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Reductive Arylation of Amides via a Nickel-Catalyzed Suzuki– Miyaura Coupling and Transfer Hydrogenation Cascade

Timothy B. Boit,[†] Milauni M. Mehta,[†] Junyong Kim, Emma L. Baker, and Neil K. Garg*

Abstract: We report a means to achieve the addition of two disparate nucleophiles to the amide carbonyl carbon in a single operational step. Our method takes advantage of non-precious metal catalysis and allows for the facile conversion of amides to chiral alcohols via a one-pot Suzuki–Miyaura cross-coupling / transfer hydrogenation process. This study is anticipated to promote the development of new transformations that allow for the conversion of carboxylic acid derivatives to functional groups bearing stereogenic centers via cascade processes.

The synthetic manipulation of carboxylic acid derivatives has become central to organic chemistry after more than a century of methodological development.^[1] Though the field has a rich history, strategies for nucleophilic addition to carboxylic acid derivatives may be largely characterized by two primary mechanisms (Figure 1a). The first involves an additionelimination sequence to produce carbonyl derivatives via a tetrahedral intermediate.^[2] Notably, this traditional strategy has limitations in the context of organometallic nucleophiles, as the ketone products resulting from initial acyl substitution are susceptible to further nucleophilic attack to give achiral alcohol products. Specialized acyl derivatives such as N-methyl-Nmethoxy amides, or "Weinreb amides," are often required to avoid such undesired reactivity and necessitate two-step protocols.^[2, 3] A complementary approach employs transition metal catalysis,^[4] where mild substrate activation affords an acyl-metal intermediate and allows for cross-coupling with a variety of nucleophiles.^[4a, 5] This alternative pathway differentiates the reactivity of the substrate from the product carbonyl to overcome the selectivity challenges mentioned above. An exciting opportunity offered by the latter strategy is the addition of a second, different nucleophile to the intermediate resulting from the initial cross-coupling reaction to generate chiral products. Cascade reactions of this type would provide efficient access to important chiral products in racemic or enantioenriched form from achiral starting materials.^[6]

Despite the widely recognized importance of cross-

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couplings, methods to leverage this platform for the addition of disparate nucleophiles to carboxylic acid derivatives remain underexplored.^[7] We envisioned that amides could provide a viable entry to address this challenge, given their recent popularization as cross-coupling handles.[4j-0,8,9] Amides have been shown to undergo a variety of couplings through the intermediacy of acyl-metal species using either non-precious or precious metal catalysis (e.g., Ni or Pd). Additionally, we viewed them as ideal substrates for one-pot cascade reactions, as their stability under non-metal catalyzed conditions could allow for the orchestration of orthogonal bond-forming events.^[10] Dixon has reported an elegant intramolecular reductive cyclization of a tertiary lactam substrate mediated by Vaska's Ir complex,[11] however, no examples exist for the intermolecular addition of two distinct nucleophiles to amides using catalysis in a single operation.^[12,13] Indeed, a reductive alkylation of aryl pyridyl esters reported by Chen and coworkers in 2019 represents the only known example of a carboxylic acid derivative undergoing direct catalytic addition of two nucleophiles through a crosscoupling approach (Figure 1b).^[14] Though mechanistically distinct and not involving acyl metal species, two additional relevant methodologies should be highlighted. Buchwald and coworkers have reported a copper-catalyzed reductive alkylation of symmetric anhydrides to afford enantioenriched secondary alcohols,^[15] and more recently the Hoveyda group reported a copper-catalyzed asymmetric reductive allylation of nitriles to access enantioenriched homoallylic amines (Figure 1b).[16] Together, these examples illustrate some of the potential advantages of cascade reactions that add disparate nucleophiles to a single reactive center of an achiral substrate and uncover synergistic reactivity beyond the capabilities of one reaction manifold.[17]



a. Strategies for nucleophilic addition to carboxylic acid derivatives

In this manuscript, we describe a synthetic method for achieving the addition of two different nucleophiles to a carboxylic acid derivative using nickel catalysis.^[18] The overall transformation relies on a Suzuki–Miyaura cross-coupling / transfer hydrogenation cascade reaction of amide starting materials to form a C–C and C–H bond,^[19,20] consecutively, and ultimately furnish alcohol products (Figure 2).^[21] The results presented herein not only reinforce the notion that amides are versatile building blocks for transition-metal catalyzed reactions, but also validate their utility as synthons for directly generating sp³ carbon centers from the amide carbonyl.





Figure 2. Overview of current study involving the conversion of aliphatic amides to alkyl–aryl alcohols via a Suzuki–Miyaura coupling / transfer hydrogenation cascade.

We initiated our study by examining the Ni-catalyzed Suzuki-Miyaura coupling and in situ reduction of dihydrocinnamic acid-derived amide 1 as shown in Figure 3. [19b] In the absence of a reducing agent, the Suzuki-Miyaura coupling with boronate 5 delivered ketone 3 in nearly quantitative yield (entry 1).^[22,23,,24] With the aim of developing the reductive variant, we questioned whether the use of a secondary alcohol reductant could effect the in situ transfer hydrogenation of ketone 3 to deliver alcohol 4. In this regard, we attempted the use of *i*-PrOH as solvent, reminiscent of common Meerwein-Ponndorf–Verley (MPV) reduction conditions.^[25,26] Unfortunately, this change resulted in low yields of 4 (entries 2 and 3).^[27] By shifting to the use of *i*-PrOH as an additive while using toluene as solvent, we obtained the desired product 4 in a slightly improved yield of 32%, with 18% of ketone 3 remaining (entry 4). Given our lab's recent success in using 1-4-(dimethylamino)phenyl)-1-ethanol (DMPE, 7) in base-catalyzed MPV reductions,^[28] we also tested this benzylic alcohol in our system.^[29] By simply replacing *i*-PrOH with 7, alcohol 4 was obtained in 51% yield (entry 5). Finally, switching the solvent to 1,4-dioxane (entry 6) and using boronate 6 in place of boronate 5 (entry 7) led to further improvements, delivering alcohol 4 in 82% yield.^[30,31,32]

It is worth noting that these optimized conditions satisfy a challenging balance of reactivity required for the success of the amide to alcohol conversion. Specifically, reducing agent **7** does not significantly impede the nickel-catalyzed cross-coupling step, yet is reactive enough to efficiently reduce ketone **3**. Furthermore, as will be shown, other carbonyl functional groups are tolerated by the methodology's mild reducing conditions.



Figure 3. Evaluation of reaction conditions for the nickel-catalyzed Suzuki–Miyaura coupling / transfer hydrogenation cascade of amide **1** with phenyl boronates and reductants. Standard conditions unless otherwise noted: amide substrate (0.20 mmol, 1.0 equiv); phenyl boronate (0.50–0.80 mmol, 2.5–4.0 equiv); reductant (0.50 equiv); 2.5 equiv); K₃PO₄ (0.80 mmol, 4.0 equiv); H₂O (0.40 mmol, 2.0 equiv); Ni(cod)₂ (0.010–0.020 mmol, 5–10 mol%); **2** (0.020–0.040 mmol, 10–20 mol%); solvent (1.0 M); 120 °C; 16 h in a sealed vial. [a] Yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

With optimized conditions in hand, we evaluated the scope of the reaction with respect to the aliphatic amide^[33] coupling partner using phenyl boronate 6, which afforded a range of alkyl-aryl alcohol products (Figure 4). Beginning with the parent dihydrocinnamic acid-derived amide substrate used in optimization studies (i.e., 1), the reductive arylation furnished alcohol 4 in 76% isolated yield. Additionally, the use of an unbranched amide derived from decanoic acid provided alcohol 8 in 82% yield. Carrying out the reaction at 130 °C allowed for the reductive arylation of sterically encumbered substrates, as demonstrated by the formation of alcohol 9 in 61% yield. The compatibility of carbocyclic amides with boronate 6 was explored as well and gave alcohols 10-14 in good yields. We also evaluated an amide substrate bearing an epimerizable stereocenter α to the amide carbonyl. As shown by the formation of alcohol 15 from the corresponding trans amide substrate, minimal erosion of stereochemistry was observed.^[34] Of note, the ester moiety was not disturbed, demonstrating both the preferential cleavage of the amide C-N bond over the ester C-O bond and the mildness of the reducing conditions.³⁵ The tolerance of the methodology toward heterocycles was also determined. Notably, tetrahydropyrans, pyrrolidines, and piperidines, all of which are valuable in medicinal chemistry,³⁶ could be employed as evidenced by the synthesis of alcohols 16-20, respectively.

With the aim of further improving the synthetic utility of the reductive arylation, we performed a robustness screen to assess the compatibility of the reaction with various functional groups and heterocycles (Figure 4).^[37] Results indicated the tolerance of functional groups including tertiary alcohols, secondary anilines,

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and secondary amides, as demonstrated by moderate to good yields of alcohol **20** and appreciable recoveries of additives **22–24**, respectively. Additionally, heterocycles such as quinoline (**25**), dibenzofuran (**26**), and *N*-methyl indole (**27**) were found to be stable under our standard reductive arylation conditions with minimal to no inhibition of reactivity.^[38] These results complement those presented in the scope of the reaction and further demonstrate the methodology's robustness toward several heteroatom-containing functional groups.



Figure 4. Scope of the reductive arylation of aliphatic amides and boronate 6. Standard conditions unless otherwise noted: amide substrate (0.20 mmol, 1.0 equiv); phenyl boronate 6 (0.80 mmol, 4.0 equiv); 7 (0.50 mmol, 2.5 equiv); K₃PO₄ (0.80 mmol, 4.0 equiv); H₂O (0.40 mmol, 2.0 equiv); Ni(cod)₂ (0.020 mmol, 10 mol%); 2 (0.040 mmol, 20 mol%); solvent (1.0 M); 120 °C; 16 h. Unless otherwise noted, yields reflect the average of two isolation experiments. [a] determined by ^{1}H NMR analysis Yield using 1,3,5trimethoxybenzene as an external standard. [b] Reaction ran at 130 °C.

The scope of the aryl boronate component was also examined by coupling pinacol boronates with various amides (Figure 5).^[31,39] Methyl substitution at the ortho, meta, or para positions of the aryl boronate was tolerated, as demonstrated by

the formation of alcohols **28–30** in synthetically useful yields. We also evaluated aryl boronic ester nucleophiles bearing either a trimethylsilyl or trifluoromethyl group, which furnished alcohols **31** and **32**, respectively, in good yields. Additionally, a naphthyl boronate ester underwent the reductive arylation to afford alcohol **33** in 58% yield. We also tested several boronates that possess functional groups that have been demonstrated to be reactive to nickel catalysis. To our delight, an aryl ester,^[35] an ether,^[40] and a dimethyl amine were tolerated,^[41] thus giving rise to alcohols **34–36**, respectively. Furthermore, a boronic ester containing a morpholinopyridine motif was employed to furnish alcohol **37**, showing the reaction's tolerance of this heteroatomrich unit.^[42]



Figure 5. Scope of the reductive arylation of aliphatic amides and aryl boronates. Standard conditions unless otherwise noted: amide substrate (0.20 mmol, 1.0 equiv); aryl boronate (0.80–1.2 mmol, 4.0–6.0 equiv); **7** (0.50 mmol, 2.5 equiv); K_3PO_4 (0.80 mmol, 4.0 equiv); H_2O (0.40 mmol, 2.0 equiv); Ni(cod)₂ (0.020–0.040 mmol, 10–20 mol%); **2** (0.040–0.080 mmol, 20–40 mol%); solvent (1.0 M); 120 °C; 16–24 h. Unless otherwise noted, yields reflect the average of two isolation experiments. [a] Yield determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

The utility of this methodology was evaluated in the synthesis of known intermediates toward two bioactive compounds (Figure 6). In the first example (Figure 6a), amide 38 underwent reductive arylation with boronate 39, despite the notable electron deficiency of this nucleophile. This delivered alcohol 40, a precursor to a known γ -secretase modulator.^[43] We also targeted the interception of a known route to fluoxetine, [44] the active ingredient in the blockbuster drug Prozac[®]. Toward this end, amide 42, derived from the corresponding commercially available carboxylic acid, was coupled with boronate 6. This transformation furnished alcohol 43 in 69% yield, providing facile access to a known intermediate in the synthesis of 44 from commercially available materials.[44] These results not only further demonstrate the viability of leveraging a cross-coupling approach to add two disparate nucleophiles into an amide carbonyl carbon, but also showcase the practical utility

of this reductive arylation protocol in the synthesis of complex chiral molecules.



Figure 6. (a) Synthesis of alcohol **40**, an intermediate in the synthesis of γ -secretase modulator **41**. (b) Synthesis of alcohol **43**, intercepting a known synthetic route toward Prozac[®] (**44**, fluoxetine). See Supporting Information for details.

In summary, we have developed the first catalytic method for the direct intermolecular addition of two distinct nucleophiles to the amide carbonyl carbon. This transformation takes advantage of non-precious metal catalysis and allows for the facile conversion of amides to chiral alcohols via a cascade involving Suzuki-Miyaura cross-coupling reaction and subsequent transfer hydrogenation. The methodology has a broad scope with respect to both the amide and boronate crosscoupling partners. Additionally, it shows tolerance toward epimerizable stereocenters, select functional groups (i.e., alcohols, amines, esters, ethers, and secondary amides,) and a range of heterocycles. Moreover, the methodology can be used to access scaffolds of value to medicinal chemistry, as shown by the syntheses of 40 and 43. This study validates the use of a cross-coupling approach to construct sp³ carbon centers from the amide carbonyl carbon in a single operational step. We hope this study will prompt the development of additional processes that allow for the direct conversion of carboxylic acid derivatives to functional groups bearing stereogenic centers^[45] via catalytic cascade processes.

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Keywords: base metal catalysis • amides • Suzuki–Miyaura coupling • transfer hydrogenation • cascade reaction

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[33] When amides derived from benzoic acids were employed, using a Ni(cod)₂ / SIPr catalyst/ligand system and 3-pentanol as the alcohol reductant in toluene at 50 °C for 16 h, the corresponding ester was observed in 85% yield as determined by ¹H NMR analysis using hexamethylbenzene as an external standard.

[34] Notably, under our standard Suzuki–Miyaura coupling conditions of the parent amide, epimerization of the stereocenter α to the amide carbonyl is observed affording a mixture of *cis* and *trans* diastereomers (see ref. 19b.)

[35] For transition metal-catalyzed cleavage of the acyl C-O bond of esters, see: (a) K. Muto, J. Yamaguchi, D. G. Musaev, K. Itami, Nat. Commun. 2015, 6, 7508; (b) N. A. LaBerge, J. A. Love, Eur. J. Org. Chem. 2015, 5546-5553; (c) T. B. Halima, J. K. Vandavasi, M. Shkoor, S. G. Newman, ACS Catal. 2017, 7, 2176-2180; (d) A. Kruckenberg, H. Wadepohl, L. H. Gade, Organometallics 2013, 32, 5153-5170; (e) H. Yue, L. Guo, H.-H. Liao, Y. Cai, C. Zhu, M. Rueping, Angew. Chem. Int. Ed. 2017, 56, 4282-4285; Angew. Chem. 2017, 129, 4346-4349; (f) H. Yu, L. Guo, S.-C. Lee, X. Liu, M. Rueping, Angew. Chem. Int. Ed. 2017, 56, 3972-3976; Angew. Chem. 2017, 129, 4030-4034; (g) T. B. Halima, W. Zhang, I. Yalaoui, X. Hong, Y. Yang, K. N. Houk, S. G. Newman, J. Am. Chem. Soc. 2017, 139, 1311-1318; (h) T. B. Halima, J. Masson-Makdissi, S. G. Newman, Angew. Chem. Int. Ed. 2018, 57, 12925-12929; Angew. Chem. 2018, 130, 13107-3111; (i) Y.-L. Zheng, S. G. Newman, ACS Catal. 2019, 9, 4426-4433; (j) Y.-L. Zheng, S. G. Newman, Angew. Chem. Int. Ed. 2019, 58, 18159-18164; Angew. Chem. 2019, 131, 18327-18322.



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[38] The robustness screen was carried out using amide 21 and boronate 6, with one equivalent of additive. Additives 22-27 were recovered in near quantitative yields and did not significantly hinder the reductive arylation reaction. See Supporting Information for details.

[39] The amide coupling partner was varied in order to simplify isolation of purified products.

[40] For nickel-catalyzed cleavage of the aryl C–O bond of aryl ethers, see:
(a) E. Wenkert, E. L. Michelotti, C. S. Swindell, J. Am. Chem. Soc. 1979, 101, 2246–2247;
(b) E. Wenkert, E. L. Michelotti, C. S. Swingdell, M. Tingoli, J. Org. Chem. 1984, 49, 4894–4899;
(c) J. W. Dankwardt, Angew. Chem. Int. Ed. 2004, 43, 2428–2432; Angew. Chem. 2004, 116, 2482–2486;
(d) B.-T. Guan, S.-K. Xiang, T. Wu, Z.-P. Sun, B.-Q. Wang, K.-Q. Zhao, Z.-J. Shi, Chem. Commun. 2008, 1437–1439;
(e) M. Tobisu, T. Shimasaki, N. Chatani, Angew. Chem. Int. Ed. 2008, 47, 4866–4869; Angew. Chem. 2008, 120, 4944–4947;
(f) A. G. Sergeev, J. F. Hartwig, Science 2011, 322, 439–443.

[41] For the nickel-catalyzed cleavage of the aryl C–N bond of dimethylanilines, see: Z.-C. Cao, S.-J. Xie, H. Fang, Z.-J. Shi, *J. Am. Chem. Soc.* **2018**, *140*, 13575–13579.

[42] When boronates bearing para electron-donating groups were employed, a significant amount of the ketone intermediate was observed. For example, the coupling of amide 1 with p-NMe₂Ph–B(pin) under our standard reaction conditions gave the corresponding ketone and alcohol in 17% and 42% yields, respectively.

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[45] An exciting opportunity lies in catalytic asymmetric variants of our strategy. In an encouraging preliminary result, we have found that the use of a chiral NHC ligand allows for the synthesis of **4** in 36% yield and 20% ee. See Supporting Information for details.

Entry for the Table of Contents

COMMUNICATION

The first catalytic intermolecular addition of two disparate nucleophiles to the amide carbonyl carbon in a single operational step is reported. The method relies on nickel catalysis and enables the conversion of amides to chiral alcohols via a Suzuki–Miyaura cross-coupling / transfer hydrogenation cascade process.



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Reductive Arylation of Amides via a Nickel-Catalyzed Suzuki–Miyaura Coupling and Transfer Hydrogenation Cascade

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