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Nickel-Catalyzed Suzuki–Miyaura Coupling of Aliphatic Amides

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Nickel-Catalyzed Suzuki–Miyaura Coupling of Aliphatic Amides

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ABSTRACT: We report the Ni-catalyzed Suzuki–Miyaura coupling of aliphatic amide derivatives. Prior studies have shown that aliphatic amide derivatives can undergo Ni-catalyzed carbon–heteratom bond formation, but Ni-mediated C–C bond formation using aliphatic amide derivatives has remained difficult. The coupling disclosed herein is tolerant of considerable variation with respect to both the amide-based substrate and the boronate coupling partner, and proceeds in the presence of heterocycles and epimerizable stereocenters. Moreover, a gram-scale Suzuki–Miyaura coupling / Fischer indolization sequence demonstrates the ease with which unique poly-heterocyclic scaffolds can be constructed, particularly by taking advantage of the enolizable ketone functionality present in the cross-coupled product. The methodology provides an efficient means to form C–C bonds from aliphatic amide derivatives using non-precious metal catalysis and offers a general platform for the hetero-arylation of aliphatic acyl electrophiles.

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

The facile unification of molecular fragments via C–C bond formation represents an important and challenging objective in transition metal catalysis.[1] Although the field has been largely dominated by the coupling of aryl electrophiles, there has been a recent resurgence in developing analogous methods using stable acyl electrophiles. More specifically, esters and amides have emerged as useful synthetic building blocks in a variety of acyl cross-coupling manifolds. Recent breakthroughs in the area include the Suzuki–Miyaura coupling of phenyl esters reported independently by Newman and Szostak, which proceeds using palladium catalysis,[2,3] in addition to numerous amide C–N bond activation studies using either palladium or nickel.[4,5,6,7,8,9]

We and others have been especially interested in using nickel catalysis to enable facile C–C bond formation from amide derivatives. Such methods provide new strategies for the synthesis of ketones which complement Weinreb's methodology,[10] but importantly avoid the use of highly basic or pyrophoric reagents. Previously, we have shown that nickel catalysis can promote the cross-coupling of Ts- or Boc- activated benzamide derivatives in C–C bond forming reactions.[4b,4d,4k] These cross-coupling platforms have allowed for the efficient coupling of *aryl* amide electrophiles, however, the corresponding activation of *aliphatic* amides is more challenging. Prior computational studies suggest that the use of aliphatic amides is inherently more difficult because of the high kinetic barrier of activation associated with oxidative addition into the resonance-stabilized C–N bond.[4a] Indeed, achievements in cross-couplings of aliphatic amides using Ni catalysis is limited to carbon-heteratom bond formation.[4h,o] Molander and coworkers have also reported an elegant coupling of *N*-acyl succinimides with alkyl trifluoroborate salts employing a dual-metal photoredox approach using nickel and an iridium photocatalyst,[9] which nicely complements the method described herein.[11,12]

With the aim of developing a general cross-coupling manifold to build C–C bonds from aliphatic amides, we targeted the Suzuki–Miyaura coupling shown in Figure 1. From the outset, we opted to focus our efforts on the coupling of heterocyclic fragments due to their prevalence in bioactive molecules. Certain heterocycles can be challenging to employ in metal-mediated cross couplings as they are known to ligate metal catalysts and inhibit reactivity.[1b] Moreover, only a handful of isolated examples of hetero-arylative Suzuki–Miyaura couplings of aliphatic acyl electrophiles exist[13] (i.e., anhydrides,[13a,b] thioesters,[13c,d] acid chlorides[13e,f]), and a general platform for the hetero-arylation of aliphatic acyl electrophiles has not been developed. In this manuscript, we describe the nickel-catalyzed Suzuki–Miyaura coupling of aliphatic amide derivatives. Importantly, this methodology provides rapid access to

functionalizable heterocyclic scaffolds, while expanding the scope of synthetically useful transformations involving amide derivatives and non-precious metal catalysis.

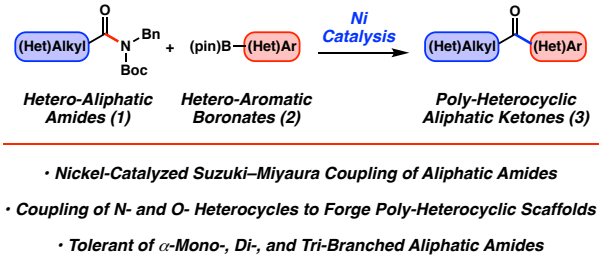
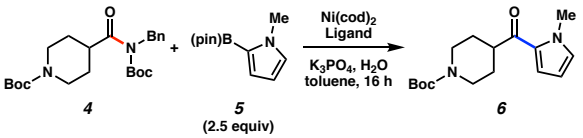


Figure 1. Suzuki–Miyaura hetero-arylation of aliphatic amides to construct poly-heterocyclic scaffolds.

To initiate our study, we examined the coupling of piperidine derivative **4** [14] with *N*-methylpyrrole-2-boronic acid pinacol ester (**5**) as shown in Figure 2. Our initial attempts to employ the *N*-heterocyclic carbene (NHC) ligand SIPr (**7**), which we had previously shown to be competent in the Suzuki–Miyaura coupling of aromatic amide derivatives,[4b] were met with difficulty, as no trace of the desired ketone product **6** was formed at 50 °C (entry 1). Moreover, increasing the temperature to 120 °C only led to partial decomposition of substrate **4** (entry 2). Next, we screened several ligand frameworks that have been used in the context of nickel-catalyzed couplings. Interestingly, efforts to utilize the ligand terpyridine (**8**), which had been shown to facilitate the nickel-catalyzed esterification of aliphatic amide derivatives,[4h] were also unfruitful (entry 3). Gratifyingly, however, use of the NHC precursor ICy•HBF_4 (**9**) was found to promote the desired Suzuki–Miyaura coupling, and delivered ketone **6** in 95% yield (entry 4). Ligand **9** has been used in other nickel-catalyzed processes,[5b,5f,15] including in the Heck reaction of benzamide derivatives.[4k] Finally, the related NHC precursor Benz-ICy•HCl (**10**) was evaluated and found to give similarly useful results (entry 5). As NHC precursor **10** was found to be broadly effective in subsequent scouting experiments, it was used in our further studies.[16] Lastly, although we focus on the use of *N*-Bn,Boc amides in this study, it should be noted that the methodology is not limited to the use of the *N*-benzyl group. For example, coupling of *N*-*i*Pr,Boc cyclohexamide with boronate **5** under the optimized conditions gave the corresponding ketone in 72% yield.



Entry[a]	Temp.	$Ni(cod)_2$	Ligand	Remaining 4	Yield of 6
1	50 °C	5 mol%	*7* (10 mol%)	100%	0%
2	120 °C	5 mol%	*7* (10 mol%)	52%	0%
3	120 °C	5 mol%	*8* (10 mol%)	50%	0%
4	120 °C	5 mol%	*9* (10 mol%)	0%	95%
5	120 °C	5 mol%	*10* (10 mol%)	0%	95%

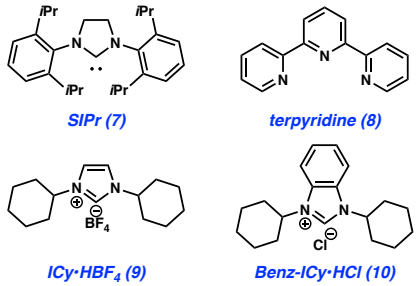


Figure 2. Evaluation of reaction conditions for the nickel-catalyzed coupling of aliphatic amide **4** with boronate **5** to furnish ketone **6**.

[a] Conditions: $Ni(cod)_2$ (5 mol%), **7**–**10** (10 mol%), substrate **4** (1.0 equiv), boronate **5** (2.5 equiv), K_3PO_4 (4.0 equiv), toluene (1.0 M), and H_2O (2.0 equiv) heated at the indicated temperature for 16 h. Yields were determined by ^1H NMR analysis using hexamethylbenzene as an internal standard.

With optimized conditions in hand, we explored the scope of the coupling with respect to both the hetero-aliphatic amide-derived substrate and the hetero-aryl boronate to afford a variety of bis-heterocyclic ketone products (Figure 3). The reaction was found to be widely tolerant of *N*-heterocyclic boronate nucleophiles, including pyrrole, quinoline, indole, pyrazole, and morpholino-pyridine moieties, as demonstrated by the formation of **6** and **11**–**16**, all in good yields. Moreover, an isomeric piperidine amide substrate could be utilized, allowing for the formation of pyrrolo- and pyrazolo-ketones **17** and **18**, respectively. Alternatively, the pyrrolidine heterocycle could also be employed to generate ketones **19** and **20** in 82% and 90% yields, respectively. Finally, substrates derived from both 4- and 3-isomers of tetrahydropyran carboxylic acid were shown to be competent in the coupling, furnishing ketones **21**–**25** in good to excellent yields. The formation of **25** highlights the use of an oxygen-containing heterocyclic boronate in the coupling reaction. It is also worth noting that non-heterocyclic aryl boronates, such as 2-naphthyl and phenyl boronic esters, could be employed in the Suzuki–Miyaura coupling as demonstrated by the formation of **26** and **27**, respectively.

In addition, *o*-Me, *p*-CF_3, and *p*-CO_2Me substituents were tolerated on the phenyl boronate, giving rise to ketones **28**–**30**, respectively.[17]

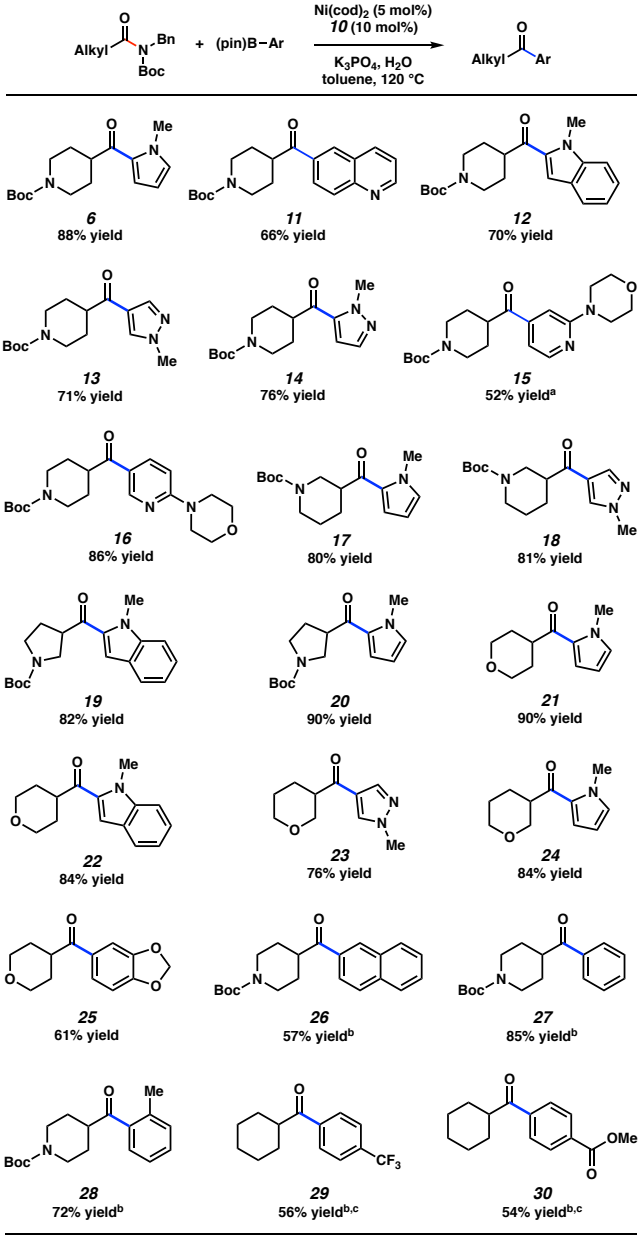


Figure 3. Scope of the Suzuki–Miyaura coupling with hetero-aliphatic amide substrates and aryl boronates.

Conditions: Ni(cod)$_2$ (5 mol%), **10** (10 mol%), substrate (1.0 equiv), boronate (2.5 equiv), K_3PO_4 (4.0 equiv), toluene (1.0 M), and H_2O (2.0 equiv) heated at 120 °C for 16 h. Unless otherwise noted, yields reflect the average of two isolation experiments. [a] The reaction was run using 3.3 equiv of the boronate. [b] Yield determined by ^{1}H NMR analysis using hexamethylbenzene as an external standard. [c] The reaction was run for 24 h using 5.0 equiv of the boronate.

The scope of the hetero-arylative coupling with boronate **5** was also evaluated with respect to several non-heterocyclic aliphatic amide derivatives (Figure 4). Substrates derived from dihydrocinnamic and decanoic acids coupled in high yields to furnish ketones **31** and **32**, respectively. Additionally, α-branched carbocyclic amides also underwent efficient couplings, providing pyrrolo-ketones **33** and **34**. Lastly, sterically encumbered carboxamides could also be employed in the coupling, as demonstrated by the production of *tert*-butyl ketone **35** in excellent yield.

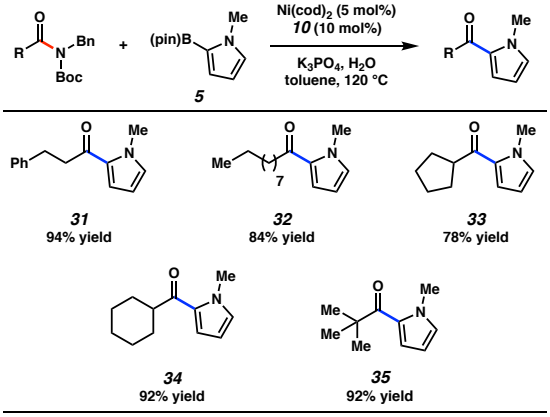
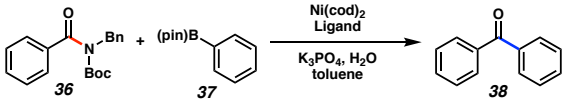


Figure 4. Scope of the coupling with non-heterocyclic aliphatic amide substrates and boronate **5**.

Conditions: Ni(cod)$_2$ (5 mol%), **10** (10 mol%), substrate (1.0 equiv), boronate **5** (2.5 equiv), K_3PO_4 (4.0 equiv), toluene (1.0 M), and H_2O (2.0 equiv) heated at 120 °C for 16 h. Yields reflect the average of two isolation experiments.

Although our manuscript focuses on *aliphatic* amides for the reasons mentioned earlier, we were curious if our optimal reaction conditions could be applied to a benzamide substrate (Figure 5). We have reported earlier the coupling of *N*-Bn,Boc benzamide **36** with phenylboronic acid pinacol ester **37** using a Ni/SIPr system at 50 °C. This gives ketone **38** in 96% yield (entry 1).[4b] We performed the corresponding coupling of **36** and **37** using the Ni/Benz-ICy catalyst system. At 50 °C, we obtained only a 14% yield of the cross-coupled product, **38** (entry 2). We also performed the cross-coupling using the Ni/Benz-ICy catalyst system at 120 °C, which furnished **38** in 60% yield (entry 3).[18] As such, for practioners of this methodology, we recommend the use of Ni/SIPr at 50 °C to achieve the Suzuki–Miyaura coupling of benzamide-type substrates[4b] and the use of the conditions reported herein (i.e., Ni/Benz-ICy at 120 °C) for aliphatic amides.



Entry	Temp.	Mol % Ni	Ligand (mol%)	Yield of 38
1[a]	50 °C	5 mol%	*SIPr* (*7*, 5 mol%)	96%
2[b,c]	50 °C	5 mol%	*Ben-ICy·HCl* (*10*, 10 mol%)	14%
3[b,c]	120 °C	5 mol%	*Ben-ICy·HCl* (*10*, 10 mol%)	60%

Figure 5. Suzuki–Miyaura coupling of amide **36** with boronate **37** using Ni/SIPr and Ni/Benz-ICy catalyst systems.

Conditions: [a] $Ni(cod)_2$ (5 mol%), **7** (5 mol%), substrate (1.0 equiv), boronate **5** (1.2 equiv), K_3PO_4 (2.0 equiv), toluene (1.0 M), and H_2O (2.0 equiv) heated at 50 °C for 24 h. [b] $Ni(cod)_2$ (5 mol%), **10** (10 mol%), substrate (1.0 equiv), boronate **5** (2.5 equiv), K_3PO_4 (4.0 equiv), toluene (1.0 M), and H_2O (2.0 equiv) heated at the indicated temperature for 16 h. [c] Yields reflect the average of two experiments; yields were determined by ^1H NMR analysis using hexamethylbenzene as an external standard.

We also questioned if the methodology would be amenable to the coupling of an amide substrate containing a defined chiral center α to the carbonyl. As such, we attempted the coupling between amide **39** and boronate **5** (Figure 6). Although the use of standard conditions (i.e., 120 °C for 16 h), gave the desired ketone product **40** in 68% yield, roughly 20% epimerization was also observed. We found that by carrying out the reaction at 90 °C for 2 h, the epimerization could be avoided. Thus, ketone **40** was obtained in 70% yield, without observable formation of the *syn* diastereomer. Moreover, the tolerance of the ester (and other functional groups)[19] underscores the complementarity of this methodology to the Weinreb ketone synthesis,[10] where such electrophilic functional groups typically do not withstand the use of highly basic and nucleophilic organometallic reagents. Importantly, this result provides the first example of an amide or ester Suzuki–Miyaura coupling that proceeds smoothly in the presence of an epimerizable stereocenter α to the amide carbonyl. The tolerance of the method to defined stereocenters α to the carbonyl was also evaluated using enantioenriched cyclohexenyl amide **41**. Using standard conditions (i.e., 120 °C for 16 h), the desired ketone **42** was obtained in 81% yield, but only in 14% *ee*. By lowering the temperature of the reaction to 70 °C, the desired coupling of **41** with boronate **5** proceeded in good yield and with significant preservation of stereochemical information. We hypothesize that the observed epimerization stems from the basicity of the deprotonated Benz-ICy•HCl (**10**). In fact, subjection of enantioenriched **42** to the free NHC in toluene at 120 °C for 4 h led to complete racemization of the substrate. In contrast, the corresponding experiments performed with Benz-ICy•HCl (**10**) or K_3PO_4 led to no or minimal observable loss in *ee*, respectively. It should also be noted that ketone product **42** was observed to racemize more readily than amide **41** under the standard reaction conditions (see the SI for details). Nonetheless, these results demonstrate the mildness of the reaction conditions and bode well for future synthetic applications.

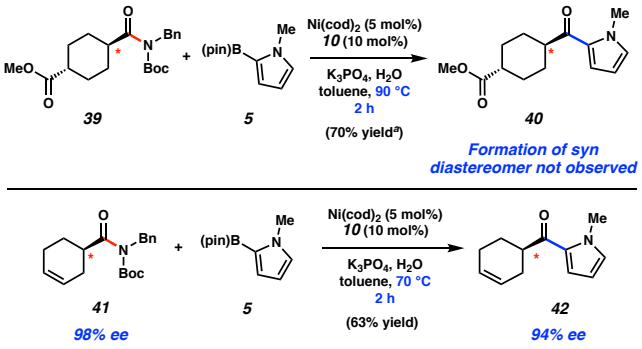


Figure 6. Stereoretentive Suzuki–Miyaura couplings of amide **39** and enantioenriched amide **41**.

Conditions: $Ni(cod)_2$ (5 mol%), **10** (10 mol%), substrate (1.0 equiv), boronate **5** (2.5 equiv), K_3PO_4 (4.0 equiv), toluene (1.0 M), and H_2O (2.0 equiv) heated at 70 °C for 2 h. Yield reflects the average of two isolation experiments. [a] Reaction was run at 90 °C for 2 h; yield was determined by ^1H NMR analysis using hexamethylbenzene as an external standard.

In comparison to more classical aryl-aryl couplings, the products obtained from this methodology possess enolizable ketones, which serve as valuable synthetic handles. As a demonstration of this benefit, we performed a gram-scale Suzuki–Miyaura coupling and subsequent Fischer indolization reaction to construct a poly-heterocyclic spiroindolenine scaffold (Figure 7). Spiroindolenines are commonly seen in bioactive molecules[20] and also serve as valuable synthetic intermediates.[21] In the event, Suzuki–Miyaura coupling of tetrahydropyran carboxamide **43** with boronate **44** took place on gram scale under conditions employing reduced boronate, catalyst, and ligand loadings (1.2 equiv, 2.5 and 5 mol%, respectively) to furnish ketone **45** in 82% yield. Next, ketone **45** was transformed into spirocycle **47** in 61% yield by reaction with phenylhydrazine (**46**) in the presence of TFA by way of a Fischer indolization.[22] The rapid construction of poly-heterocyclic spiroindolenine **47**,[23] hinging upon the classical reactivity of enolizable ketones, underscores the utility of the Suzuki–Miyaura coupling of aliphatic amides and further

demonstrates the ease with which a variety of unique heterocyclic compounds can be fashioned.

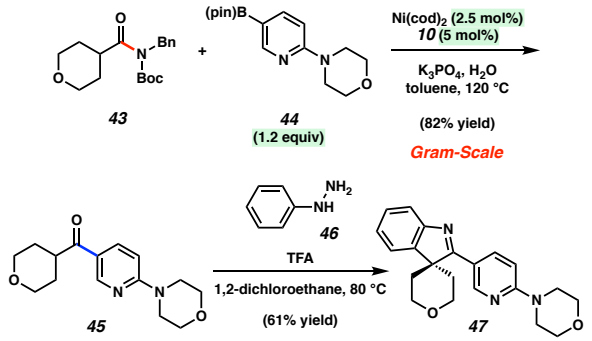


Figure 7. Sequential gram-scale Suzuki–Miyaura coupling and Fischer indolization to provide **47**.

We have developed the nickel-catalyzed Suzuki–Miyaura coupling of aliphatic amides. The coupling was found to be tolerant of variation in both coupling partners, and can be employed in the presence of heterocycles, epimerizable stereocenters, and sensitive functional groups (e.g., esters). The synthetic utility of this methodology was further demonstrated on gram-scale via a Suzuki–Miyaura coupling / Fischer indolization sequence to form polyheterocyclic spiroindolenine **47**. These studies offer a general platform for the hetero-arylation of aliphatic acyl electrophiles, while contributing to the repertoire of synthetic transformations involving amide derivatives and non-precious metal catalysis. Moreover, given their stability towards a variety of conditions, we view amides as having significant potential utility as synthons in the derivatization of biomolecules and multistep synthetic efforts.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, analytical, and spectral data including control experiments and robustness screen.

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Author Contributions

† T.B.B., N.A.W., and J.K. contributed equally.

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The authors declare no competing financial interests.

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SYNOPSIS TOC