

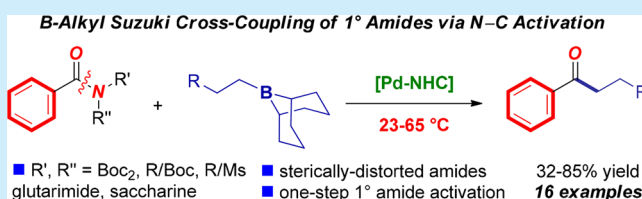
Palladium/NHC (NHC = *N*-Heterocyclic Carbene)-Catalyzed B-Alkyl Suzuki Cross-Coupling of Amides by Selective N–C Bond Cleavage

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S Supporting Information

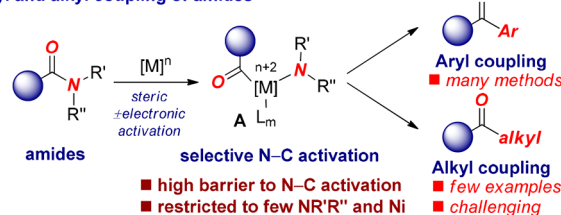
ABSTRACT: A highly chemoselective, palladium-NHC (NHC = *N*-heterocyclic carbene)-catalyzed, direct cross-coupling between B-*sp*³-alkyl reagents and activated amides by N–C(O) cleavage is reported. Palladium-NHC precatalysts promote chemoselective alkylations of amides that are inaccessible by applying 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 the Weinreb amide-type reactivity of amides⁹ 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 (1°) and secondary (2°) 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/protodemetalation decomposing the organometallic and slower transmetalation.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-coupling¹⁵ 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

A. Aryl and alkyl coupling of amides



B. B-Alkyl Suzuki Cross-Coupling of 1° Amides via N–C Activation

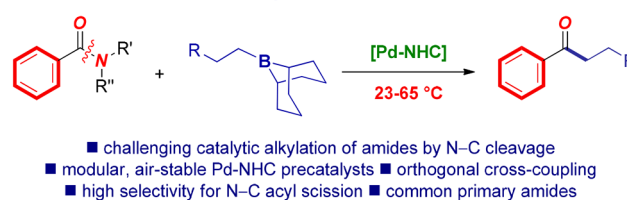


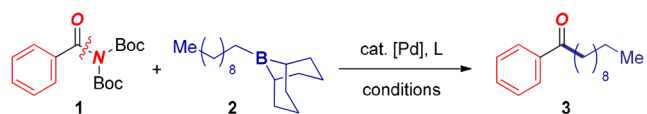
Figure 1. Palladium/NHC-catalyzed B-alkyl Suzuki–Miyaura cross-coupling of amides by selective N–C cleavage (previous and this work).

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

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Table 1 presents key results obtained during the optimization of the reaction conditions. To test the B-alkyl-

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



entry	catalyst	base	solvent	<i>t</i> (°C)	yield (%)
1	(IPr)Pd(cin)Cl	K ₂ CO ₃	THF	23	56
2	(IPr)Pd(cin)Cl	K ₂ CO ₃	THF	65	67
3 ^b	(IPr)Pd(cin)Cl	K ₂ CO ₃	THF	65	48
4 ^c	(IPr)Pd(cin)Cl	K ₂ CO ₃	THF	23	70
5 ^d	(IPr)Pd(cin)Cl	K ₂ CO ₃	THF	23	53
6	(IPr)Pd(cin)Cl	K ₂ CO ₃	THF	23	84
7	(IPr)Pd(cin)Cl	K ₂ CO ₃	THF	65	91
8	(IPr)Pd(cin)Cl	Cs ₂ CO ₃	THF	23	<5
9	(IPr)Pd(cin)Cl	K ₃ PO ₄	THF	23	27
10	(IPr)Pd(cin)Cl	K ₂ CO ₃	toluene	23	28
11	(IPr)Pd(cin)Cl	K ₂ CO ₃	Et ₂ O	23	21
12	(IPr)Pd(allyl)Cl	K ₃ PO ₄	THF	23	5
13	(IMes)Pd(cin)Cl	K ₂ CO ₃	THF	23	7
14	(SIPr)Pd(cin)Cl	K ₂ CO ₃	THF	23	21
15	Pd-PEPPSI-IPr	K ₂ CO ₃	THF	23	15
16	(IPr)Pd(1- <i>t</i> -Bu-ind)Cl	K ₂ CO ₃	THF	23	57
17	–	K ₂ CO ₃	THF	23	<5
18 ^e	Pd(PPh ₃) ₄	Cs ₂ CO ₃	THF	110	<5

^aConditions: **1** (1.0 equiv), *n*-C₁₀H₂₁-9-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 6–16: [Pd] (6 mol %). ^bK₂CO₃ (4.5 equiv). ^cH₂O (10 equiv). ^dEt₃N (30 mol %). ^e[Pd] (5 mol %). See Supporting Information (SI) for experimental details.

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 toward metal insertion. To our delight, we observed the desired B-alkyl Suzuki alkylation product using the [(IPr)Pd(cin)Cl] precatalyst¹⁷ (3 mol %) in a promising 56% yield at room temperature (Table 1, entry 1) using *n*-C₁₀H₂₁-9-BBN (2.0 equiv) in the presence of K₂CO₃ 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-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 K₂CO₃ 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–

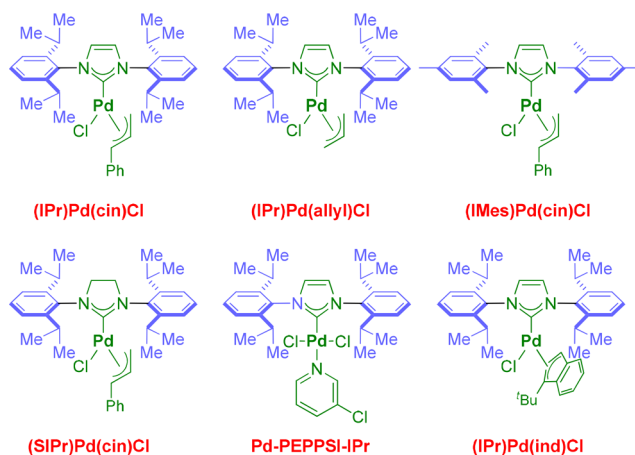


Figure 2. Structures of palladium-NHC precatalysts.

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] precatalyst¹⁹ 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-PR₃ 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 are tolerated in this B-alkyl-Suzuki cross-coupling. Most interestingly, *N*-acyl-glutarimides that feature two activated carbonyl groups²⁰ were selectively cross-coupled at the exocyclic *N*-acyl bond, attesting that this catalytic system is selective for cleavage of activated 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 SO₂ 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 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(sp²)–C(sp²)/C(sp²)–C(sp³) cross-couplings employing amides derived from common primary amide bonds. To this end, site-selective

Table 2. Palladium-NHC-Catalyzed Alkylation of Amides by N–C Cleavage^{a,b}

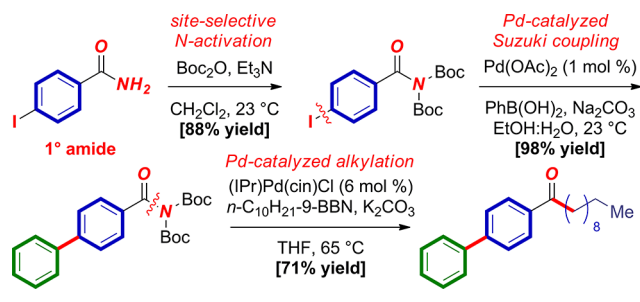
entry	amide	alkyl-9-BBN	product	3	conditions	yield (%)
1				3a	A	73
2				3b	B	48
3				3c	C	75
4				3d	B	46
5				3e	B	32
6				3f	C	71
7				3a	A	85
8				3g	A	79
9	R = CF ₃			3h	B	61
10	R = MeO			3i	A	74
11				3b	B	72
12				3e	B	81
13				3a	B	72
14				3a	B	84
15				3a	A	34

^aConditions: (A) **1** (1.0 equiv), **2** (2.0 equiv), (IPr)Pd(cin)Cl (6 mol %), K₂CO₃ (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. ^bIsolated yields.

N,N-di-Boc activation of 4-iodobenzamide, followed by aryl Suzuki cross-coupling and C(acyl)–B-alkyl Suzuki cross-coupling, has 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-sp³-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(sp²)–C(sp²)/C(sp²)–C(sp³) 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs-orglett.8b02911.

Procedures and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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