General Method for the Suzuki-Miyaura Cross-Coupling of Primary Amide-Derived Electrophiles Enabled by [Pd(NHC)(cin)Cl] at Room Temperature

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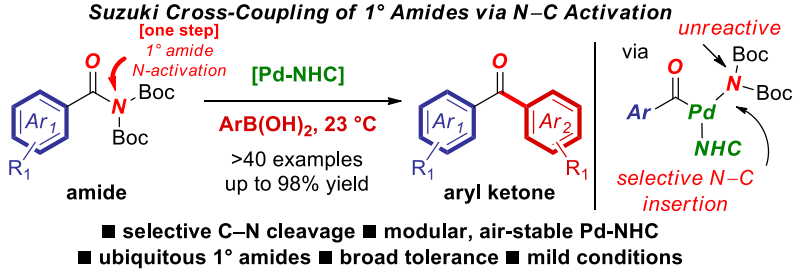
Supporting Information



ABSTRACT: A general, highly selective method for the room temperature Suzuki-Miyaura cross-coupling of commonly encountered primary benzamides is reported. A combination of site-selective *N*,*N*-di-Boc-activation (*tert*-butoxycarbonyl activation) of the amide nitrogen with practical air- and moisture-stable, well-defined and highly reactive [Pd(NHC)(cin)Cl] (NHC = N-heterocyclic carbene; cin = cinnamyl) provides a highly effective route to biaryl ketones from primary amides in high yields. For the first time, a TON of >1,000 has been achieved in amide acyl cross-coupling.

In the past two years, tremendous progress has been reported in the development of new methods for the cross-coupling of amides by N–C bond activation.[1–5] Typically, amides have long been considered unreactive for the powerful metal insertion into the acyl N–C(O)amide bond due to amidic resonance ($n_N \rightarrow \pi^*_{C=O}$ conjugation, a barrier to rotation in planar amides of 15-20 kcal/mol).[6,7] More recently, efforts to enhance amide reactivity by steric and electronic ground-state-destabilization have been reported,[8] enabling direct access acyl-metal intermediates from amides.[9] While a range of methods to activate the amide bond towards selective metal insertion has been developed,[1–5] by far the most synthetically useful are *N*,*N*-di-Boc-activated amides (Figure 1),[10] allowing direct engagement with common primary amides[10–12] in a range of cross-coupling methods after double *N*-*tert*-butoxycarbonylation under mild conditions.[13] Given that primary amides are among the most ubiquitous amide derivatives in organic synthesis[11] and constitute widespread structural motifs in medicinal chemistry,[12] selective methods that allow for the cross-coupling of primary amides under mild conditions are in high demand.[14]

As part of our program on amide bond activation, we report the first direct Suzuki-Miyaura cross-coupling of common primary benzamides[10-12] under exceedingly mild conditions enabled by the merger of site-selective *N*,*N*-di-Boc-activation[13] and the use of highly-selective [Pd(NHC)(cin)Cl] precatalysts.[15] This user-friendly method, employing air- and moisture-stable, commercially available reagents and catalysts,[16] provides a highly effective protocol to access biaryl ketones[17] from primary amides. We show that a broad range of electronically-diverse amides can be cross-coupled with an array of boronic acids in high yields. Moreover, we demonstrate for the first time a TON of >1,000 in amide/acyl cross-coupling. Considering the importance of the primary amide bond in organic synthesis and pharmaceutical industry,[11,12] we anticipate that the method will be of broad synthetic interest.

Notable features of this study include: (1) the first general method for the room temperature Suzuki-Miyaura cross-coupling of *N*,*N*-di-Boc amides that are equivalent to unactivated NH_2 benzamides, and (2) the establishment of a new catalytic system based on [Pd(IPr)(cin)Cl]/KF/H_2O in a non-polar, aprotic solvent.

The key challenges in direct activation of the amide bond in *N*,*N*-di-Boc-amides are (1) selective metal insertion into the acyl amide bond (cf. N-carbamate bond);[1a-d] (2) undesired cleavage of the N-Boc moiety switching off the capacity of the amide bond to engage in cross-coupling under redox-neutral conditions;[8] and (3) stability of the acyl-metal intermediate after metal insertion.[9] Seeking to take advantage of the well-

established propensity of NHC ligands[18-20] (as strong σ-donors) to facilitate oxidative addition in combination with flexible steric bulk that stabilizes the active catalyst and promotes reductive elimination, we hypothesized that well-defined Pd(II)-NHC precatalysts[21] might represent a general class of highly-practical catalysts for the desired coupling.

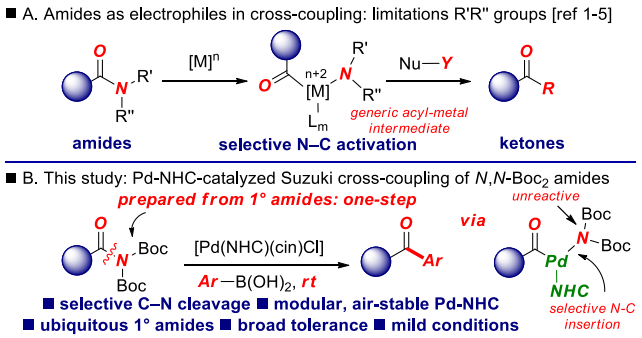
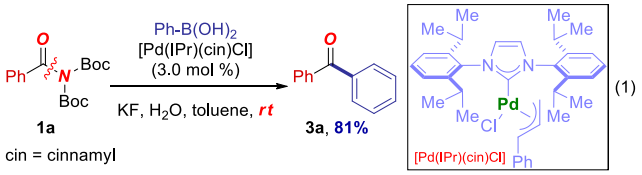


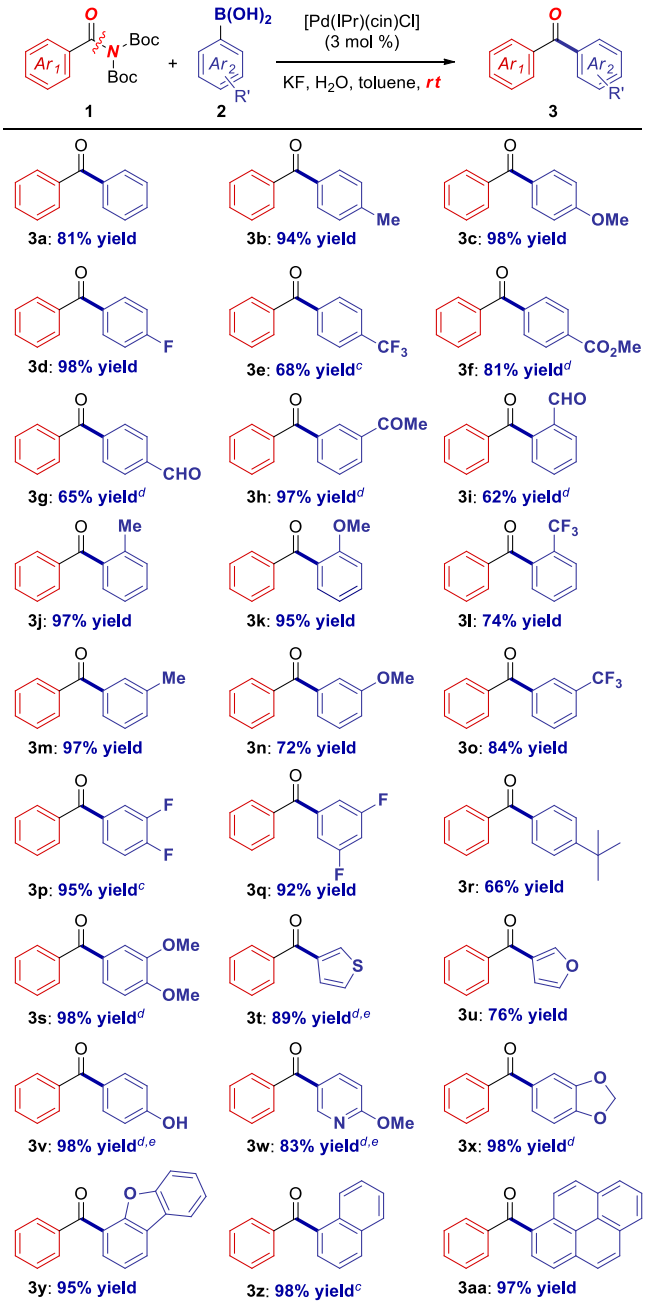
Figure 1. (a) Activation of amides and derivatives. (b) This work: coupling of common primary amides enabled by [Pd(NHC)(cin)Cl] catalysts.

Our previous conditions for acyl-coupling using Pd-NHCs were ineffective,[3d] highlighting the challenge of the direct Suzuki-Miyaura coupling of *N*,*N*-di-Boc-amides. After very extensive optimization that was focused on examination of sterically-demanding NHC ligands with variable steric bulk and flexibility, such as IPr*,[22] we discovered a catalytic system that facilitates the desired coupling (eq 1, [Pd(IPr)(cin)Cl] (3 mol %), KF (3 equiv), water (5 equiv), toluene, rt, 15 h). The high reactivity of [Pd(IPr)(cin)Cl] under these conditions allows the coupling to be conducted at ambient temperature.



With the optimal conditions in hand, the scope of this protocol was next evaluated by varying the boronic acid component (Scheme 1). As shown, a broad range of aryl boronic acids serves as highly effective nucleophile in the reaction. Neutral (**3a**), electron-donating (**3b-c**), and electron-withdrawing (**3d-f**) boronic acids afforded the desired products in high to excellent yields. Importantly, a range of electrophilic carbonyl functional groups that would be problematic in the classic Weinreb amide synthesis, including ester (**3f**), aldehydes (**3g, 3i**) and ketone (**3h**) situated at various positions around the aromatic ring are readily compatible, highlighting a distinct advantage of our catalytic protocol. Notably, the reaction is highly efficient for the cross-coupling of electronically-diverse ortho-sterically-hindered boronic acids (**3j-l**), including deactivating ortho-CF_3-substituent on the aromatic ring (**3l**), attesting to the high catalytic activity of [Pd(IPr)(cin)Cl] under these conditions. Electronically-diverse substitution at the meta-position (Me, OMe, CF_3) is also well-tolerated (**3m-o**). Furthermore, fluorinated boronic acids, relevant to medicinal and agrochemistry, furnish the desired products in high yields (**3p-q**). A tertiary alkyl substituent on the aromatic ring is well-tolerated (**3r**), providing an alternative to the direct cross-coupling.[23] Highly electron-rich arene (**3s**), five-membered heterocycles (**3t-u**), phenol (**3v**), pyridine (**3w**) and dioxolane (**3x**) were converted with high catalytic efficiency. Finally, sterically-hindered heterocycles, such as dibenzofuran (**3y**), and poly-aromatics, such as 1-naphthalene (**3z**) and 1-pyrene (**3aa**) are competent nucleophiles in this direct cross-coupling. We determined that is some cases the reaction is more efficient using a combination of K_3PO_4/toluene (e.g. **3e**) or K_2CO_3/THF (e.g. **3f-i**), presumably due to solubility issues. At this stage, vinyl boronic acids have not been tested.[3b]

Scheme 1. Boronic Acid Scope in the Pd-NHC-Catalyzed Direct Cross-Coupling of *N*,*N*-Boc$_2$-Amides[a,b]



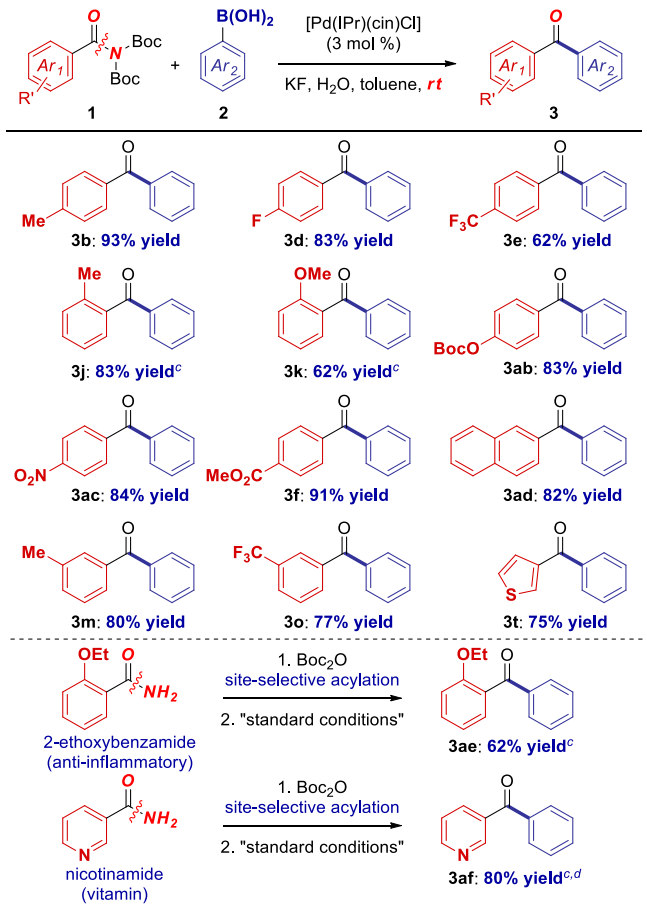
[a]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd(IPr)(cin)Cl] (3 mol %), KF (3.0 equiv), H_2O (5.0 equiv), toluene (0.25 M), 23 °C, 15 h. [b]Isolated yields. [c]K_3PO_4. [d]K_2CO_3, THF. [e][Pd(IPr)(1-*t*-Bu-indenyl)Cl].

Furthermore, for some heteroatom-containing boronic acids (e.g., **3t**), [Pd(IPr)(η^3-1-*t*-Bu-indenyl)Cl][24] is beneficial. To the

best of our knowledge, the present method represents the broadest scope for the Suzuki-Miyaura cross-coupling by amide bond N–C activation reported to date[1–5] and additionally and pleasingly is conducted at room temperature.

We next turned our attention to the scope of amides that can participate in this protocol (Scheme 2). Note that all *N*,*N*-di-Boc amides are prepared directly in one-step from the corresponding benzamides.[25] This represents a major shift from the cross-coupling of other types of amides, largely limited thus

Scheme 2. Amide Scope in the Pd-NHC-Catalyzed Direct Cross-Coupling of *N*,*N*-Boc$_2$-Amides[a,b]



[a]Conditions: amide (1.0 equiv), Ph-B(OH)$_2$ (2.0 equiv), [Pd(IPr)(cin)Cl] (3 mol %), KF (3.0 equiv), H_2O (5.0 equiv), toluene (0.25 M), 23 °C, 15 h. [b]Isolated yields. [c]60 °C. [d]K_2CO_3, THF.

far to the coupling of less common secondary or tertiary amides that typically originate from carboxylic acids or aroyl chlorides (cf. ubiquitous primary amides).

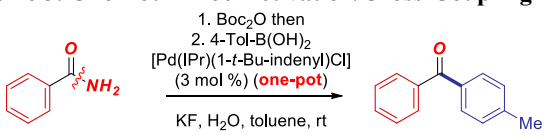
We were pleased to find a very broad scope of amides can participate in this new protocol. Electron-donating (**3b**), electron-withdrawing (**3d-e**) and sterically-hindered (**3j-k**) amides can be readily employed with good efficiency. Furthermore, substrates containing electrophilic functional groups, such as protected phenol (**3ab**), nitro (**3ac**) and ester (**3f**), undergo the cross-coupling in high yields, providing functional handles for further modification. As expected, meta-substitution (**3m**, **3o**) and heterocycles (**3t**) are well-tolerated. Perhaps most notably, the present method can be employed to directly engage pharmaceuticals, such as 2-ethoxybenzamide (**3ae**, anti-inflammatory drug) and nicotinamide (**3af**, essential vitamin) under mild, practical reaction conditions. For sterically-demanding (e.g. **3j-k**) and heterocyclic (**3af**) amides slight increase of the reaction temperature leads to optimum results. At present, alkyl and vinyl amides have not been examined under these conditions.[3b] Finally, it is important to note that the reaction employs well-defined Pd-NHC precatalyst,[26] avoiding excess ligand, and is conducted under mild, redox-neutral conditions enabled by the site-selective *N*,*N*-di-Boc activation of the 1° amide bond.

The robust nature of Pd-NHCs permits one-pot site-selective *N*-Boc *tert*-butoxycarbonylation, followed by N–C(O) cross-coupling in high yield (Scheme 3). To our knowledge this is the first example of one-pot catalytic process engaging primary amides without purification of the intermediates.

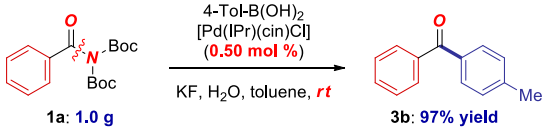
Pleasingly, the cross-coupling was carried out on a gram-scale using lower catalytic loading (0.50 mol %) without difficulty (Scheme 4), attesting to the practicality of the method.

We were further interested in the activity of the Pd-NHC catalyst at even lower loadings. We determined that the cross-coupling at 0.05 mol % [Pd] proceeds with TON of 1,200 (Scheme 5, 110 °C, TON of 600 at 23 °C). This is the highest TON reported to date for amide acyl cross-coupling. The finding bodes well for the development of even more efficient catalytic systems for amide cross-coupling using NHC ligands.

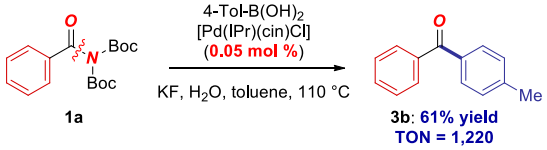
Scheme 3. One-Pot *N*-Boc-Activation/Cross-Coupling



Scheme 4. Scale-up at Low Catalyst Loading

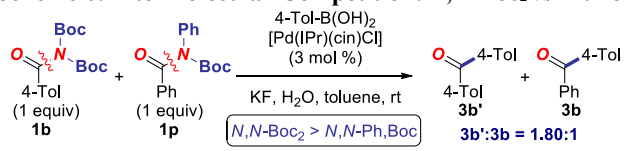


Scheme 5. Determination of TON



Intermolecular competition studies demonstrate that the activity of *N*,*N*-di-Boc amides under these conditions supersedes the reactivity of benchmark *N*-Ph/Boc amides[1a-d] (Scheme 6). The high reactivity of *N*,*N*-di-Boc amides using Pd-NHCs opens the door to a range of catalytic cross-coupling methods of primary amides via acyl-metal intermediates using the well-established Pd-NHC catalytic manifold. We hypothesize that the high reactivity of *N*,*N*-di-Boc amides results from the weakened N–C amide bond in these precursors.[1c]

Scheme 6. Intermolecular Competition: *N*,*N*-Boc$_2$ vs Ph/Boc



In conclusion, we have developed the first general method for the room-temperature Suzuki-Miyaura cross-coupling of common primary benzamides,[10a] which are among the most important amide derivatives in organic synthesis. This versatile and operationally-convenient method employs bench-stable and commercially available catalysts and reagents. The reaction tolerates a wide range of sensitive functional groups and shows broad substrate scope with respect to both the amide and boronic acid components. The reaction can be conducted in a one-pot fashion, is scalable and proceeds with the highest TON reported to date for amide acyl cross-coupling. The single-component, readily available,[27] air- and moisture-stable Pd-NHC precatalyst enables direct Pd insertion into the amide acyl bond with high selectivity, aided by the electronic properties and flexible bulk of the NHC ligand. The reaction highlights the potential of NHC ligands in Pd-catalyzed coupling of stable acyl electrophiles.[1a] Studies to expand the scope and generality of the cross-coupling of primary amides are currently ongoing.

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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