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Nickel-Catalyzed Suzuki–Miyaura Couplings in Green Solvents

Stephen D. Ramgren, Liana Hie, Yuxuan Ye, and Neil K. Garg*

Department of Chemistry and Biochemistry, University of California, Los Angeles,
Los Angeles, California 90095-1569, United States

neilgarg@chem.ucla.edu

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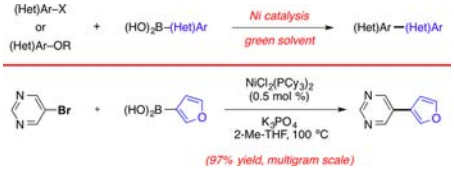
ABSTRACT



The nickel-catalyzed Suzuki–Miyaura coupling of aryl halides and phenol-derived substrates with aryl boronic acids using green solvents, such as 2-Me-THF and *tert*-amyl alcohol, is reported. This methodology employs the commercially available and air-stable precatalyst, NiCl$_2$(PCy$_3$)$_2$, and gives biaryl products in synthetically useful to excellent yields. Using this protocol, bis(heterocyclic) frameworks can be assembled efficiently.

Transition-metal-catalyzed cross-coupling reactions are widely used in the pharmaceutical industry in both medicinal chemistry and drug manufacturing.[1] Although the use of Pd catalysis is most common, complementary approaches are highly sought after. Specifically, cost-effective catalyst systems that allow for unconventional couplings to take place smoothly are of great value. Additionally, the ability to efficiently carry out cross-coupling reactions in more environmentally friendly solvents[2,3] remains an important goal of green chemistry research.[4] It should be noted that organic solvents comprise up to 85% of the waste produced from a drug synthesis.[5]

Recently, the field of nickel-catalyzed cross-coupling reactions has gained considerable attention. The low cost and high reactivity of nickel is attractive, and a range of substrates has been shown to undergo nickel-catalyzed carbon–carbon and carbon–heteroatom bond forming reactions, including halides[6] and a variety of oxygen-based

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(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Meijere, A., Eds.; Wiley-VCH: Weinheim, 2004. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469. (c) *Topics in Current Chemistry*, Vol. 219; Miyaura, N., Ed.; Springer-Verlag: New York, 2002. (d) Corbet, J.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710. (e) Negishi, E. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233–257. (f) *Application of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective*; Shen, H. C., Crawley, M. L., Trost, B. M., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2012.

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(5) Fortunak, J. M. *Future Med. Chem.* **2009**, *1*, 571–575.

(6) For selected examples involving aryl halides, see: (a) Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*, 5908–5910. (b) Klein, A.; Budnikova, Y. H.; Sinyashin, O. G. *J. Organomet. Chem.* **2007**, *692*, 3156–3166. (c) Jennings, P. W.; Pillsbury, D. G.; Hall, J. L.; Brice, V. T. *J. Org. Chem.* **1976**, *41*, 719–722. (d) Zembayashi, M.; Tamao, K.; Yoshida, J.; Kumada, M. *Tetrahedron Lett.* **1977**, 4089–4092. (e) Wilson, D. A.; Wilson, C. J.; Rosen, B. M.; Percec, V. *Org. Lett.* **2008**, *10*, 4879–4882. (f) Golding, G. M.; Smidrkal, J.; Weichold, O.; Percec, V. *J. Org. Chem.* **2004**, *69*, 3442–3452. (g) Zhang, N.; Hoffman, D. J.; Gutsche, N.; Gupta, J.; Percec, V. *J. Org. Chem.* **2012**, *77*, 5956–5964. (h) Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993–2996. (i) Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513–3516. (j) Moldoveanu, C.; Wilson, D. A.; Wilson, C. J.; Leowanawat, P.; Resmerita, A.-M.; Liu, C.; Rosen, B. M.; Percec, P. *J. Org. Chem.* **2010**, *75*, 5438–5454. (k) Moldoveanu, C.; Wilson, D. A.; Wilson, C. J.; Corcoran, P.; Rosen, B.M.; Percec, V. *Org. Lett.* **2009**, *11*, 4974–4977. (l) Leowanawat, P.; Resmerita, A.-M.; Moldoveanu, C.; Liu, C.; Zhang, N.; Wilson, D. A.; Hoang, L. M.; Rosen, B. M.; Percec, V. *J. Org. Chem.* **2010**, *75*, 7822–7828. (m) Wolfe, J. P.; Buchwald, S. P. *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058.

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electrophiles (e.g., aryl-esters,[7] -ethers,[8] -carbamates,[9] -sulfamates[10]).[11,12] Considering the promise of nickel-catalyzed couplings and the need to make industrial processes more environmentally friendly, we explored coupling reactions in green solvents. Herein, we demonstrate that a range of substrates, including heterocycles, participate in the nickel-catalyzed Suzuki–Miyaura coupling in solvents that are attractive for industrial applications (Figure 1).

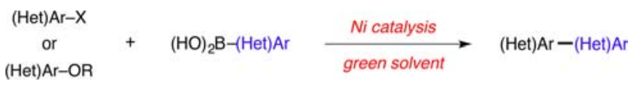
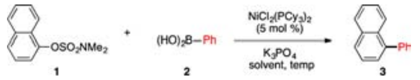


Figure 1. Suzuki–Miyaura cross-coupling of aryl halides and phenol derivatives in green solvents.

We initiated our efforts by examining the cross-coupling of naphthyl sulfamate **1** and phenylboronic acid (**2**) using the commercially available $NiCl_2(PCy_3)_2$ precatalyst (Table 1). Although solvents such as 1,4-dioxane and *N*-methyl-2-pyrrolidone (NMP), which have been deemed as environmentally unfriendly solvents,[2] are commonly used in nickel-catalyzed cross-couplings, we were delighted to find that many other solvents may be employed in the coupling to give biaryl **3**. Of the > 30 solvents that were surveyed, more than half gave quantititative yields of **3**, while many others also showed promise.[13] A subset of our findings are summarized in Table 1. The solvent used in our previous studies,[7c,9b,9d] toluene, gave biaryl **3** in quantitative yield (entry 1). Acetone, ethyl acetate, and isopropyl acetate (entries 2–4, respectively) also gave product in comparable yields. In addition, alcohol solvents were examined. Whereas the use of *n*-BuOH proved ineffective (entry 5), *tert*-amyl alcohol was found to be an excellent solvent for the cross-coupling (entry 6). Ethereal solvents also provided biaryl **3** in quantitative yield (entries 7–8). Mixed results were observed for highly coordinating solvents; for example, the use of DMSO was unsuccessful (entry 9), but the use of acetonitrile led to the desired coupling. Although many solvents could be employed, we opted to pursue *tert*-amyl alcohol and 2-Me-THF (entries 6 and 8, respectively) for further studies.[3,14]

Table 1. Survey of Solvents in the Suzuki–Miyaura Coupling[a]



entry	solvent, temp	yield[b]	entry	solvent, temp	yield[b]
1	toluene, 110 °C	100%	6	*t*-amyl alcohol, 100 °C	100%
2	acetone, 75 °C	96%	7	MTBE, 80 °C	100%
3	EtOAc, 100 °C	100%	8	2-Me-THF, 80 °C	100%
4	*i*-PrOAc, 110 °C	100%	9	DMSO, 110 °C	0%
5	*n*-BuOH, 110 °C	0%	10	acetonitrile, 100 °C	99%

[a] Conditions: $NiCl_2(PCy_3)_2$ complex (5 mol %), sulfamate substrate **1** (1.00 equiv), **2** (2.50 equiv), K_3PO_4 (4.50 equiv), hexamethylbenzene (0.10 equiv), 12 h. [b] Yield of **3** determined by ^1H NMR analysis of crude reaction mixtures using hexamethylbenzene as an internal standard.

With promising results in hand, we tested the analogous cross-coupling of several other electrophilic partners (Table 2). In addition to the naphthyl sulfamate (entry 1), the corresponding carbamate[15] and pivalate ester were deemed competent substrates (entries 2–3). Furthermore, sulfonate derivatives of 1-naphthol also gave high yields

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(7) For selected examples involving aryl esters, see: (a) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468–14470. (b) Li, B.-J.; Li, Y.-Z.; Lu, X.-Y.; Liu, J.; Guan, B.-T.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 10124–10127. (c) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748–17749. (d) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307–3310.

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(9) For selected examples involving aryl carbamates, see: (a) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066–4068. (b) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422–14423. (c) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750–17752. (d) Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352–6363. (e) Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Fine Nathel, N. F.; Hong, X.; Garg, N. K. *Chem. Sci.* **2011**, *2*, 1766–1771. (f) Hie, L.; Ramgren, S. D.; Mesganaw, T.; Garg, N. K. *Org. Lett.* **2012**, *14*, 4182–4185.

(10) For selected examples involving aryl sulfamates, see: (a) Macklin, T. K.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519–2522. (b) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 1507–1510. (c) Ramgren, S. D.; Silberstein, A. L.; Yang, Y.; Garg, N. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2171–2173. (d) Ackerman, L.; Sandmann, R.; Song, W. *Org. Lett.* **2011**, *13*, 1784–1786. (e) Zhang, N.; Hoffman, D. J.; Gutsche, N.; Gupta, J.; Percec, V. *J. Org. Chem.* **2012**, *77*, 5956–5964. (f) Chen, G.-J.; Han, F.-S. *Eur. J. Org. Chem.* **2012**, 3575–3579. (g) Wehn, P. M.; Du Bois, J. *Org. Lett.* **2005**, *7*, 4685–4688.

(11) For selected examples involving aryl sulfonates, see: (a) Wilson, D. A.; Wilson, C. J.; Moldoveanu, C.; Resmerita, A.-M.; Corcoran, P.; Hoang, L. M.; Rosen, B. M.; Percec, V. *J. Am. Chem. Soc.* **2010**, *132*, 1800–1801. (b) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060–1065. (c) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H.; Percec, V. *J. Org. Chem.* **1995**, *60*, 1066–1069. (d) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H.; Percec, V. *J. Org. Chem.* **1995**, *60*, 176–185. (e) Fan, X.-H.; Yang, L.-M. *Eur. J. Org. Chem.* **2011**, 1467–1471. (f) Gao, C.-Y.; Yang, L. M. *J. Org. Chem.* **2008**, *73*, 1624–1627. (g) Percec, V. J.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447–3452. (h) Tang, Z.-Y.; Fu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058–3059. (i) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049–3051; see also references 6e-g and 10d.

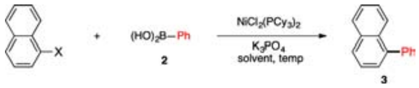
(12) For recent reviews, see: (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346–1416. (b) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 1728–1759. (c) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29–39. (d) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19–30.

(13) Solvents were selected from the ACS Green Chemistry Institute Roundtable Solvent Selection Guide. See Supporting Information for details.

(14) *tert*-Amyl alcohol and 2-Me-THF were selected in consultation with the ACS Green Chemistry Institute. *tert*-Amyl alcohol is attractive due to its safety profile, low freezing point (in comparison to *t*-BuOH), and ability to solubilize polar compounds. 2-Me-THF is advantageous because it is obtained from renewable feedstocks and possesses many process chemistry-related over THF. For a discussion of 2-Me-THF, see: Aycock, D. F. *Org. Process Res. Dev.* **2007**, *11*, 156–159.

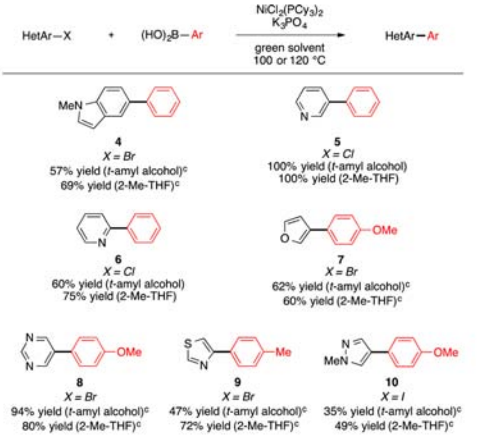
(15) Under standard conditions using 5% Ni, 50–60% yields of **3** were obtained, with the remaining mass being an unreacted carbamate substrate.

Table 2. Survey of Cross-Coupling Partners[a]



entry	X	yield (*tert*-amyl alcohol)[b]	yield (2-Me-THF)[b,c]
1	OSO_2NMe_2	100	100
2	$OCONEt_2$	57	50
3	OPiv	94	100
4	OMs	97	95
5	OTs	100	98
6	OTf	100	100
7	Cl	100	94
8	Br	97	92
9	I	100	97

[a] Conditions: $NiCl_2(PCy_3)_2$ complex (5 mol %), substrate (1.00 equiv), **2** (2.50 equiv), K_3PO_4 (4.50 equiv), hexamethylbenzene (0.10 equiv), 100 °C, 12 h. [b] Yield of **3** determined by ^{1}H NMR analysis of the crude reaction mixtures using hexamethylbenzene as an internal standard. [c] 66 °C.



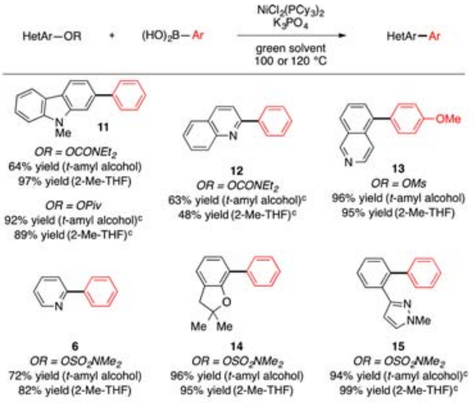
[a] Conditions: $NiCl_2(PCy_3)_2$ complex (5 mol %), halide substrate (1.00 equiv), aryl boronic acid (2.50 equiv), K_3PO_4 (4.50 equiv), hexamethylbenzene (0.10 equiv), 100 or 120 °C, 12 h. [b] Yield of product determined by ^{1}H NMR analysis of the crude reaction mixtures using hexamethylbenzene as an internal standard. [c] Conditions: $NiCl_2(PCy_3)_2$ complex (10 mol %), halide substrate (1.00 equiv), aryl boronic acid (4.00 equiv), K_3PO_4 (7.20 equiv), hexamethylbenzene (0.10 equiv), 100 or 120 °C, 12 h.

Figure 2. Coupling of heterocyclic halides with aryl boronic acids.[a,b]

of coupled product (entries 4–6). Moreover, the use of 1-naphthyl chloride, bromide, and iodide each delivered the desired product under our optimized conditions (entries 7–9, respectively).

An array of heterocyclic aryl halide substrates underwent the desired cross-coupling with aryl boronic acids in *tert*-amyl alcohol and 2-Me-THF (Figure 2). Nitrogen-containing heterocycles, such as indole and pyridine, were tolerated to give products **4**–**6**, respectively. 3-Bromofuran also underwent the desired coupling to give cross-coupled product **7**. In addition, the methodology was found to be tolerant of substrates that contain multiple heteroatoms, as demonstrated by the formation of products **8**–**10**.

As shown in Figure 3, heterocyclic phenol-derived electrophiles participate in the Suzuki–Miyaura coupling in green solvents.[16] Both the carbamate and ester derivatives of 2-hydroxy-*N*-Me-carbazole coupled smoothly with phenyl boronic acid to give **11** in good yields. Quinoline, isoquinoline, and pyridine derivatives were also tolerated, as demonstrated by the formation of **12**, **13**, and **6**, respectively. Dihydrobenzofuran- and pyrazole-based sulfamate substrates gave excellent yields of products **14** and **15**, respectively.



[a] Conditions: $NiCl_2(PCy_3)_2$ complex (5 mol %), phenolic-substrate (1.00 equiv), aryl boronic acid (2.50 equiv), K_3PO_4 (4.50 equiv), hexamethylbenzene (0.10 equiv), 100 or 120 °C, 12 h. [b] Yield of product determined by ^{1}H NMR analysis of the crude reaction mixtures using hexamethylbenzene as an internal standard. [c] Conditions: $NiCl_2(PCy_3)_2$ complex (10 mol %), sulfamate substrate **1** (1.00 equiv), aryl boronic acid (4.00 equiv), K_3PO_4 (7.20 equiv), hexamethylbenzene (0.10 equiv), 100 or 120 °C, 12 h.

Figure 3. Coupling of heterocyclic phenolic derivatives with aryl boronic acids.[a,b]

We also tested our cross-coupling procedure for the assembly of bis(heterocyclic) scaffolds (Figure 4), which are prevalent in numerous drugs and natural products, but are sometimes difficult to access using Pd-catalyzed methods.[17] 3-Cl-Pyridine readily underwent coupling with pyridyl-,[18] furyl-, and thiophenyl-boronic acid derivatives to provide bis(heterocyclic) compounds **16**–**18**. Likewise, 5-Br-pyrimidine was coupled to deliver compounds **19**–**21**.[19]

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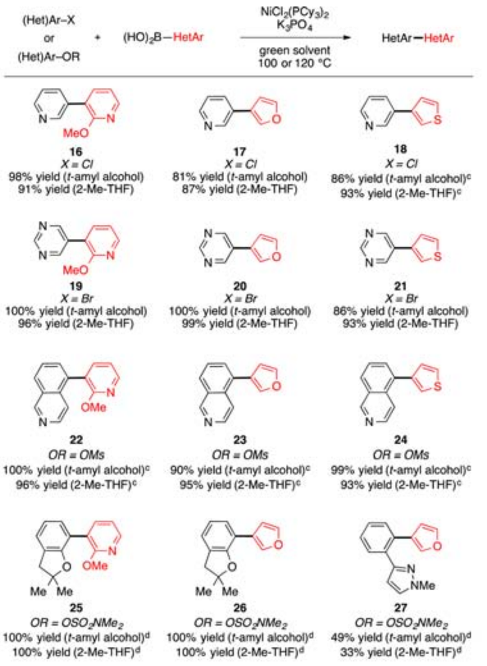
(16) The specific combination of heterocyclic framework and leaving group was chosen at random or based on substrate availability to span a broad range of coupling partners for this Letter. As such, the absence of a specific combination should not imply that such a combination would not lead to a successful Ni-catalyzed cross-coupling.

(17) For examples of Pd-catalyzed cross-coupling to access bis-heterocycles, see: (a) Zhao, D.; You, J.; Hu, C. *Chem.—Eur. J.* **2011**, *17*, 5466–5492. (b) Molander, G. A.; Shin, I. *Org. Lett.* **2013**, *15*, 2534–2537.

(18) The corresponding coupling between 2-chloropyridine and 2-methoxy-3-pyridinylboronic acid gave the desired bis(heteroaryl) in 60% yield (*tert*-amyl alcohol) and 71% yield (2-Me-THF).

(19) Microwave conditions were also tested for comparison. Cross-coupling of bromopyrimidine **30** with 3-furylboronic acid (**31**) using microwave conditions gave compound **20** in quantitative yield (using either *tert*-amyl alcohol or 2-Me-THF). See the Supporting Information for details. For Suzuki–Miyaura couplings of aryl carbamates and sulfamates under microwave conditions, see: References 10b.

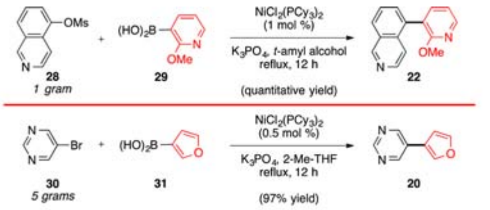


[a] Conditions: $\mathrm{NiCl_2(PCy_3)_2}$ complex (1 mol %), substrate (1.00 equiv), aryl boronic acid (2.50 equiv), $\mathrm{K_3PO_4}$ (4.50 equiv), hexamethylbenzene (0.10 equiv), 100 or 120 °C, 12 h. [b] Yield of product determined by ^{1}H NMR analysis of the crude reaction mixtures using hexamethylbenzene as an internal standard. [c] Conditions: $\mathrm{NiCl_2(PCy_3)_2}$ complex (5 mol %), substrate (1.00 equiv), aryl boronic acid (2.50 equiv), $\mathrm{K_3PO_4}$ (4.50 equiv), hexamethylbenzene (0.10 equiv), 100 or 120 °C, 12 h. [d] Conditions: $\mathrm{NiCl_2(PCy_3)_2}$ complex (10 mol %), substrate (1.00 equiv), aryl boronic acid (4.00 equiv), $\mathrm{K_3PO_4}$ (7.20 equiv), hexamethylbenzene (0.10 equiv), 100 or 120 °C, 12 h.

Figure 4. Coupling of heterocyclic substrates with heterocyclic aryl boronic acids.[a,b]

The mesylate derived from 5-hydroxyisoquinoline also underwent facile coupling, thus affording **22**–**24** in excellent yields. Additionally, the coupling of a benzofuranyl sulfamate was explored to give bis(heterocycles) **25** and **26**.[20] We also tested the coupling of a pyrazole derived sulfamate with 3-furanyl boronic acid, which afforded **27** in moderate yield. Our methodology complements the recently disclosed Ni-catalyzed cross-couplings to form bis(heterocycles) reported by Hartwig.[6e]

The nickel-catalyzed Suzuki–Miyaura coupling shows promise for the assembly of bis(heterocyclic) frameworks on preparative scale (Figure 5).[21] Using 1 mol % Ni catalyst, isoquinoline **28** was coupled with pyridylboronic acid **29** to provide adduct **22** in quantitive yield on gram scale. Additionally, bromopyrimidine **30** underwent Ni-catalyzed cross-coupling with furanylboronic acid **31** using 0.5 mol % catalyst. This transformation, which was performed on 5 g scale, delivered **20** in 97% yield.



[a] Conditions: $\mathrm{NiCl_2(PCy_3)_2}$ complex (1 or 5 mol %), substrate (1.00 equiv), aryl boronic acid (2.50 equiv), $\mathrm{K_3PO_4}$ (4.50 equiv), reflux, 12 h. [b] Isolated yields.

Figure 5. Gram scale couplings.[a,b]

In summary, we have demonstrated the efficient Ni-catalyzed Suzuki–Miyaura cross-coupling of aryl halides and phenolic derivatives in green solvents. The scope of these reactions is broad with respect to both coupling partners, and heterocycles are well-tolerated. Additionally, the potential for these couplings to be performed on preparative scale has been demonstrated by the gram scale assembly of bis(heterocycles) using low catalyst loadings (i.e., 0.5–1 mol % Ni). Given the appeal of Ni catalysis and the favorable green solvents that may be employed, we expect the methodology presented will find utility in academic and industrial applications.

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

The authors declare no competing financial interest.

(20) Interestingly, the corresponding cross-coupling with thiophene-3-boronic acid resulted in no product formation.

(21) The choice of solvents for these transformations was arbitrary to showcase that either *tert*-amyl alcohol or 2-Me-THF can be employed on preparative scale. As shown in Figure 4, the couplings to prepare **22** and **20** readily proceed in either solvent.