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Nickel-Catalyzed Suzuki–Miyaura Couplings in Green Solvents

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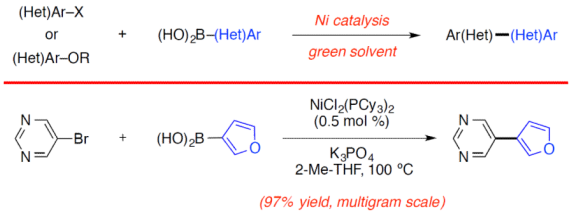
Abstract



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 *t*-amyl alcohol, is reported. This methodology employs the commercially available and air-stable pre-catalyst $NiCl_2(PCy_3)_2$ 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 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).

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 enviromentally unfriendly solvents,[2] are commonly used in nickel-catalyzed

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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.

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,[7,9] 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. Alcohol solvents were also examined. Whereas the use of *n*-BuOH proved ineffective (entry 5), *t*-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 *t*-amyl alcohol and 2-Me-THF (entries 6 and 8, respectively) for further studies.[2,14]

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 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 *t*-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.

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] 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 Nicatalyzed 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 Nicatalyzed 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.

In summary, we have demonstrated the efficient Nicatalyzed 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Diederich, F.; Meijere, A., editors. Metal-Catalyzed Cross-Coupling Reactions. Wiley-VCH; Weinheim: 2004. (b) Hassan J, Sevignon M, Gozzi C, Schulz E, Lemaire M. Chem. Rev. 2002; 102:1359–1469. [PubMed: 11996540] (c) Miyaura, N., editor. Topics in Current Chemistr. Vol. Vol. 219. Springer-Verlag; New York: 2002. (d) Corbet J, Mignani G. Chem. Rev. 2006; 106:2651–2710. [PubMed: 16836296] (e) Negishi E. Bull. Chem. Soc. Jpn. 2007; 80:233–257.(f) Shen, HC.; Crawley, ML.; Trost, BM., editors. Application of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective. John Wiley & Sons, Inc.; Hoboken: 2012.
2. For solvent selection guide in medicinal chemistry, see: Alfonsi K, Colberg J, Dunn PJ, Fevig T, Jennings S, Johnson TA, Kleine HP, Knight C, Nagy MA, Perry DA, Stefaniak M. Green Chem. 2008; 10:31–36.. Henderson RK, Jiménez-Gonález C, Constable DJC, Alston SR, Inglis GGA, Fisher G, Sherwood J, Binks SP, Curzons AD. Green Chem. 2011; 13:854–862.
3. For examples of cross-coupling reactions in aqueous media, see Bussolari JC, Rehborn DC. Org. Lett. 1999; 1:965–967.. Hesse S, Kirsch G. Synthesis. 2001:755–759.. Anderson KW, Buchwald SL. Angew. Chem. Int. Ed. 2005; 44:6173–6177.. Lipshutz BH, Ghorai S. Aldrichim. Acta. 2008; 41:59–72.. Alacid E, Nájera C. J. Org. Chem. 2009; 74:2321–2327. [PubMed: 19216543] . Han J, Liu Y, Guo R. J. Am. Chem. Soc. 2009; 131:2060–2061. [PubMed: 19170490] . Chalker JM, Wood CS, Davis BG. J. Am. Chem. Soc. 2009; 131:16346–16347. [PubMed: 19852502] .
4. (a) Anastas, PT.; Warner, JC., editors. Green Chemistry: Theory and Practice. Oxford University Press; New York: 1998. (b) Anastas PT, Kirchhoff MM. Acc. Chem. Res. 2002; 35:686–694. [PubMed: 12234198]
5. Fortunak JM. Future Med. Chem. 2009; 1:571–575. [PubMed: 21426025]
6. For selected examples examples involving aryl halides, see: Powell DA, Maki T, Fu GC. J. Am. Chem. Soc. 2005; 127:510–511. [PubMed: 15643860] . Yoshikai N, Matsuda H, Nakamura E. J. Am. Chem. Soc. 2009; 131:9590–9599. [PubMed: 19522507] . Everson DA, Shrestha R, Weix DJ. J. Am. Chem. Soc. 2010; 132:920–921. [PubMed: 20047282] . Fan X-H, Yang L-M. Eur. J. Org. Chem. 2011:1467–1471.. Ge S, Hartwig JF. Angew. Chem. Int. Ed. 2012; 51:12837–12841.. Zultanski SL, Fu GC. J. Am. Chem. Soc. 2013; 135:624–627. [PubMed: 23281960] .

7. For selected examples examples involving aryl esters, see: Guan B-T, Wang Y, Li B-J, Yu D-G, Shi Z-J. J. Am. Chem. Soc. 2008; 130:14468–14470. [PubMed: 18847272] . 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.. Quasdorf KW, Riener M, Petrova KV, Garg NK. J. Am. Chem. Soc. 2009; 131:17748–17749. [PubMed: 19928764] . Zhou Q, Srinivas HD, Dasgupta S, Watson MP. J. Am. Chem. Soc. 2013; 135:3307–3310. [PubMed: 23425080] .
8. For selected examples involving aryl ethers, see: Tobisu M, Shimasaki T, Chatani N. Angew. Chem. Int. Ed. 2008; 47:4866–4869.. Shimasaki T, Konno Y, Tobisu M, Chatani N. Org. Lett. 2009; 11:4890–4892. [PubMed: 19810683] . Shimasaki T, Tobisu M, Chatani N. Angew. Chem. Int. Ed. 2010; 49:2929–2932.. Li X-J, Zhang J-L, Geng Y, Jin Z. J. Org. Chem. 2013; 78:5078–5084. [PubMed: 23627776] .
9. For selected examples involving aryl carbamates, see: Sengupta S, Leite M, Raslan DS, Quesnelle C, Snieckus V. J. Org. Chem. 1992; 57:4066–4068.. Quasdorf KW, Tian X, Garg NK. J. Am. Chem. Soc. 2008; 130:14422–14423. [PubMed: 18839946] . Antoft-Finch A, Blackburn T, Snieckus V. J. Am. Chem. Soc. 2009; 131:17750–17752. [PubMed: 19928763] . Quasdorf KW, Antoft-Finch A, Liu P, Silberstein AL, Komaromi A, Blackburn T, Ramgren SD, Houk KN, Snieckus V, Garg NK. J. Am. Chem. Soc. 2011; 133:6352–6363. [PubMed: 21456551] . Mesganaw T, Silberstein AL, Ramgren SD, Fine Nathel NF, Hong X, Garg NK. Chem. Sci. 2011; 2:1766–1771.. Hie L, Ramgren SD, Mesganaw T, Garg NK. Org. Lett. 2012; 14:4182–4185. [PubMed: 22849697] .
10. For selected examples involving aryl sulfamates, see: Macklin TK, Snieckus V. Org. Lett. 2005; 7:2519–2522. [PubMed: 15957880] . Baghbanzadeh M, Pilger C, Kappe CO. J. Org. Chem. 2011; 76:1507–1510. [PubMed: 21250707] . Ramgren SD, Silberstein AL, Yang Y, Garg NK. Angew. Chem. Int. Ed. 2011; 50:2171–2173.. Ackerman L, Sandmann R, Song W. Org. Lett. 2011; 13:1784–1786. [PubMed: 21351758] . Zhang N, Hoffman DJ, Gutsche N, Gupta J, Percec V. J. Org. Chem. 2012; 77:5956–5964. [PubMed: 22712768] . Chen G-J, Han F-S. Eur. J. Org. Chem. 2012:3575–3579..
11. For selected examples involving aryl sulfonates, see: Bhayana B, Fors BP, Buchwald SL. Org. Lett. 2009; 11:3954–3957. [PubMed: 19663467] . Limmert ME, Roy AH, Hartwig JF. J. Org. Chem. 2005; 70:9364–9370. [PubMed: 16268609] . Naber JR, Fors BP, Wu X, Gunn JT, Buchwald SL. Heterocycles. 2010; 80:1215–1226. [PubMed: 23596345] . Chow WK, So CM, Lau CP, Kwong FY. J. Org. Chem. 2010; 75:5109–5112. [PubMed: 20590104] .
12. For recent reviews, see: Rosen BM, Quasdorf KW, Wilson DA, Zhang N, Resmerita A-M, Garg NK, Percec V. Chem. Rev. 2011; 111:1346–1416. [PubMed: 21133429] . Li B-J, Yu D-G, Sun C-L, Shi Z-J. Chem. Eur. J. 2011; 17:1728–1759. [PubMed: 21274921] . Mesganaw T, Garg NK. Org. Process Res. Dev. 2013; 17:29–39.. 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. *t*-Amyl alcohol and 2-Me-THF were selected in consultation with the ACS Green Chemistry Institute. *t*-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 advantages over THF. For a discussion of 2-Me-THF, see: Aycock DF. 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 unreacted carbamate substrate.
16. The specific combination of heterocyclic framework and leaving group were 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 bisheterocycles, see: Zhao D, You J, Hu C. Chem. Eur. J. 2011; 17:5466–5492. [PubMed: 21506178] . Molander GA, 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 (*t*-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 (*t*-amyl alcohol) and 100% yield (2-Me-THF). See the Supporting Information for details. For Suzuki–Miyaura couplings of aryl carbamates and sulfamates under microwave conditions, see: ref. 10b.

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 *t*-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.

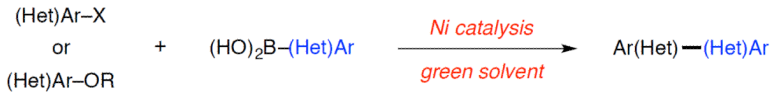
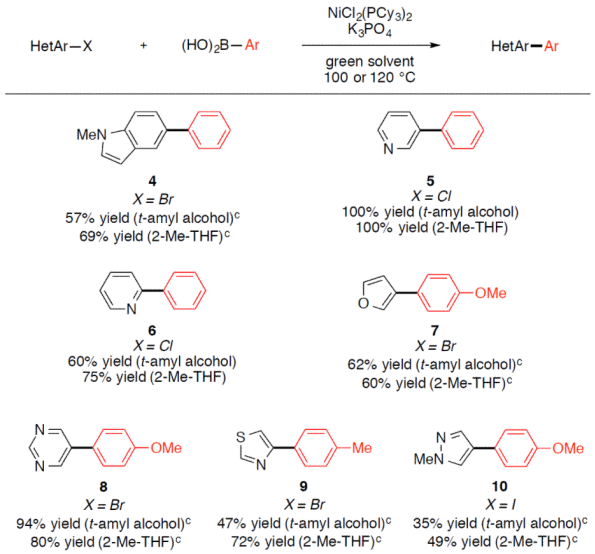
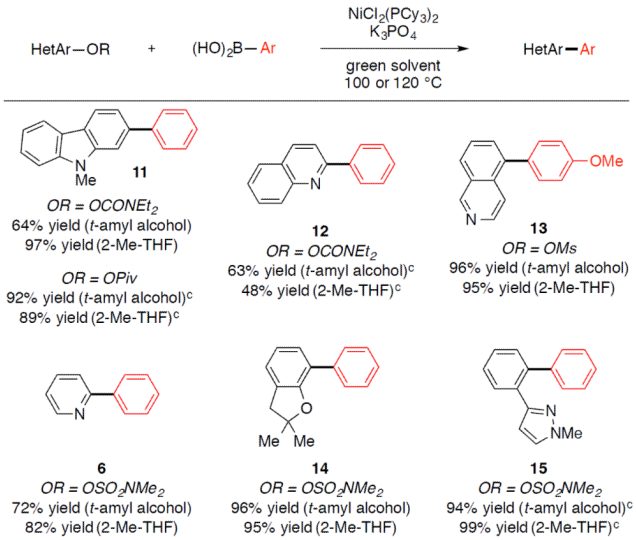


Figure 1.
Suzuki–Miyaura cross-coupling of aryl halides and phenol derivatives in green solvents.



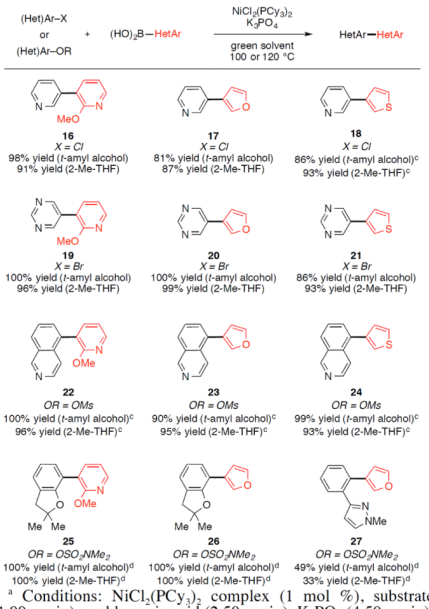
[a] Conditions: $NiCl_2(PCy_3)_2$ complex (5 mol %), halide substrate (1.00 equiv), aryl boronic acid (2.50 equiv), K_3PO_4 (4.50 equiv), hexamethylbenzene (0.10 equiv), 100 or 120 °C, 12 h. [b] Yield of product determined by ^1H NMR analysis of the crude reaction mixtures using hexamethylbenzene as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



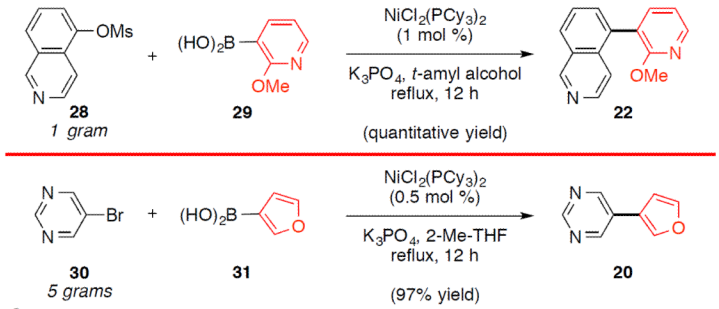
[a] Conditions: $NiCl_2(PCy_3)_2$ complex (5 mol %), phenolic-substrate (1.00 equiv), aryl boronic acid (2.50 equiv), K_3PO_4 (4.50 equiv), hexamethylbenzene (0.10 equiv), 100 or 120 °C, 12 h. [b] Yield of product determined by ^1H NMR analysis of the crude reaction mixtures using hexamethylbenzene as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



[a] Conditions: $NiCl_2(PCy_3)_2$ complex (1 mol %), 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 ^1H NMR analysis of the crude reaction mixtures using hexamethylbenzene as an internal standard. [c] Conditions: $NiCl_2(PCy_3)_2$ complex (5 mol %), 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. [d] Conditions: $NiCl_2(PCy_3)_2$ complex (10 mol %), 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 4.
Coupling of heterocyclic substrates with heterocyclic aryl boronic acids.[a,b]

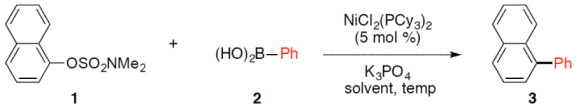


[a] Conditions: $NiCl_2(PCy_3)_2$ complex (1 or 5 mol %), substrate (1.00 equiv), aryl boronic acid (2.50 equiv), K_3PO_4 (4.50 equiv), reflux, 12 h. [b] Isolated yields.

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

Table 1

Survey of solvents in the Suzuki–Miyaura coupling.[a]



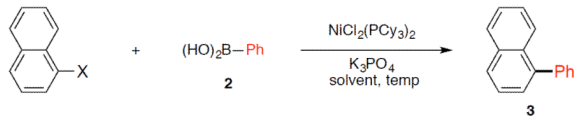
entry	solvent, temp	yield[b]	entry	solvent, temp	yield[b]
1	toluene, 110 °C	100%	6	*t*-amyl alcohol, 100 °C	100%
2	acetone, 75 °C	96%	7	MTBE, 80 °C	100%
3	EtOAc, 100 °C	100%	8	2-Me-THF, 80 °C	100%
4	*i*-PrOAc, 110 °C	100%	9	DMSO, 110 °C	0%
5	*n*-BuOH, 110 °C	0%	10	acetonitrile, 100 °C	99%

[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.

Table 2

Survey of cross-coupling partners.[a]



entry	X	yield (*t*-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 ^1H NMR analysis of the crude reaction mixtures using hexamethylbenzene as an internal standard.

[c]66 °C