Letter

Nickel-Catalyzed Alkylation of Amide Derivatives

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Nickel-Catalyzed Alkylation of Amide Derivatives

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ABSTRACT: We report the catalytic alkylation of amide derivatives, which relies on the use of non-precious metal catalysis. Amide derivatives are treated with organozinc reagents utilizing nickel catalysis to yield ketone products. The methodology is performed at ambient temperature and is tolerant of variation in both coupling partners. A precursor to a nanomolar glucagon receptor modulator was synthesized using the methodology, underscoring the mild nature of this chemistry and its potential utility in pharmaceutical synthesis. These studies are expected to further promote the use of amides as synthetic building blocks.

KEYWORDS: nickel, catalysis, alkylation, amides, cross-coupling

The ability to activate traditionally unreactive functional groups as synthons continues to be a vital area of research. One particularly stable functionality is the amide.[1] The resonance stabilization of amides has been well understood for decades;[1,2] consequently, the use of amides in C–N bond cleavage reactions has remained limited. Recently, however, there has been much interest in breaking amide C–N bonds to forge new C–heteroatom and C–C bonds.[3,4,5,6,7] Such methodologies provide new tactics to prepare acyl derivatives, but with the key benefit of amide stability. The use of amides in multistep synthesis, followed by selective C–N bond activation and coupling, should ultimately prove advantageous in the synthesis of complex molecules.

The present study focuses on activating and coupling amides to build acyl C–C bonds in an intermolecular fashion (Figure 1).

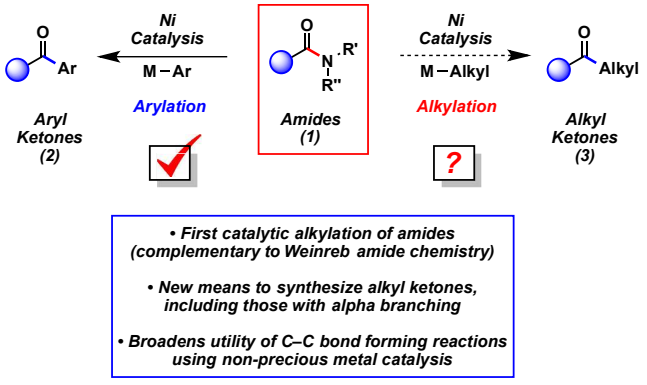


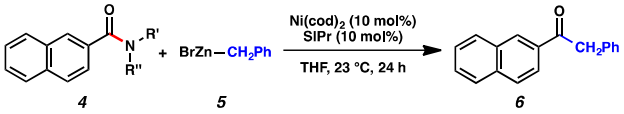
Figure 1. Nickel-catalyzed C–C bond forming reactions from amides.

Such catalytic methodology would complement Weinreb amide chemistry, but without the use of highly basic and pyrophoric organometallic reagents.[8] Prior contributions in this area include Suzuki–Miyaura couplings (**1**→**2**) reported by Zou (Pd),[4] Szostak (Pd),[5] and our laboratory (Ni).[3b] In each of these cases, the nucleophilic coupling partner was restricted to *aryl* boronate species, thus limiting the application of this methodology. The corresponding *alkylative* coupling (**1**→**3**) would be highly desirable given the prevalence of alkyl ketones in molecules of biological importance and the versatility of alkyl ketones as synthetic building blocks. Herein, we report the first alkylative cross-coupling of amide derivatives.

Following unsuccessful attempts to couple amide derivatives with aliphatic boronic acids and esters, we opted to pursue the use of organozinc reagents as cross-coupling partners.[9] Our earlier studies have relied on the use of nickel catalysis for amide C–N bond activation,[3] which is notable given that nickel is less expensive, more abundant, and displays a lower CO_2 footprint compared to its precious metal counterpart, palladium.[10] Catalytic acyl couplings[11] with organozinc reagents are well precedented using acid halides (Pd or Ni),[12] anhydrides (Pd, Ni, or Rh),[12a,13] and thioesters (Pd or Ni),[12a,b,14] but the corresponding coupling of amides has not been reported.

To initiate our study, we examined the coupling of naphthamides **4** with benzylzinc bromide (**5**) in the presence of catalytic $Ni(cod)_2$ and the NHC ligand SIPr in THF (Scheme 1). Although several amide derivatives failed to undergo the coupling (entries 1–3), we were delighted to find that *N*-alkyl,Boc and *N*-alkyl,Ts derivatives could be utilized (entries 4–5, respectively).[15] *N*-Alkyl,Ts amides (e.g., **4e**) are well suited for use in mul-

tistep synthesis.[16] It should be noted that the successful reactions of **4d** and **4e** proceeded at room temperature, which compares favorably to the few existing examples of catalytic amide C–N bond activation (ca. 50–160 °C) [3,4,5,6,7] and highlights the mild nature of this coupling.



Entry			Recovered 4	Yield of Ketone 6[b]
1		4a	100%	0%
2		4b	51%	0%
3		4c	100%	0%
4		4d	40%	60%
5		4e	17%	81%

Scheme 1. Survey of amide *N*-substituents in the coupling of substrates **4** with **5**.[a]

[a] Conditions: $Ni(cod)_2$ (10 mol%), SIPr (10 mol%), substrate **4** (1.0 equiv), benzylzinc bromide (**5**, 1.5 equiv) and THF (1.0 M) at 23 °C for 24 h. [b] Yields determined by ^1H NMR analysis using hexamethylbenzene as an internal standard.

Having found that the alkylative coupling of amide derivatives was indeed possible,[17] we evaluated the scope of the amide substrate (Figure 2). The use of the parent naphthyl substrate gave **6** in 80% isolated yield. Additionally, it was found that the methodology was not restricted to extended aromatics. For example, the substrate derived from benzoic acid coupled smoothly to furnish **7** in 74% yield. Substrates bearing electron-donating groups could also be employed, as demonstrated by the formation of **8**–**10**. From the latter two cases, it should be emphasized that the presence of tertiary amines does not hinder catalysis. As shown by the formation of **11** and **12**, the electron-withdrawing –F and –CF_3 substituents were also tolerated.[18]

We also examined the scope of the organozinc reagent in this methodology (Figure 3).[19,20] *n*-Propylzinc bromide was successfully employed to furnish **13** in 80% yield. To assess the tolerance of the methodology toward β-branching, neopentylzinc iodide, a very hindered nucleophile was tested and found to undergo the desired coupling to furnish **14**. α-Branched nucleophiles could also be employed, as judged by the formation of **15** and **16**.

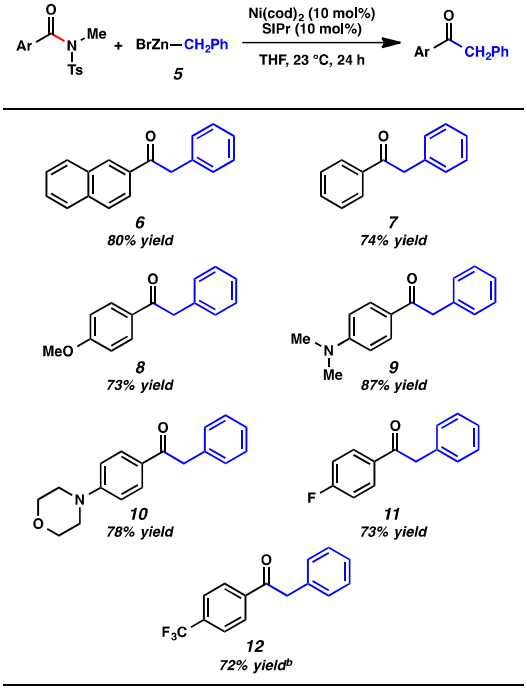


Figure 2. Scope of the amide substrate.[a]

[a] Conditions unless otherwise stated: $Ni(cod)_2$ (10 mol%), SIPr (10 mol%), substrate (1.0 equiv), benzylzinc bromide (**5**, 1.5 equiv) and THF (1.0 M) at 23 °C for 24 h. Yields shown reflect the average of two isolation experiments. [b] The corresponding *N*-Bn,Boc benzamide derivative was used.

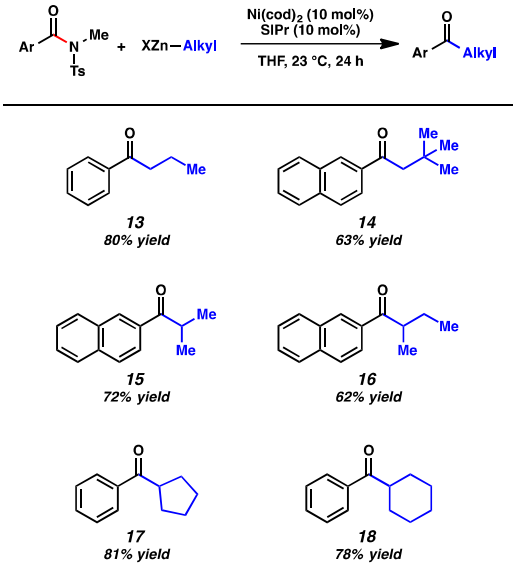


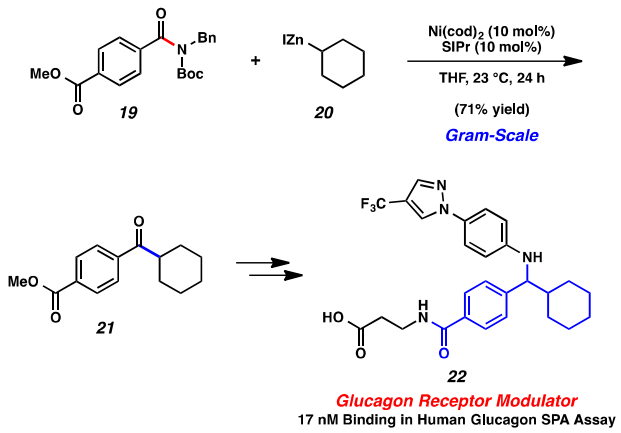
Figure 3. Scope of the organozinc coupling partner.[a]

[a] Conditions unless otherwise stated: $Ni(cod)_2$ (10 mol%), SIPr (10 mol%), substrate (1.0 equiv), organozinc reagent (1.5 equiv) and THF (1.0 M) at 23 °C for 24 h. Yields shown reflect the average of two isolation experiments.

Notably, couplings utilizing secondary organozinc reagents are known to be challenging.[21] Finally, cyclopentyl and cyclohexyl organozinc reagents underwent the

desired coupling in good yield to deliver products **17** and **18**, respectively.

The alkylative cross-coupling methodology was further probed in a synthetic application (Scheme 2). On gram-scale, amide derivative **19** was coupled with cyclohexylzinc iodide (**20**) using our optimal nickel-catalyzed reaction conditions. This transformation provided ketone **21** in 71% yield without disturbing the ester.[22] Ketone **21** is an intermediate in Pfizer's synthesis of the glucagon receptor modulator **22**.[23] The cross-coupling route to **21** provides a favorable alternative to the known Weinreb amide displacement chemistry described in the literature, which proceeds in 34% yield.[23]



Scheme 2. Gram-scale coupling to form ketone **21**.

In summary, we have developed the first catalytic alkylation of amide derivatives. The transformation involves the coupling of *N*-alkyl,Ts or *N*-alkyl,Boc amides with organozinc reagents using nickel catalysis. The methodology proceeds at room temperature and is tolerant of variation in both the substrate and nucleophilic coupling partner. The synthesis of **21** underscores the mildness and scalability of this methodology, along with the applicability of this technology to pharmaceutical synthesis. As such, we expect these studies will further promote the use of amides as synthetic building blocks for use in drug and natural product synthesis.

ASSOCIATED CONTENT

Supporting Information Available. Detailed experimental and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interests.

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[17] Substrates derived from aliphatic carboxylic acids do not couple under the reported reaction conditions; studies to overcome this limitation are currently underway.

[18] Lower yields of **12** were obtained using the corresponding *N*-Me,Ts benzamide substrate. Generally, amides derived from electron-poor arenes were found to couple in higher yields when the *N*-Bn,Boc derivatives were employed.

[19] The organozinc bromide or iodide was used in accord with literature precedent for the formation of each organozinc species. Generally, alkyl bromides and iodides are known to undergo organozinc formation more readily than alkyl chlorides; see ref. 9b.

[20] Although primary and secondary organozinc species were well tolerated in the coupling, it was found that couplings with tertiary organozinc halides and organozinc reagents bearing heterocycles, acetals, and esters gave only trace amounts of product.

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SYNOPSIS TOC