# Palladium/NHC (NHC = *N*-Heterocyclic Carbene)-Catalyzed B-Alkyl Suzuki Cross-Coupling of Amides by Selective N–C Bond Cleavage

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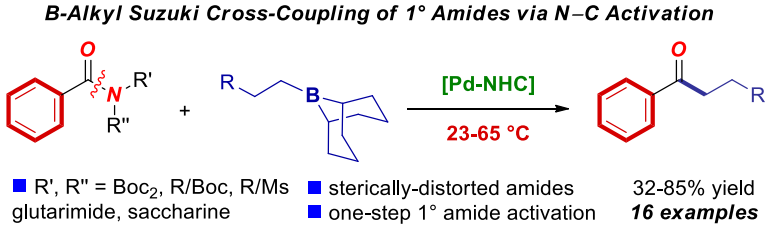
*Supporting Information*




**ABSTRACT:** A highly chemoselective, palladium-NHC (NHC = *N*-heterocyclic carbene)-catalyzed, direct cross-coupling between B-sp$^3$-alkyl reagents and activated amides by N–C(O) cleavage is reported. Palladium-NHC precatalysts promote chemoselective alkylations of amides that are inaccessible by applying strong organometallic reagents. Various amides, including challenging primary amides after direct and site-selective N,N-di-Boc activation are compatible with this method. The potential of this mild protocol is demonstrated in sequential C(sp$^2$)–C(sp$^2$)/C(sp$^2$)–C(sp$^3$) cross-couplings deploying a di-Boc amide derived from a common primary amide bond. The method provides a rare example of air- and moisture-stable, well-defined and highly reactive Pd-NHC precatalysts in B-alkyl-Suzuki cross-couplings.

The cross-coupling of amides represents a powerful route to carbon–carbon and carbon–heteroatom bond formation by engaging traditionally inert amide bonds (amidic resonance, 15-20 kcal/mol, $n_N \rightarrow \pi^*_{C=O}$ conjugation).[1–3] Direct functionalization of amides has recently become an important goal in organic synthesis[4–8] especially due to the potential to unlock Weinreb amide-type reactivity of amides[9] by catalytic metal insertion with much improved functional group tolerance, chemoselectivity[10] and operational convenience by avoiding strong organometallic reagents. Furthermore, the direct activation of amides by N–Boc or N–Ts protection offers significant advantages to manipulate common primary and secondary amide bonds,[11] providing a new synthetic disconnection for the construction of functionalized molecules from ubiquitous amides.[12] Despite recent progress in C(acyl)–aryl cross-couplings of amides[3,4,6–8], alkylation of amide bonds by transition-metal-catalysis remains a significant challenge due to competing β-hydride elimination/protodemetallation decomposing the organometallic and slower transmetallation.[13] In previous work, Ni-catalyzed alkylation of N-Ts activated amides using alkylzinc reagents and Ni-catalyzed alkylation of N-Ph/Me activated amides using alkylborane reagents has been reported.[14] Furthermore, a Ni-catalyzed reductive C(acyl)–alkyl cross-coupling of N-acyl-succinimide amides has been reported.[4e] We turned our attention to the B-alkyl Suzuki cross-coupling[15] of amides using Pd-catalysis to promote selective formation of acyl-metal from more challenging N-Boc and N-cyclic amides that are inaccessible by Ni-catalysis.

Herein, we report a highly chemoselective, palladium-NHC (NHC = *N*-heterocyclic carbene)-catalyzed, direct cross-coupling between B-sp$^3$-alkyl reagents and activated amides by N–C(O) cleavage (Figure 1). Various amides, including challenging primary amides after direct and site-selective N,N-di-Boc activation and sensitive N-glutarimide amides,[3a,b] are compatible with this method. The potential of this mild protocol is demonstrated in sequential C(sp$^2$)–C(sp$^2$)/C(sp$^2$)–C(sp$^3$) cross-couplings deploying a common primary amide bond. Most importantly, the method expands the well-developed manifold of Pd-catalyzed Suzuki-Miyaura aryl cross-coupling of amides to the B-alkyl cross-coupling using versatile organoboron reagents.[15] Furthermore, the method provides a rare example of air- and moisture-stable, well-defined and highly reactive Pd-NHC precatalysts in B-alkyl-Suzuki cross-couplings.[16]

Table 1 presents key results obtained during the optimization of the reaction conditions. To test the B-alky-Suzuki cross-coupling, we selected N,N-di-Boc activated benzamide. The site-selective *N*,*N*-diacylation of the 1° amide bond allows a significant decrease in amidic resonance ($E_R$ = 7.6 kcal/mol) and engages common benzamides in general cross-coupling manifolds.[11] However, the major challenge is the propensity of the N-Boc group to undergo scission, deactivating the acyl amide bond towards metal insertion. To our delight, we observed the desired B-alkyl Suzuki alkylation product using [(IPr)Pd(cin)Cl] precatalyst[17] (3 mol%) in a promising 56% yield at room temperature (Table 1, entry 1) using *n*-$C_{10}H_{21}$-9-

BBN (2.0 equiv) in the presence of $K_2CO_3$ as a base. Improvement in the reaction efficiency was realized by increasing the reaction temperature to 65 °C (entry 2); however, the reaction was less efficient using an excess of base (entry 3), consistent with facile decomposition of the alkyl-

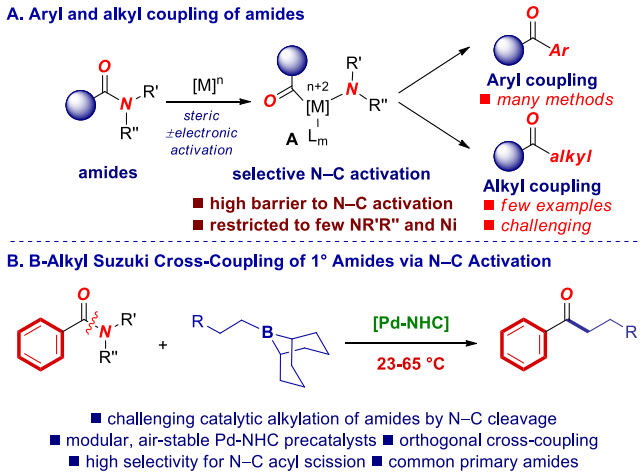
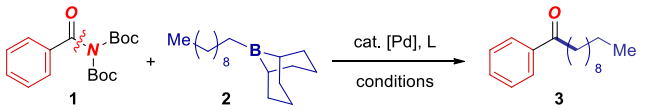



**Figure 1.** Palladium/NHC-catalyzed B-alkyl Suzuki-Miyaura cross-coupling of amides by selective N–C cleavage (previous and this work).

organometallic.[13] The addition of water had a minor, but positive effect on the reaction efficiency (entry 4); however, our attempts to generate the more reactive acylammonium species in situ by using Lewis bases[4c] did not result in noticeable improvements of the reaction efficiency (entry 5). Further optimization revealed that yields could be dramatically improved by employing 6 mol% of the Pd-NHC precatalyst (entries 6-7), consistent with the difficulty of the cross-coupling. Tuning of different bases and solvents demonstrated that a combination of $K_2CO_3$ and THF is preferred for this coupling (entries 8-11). An extensive screen of various Pd-NHC precatalysts (Figure 2) identified [(IPr)Pd(cin)Cl] as essential for this coupling (Table 2, entries 12-16). Of note, changes in the throw-away ligand ([(IPr)Pd(allyl)Cl], [Pd-PEPPSI-IPr]) and in the NHC scaffold ([(IMes)Pd(cin)Cl], [(SIPr)Pd(cin)Cl]) resulted in significantly diminished yields.[18] However, we identified the [(IPr)Pd(1-*t*-Bu-ind)Cl] precatalyst as a promising Pd(II)-NHC precatalyst[19] for the B-alkyl-Suzuki cross-coupling of amides. In line with previous studies and the high reactivity of the preformed Pd(II)-NHC precatalysts, control experiments in the absence of the catalyst and using representative Pd-$PR_3$ conditions,[14e] revealed the requirement for a strong σ-donating Pd–NHC in this cross-coupling protocol.

With the optimized conditions in hand, we tested the preparative scope of the reaction using N,N-di-Boc amide as a standard electrophile (Table 2). Pleasingly, this challenging alkylation reaction tolerates a range of B-alkyl-9-BBN reagents, including those with simple (entries 1-2) and sensitive functional groups such as ether (entry 3), imide (entry 4), indole (entry 5) and ester (entry 6). While in some cases the yield is modest, the reaction provides a proof-of-concept and a simple method for selectively installing functionalized alkyl groups from amides derived from common primary benzamides in a catalytic manner. Furthermore, we were pleased to find that a variety of amides is tolerated in this B-alkyl-Suzuki cross-coupling. Most interestingly, N-acyl-glutarimides that feature two activated carbonyl groups[20] were selectively cross-

**Table 1. Optimization of Palladium-NHC-Catalyzed Cross-Coupling by N–C Cleavage[a]**




1 2 3

| entry | catalyst | base | solvent | *t* (°C) | yield (%) |
|---|---|---|---|---|---|
| 1 | (IPr)Pd(cin)Cl | $K_2CO_3$ | THF | 23 | 56 |
| 2 | (IPr)Pd(cin)Cl | $K_2CO_3$ | THF | 65 | 67 |
| 3[b] | (IPr)Pd(cin)Cl | $K_2CO_3$ | THF | 65 | 48 |
| 4[c] | (IPr)Pd(cin)Cl | $K_2CO_3$ | THF | 23 | 70 |
| 5[d] | (IPr)Pd(cin)Cl | $K_2CO_3$ | THF | 23 | 53 |
| 6 | (IPr)Pd(cin)Cl | $K_2CO_3$ | THF | 23 | 84 |
| 7 | (IPr)Pd(cin)Cl | $K_2CO_3$ | THF | 65 | 91 |
| 8 | (IPr)Pd(cin)Cl | $Cs_2CO_3$ | THF | 23 | <5 |
| 9 | (IPr)Pd(cin)Cl | $K_3PO_4$ | THF | 23 | 27 |
| 10 | (IPr)Pd(cin)Cl | $K_2CO_3$ | toluene | 23 | 28 |
| 11 | (IPr)Pd(cin)Cl | $K_2CO_3$ | $Et_2O$ | 23 | 21 |
| 12 | (IPr)Pd(allyl)Cl | $K_3PO_4$ | THF | 23 | 5 |
| 13 | (IMes)Pd(cin)Cl | $K_2CO_3$ | THF | 23 | 7 |
| 14 | (SIPr)Pd(cin)Cl | $K_2CO_3$ | THF | 23 | 21 |
| 15 | Pd-PEPPSI-IPr | $K_2CO_3$ | THF | 23 | 15 |
| 16 | (IPr)Pd(1-*t*-Bu-ind)Cl | $K_2CO_3$ | THF | 23 | 57 |
| 17 | - | $K_2CO_3$ | THF | 23 | <5 |
| 18[e] | $Pd(PPh_3)_4$ | $Cs_2CO_3$ | THF | 110 | <5 |

[a]Conditions: **1** (1.0 equiv), *n*-$C_{10}H_{21}$-9-BBN (2.0 equiv), catalyst (3-6 mol %), base (3.0 equiv), solvent (0.25 M), 23-110 °C, 15 h. Entries 1-5: [Pd] (3 mol %), entries 6-17: [Pd] (6 mol %). [b]$K_2CO_3$ (4.5 equiv). [c] $H_2O$ (10 equiv). [d]$Et_3N$ (30 mol %). [e][Pd] (5 mol %). See SI for experimental details.

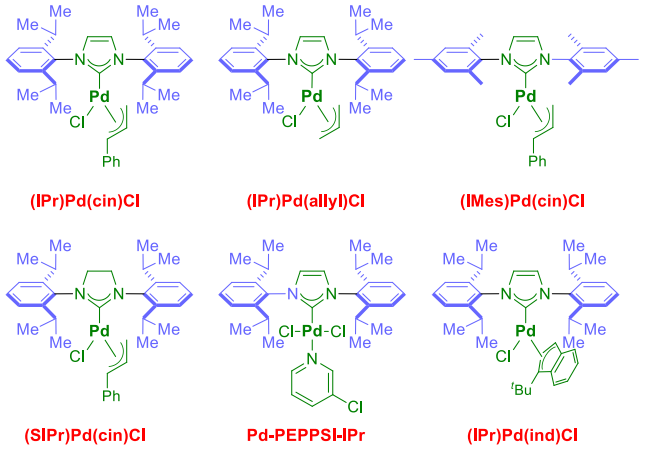
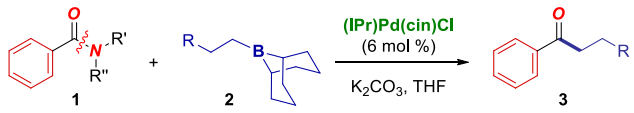


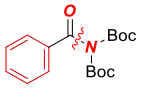
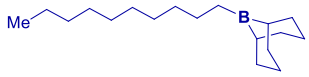
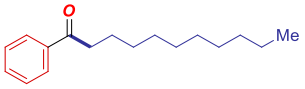
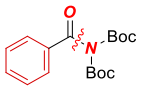
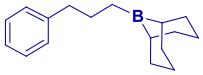
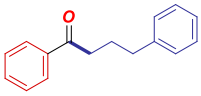
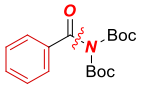
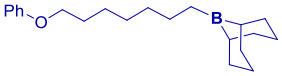
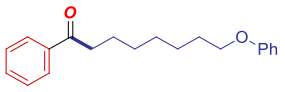
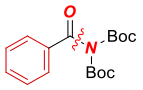
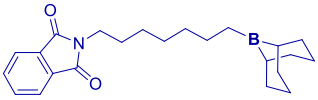
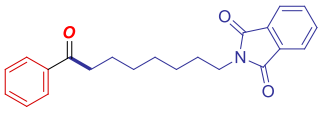
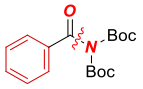
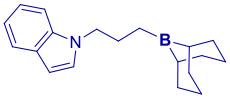
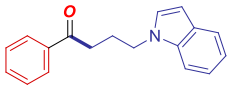
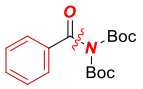
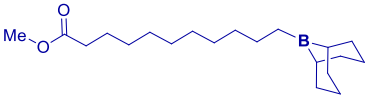
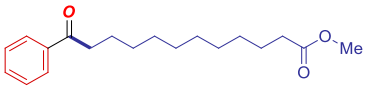
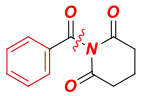
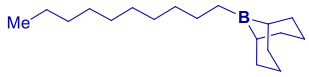
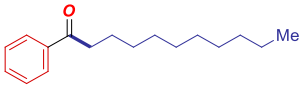
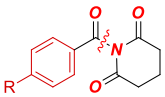
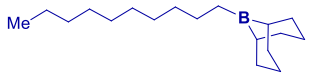
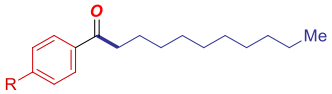
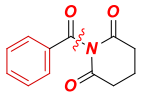
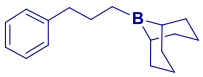
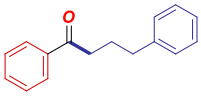
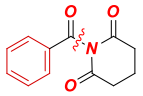
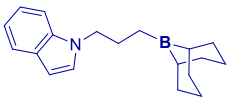
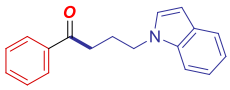
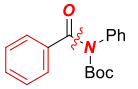
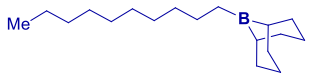
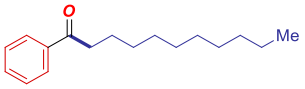
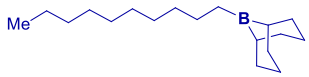
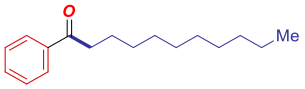
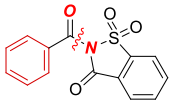
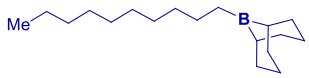
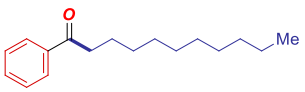

**Figure 2. Structures of palladium-NHC precatalysts.**

coupled at the exo-cyclic N-acyl bond, attesting that this catalytic system is selective for cleavage of N–C(O) bonds (entries 7-12). Furthermore, N-Ph/Boc and atom-economical N-Ph/Ms amides that can be prepared directly from common secondary amides readily participated in this coupling (entries 13-14).[3a,b] Finally, we found that even sensitive N-benzoyl-saccharin that typically undergoes CO addition to the saccharine ring and $SO_2$ cleavage with strong organometallics,[3a,b] delivered the

desired coupling product, albeit in a modest yield (entry 15).
At present, ortho-methyl benzoic acid derived amides have not

**Table 2. Palladium-NHC-Catalyzed Alkylation of Amides by N–C Cleavage**[a,b]



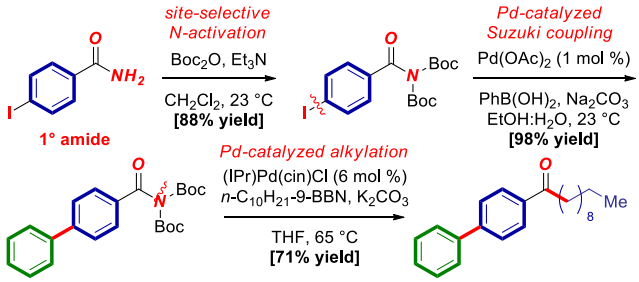

| entry | amide | alkyl-9-BBN | product | 3 | conditions | yield (%) |
|---|---|---|---|---|---|---|
| 1 |  |  |  | **3a** | A | 73 |
| 2 |  |  |  | **3b** | B | 48 |
| 3 |  |  |  | **3c** | C | 75 |
| 4 |  |  |  | **3d** | B | 46 |
| 5 |  |  |  | **3e** | B | 32 |
| 6 |  |  |  | **3f** | C | 71 |
| 7 |  |  |  | **3a** | A | 85 |
| 8 |  R = $CF_3$ |  |  | **3g** | A | 79 |
| 9 | R = MeO | | | **3h** | B | 61 |
| 10 | R = $CO_2$Me | | | **3i** | A | 74 |
| 11 |  |  |  | **3b** | B | 72 |
| 12 |  |  |  | **3e** | B | 81 |
| 13 |  |  |  | **3a** | B | 72 |
| 14 |  |  |  | **3a** | B | 84 |
| 15 |  |  |  | **3a** | A | 34 |

[a]Conditions: A: **1** (1.0 equiv), **2** (2.0 equiv), (IPr)Pd(cin)Cl (6 mol %), $K_2CO_3$ (3.0 equiv), THF (0.25 M), 23 °C, 15 h. B: 65 °C. C: (IPr)Pd(1-*t*-Bu-ind)Cl (6 mol %), 65 °C. See SI for experimental details. [b]Isolated yields.

been tested. At this stage, α-branched alkyl boron reagents are not tolerated. The reaction can be routinely set up under open air conditions. Future studies will be focused on further optimization of reaction conditions and application to multicomponent reactions.

We speculated that the potential of this mild alkylation protocol could be demonstrated in sequential $C(sp^2)$–$C(sp^2)$/$C(sp^2)$–$C(sp^3)$ cross-couplings employing amides derived from common primary amide bonds. To this end, site-selective N,N-di-Boc activation of 4-iodobenzamide, followed by aryl Suzuki cross-coupling and C(acyl)–B-alkyl Suzuki cross-coupling have been accomplished with a high degree of efficiency and excellent chemoselectivity (Scheme 1). Of note, aryl Suzuki cross-coupling could be readily performed in the presence of the electrophilic N,N-di-Boc amide, which together with the B-alkyl regime allows for a strategically valuable disconnection typical to Weinreb amides, but in a catalytic manner.

**Scheme 1. Sequential Cross-Coupling of 1° Amides**




In conclusion, we have reported a new method for highly chemoselective, palladium-NHC-catalyzed, direct cross-coupling between B-$sp^3$-alkyl reagents and activated amides by N–C acyl cleavage. This protocol is compatible with various amides, including challenging primary amides after direct and site-selective N,N-di-Boc activation and sensitive N-cyclic amides. The method delivers chemoselective alkylation products of amides that are inaccessible by applying strong organometallic reagents. We have further demonstrated the utility of the method in sequential $C(sp^2)$–$C(sp^2)$/$C(sp^2)$–$C(sp^3)$ cross-couplings employing amides derived from common primary amide bonds. Further studies will focus on optimization of the catalyst system and reaction parameters to expand the substrate scope and mechanistic investigations to facilitate further reaction development.

## ASSOCIATED CONTENT

### Supporting Information

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

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