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Nickel-Catalyzed Diaryl Ketone Synthesis by N−C Cleavage: Direct Negishi Cross-Coupling of Primary Amides by Site-Selective *N,N*-Di-Boc Activation

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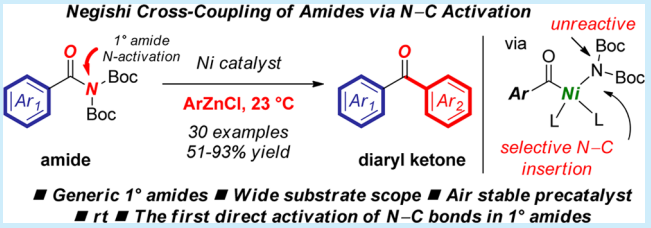
Supporting Information

ABSTRACT: A general Negishi acylation of primary amides enabled by a combination of site-selective *N,N*-di-Boc activation and nickel catalysis is reported for the first time. The reaction is promoted by a bench-stable, inexpensive Ni catalyst. The reaction shows excellent functional group compatibility, affording functionalized diaryl ketones by selective N−C cleavage. Most notably, this protocol represents the first amide cross-coupling by direct metal insertion of simple and readily available primary amides. The overall strategy by *N,N*-di-Boc activation/metal insertion is suitable for a broad range of coupling protocols via acylmetals. Mechanistic experiments suggest high reactivity of *N,N*-di-Boc activated 1° amides in direct amide C−N cross-couplings.



The catalytic activation of amide N−C bonds represents one of the most challenging transformations in organic synthesis as a consequence of amidic resonance.[1,2] Due to the prevalence of amides in bioactive molecules, synthetic polymers, and proteins,[3,4] methods to engage common amide functional groups catalytically in generic transition-metal-catalyzed transformations are in great demand.[5] In this context, catalytic cross-coupling reactions by activation of amide N−C bonds have gained significant attention.[6] Following the breakthrough report by Garg on the Ni-catalyzed esterification of amides,[7] several notoriously challenging transformations by N−C amide cleavage have been developed.[8−10] In particular, the unconventional amide N−C bond disconnection has enabled new strategies for constructing C−C,[8] C−N,[9] and C−B[10] bonds using extremely versatile cross-coupling protocols (Figure 1A). However, this approach has been largely limited to the use of Boc-activated secondary amides and less common tertiary amides.[7−10] Transformations that allow catalytic functionalization of ubiquitous primary amides[11] in a modular fashion[8l] hold particular promise to revolutionize synthetic strategies by the catalytic amide bond disconnection.[7−10] We describe a new activation mode of N−C bonds in primary amides by site-selective *N,N*-di-Boc activation of the amide nitrogen atom and direct nickel insertion into the N−C bond to enable the first functional group tolerant Negishi cross-coupling of primary amides (Figure 1B). The reaction enables us to engage generic primary amides (cf. glutarimides or less common secondary amides)[8e] in transition-metal-catalyzed amide N−C cross-coupling by direct metal insertion (cf. transacylation).[8l]

The challenge of cross-coupling of amide N−C bonds arises from structural limitations inherent in the partial double-bond character of amides.[1,2] As a consequence, coordination of

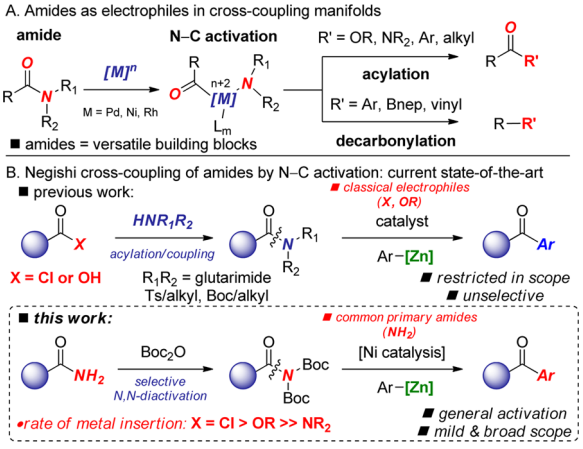


Figure 1. (a) Cross-coupling of amides by N−C activation. (b) Negishi cross-coupling of amides: previous and this work.

electrophiles is electronically biased toward the amide oxygen atom.[12] O-Coordination reinforces the double-bond character of amides, thereby decreasing the susceptibility of N−C amide bonds to direct metal insertion.[13] Although the O-activation has been well-recognized, resulting in electrophilic imidoyl cations,[14] this chemistry is limited to secondary and tertiary amides and reactive organometallic nucleophiles.[15] We hypothesized that site-selective N-activation[12] of amides in conjunction with transition-metal catalysis might enable the first general method for the modular functionalization of primary amides[11] by direct metal insertion under mild

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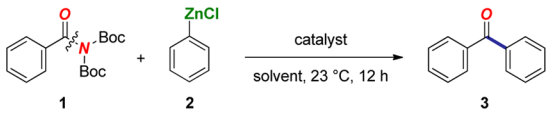
conditions. Specifically, we proposed that the double N-functionalization with an electron-withdrawing group[16] would decrease the double-bond character of primary amides (barrier to resonance of 15−20 kcal/mol; acetamide, 18.4 kcal/mol),[17] thus allowing this high energy precursor to undergo metal insertion into the amidic N−C bond. Importantly, if successful, this reaction design would generate versatile acylmetal intermediates from primary amides[11] and set the stage for diverse cross-coupling techniques utilizing well-established manifolds of acylmetals.[18] The proposed approach presents a significant challenge: (i) selective double N-activation of the amide bond must be realized, and the activating group must be stable to the reaction conditions.[19] (ii) Metal insertion into the N−C bond must be favored over scission of the now weakened σ N−C bond adjacent to N−C(O).[20] This would shut down the desired reaction pathway by producing the unreactive NHR precursor (R = H, Boc). (iii) Transmetalation must be facile to avoid decomposition of the sensitive acylmetal intermediate.[18]

In this paper, we report realization of this approach in the first modular Negishi cross-coupling[21] of primary amides under exceedingly mild conditions. The method employs cheap and bench-stable Ni catalysts that are economically advantageous over Pd catalysts.[22] We have identified *N*,*N*-di-Boc amides as readily accessible precursors for highly selective, direct Ni insertion into the amide N−C bond. The Negishi coupling reaction represents one of the most powerful transition-metal-catalyzed transformations.[21] The product diaryl ketones are prevalent in biologically active compounds, agrochemicals, dyes, and organic materials.[23] The combination of high transmetalation activity with broad functional group tolerance of organozinc reagents has contributed to the widespread industrial and academic application of the Negishi coupling manifold.[21a−c] Our study demonstrates the first Negishi cross-coupling engaging primary amides.[7−10] The overall strategy of activating 1° amide bonds is suitable for a broad range of coupling protocols via acylmetal intermediates.[5,18]

Our study commenced by evaluating the coupling of *N*,*N*-di-Boc-benzamide (**1**) with organozinc reagents under various conditions (Table 1). All *N*,*N*-di-Boc-benzamides employed in the current study were prepared by site-selective double N-acylation of the amide bond in an average yield of 73%, including substrates bearing Lewis basic groups (Boc_2O, DMAP, CH_2Cl_2, rt).[16] Traces or low yields of the desired product **3** were detected under conditions for Pd-catalyzed Negishi coupling (entries 1−4). After extensive experimentation, Ni-based catalysts provided the best results. The nature of the ligand had a significant influence of the coupling efficiency (entries 5−10). We established that the inexpensive and bench-stable $NiCl_2(PPh_3)_2$ catalyst afforded the product in good yield and with excellent N−C coupling selectivity. An extensive evaluation of solvents revealed Et_2O to be the most effective (entries 10−15). Nucleophilic and inorganic additives afforded the product in lower yields (entries 16−19). The optimum results were obtained using $NiCl_2(PPh_3)_2$ (10 mol %) in Et_2O at 23 °C, delivering **3** in 81% isolated yield (entry 20). Control experiments revealed that the reaction does not proceed without the catalyst (entry 21). Notably, the product was formed with exclusive C−N acylation selectivity (cf. decarbonylation)[8g−i] with no byproducts resulting from the σ C−N bond scission observed.[20] The developed process represents the first example of converting readily available primary amides to diaryl ketones by direct metal insertion.[7−10]

Table 1. Optimization of the Reaction Conditions[a]



1 2 3

entry	catalyst	additive	solvent	yield[b] (%)
1	$Pd(PPh_3)_4$		Et_2O	18
2	$PdCl_2(PPh_3)_2$		toluene	20
3	$PdCl_2(PPh_3)_2$		Et_2O	23
4[c]	$PdCl_2(PPh_3)_2$		Et_2O	<5
5	$NiCl_2$(dppe)		Et_2O	46
6	$NiCl_2$(dppf)		Et_2O	43
7	$Ni(OAc)_2$		Et_2O	15
8	$NiCl_2(PCy_3)_2$		Et_2O	45
9	$Ni(acac)_2$		Et_2O	18
10	$NiCl_2(PPh_3)_2$		Et_2O	74
11	$NiCl_2(PPh_3)_2$		toluene	64
12	$NiCl_2(PPh_3)_2$		THF	62
13	$NiCl_2(PPh_3)_2$		DMF	19
14	$NiCl_2(PPh_3)_2$		dioxane	55
15	$NiCl_2(PPh_3)_2$		CH_3CN	42
16[c]	$NiCl_2(PPh_3)_2$		Et_2O	48
17[d]	$NiCl_2(PPh_3)_2$	Et_3N	Et_2O	42
18[e]	$NiCl_2(PPh_3)_2$	LiCl	Et_2O	69
19[f]	$NiCl_2(PPh_3)_2$	PPh_3	Et_2O	42
20[g]	$NiCl_2(PPh_3)_2$		Et_2O	85
21			Et_2O	<5

[a]Conditions: amide (1.0 equiv), Ph-ZnCl (1.5 equiv), catalyst (5 mol %), solvent (0.20 M), 23 °C, 12 h. [b]GC and/or ^{1}H NMR [c]PhZnCl (3.0 equiv). [d]Et_3N (0.30 equiv). [e]LiCl (1.0 equiv). [f]PPh_3 (0.30 equiv). [g]$Ni(PPh_3)_2Cl_2$ (10 mol %). See the Supporting Information (SI) for full details.

Having identified the optimum conditions for the Negishi acylation of *N*,*N*-di-Boc amides, the scope of the reaction was next explored with respect to the amide-coupling partner. As shown in Scheme 1, a broad range of simple primary amides undergoes efficient coupling upon *N*,*N*-di-Boc activation. Diverse functional groups, including electronically diverse (**3a−j**), sterically hindered (**3b**,**n**), and various electrophilic functional handles, such as halides (**3e**,**f**), esters (**3i**), ethers (**3j**), protected alcohols (**3k**), nitriles (**3l**), heterocycles (**3m**), and polyarenes (**3o**), are readily tolerated. Perhaps most notable is the capacity of the reaction to tolerate functional groups that are problematic in the addition to classic Weinreb amides[15] and employ simple 1° amides as precursors.[1,2,11] The reaction provides a conceptually new method for the synthesis of ketones from primary amides under mild conditions.[7−10] Noteworthy is direct functionalization of 4-hydroxybenzamide (**3k**, pharmaceutical intermediate, with a concomitant O-Boc protection) and 2-ethoxybenzamide (**3n**, anti-inflammatory drug), highlighting the potential impact of the method on catalytic cross-coupling.[24]

Next, we focused on the evaluation of the scope of the nucleophilic coupling partner. As shown in Scheme 2, an array of arylzinc reagents perform well in the reaction. Electronically diverse organozinc reagents readily undergo the coupling (**3j−e**). Sterically hindered nucleophiles are readily tolerated (**3p**,**b**). Nucleophiles bearing functional handles for further functionalization by S_NAr (**3e**) or cross-coupling (**3r**) perform well in the reaction. Furthermore, indole-containing nucleophiles readily participate in the reaction (**3s**). Importantly, exclusive

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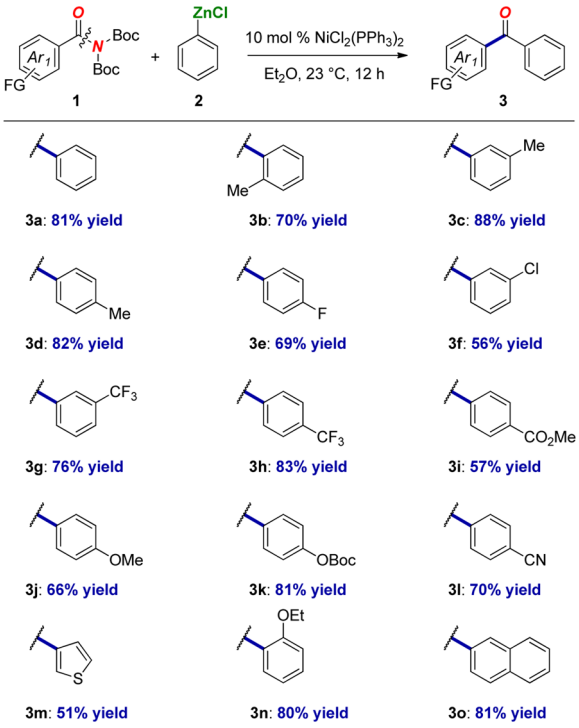
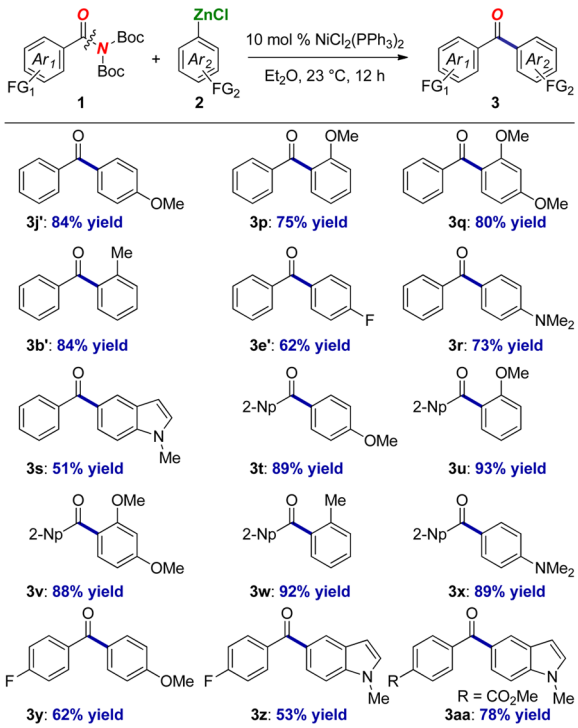
Scheme 1. Ni-Catalyzed Negishi Cross-Coupling of Amides: Amide Scope[a,b]



[a]Conditions: amide (0.10 mmol), R-ZnCl (1.5 equiv), $Ni(PPh_3)_2Cl_2$ (10 mol %), Et_2O (0.20 M), 23 °C, 12 h. [b]Isolated yields.

Scheme 2. Ni-Catalyzed Negishi Cross-Coupling of Amides: Organozinc Scope[a,b]

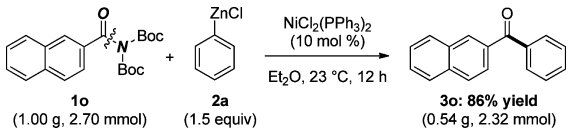


[a,b]See Scheme 1.

acylation selectivity was observed using 2-naphthalene-containing electrophiles prone to decarbonylation, attesting to the generality of this coupling (**3t**–**x**).[8g−i] The utility of this method is demonstrated by facile synthesis of functionalized ketones serving as precursors to electrochromic materials (**3x**),[23b] agrochemical intermediates (**3y**),[23c] and biological pharmacophores (**3aa**),[23d] directly from 1° amides. The broad functional group tolerance is in line with the well-established mild conditions for the Negishi cross-coupling[21] and bodes well for future applications of the method.

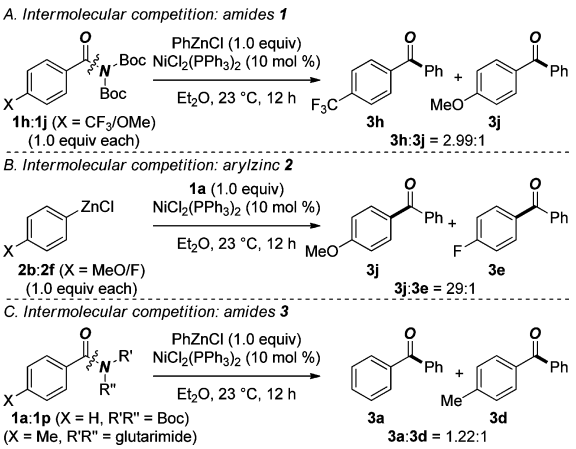
To assess the scalability of the process, the coupling was performed on a gram scale and gave **3o** in 86% isolated yield (Scheme 3), attesting to the synthetic utility of the method.

Scheme 3. Scale-up Experiment



We conducted preliminary studies to gain insight into the nature of the product determining step (Scheme 4).

Scheme 4. Mechanistic Studies



Intermolecular competition experiments between differently substituted amides (1:1 stoichiometry) revealed that electron-deficient amides are inherently more reactive (Scheme 4A), consistent with the facility of metal insertion into the N−C bond.[6] Further competition experiments between differently substituted nucleophiles indicated that electron-rich nucleophiles react preferentially (Scheme 4B). Assuming reversible oxidative addition,[8d] this experiment is consistent with rate-limiting transmetalation.[25] Intermolecular competition experiments between *N*,*N*-di-Boc-amides and *N*-glutarimide amides indicated that the former react preferentially (Scheme 4C).[8c−e] This observation, in conjunction with the ease of site-selective *N*,*N*-di-Boc-activation of simple primary amides, clearly demonstrates the synthetic potential of this method.[8c−e,g−i] The key step in the proposed mechanism involves direct Ni(0) insertion into the weakened N−C amide π bond.[7−10]

In summary, we have developed the first Negishi cross-coupling of primary amides enabled by the combined site-selective *N*,*N*-di-Boc activation and use of nickel catalysis through direct metal insertion into the N−C bond. The reaction shows excellent functional group tolerance, providing rapid access to functionalized ketones from simple and readily available primary amides, which are among the most commonly utilized building blocks in organic chemistry. Given the

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importance of N−C bond activation manifolds,[6] we expect that the site-selective *N,N*-di-Boc activation/metal insertion strategy will find broad applications in organic synthesis. Studies on general activation of amide bonds are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02952.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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