling reactions represent a most powerful tool for the rapid construction of C–C and C–X bonds available to synthetic chemists. Recently, tremendous progress has been made in the burgeoning area of cross-coupling reactions of amides and esters enabled by regio- and chemoselective acyl C–X (X = N, O) cleavage using well-defined Pd(II)–NHC complexes. The use of N-heterocyclic carbenes as ligands in palladium-catalyzed cross-couplings permits reactions of amides and esters that were previously impossible using palladium or could be achieved only under harsh conditions. These reactions provide an attractive method to synthetic chemists to manipulate the traditionally inert amide and ester bonds with the broad cross-coupling generality inherent to palladium catalysis. Research in the area of cross-coupling of stable acyl electrophiles can be broadly categorized by the type of electrophile undergoing the cross-coupling. Recent studies have shown that cross-coupling of amides by transition metal catalysis represents one of the most straightforward and wide-ranging ways of manipulating the classically inert amide bonds into generic acyl-metal intermediates that can be systematically exploited in cross-coupling reactions as a new paradigm in organic synthesis. The key to achieving high chemoselectivity of the process is control of amidic resonance (n_N to $\pi^*_{C=O}$ conjugation, rotation of ca. 15–20 mol/kcal in planar amides), enabling oxidative addition of the N–C amide bond to a metal in a rational and predictable manner. This mode of catalysis has been extended to C(acyl)–O cross-coupling reactions of aryl esters, where selective C–O bond cleavage is accomplished through a rational match of aryl ester electrophiles and nucleophilic metal catalysts. These two types of transition-metal-catalyzed cross-coupling reactions represent an attractive concept in synthetic chemistry due to the ubiquity of esters and amides as precursors in organic synthesis. Furthermore, the high stability of amides and esters provides unprecedented opportunities for orthogonal cross-coupling strategies in the presence of other electrophiles.

In this Account, we highlight advances that have taken place in the last few years in the field of cross-coupling of amides and esters, focusing on both (1) the stereo-electronic properties of well-defined Pd(II)–NHC complexes that have been critical to realize this challenging cross-coupling manifold, and (2) the role of isomerization barrier of acyl electrophiles undergoing the cross-coupling. In a broader sense, the chemistry described here, provides a practical approach to functionalize common amide and ester functional groups in organic synthesis, as well as establishes straightforward access to acyl-metal intermediates that enable non-conventional cross-coupling strategies.

1. Introduction

The amide bond represents a privileged motif in organic synthesis.[1] Traditionally, the amide bond has been considered as one of the most stable functional groups in organic synthesis as a result of amidic resonance (n_N to $\pi^*_{C=O}$ conjugation, rotation of ca. 15–20 mol/kcal in planar amides).[2] Given the key role of the amide bond in chemical sciences, including biochemistry, polymer synthesis, pharmaceuticals, drug development and materials science,[3−5] new methods that utilize bench-stable amides as synthetic intermediates provide fundamental tools for molecular assembly.

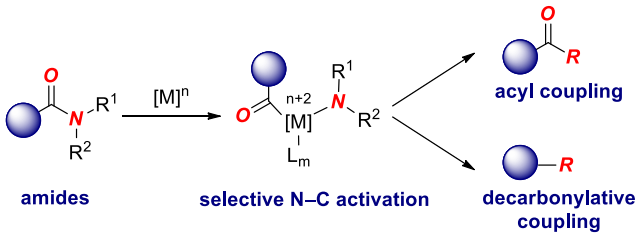
In the context of amide bond functionalization, palladium-catalyzed cross-coupling reactions[6−10] that proceed through selective insertion of a metal into the N–C bond have become a thriving area of research.[11] Recent research demonstrates that well-defined, air- and moisture-stable, Pd(II)–NHC (NHC = N-heterocyclic carbene) precatalysts[12−15] provide a significant improvement over all current catalytic systems in the cross-coupling of bench-stable amide electrophiles. The strong σ-donation and variable steric bulk around palladium in Pd-NHC complexes[16−18] facilitate oxidative addition and reductive elimination steps, enabling for the first time a broad range of cross-coupling reactions of amides in a general fashion. Moreover, this catalytic manifold enables various types of reactions of amides with high turnover numbers for the first time,[19] including industrially-valuable Suzuki-Miyaura[20] and Buchwald-Hartwig reactions,[21] and permits the cross-coupling of amide and ester electrophiles under one set of practical reaction conditions, which greatly simplifies the cross-coupling paradigm and avoids restriction to a particular acylmetal precursor.

Broadly speaking, Pd-NHC precatalysts represent a critical area of cross-coupling that are routinely utilized by scientists working in all facets of chemical research, including organic synthesis, drug discovery and polymer science. In this Account we demonstrate that Pd-NHC precatalysts are the first practical as well as the most reactive catalyst system for cross-coupling reactions of amides and esters. Both of these

functional groups are of paramount importance to all areas of chemical research.

Mechanistically, the activation of the N–C amide bond proceeds through ground-state destabilization of the amide bond by steric and/or electronic factors,[22–24] which allows facile insertion of a low valent metal into the N–C bond furnishing acyl-metal intermediate (Scheme 1).

Scheme 1. Amide Bond Cross-Coupling Reactions



In this Account, we highlight advances in the field of cross-coupling of amides and esters, focusing on both (1) the stereo-electronic properties of well-defined Pd(II)–NHC complexes that have been critical to realize this challenging cross-coupling manifold, and (2) the role of isomerization barrier of acyl electrophiles undergoing the cross-coupling. In a broader sense, the chemistry described here, provides a practical avenue to functionalize common amide and ester functional groups in organic synthesis, as well as establishes straightforward access to acyl-metal intermediates that enable non-conventional cross-coupling strategies. The Account has been arranged by the type of transformation (Suzuki-Miyaura, Buchwald-Hartwig), and the type of functional group that undergoes the coupling (amides, esters).

2. Suzuki-Miyaura Cross-Coupling of Amides

2.1. Historical Perspective on Amide Bond Cross-Coupling. The origin of amide bond cross-coupling reactions can be traced to the classic studies on modulating amidic resonance in bridged non-planar lactams.[22] The seminal work by Greenberg,[25] Kirby,[26] Stoltz[27] and others has amply demonstrated the facility of nucleophilic addition to the resonance destabilized amide bond constrained in a variety of cyclic bridged scaffolds. In the early 1990s, Yamada found that acyclic *N*-acyl-1,3-thiazolidine-2-thiones feature unusual twisted amide bonds that activate the amide moiety towards nucleophilic reactivity, thus advancing the concept of amide bond twist to acyclic amides.[28] In another important development, elegant studies on metal-catalyzed cleavage of the σ N–C bond by Aubé demonstrated the facility of transition-metal-catalysis to promote unusual reactivity of non-planar amides.[29] Despite these observations, the extraordinary capacity of the amide bond to participate in the direct metal insertion/cross-coupling remained unrecognized until 2015, when the field of amide bond cross-coupling was initiated by independent reports by Garg on nickel-catalyzed esterification of amides[30] and our group on palladium-catalyzed Suzuki-Miyaura cross-coupling of amides.[31] The research rationale on ground-state-destabilization of the amide bond in easily available acyclic amide precursors put forward by our group has effectively provided the basis for the development of a wide range of acyl- and decarbonylative cross-coupling reactions of amides.[31,32] Closely related cross-coupling reported by Zou further supported this concept.[33] In a general sense, amide cross-coupling manifold by direct metal insertion complements and expands the potential of the ubiquitous amide bond to participate in a wide range of Ni-catalyzed,[34] electrophilic,[35] Lewis acid,[36] radical[37] and nucleophilic[38] reaction pathways to achieve a myriad of high value transformations.

In contrast to amide cross-coupling, one of the first reports on ester bond activation involved a mechanistic study of oxidative addition of aryl carboxylates to Ni(0) disclosed in 1976 by Yamamoto.[39] This observation lay dormant until Yamaguchi and Itami found in 2012 that simple and abundant aryl esters participate in a Ni(0)-catalyzed C–H arylation of heterocycles by selective scission of the acyl C–O bond.[40] The work by Yamaguchi/Itami is significant because it demonstrated that non-conventional aryl ester electrophiles could be applied in the classical aryl cross-coupling reactivity by a decarbonylative pathway. While the inherent facility of cross-coupling of esters (cf. amides) can be attributed to the diminished n_O to $\pi^*_{C=O}$ conjugation as result of maintaining resonance during the isomerization pathway,[41] recent research has demonstrated that transition-metal-catalyzed cross-coupling of amides and esters proceeds under a unified reaction manifold. This generality provides one of the most important considerations in the cross-coupling of amides and esters and enables the productive engagement of both types of valuable electrophiles, while avoiding restriction to a particular acylmetal precursor.

2.2. Pd(II)–NHC Precatalysts in Cross-Coupling of Deactivated Substrates. Since the seminal discovery of stable N-heterocyclic carbenes by Arduengo, NHCs have found invaluable applications as strong σ-donor ligands in transition-metal-catalysis.[12–15] Fuelled by the interest to provide innovations in the synthesis of pharmaceuticals, materials science and agrochemical industry,[6–10] well-defined Pd(II)–NHC precatalysts have become attractive alternatives to Pd/phosphine precatalysts owing to the improved catalytic activity than electron-rich phosphines due to strong σ-donating properties. As further important characteristics, Pd(II)–NHC complexes are air- and moisture-stable, which makes their handling operationally-convenient, many of the Pd(II)–NHC complexes are commercially available, which facilitates ligand screening and reaction optimization, and well-defined Pd(II)–NHC precatalysts feature 1:1 Pd:NHC ratio. This avoids using excess of expensive ligand and is optimal for the formation of catalytically-active monoligated Pd(0) species. Optimization of steric demand around the metal has resulted in the discovery of novel precatalysts with better efficiency, selectivity and allowing higher turnover numbers.[12–18]

Current evidence supporting the high reactivity of Pd(II)-NHC precatalysts in amide and ester cross-coupling reactions is consistent with strong σ-donation to the Pd center,[12–14] facilitating activation of relatively strong C(acyl)–X (X = N, O) bonds. In contrast to the well-defined Pd(II)-NHC precatalysts, Ni catalysts based on NHC ligands have been slower to develop predominantly due to challenges in reducing Ni(II) precursors and handling air-sensitive Ni(0) complexes.[12] However, the reactivity of Ni-catalysts in activation of amide and ester bonds is promising.[34] It should also be noted that cleavage of the aryl C–O bond is feasible using, in particular, Ni catalysis.[6,7] The activity of Pd-NHC precatalysts is

often sensitive to reaction conditions. Examples presented in this account have been selected to emphasize the differences and, in some cases, complementarity of Pd-NHCs used for a given transformation.

Two major classes of Pd(II)–NHC precatalysts have been developed: (1) [Pd(NHC)(allyl)Cl] complexes pioneered by Nolan and co-workers;[42–44] and (2) Pd–PEPPSI complexes introduced by Organ and co-workers[45,46] (Figure 1). These complexes offer complementary reactivity in terms of rate and mechanism of activation, stabilization of the NHC–Pd(0) species, synthesis and reaction scope. More recently, Pd(II)–NHCs bearing a substituted indenyl-type ligand, [Pd(NHC)(ind)Cl], were reported.[47] The high reactivity of [Pd(NHC)(ind)Cl] complexes results from fast reduction of Pd(II) to Pd(0) and preventing the formation of catalytically inactive Pd(I) dimer, depending on reaction conditions.[48] Implementation of Pd(II)–NHC precatalysts with different throw-away ligands offers new opportunities for developing efficient amide and ester cross-coupling reactions.

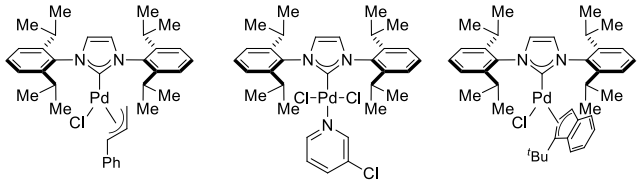


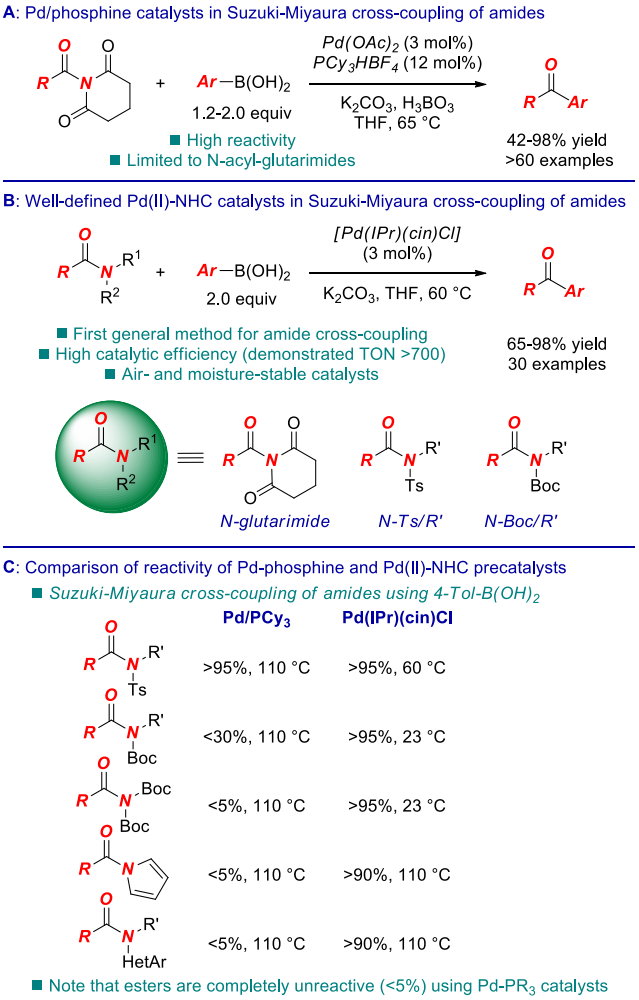
Figure 1. Structures of Pd(II)–NHC precatalysts. NHC = IPr.

2.3. Implementation of Pd/PR_3 and Pd/NHC Precatalysts in Amide Bond Activation: High Activity of [Pd(NHC)(cin)Cl] Precatalysts. In 2015, we reported the first Suzuki-Miyaura cross-coupling of *N*-glutarimide amides with boronic acids via ground-state-destabilization of the amide bond.[31] This transformation proceeded smoothly in the presence of $Pd(OAc)_2$ (3 mol%), PCy_3HBF_4 (12 mol%), K_2CO_3/H_3BO_3 in THF at 65 °C (Scheme 2A). The reaction showed good functional group compatibility with respect to both the amide and boronic acid components; however, among various amides screened, only highly-twisted *N*-glutarimide amides (τ = 85.7°; χ_N = 5.6°, Winkler-Dunitz parameters describing twist around the N–C(O) bond and *N*-pyramidalization angle)[24] showed high reactivity. Furthermore, the optimal 1:4 Pd/phosphine ratio was less than practical in terms of applications.

Meanwhile, to improve the generality of amide bond cross-couplings, a large number of amide precursors, ligands and catalytic conditions were tested.[49] In 2017, we reported [Pd(IPr)(cin)Cl] (3 mol%) in the presence of a mild carbonate base, K_2CO_3 (3.0 equiv), in THF at 60 °C for Suzuki-Miyaura cross-coupling of amides under simple, as operationally-convenient conditions (Scheme 2B).[50]

This method showed good functional group tolerance for both the amide and boronic acids components. More importantly, the developed catalytic system promoted the N–C amide bond activation of various amides, including *N*-glutarimide, *N*-Boc-carbamate and *N*-Ts-sulfonamide, under the same reaction conditions, for the first time. Cross-couplings applied across a broad range of amides activated with readily installed *N*-activating groups render the amide bond cross-coupling manifold of great use for academic and industrial applications.[6–10,19–21] This Pd(II)–NHC catalytic system benefits from the strong σ-donation, which facilitates

Scheme 2. Pd/PR_3 and Pd/NHC Precatalysts in Amide Bond Cross-Coupling: High Activity of [Pd(NHC)(cin)Cl] Precatalysts



oxidative addition, while flexible steric bulk around Pd promotes reductive elimination,[16–18] triggering high reactivity with less activated amide precursors.

The fact that Pd(II)–NHC precatalysts are single-component, commercially-available, air- and moisture-stable establishes operational simplicity and provides important benefits in terms of cost, safety and modularity.[7–10] The cross-coupling of various amides under the same reaction conditions allowed us to develop a general reactivity scale of different amides in cross-coupling reactions (Figure 2).[50] *N*-glutarimide amides have the highest reactivity, as expected from the lowest resonance energy and high twist angle;[51] however, the easily prepared *N*-Boc and *N*-Ts amides were not far off in terms of reactivity using [Pd(NHC)(cin)Cl] precatalysts. Under the optimized conditions, these three precursors cross-coupled with turnover numbers of 740–870, thus bringing the amide bond cross-coupling manifold for the first time close to the practical levels required for general use.[19]

The initial finding that Pd(II)–NHC precatalysts promote N–C bond activation of amides enabled us to discover mild conditions for amide bond cross-coupling and has been critical in expanding the application of acyl cross-coupling reactions in synthetic chemistry.

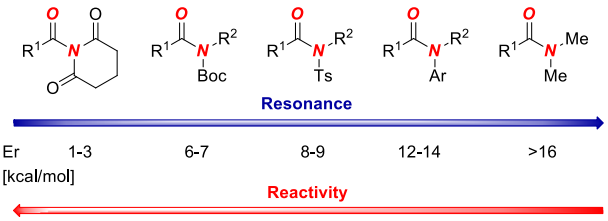


Figure 2. Correlation of amide bond reactivity with resonance energies.

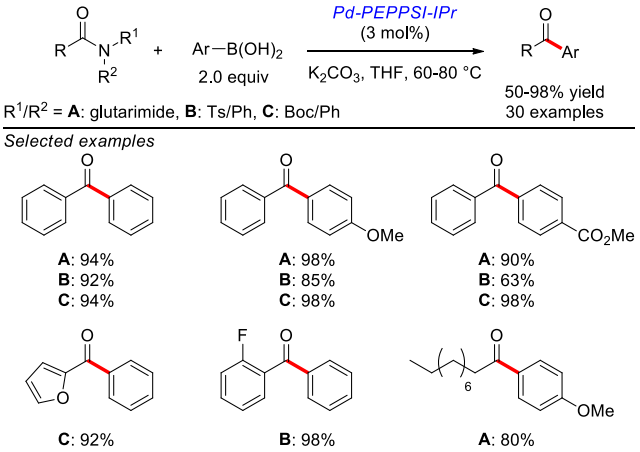
2.4. Pd–PEPPSI Precatalysts in Suzuki-Miyaura Cross-Coupling of Amides. To develop a diverse toolbox of Pd(II)–NHC precatalysts for amide bond cross-coupling, we reported the first example of Pd–PEPPSI precatalysts for Suzuki-Miyaura cross-coupling of amides (Scheme 3).[52] Pioneered by Organ and co-workers, Pd–PEPPSI complexes represent another important type of air- and moisture-stable, commercially-available Pd(II)–NHC precatalysts.[45,46] One of the benefits is their straightforward synthesis (only one-step from corresponding NHC salts; however, a recent report on facile synthesis of [Pd(NHC)(cin)Cl] precatalysts also should be noted[53]), and a variety of Pd–PEPPSI precatalysts bearing different throw-away ligands have been reported.[12] Pd–PEPPSI complexes have different activation pathway,[46] which provides new opportunities for fine-tuning supporting ligands in amide cross-coupling.

Under our optimized conditions (Pd–PEPPSI–IPr, 3 mol%, K_2CO_3, 3.0 equiv, THF, 60-110 °C), both the amide and boronic acid components showed good functional group tolerance. In agreement with the high activity of Pd–NHC complexes, diverse amides could be cross-coupled under identical reaction conditions. High turnover numbers were obtained for all amide precursors (TON = 480–760). This study further highlighted the robustness of Pd(II)–NHC catalytic system over Pd/phosphines in selective amide N–C bond activation.

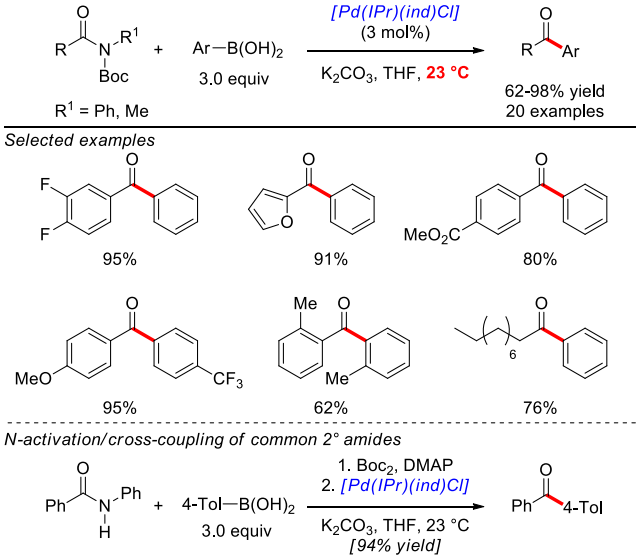
2.5. [Pd(NHC)(ind)Cl] Precatalysts in Suzuki-Miyaura Cross-Coupling of Amides. Cross-coupling reactions under mild, room temperature conditions are vastly preferred due to low overall cost and operational convenience.[6–10] To further establish the versatility of Pd(II)–NHC precatalysts in amide N–C bond activation, we reported [Pd(NHC)(ind)Cl]-promoted Suzuki-Miyaura cross-coupling of amides (Scheme 4).[54] The reaction is notable as the first example of Suzuki-Miyaura cross-coupling of amides at room temperature. The developed catalytic system based on [Pd(NHC)(ind)Cl] represents a significant improvement over our initial Pd/phosphine system. Previous work indicated that [Pd(NHC)(ind)Cl] precatalysts undergo fast reduction to Pd(0) and that off-cycle Pd(I) dimers that account for the loss of catalytic reactivity are not formed.[47,48] The robust nature of Pd(II)–NHC allowed us to perform one-pot *N*-activation/cross-coupling for the first time, thus providing a streamlined route to biaryl ketone products directly from 2° amides. Kinetic studies showed that *N*-Boc amides have higher reactivity than *N*-Ts amides, which is consistent with ground-state-destabilization of the amide bond.[55]

Clearly, these studies established that by fine-tuning of the throw-away ligand in Pd(II)–NHC precatalysts, it is possible to develop highly efficient N–C bond cross-coupling reactions of amides in a predictable and highly selective manner.

Scheme 3. Activity of Pd–PEPPSI–IPr in Cross-Coupling of Amides



Scheme 4. Activity of [Pd(IPr)(ind)Cl] in Cross-Coupling of Amides at Room Temperature



3. Scope of New Amide Precursors in Cross-Coupling Reactions Catalyzed by Pd(II)–NHC Precatalysts

Different amide precursors have been developed for amide cross-coupling manifold (Figure 3).[11] These amides can be synthesized from carboxylic acids or, more importantly, directly from secondary or primary amides in several cases. The development of new amide bond precursors is guided by the principle of amide bond resonance destabilization,[23] which conceptualizes the amide bond cross-coupling area of research and provides a benchmark for the continuum of reactivity of the amide bond.

The role of new amide precursors is two-fold: (1) to enable the catalytic mode of reactivity, wherein the amide bond is ultimately derived from carboxylic acids, and (2) to permit non-classical, electrophilic reactivity of the amide bond, through metal-catalyzed as well as metal-free pathways, wherein the reactive amide bond originates from common primary or secondary amides. The introduction of practical, robust Pd(II)–NHC precatalysts significantly expands the scope of amides that can be employed in cross-coupling due

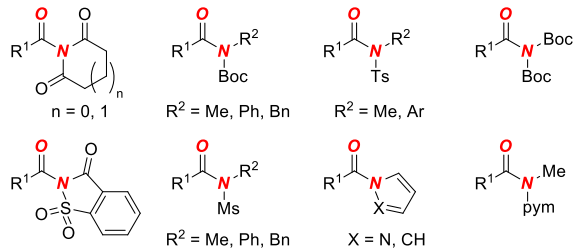
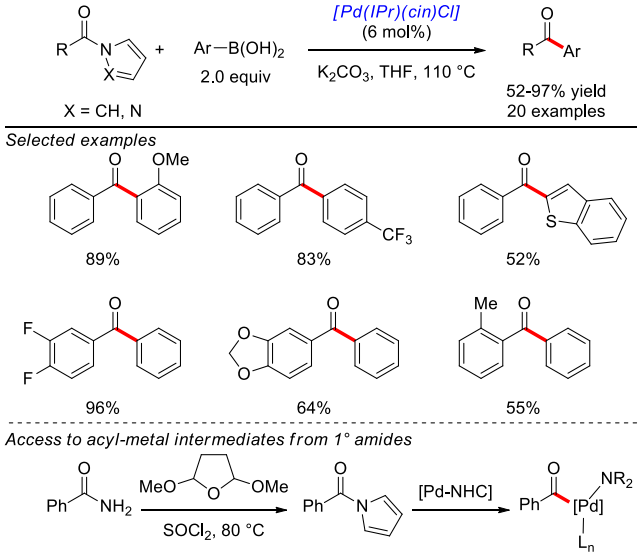
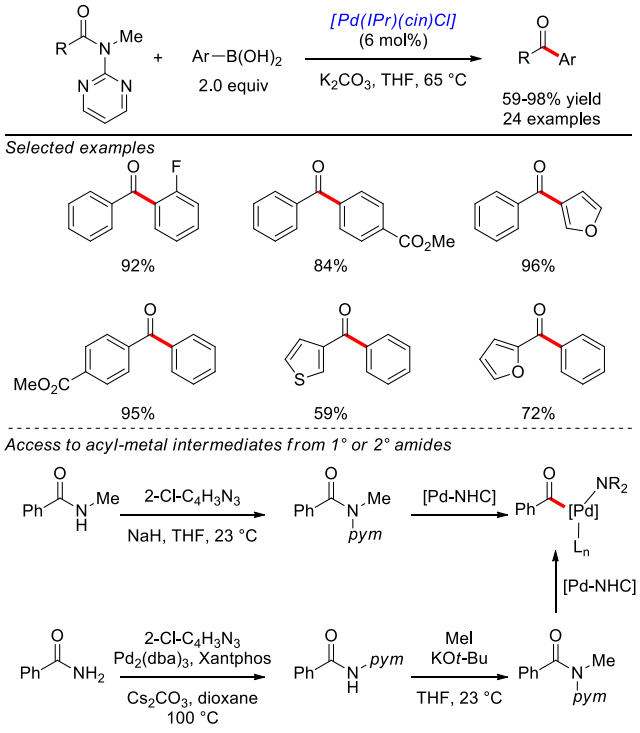


Figure 3. Amide bond precursors in Suzuki-Miyaura cross-coupling.

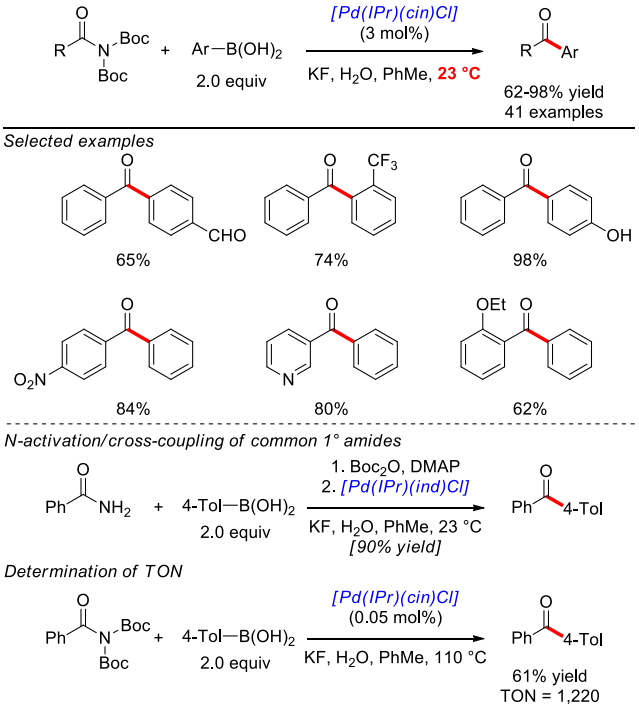
Scheme 5. Activity of [Pd(NHC)(cin)Cl] in Cross-Coupling of *N*-Acylpyrroles and Pyrazoles



Scheme 6. Activity of [Pd(NHC)(cin)Cl] in Cross-Coupling of *N*-Methylamino-Pyrimidyl-Amides (MAPA)



Scheme 7. Activity of [Pd(NHC)(cin)Cl] in Cross-Coupling of *N*,*N*-Boc$_2$-Amides Derived Directly from 1° Amides



to high σ-donation and operationally-convenient conditions.[16–18]

In this context, Pd(II)-NHC have been used to cross-couple planar amides (Scheme 5),[56] *N*-heteroaryl amides (Scheme 6)[57] and 1° amides (Scheme 7).[58]

As a further illustration, Zou reported a Pd–PEPPSI–IPr-enabled Suzuki-Miyaura cross-coupling of *N*-Ts amides with diarylborinic acids.[59] These reactions are not easily achieved using Pd/phosphine precatalysts.

4. Suzuki-Miyaura Cross-Coupling of Esters

Aromatic esters have emerged as increasingly important precursors to generate acyl-metal intermediates in organic synthesis.[11,39,60] The ubiquity of esters as common intermediates in synthetic endeavors makes the development of catalytic cross-coupling methods by C–O acyl cleavage appealing. As part of our interest in generating acyl-metal intermediates, we have made significant progress in activating ester C–O bonds under mild and practical conditions by using Pd(II)–NHC precatalysts. These studies explore new acyl-metal precursors with the selectivity complementing reactions of amides in terms of synthesis of C–O electrophiles (cf. amides), catalytic performance, reaction scope and relative facility of oxidative addition in the catalytic cycle.

Based on the lessons drawn from Pd(II)–NHC catalysis, we reported the first Suzuki-Miyaura cross-coupling of esters by selective C–O bond activation to give biaryl ketones at room temperature (Scheme 8).[54] The reaction was catalyzed by [Pd(IPr)(ind)Cl] in the presence of a mild carbonate base. Notably, the method established the first example of efficient acyl cross-coupling of common amide and ester electrophiles promoted by a single commercially-available, air- and moisture-stable Pd(II)–NHC precatalyst under identical reaction conditions. Kinetic studies allowed us to correlate the reac-

tivity with low barriers to isomerization around the C–X bond (Figure 4). Esters feature considerable stabilization in the ground-state countered by significant stabilization in the transition-state.[41] This study provides a unified manifold for the development of cross-coupling reactions of ester and amide electrophiles by selective activation of C–O and C–N bonds under the same reaction conditions.

Our subsequent studies have determined that Pd–PEPPSI type precatalysts catalyze the cross-coupling of amides with comparable reactivity to [Pd(IPr)(cin)Cl] (Scheme 9).[61]

In an effort to find general and operationally-simple conditions for C–O bond activation, we reported an exceedingly mild method for Suzuki-Miyaura cross-coupling of aryl esters using Pd–PEPPSI at room temperature (Scheme 10 and Figure 5).[62] Low cost, accessibility and broad applicability of PEPPSI catalysts provide additional impetus to study Pd(II)–NHCs containing different throw-away ligands.

Scheme 8. Activity of [Pd(IPr)(ind)Cl] in Cross-Coupling of Esters at Room Temperature

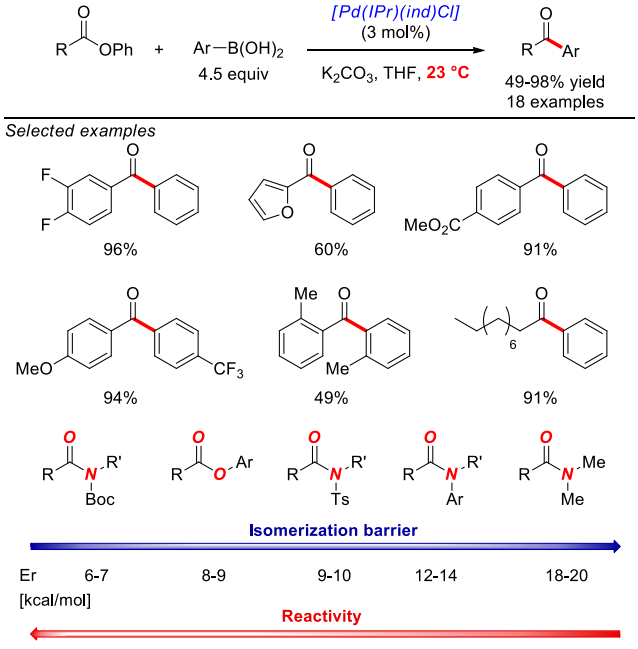
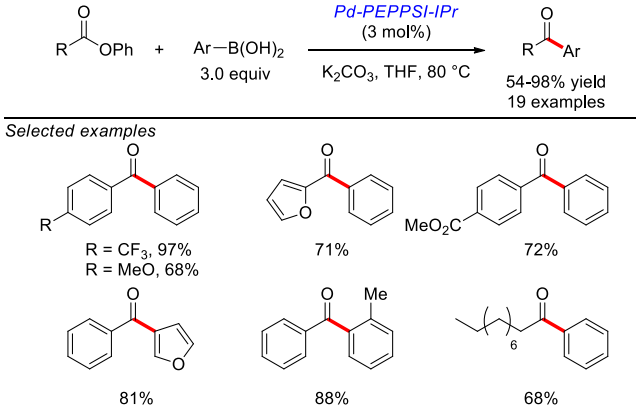


Figure 4. Correlation of amide and ester bond reactivity with isomerization barriers.

Scheme 9. Activity of Pd–PEPPSI–IPr in Cross-Coupling of Esters



In their seminal work, Newman, Houk and co-workers reported the first Suzuki-Miyaura cross-coupling of aryl esters catalyzed by [Pd(NHC)(cin)Cl] (Scheme 11).[64] This finding was of central importance because it demonstrated that Pd-NHC precatalysts are capable of cleaving strong C–O bonds in phenolic esters. A sequential C–N amide bond activation using Pd/PCy_3HBF_4 (Scheme 2A),[31] followed by C–O bond activation of aryl ester using Pd(II)–NHC was achieved with

Scheme 10. Activity of Pd–PEPPSI–IPr and Related Pd(II)–NHC Precatalysts in Cross-Coupling of Esters at Room Temperature

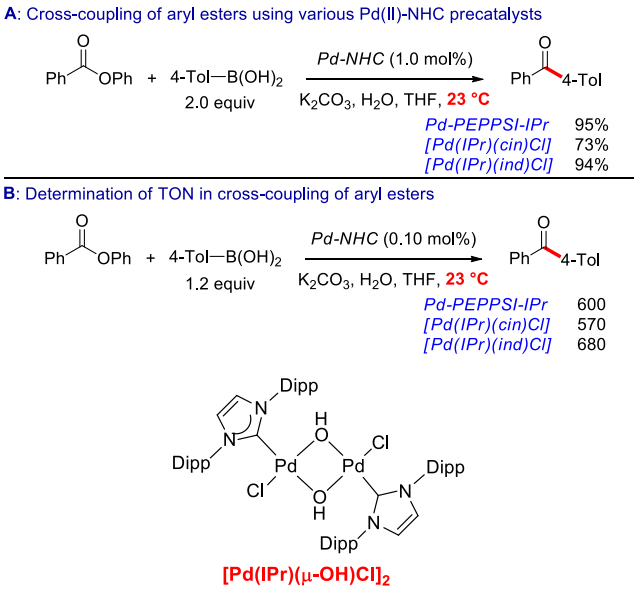
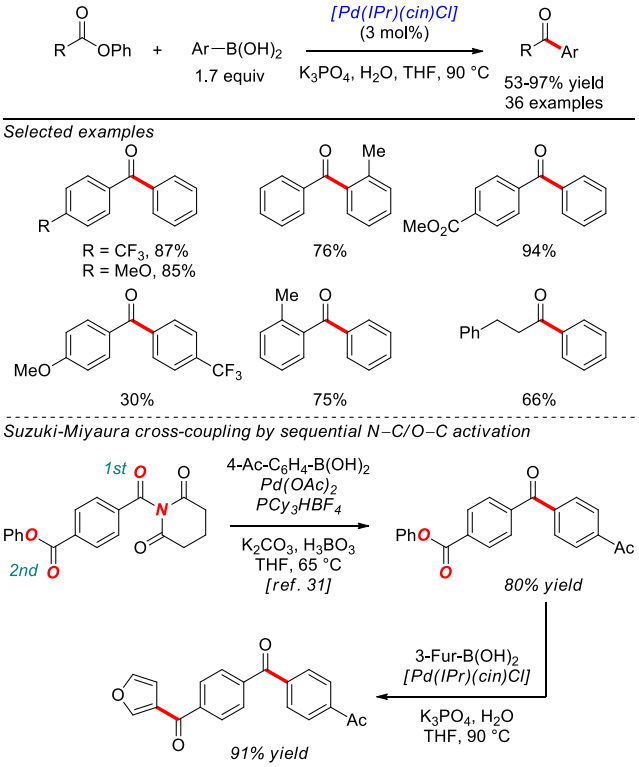
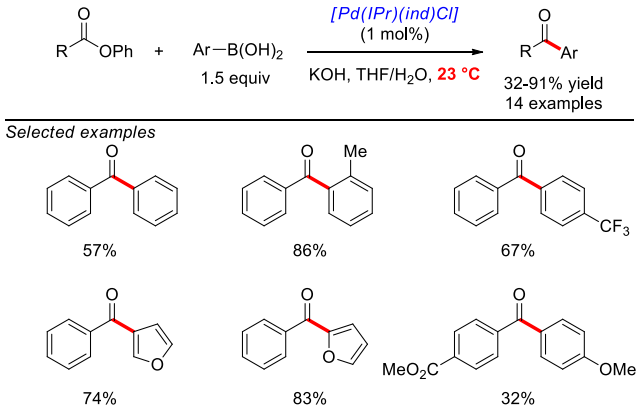


Figure 5. Structure of Pd(II)–NHC hydroxide dimer. NHC = IPr.

Scheme 11. Activity of [Pd(IPr)(cin)Cl] in Cross-Coupling of Esters at Elevated Temperatures



Scheme 12. Activity of [Pd(IPr)(ind)Cl] in Cross-Coupling of Esters using Hydroxide Bases



exquisite chemoselectivity, demonstrating the synthetic value of cross-coupling of bench-stable acyl derivatives with a varying degree of n_X to $\pi^*_{C=O}$ delocalization.

Hazari and co-workers have reported Suzuki-Miyaura cross-coupling of aryl esters catalyzed by [Pd(NHC)(ind)Cl] precatalysts (Scheme 12).[65] The reaction proceeds at room temperature in the presence of strong bases. The high efficiency of their catalytic system benefits from rapid activation of [Pd(NHC)(ind)Cl] under the reaction condition.

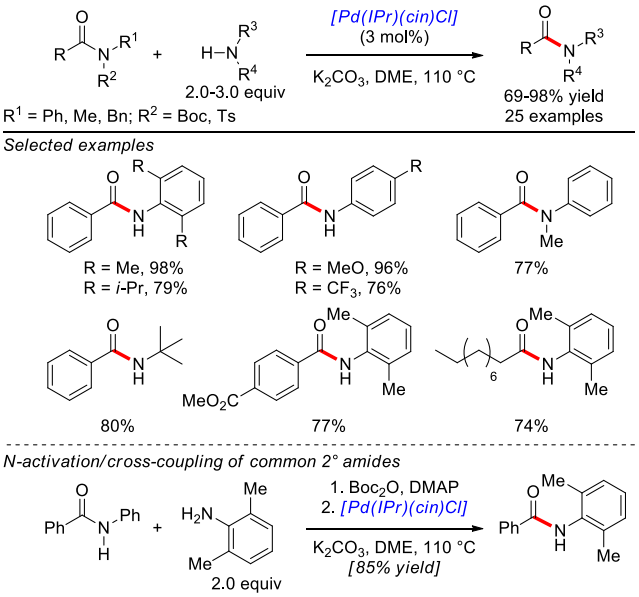
5. Acyl-Buchwald–Hartwig Cross-Coupling of Amides (Transamidation) and Esters

On the basis of efficient formation of acyl-metal intermediates enabled by Pd(II)–NHC precatalysts, new types of synthetically valuable reactions hinging on Pd–NHCs are feasible. Adapting the general, well-established Buchwald-Hartwig $C_{(aryl)}$ amination reaction mechanism[21] to common amides and esters by chemoselective $C_{(acyl)}$–X cleavage affords amides through a unique synthetic pathway.[66] This mode of reactivity is particularly attractive to achieve transamidation of the amide bond under mild conditions with selectivity orthogonal to other known methods.

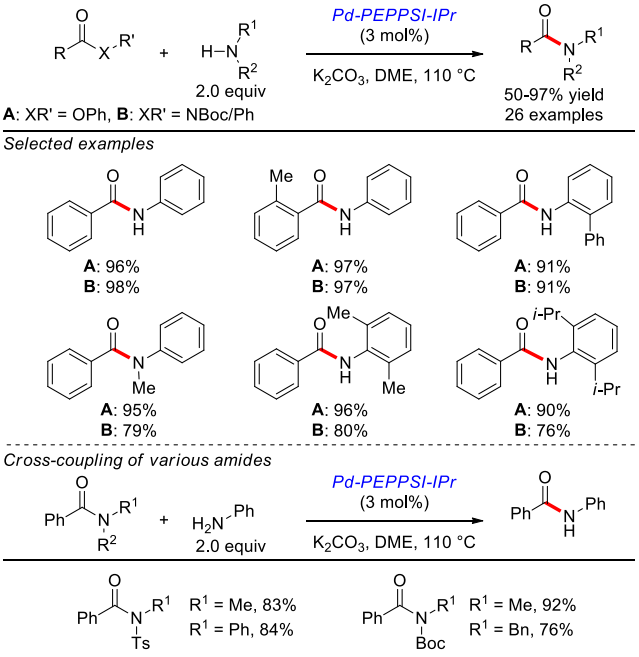
5.1. [Pd(NHC)(cin)Cl] Precatalysts in Buchwald-Hartwig Transamidation of Amides. Based on the excellent reactivity of Pd(II)–NHC precatalysts in amide N–C bond activation, we reported the first acyl-Buchwald-Hartwig reaction of amides (transamidation) (Scheme 13).[67] The reaction was catalyzed by [Pd(NHC)(cin)Cl] in DME at 110 °C. Unlike the typical $C_{(aryl)}$–aminations, which require strong bases, a weak carbonate base performed best under the reaction conditions. The robust nature of Pd(II)–NHCs allowed us to perform one-pot *N*-activation/transamidation, resulting in a net amide exchange of common 2° amides. The catalytic system was found applicable to a broad range of amides, highlighting the generality of Pd(II)–NHC precatalysts in N–C bond activation. This study provides a new approach to the synthesis of valuable amide building blocks facilitated by the versatility of Pd(II)–NHC complexes in amide N–C bond activation.

5.2. Pd–PEPPSI Precatalysts in Buchwald-Hartwig Amidation of Esters and Transamidation of Amides under Identical Reaction Conditions. In our efforts to develop a unified manifold for amide and ester cross-coupling, we reported the first selective $C_{(acyl)}$–N and $C_{(acyl)}$–O cleavage/Buchwald-Hartwig amination under the same reaction

Scheme 13. Activity of [Pd(IPr)(cin)Cl] in Transamidation of Amides



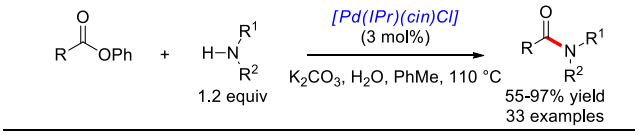
Scheme 14. Activity of Pd–PEPPSI–IPr in Amidation of Esters and Transamidation of Amides



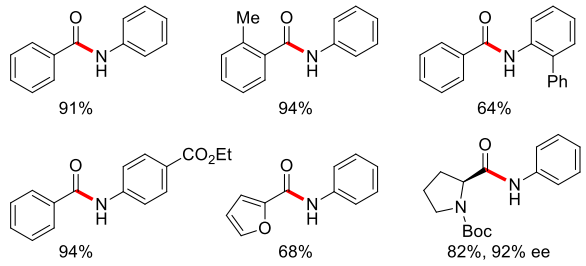
conditions (Scheme 14).[68] The selection of NHC ligand was important for this reaction. The IPr[69] ligand performed best under optimized conditions, while bulkier IPent and less sterically-demanding IMes resulted in a significant decrease of activity. Kinetic studies demonstrated that cross-coupling of amides and esters follows almost identical kinetics. This study conceptualized the common manifold for Buchwald-Hartwig amination of amides and esters.

5.3. [Pd(NHC)(cin)Cl] Precatalysts in Buchwald-Hartwig Amidation of Esters. Newman and co-workers reported Buchwald-Hartwig amination of aryl esters using [Pd(NHC)(cin)Cl] (Scheme 15).[70] They found that water was crucial for the reaction but the reason for this unclear. Interestingly, water has no effect on the related Buchwald-

Scheme 15. Activity of [Pd(IPr)(cin)Cl] in Amidation of Esters



Selected examples



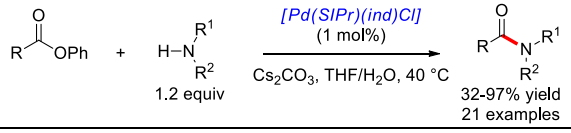
Hartwig reactions of amides.[67,68] The reaction was applicable to diverse esters using anilines, while aliphatic amines were found to react with aryl esters in the absence of precatalyst.[71]

5.4. [Pd(NHC)(ind)Cl] Precatalysts in Buchwald-Hartwig Amidation of Esters. Hazari and co-workers have reported Buchwald-Hartwig cross-coupling of esters promoted by [Pd(NHC)(ind)Cl] (Scheme 16).[65] Under the optimized conditions, SIPr ligand performed best, and the cross-coupling was achieved at 40 °C in THF:H_2O.

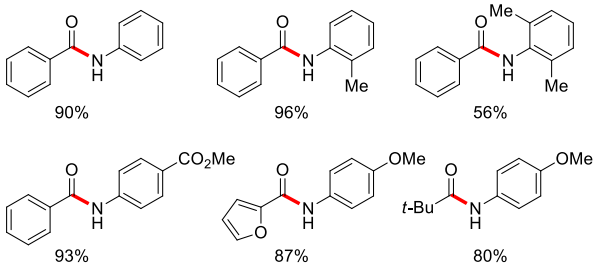
6. Cross-Coupling Mechanism

To better understand the mechanism of Pd(II)–NHC-promoted Suzuki-Miyaura cross-coupling of amides, we

Scheme 16. Activity of [Pd(SIPr)(ind)Cl] in Amidation of Esters



Selected examples



reported a detailed investigation with [Pd(NHC)(allyl)Cl] precatalysts.[72] The study demonstrated the crucial role of water using [Pd(NHC)(cin)Cl]. Experimental results indicated that bulkier [Pd(IPr*)(cin)Cl][73] showed similar or in some cases even superior reactivity than [Pd(IPr)(cin)Cl]. DFT calculations suggested that the rate-determining step involves (1) activation of the precatalyst by formation of the C–O bond between the cinnamyl moiety and the carbonate moieties for [Pd(IPr)(cin)Cl], and (2) transmetallation in the catalytic cycle with [Pd(IPr*)(cin)Cl] (Figure 6). Further mechanistic studies should lead to the discovery of more efficient Pd–NHC precatalysts for the cross-coupling of amides.

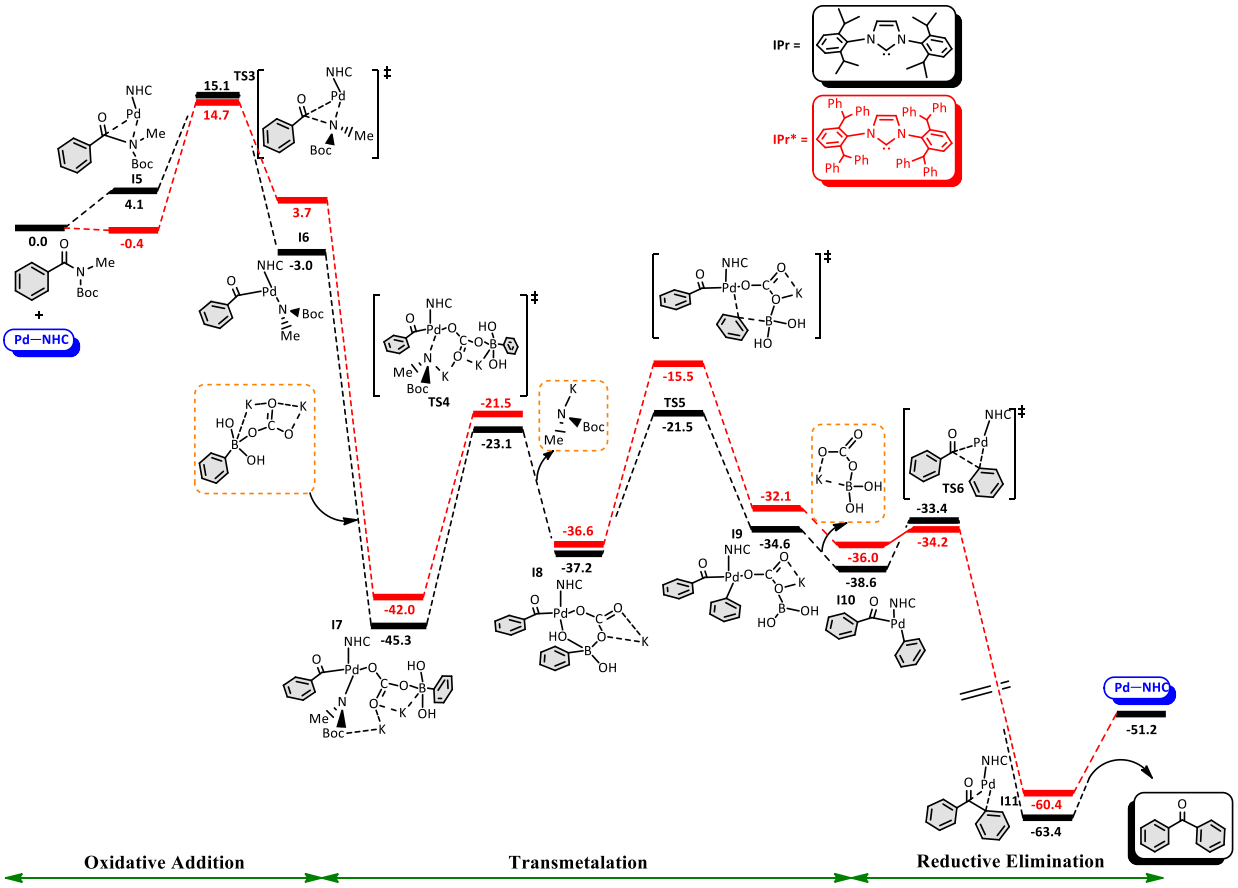


Figure 6. Reaction profile (kcal/mol) of the Suzuki-Miyaura cross-coupling of amides catalyzed by [Pd(NHC)(cin)Cl]. Note that activation of precatalyst is rate-determining in the case of IPr-supported cinnamyl precatalyst.

7. Outlook

In summary, the use of well-defined Pd(II)–NHC precatalysts to enable cross-coupling reactions of bench-stable amides and esters by C–X activation has emerged as a novel and valuable method for catalytic functionalization of the ubiquitous amide and ester bond. Most crucially, the use of N-heterocyclic carbenes permits reactions of amides and esters that were previously impossible or could be achieved only under very harsh conditions. To date, four important types of cross-coupling reactions have been developed. Each of these methods shows broad generality, unrivalled catalytic efficiency and each is performed with commercially-available, air- and moisture-stable Pd(II) precatalysts.

Broadly speaking, cross-coupling of amides and esters should be placed in the context of cross-coupling reactions of acyl electrophiles. The use of amides and esters presents several unique advantages due to (1) superior stability of these functional groups as compared to less stable acyl chlorides, thioesters and anhydrides, (2) ubiquitous presence of the ester and, in particular, the amide bond in common synthetic molecules.

We speculate that, in the future, this chemistry will become important in the site-selective manipulation of biomolecules, post-polymer modification as well as the synthesis of important targets that are not readily available by other methods. The very exciting recent breakthroughs enabled by Pd(II)–NHC catalysis should pave the way for the general use of common amide and ester electrophiles in catalytic assembly of valuable molecules.

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Funding Sources

Rutgers University and the NSF (CAREER CHE-1650766) are gratefully acknowledged for support.

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Shicheng Shi was born in Xuancheng, P. R. of China. In 2010, he received his B.Sc. degree from Nanjing Agriculture University. In 2013, he received his M.Sc. degree from the Shanghai Institute of Organic Chemistry. After a short experience in industry, he joined the group of Professor Michal Szostak at Rutgers University, in 2014, and is currently working toward his Ph.D. His research focuses on developing new reactions based on transition-metal catalysis.

Steven P. Nolan received his B.Sc. in Chemistry from the University of West Florida and his Ph.D. from the University of Miami where he worked under the supervision of Professor Carl D. Hoff. After a postdoctoral stay with Professor Tobin J. Marks at Northwestern University, he joined the Department of Chemistry of the University of New Orleans in 1990. In 2006, he joined the Institute of Chemical Research of Catalonia (ICIQ). In early 2009, he joined the School of Chemistry at the University of St Andrews. In 2015 he moved to the Ghent University. His research interests include organometallic chemistry and catalysis.

Michal Szostak received his Ph.D. from the University of Kansas with Professor Jeffrey Aubé in 2009. After postdoctoral stints at Princeton University with Prof. David MacMillan and at the University of Manchester with Prof. David Procter, in 2014, he joined the faculty at Rutgers University. His research group is focused on the development of new synthetic methodology based on transition-metal catalysis, transition-metal-mediated free-radical chemistry, and application to the synthesis of biologically active molecules.

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