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Nickel-Catalyzed Amination of Aryl Chlorides and Sulfamates in 2-Methyl-THF

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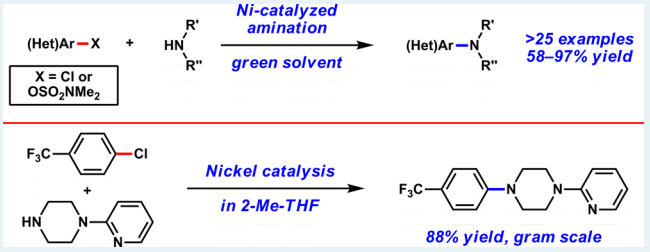
Supporting Information

ABSTRACT: The nickel-catalyzed amination of aryl *O*-sulfamates and chlorides using the green solvent 2-methyl-THF is reported. This methodology employs the commercially available and air-stable precatalyst $NiCl_2(DME)$, is broad in scope, and provides access to aryl amines in synthetically useful yields. The utility of this methodology is underscored by examples of gram-scale couplings conducted with catalyst loadings as low as 1 mol % nickel. Moreover, the nickel-catalyzed amination described is tolerant of heterocycles and should prove useful in the synthesis of pharmaceutical candidates and other heteroatom-containing compounds.



KEYWORDS: *nickel, catalysis, amination, cross-coupling, 2-methyl-THF, green chemistry*

Transition metal-catalyzed cross-couplings have had a profound impact on chemical synthesis.[1] As mild and useful alternatives to classical fragment couplings, cross-couplings have become one of the most frequently employed transformations for the construction of carbon−carbon (C−C) and carbon−heteroatom (C−X) bonds in both academic and industrial settings.[1] Although palladium-catalyzed couplings dominate the field, there has been growing interest in the development of related couplings that employ nonprecious metals.[2] Nickel, in particular, is very attractive in part due to its wide availability and low cost.[2d−h] Additionally, certain nickel catalysts have the unique ability to activate a wide range of electrophilic coupling partners, well beyond the scope of traditional cross-couplings that use palladium catalysis.[2d−h] Moreover, in addition to cost and reactivity benefits, nickel catalysis has shown great promise for operating under green reaction conditions,[3] particularly in green solvents.[4]

Our research group and others have developed new protocols for aryl C−C and C−N bond formation[5] using nickel catalysis.[2d−h,4,6−8] These procedures not only enable the desired bond formations but often also utilize air and moisture stable Ni(II) precatalysts that do not require glovebox handling. To render these transformations more practical, we have recently focused our efforts on developing greener variants. This has led to a general nickel-catalyzed Suzuki−Miyaura coupling procedure that takes place in a variety of green solvents, is scalable at low catalyst loadings, and possesses an unusually broad substrate scope.[4] Herein, we report a complementary procedure for the efficient formation of aryl C−N bonds that proceeds in a green solvent using nickel catalysis (Figure 1).

Having previously established the nickel-catalyzed amination of aryl sulfamates,[7g,j] albeit not in a green solvent, we sought to

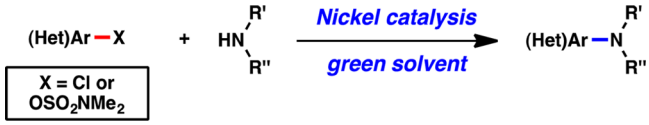


Figure 1. Amination of (hetero)aryl chlorides and sulfamates in a green solvent using nickel catalysis.

first develop the corresponding coupling of aryl chlorides. We chose naphthyl chloride **1a** for our studies and tested its coupling with morpholine (**2**) using nickel catalysis (Table 1). Indeed, upon exposure of **1a** and **2** to our previously disclosed sulfamate amination conditions,[7g,j,9,10] product **4** was obtained when toluene was used as the solvent (entry 1). Other solvents that have some attractive attributes were also tested.[11,12] The use of DMF gave **4** in 50% yield (entry 2). We also examined alcohol solvents. Although the desired coupling did not take place when *n*-butanol was employed (entry 3), we found that the use of *t*-amyl alcohol gave the aminated product in good yield (entry 4). Ethereal solvents were also tested. Fortunately, the use of THF, MTBE, CPME,[13] or 2-Me-THF (entries 5−8, respectively) uniformly furnished **4** in excellent yield.

Of the solvents surveyed, we elected to focus on the use of 2-Me-THF for our subsequent studies.[14] 2-Me-THF has gained attention as a promising solvent for industrial applications[15] due to several salient features, including the following: (a) it is not easily oxidized; (b) it readily phase-separates from aqueous layers (in contrast to THF); (c) it is obtained from furfural, which in turn comes from renewable feedstock; (d) it has a

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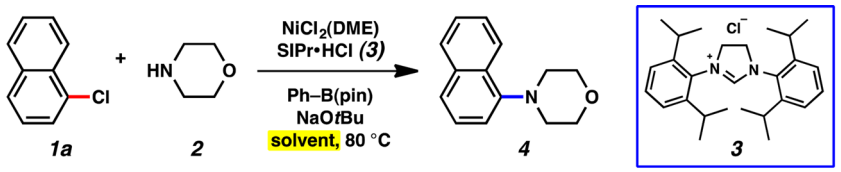
Table 1. Examination of Solvents in the Amination of 1-Chloronaphthalene[a]

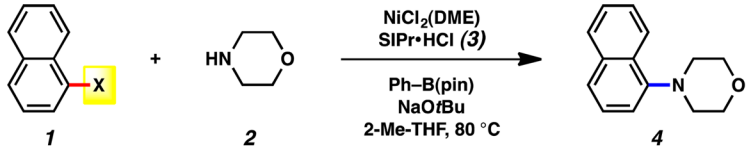


1a 2 4 3

Entry	Solvent	Yield[b]	Entry	Solvent	Yield[b]
1	toluene	95%	5	THF	88%
2	DMF	50%	6	MTBE	96%
3	*n*-BuOH	0%	7	CPME	100%
4	*t*-amyl alcohol	78%	8	2-Me-THF	95%

[a]Reactions were carried out with $NiCl_2$(DME) (5 mol %), SIPr·HCl (10 mol %), Ph-B(pin) (0.55 equiv), substrate (0.5 mmol, 1.00 equiv), morpholine (1.80 equiv), NaO*t*Bu (1.85 equiv), hexamethylbenzene (0.10 equiv), and solvent (used as received, 2.5 mL), for 3 h. [b]Yields were determined using hexamethylbenzene as an internal standard.

Table 2. Evaluation of Various Electrophiles[a]



1 2 4

Entry	X	Yield[b]	Entry	X	Yield[b]
1	Cl	95%	5	OTs	71%
2	Br	62%	6	OPiv	4%
3	I	27%	7	$OC(O)NEt_2$	76%
4	OTf	6%	8	OSO_2NMe_2	87%

[a]Reactions were carried out with $NiCl_2$(DME) (5 mol %), SIPr·HCl (10 mol %), Ph−B(pin) (0.55 equiv), substrate (0.5 mmol, 1.00 equiv), morpholine (1.80 equiv), NaO*t*Bu (1.85 equiv), hexamethylbenzene (0.10 equiv), and solvent (used as received, 2.5 mL), for 3 h. [b]Yields were determined using hexamethylbenzene as an internal standard.

higher boiling point compared to THF, which can be advantageous in some instances; and (e) it poses minimal health risks.

After establishing suitable reaction conditions for the amination of **1a** with morpholine (**2**), we probed the use of other 1-naphthyl-based electrophilic coupling partners **1** in this methodology (Table 2). We were delighted to find that 1-bromonaphthalene could also be employed (entry 2). However, the corresponding iodide and triflate substrates gave only modest yields of **4** (entries 3 and 4). The use of a tosylate coupling partner, on the other hand, led to the desired product in 71% yield (entry 5). Finally, whereas the pivalate ester substrate failed (entry 6), we found that the corresponding carbamate and sulfamate substrates could be employed in the methodology (entries 7 and 8). Overall, the chloride and sulfamate substrates gave the best yields of product **4**; thus, we elected to evaluate the scope of the methodology for these two types of electrophiles.[16,17]

Figure 2 highlights the scope of the methodology with regard to the coupling of aryl sulfamate substrates using morpholine (**2**) as the amine partner and 2-Me-THF as the solvent. Simple aryl hydrocarbon substrates, such as naphthyl and phenyl sulfamates, were readily aminated as demonstrated by the high yielding formation of **4** and **5**, respectively. Additionally, the generation of products **6**−**9** in good yields shows the methodology's tolerance of electron-donating, electron-withdrawing, and ortho substituents. Given the prevalence of heterocycles in pharmaceuticals, where amination reactions are widely employed, we also tested several heterocyclic sulfamate substrates. Both 2- and 3-substituted pyridines were well tolerated, as demonstrated by the formation of products **10** and **11**, respectively. Moreover, indole-, isoquinoline-, and dihydrobenzofuran-containing substrates were suitable coupling partners, as judged by the formation of **12**−**14** in synthetically useful yields.

Similarly, an array of aryl chlorides underwent the nickel-catalyzed amination reaction with morpholine (**2**) in 2-Me-THF (Figure 3). Nonheterocyclic substrates, including those containing electronically or sterically biasing substituents, coupled smoothly, as shown by the formation of adducts **4** and **6**−**9**. Of note, commercially available heterocyclic aryl chlorides could also be employed, thus giving rise to products **10**, **11**, **15**, and **16**. The tolerance of the methodology to pyridines, quinolines, and benzothiophenes suggests the utility of our coupling conditions for applications in drug discovery.

As shown in Figure 4, the scope of this amination methodology is not limited to the use of morpholine as the amine coupling partner. For example, pyrrolidine could be employed to give aminated product **17**. As demonstrated by the formation of **18**, the acyclic amine *n*-methylbutylamine was also tolerated in this methodology. Additionally, we found that 2,6-dimethylaniline, despite its steric hindrance, underwent the desired amination to give the unsymmetrical biaryl amine product **19**. We were also delighted to find that a piperazine nucleophile bearing a pyridine ring coupled smoothly to give product **20** in 94% yield.

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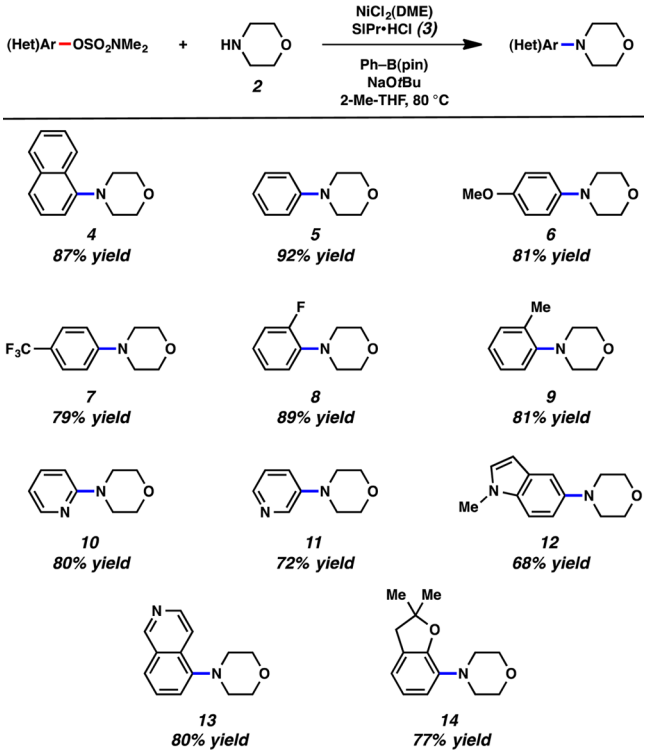

Figure 2. Coupling of (hetero)aryl sulfamates with morpholine in 2-Me-THF. Reactions were carried out with $NiCl_2$(DME) (5−15 mol %), SIPr·HCl (10−30 mol %), Ph−B(pin) (0.30−0.45 equiv), substrate (0.5 mmol, 1.00 equiv), morpholine (1.80 equiv), NaO*t*Bu (2.25−2.55 equiv), hexamethylbenzene (0.10 equiv), and solvent (used as received, 2.5 mL), for 3 h. Yields were determined using hexamethylbenzene as an internal standard.

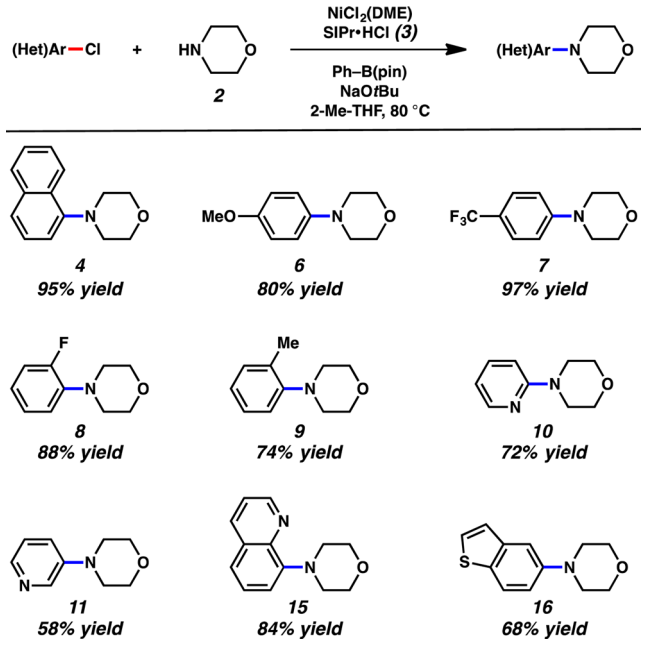

Figure 3. Coupling of (hetero)aryl chlorides with morpholine in 2-Me-THF. Reactions were carried out with $NiCl_2$(DME) (5−15 mol %), SIPr·HCl (10−30 mol %), Ph−B(pin) (0.35−0.70 equiv), substrate (0.5 mmol, 1.00 equiv), morpholine (1.80 equiv), NaO*t*Bu (2.25−2.70 equiv), hexamethylbenzene (0.10 equiv), and solvent (used as received, 2.5 mL), for 3 h. Yields were determined using hexamethylbenzene as an internal standard.

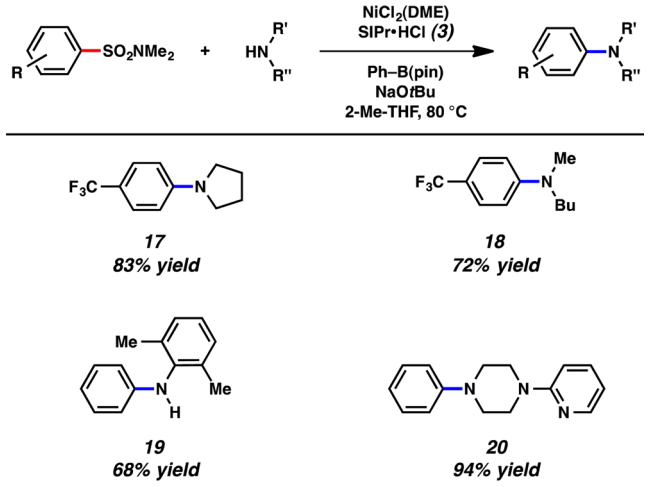

Figure 4. Scope of amine component in the coupling reaction. Reactions were carried out with $NiCl_2$(DME) (5−15 mol %), SIPr·HCl (10−30 mol %), Ph−B(pin) (0.35−0.75 equiv), substrate (0.5 mmol, 1.00 equiv), morpholine (1.20−2.40 equiv), NaO*t*Bu (2.10−3.45 equiv), hexamethylbenzene (0.10 equiv), and solvent (used as received, 2.5 mL), for 3 h. Yields were determined using hexamethylbenzene as an internal standard.

One general limitation pertaining to nickel-catalyzed cross-couplings is the frequent use of high catalyst loadings (i.e., often >10%).[2d−h] Whereas progress has been made in rendering nickel-catalyzed Suzuki−Miyaura couplings more efficient,[4,6i] corresponding achievements in nickel-mediated amination reactions have been lacking. To address this challenge, we tested the coupling of trifluoromethyl-containing sulfamate and chloride substrates **21a** and **21b**, respectively, in the amination reaction with **2** using 2-Me-THF as the solvent (Figure 5). Using 3 and 1 mol % Ni, respectively, we found that gram-scale couplings could be achieved to give the arylated morpholine product **7** in excellent yields.

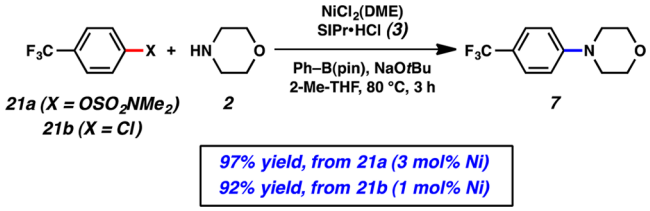

Figure 5. Gram-scale couplings of trifluoromethyl-containing substrates.

As noted earlier, the amination of heterocyclic substrates in 2-Me-THF provides a promising tool for synthesizing pharmaceutical candidates. To further probe this notion, we tested the gram-scale couplings of heterocycle-containing substrates, as shown in Figure 6. Chloroquinoline **22** underwent facile coupling with morpholine (**2**) to generate aminated product **15** in 94% yield. This coupling was performed on gram-scale using 3 mol % Ni. Finally, we tested the gram-scale coupling of trifluoromethylated aryl chloride **21b** with pyridyl piperazine derivative **23**. This reaction provided adduct **24** in 88% yield; of note, **24** contains two heterocycles and a trifluoromethyl group, all of which are motifs commonly seen in pharmaceuticals.

In summary, we have developed the nickel-catalyzed coupling of a variety of electrophilic substrates (e.g., halides

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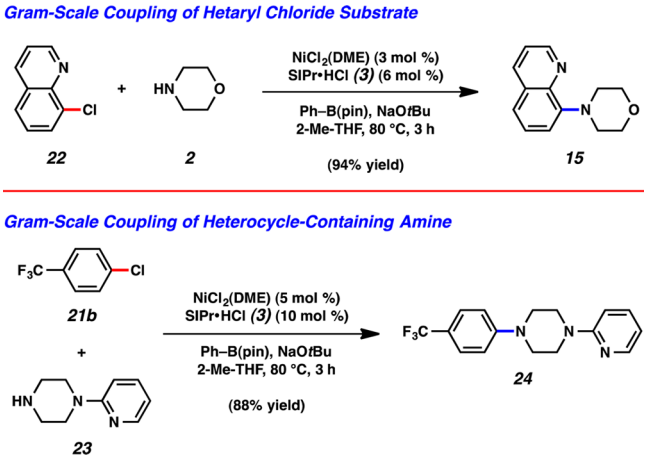

Figure 6. Gram-scale couplings of heterocyclic substrates.

and pseudohalides) with amines using the attractive, green solvent 2-Me-THF. The couplings of aryl *O*-sulfamates and aryl chlorides proceed in the highest yields and may be achieved using an air-stable nickel precatalyst. The methodology has a broad scope and is tolerant of electronically biasing substituents, sterics, and even pharmaceutically relevant heterocycles. The scalability of the nickel-catalyzed amination in 2-Me-THF using low catalyst loading bodes well for future synthetic applications in drug discovery and other arenas.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) For discussion on 2-Me-THF, see: (a) Aycock, D. F. *Org. Process Res. Dev.* **2007**, *11*, 156−159. (b) Pace, V.; Hoyos, P.; Castoldi, L.; Domínguez de María, P.; Alcántara, A. R. *ChemSusChem* **2012**, *5*, 1369−1379 see also ref 13b.
(16) Aryl chlorides are attractive substrates as they are often available commercially or are easily synthesized. Additionally, aryl chlorides are often robust enough to be carried through multiple synthetic operations.
(17) Aryl sulfamates bear many notable features. They are easily synthesized from their corresponding phenols, which are often commercially available, and are generally stable to acidic and basic reaction conditions. Moreover, aryl sulfamates may be used to direct arene functionalization through electrophilic aromatic substitution or *ortho*-lithiation processes. For a discussion of these features, see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (b) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: New York, 2002; pp 330−367. (c) Macklin, T. K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519−2522. (d) Snieckus, V.; Macklin, T. In *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: New York, 2005; Vol. *1*, pp 106−118; see also ref 6d.