Green Chemistry

International Edition: DOI: 10.1002/anie.201505136
German Edition: DOI: 10.1002/ange.201505136

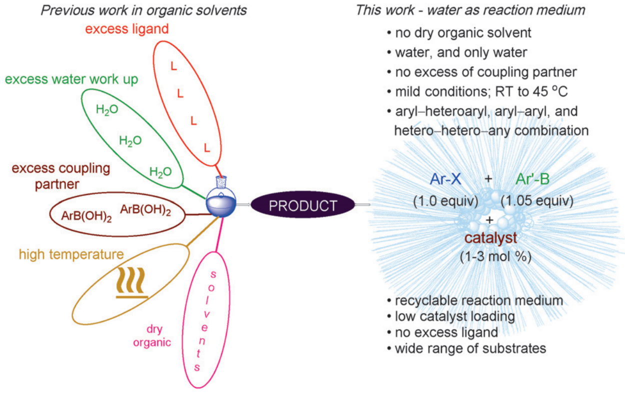
Nanonickel-Catalyzed Suzuki–Miyaura Cross-Couplings in Water

*Sachin Handa, Eric D. Slack, and Bruce H. Lipshutz**

Abstract: *Nickel nanoparticles, formed in situ and used in combination with micellar catalysis, catalyze Suzuki–Miyaura cross-couplings in water under very mild reaction conditions.*

Transition-metal-mediated cross-couplings, especially those catalyzed by palladium, have become truly fundamental tools in organic synthesis. Most heavily utilized this decade have been Suzuki–Miyaura (SM) reactions, especially those that provide rapid entry to biaryl frameworks.[1] Over the past 35 + years, since this Nobel-Prize-winning chemistry was introduced, circumstances surrounding use of all such palladium-mediated bond constructions have changed, that is, from an environmental perspective, as well as a developing awareness of the finite levels of platinoids accessible by current technologies which are being quickly depleted. The cost of this precious metal is almost always a factor, especially in process research, thus further encouraging alternative methodologies that accomplish similar goals.[2] The National Science Foundation has already begun to encourage research into less costly and earth-abundant alternative metals.[3]

Beginning in 2008, we introduced several palladium-catalyzed SM processes which take advantage of the hydrophobic effect operating within newly engineered nanoparticles in water. This approach dramatically reduces organic waste associated with use of organic solvents as reaction media.[2] A switch to nickel under such micellar catalysis conditions represents another opportunity to replace a precious metal with its base metal alternative. The virtues of nickel, including its greater nucleophilicity relative to palladium because of its smaller size, and its heightened reactivity towards aromatic chlorides because of the strength of the resulting Ni−Cl bond, might be further accentuated given the high concentrations typically found within nanomicelles.[4] Herein we describe new technology that offers not only the most general solution available for such valued nickel-based cross-couplings, but also a process that advances the capabilities of prior art in this field and is, by far, the most environmentally responsible reported to date (Scheme 1).



Scheme 1. Nanoparticle approach to nickel-catalyzed SM couplings in water.

Since the initial disclosure by Miyaura and co-workers in 1996, nickel-catalyzed Suzuki–Miyaura couplings have been extensively investigated.[5] Many literature reports require relatively high reaction temperatures (usually ≥ 100 °C),[6] are limited to either heteroaryl or homoaryl partners,[7] and involve ligand loadings beyond that of the metal[6c,8] and can poison the catalyst over time.[5c,9] In addition, all are conducted in organic solvents. In the composite, these features tend to drive synthetic chemists back towards reliance on palladium.[1,10] An early report by Genet et al. did focus on a water-soluble nickel catalyst, but the couplings were limited to aryl chlorides, required 10 mol % $NiCl_2$ and 50 mol % ligand loading, as well as significant heating to accommodate water-insoluble coupling partners.[11] More recently, significant advances by the groups of Hartwig,[12] Buchwald,[13] Garg,[6a,b] and others[2] provide solutions to some of these limitations, in particular the issues of catalyst stability and sensitivity, loadings, substrate scope, and reproducibility on somewhat larger scales. However, these protocols still all involve organic solvents, an excess of heavy base, elevated temperatures, and importantly, an excess of a coupling partner, while none offers recycling of either the solvent or catalyst.

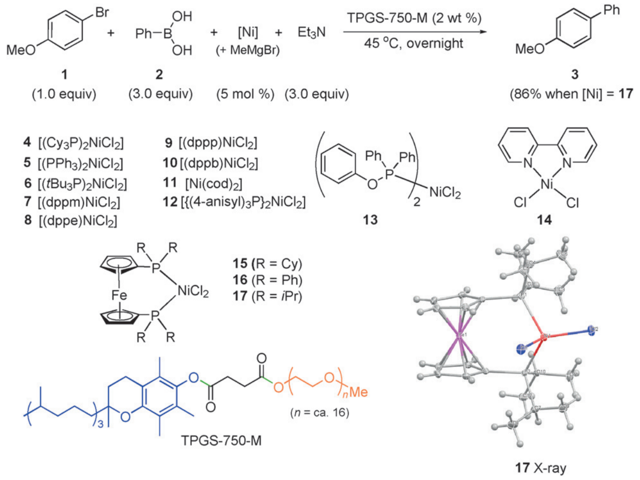
Our study began with the model reaction between aryl bromide **1** and phenylboronic acid (**2**) using various nickel catalysts, along with triethylamine as a base in an aqueous solution containing 2 wt % of the commercially available designer surfactant TPGS-750-M at 45 °C (Scheme 2). Screening of several catalysts revealed the active nature of species **4**, **6**, and **14**–**17**. Catalyst **17** (see X-ray) was found to be the most effective, with the biaryl **3** being obtained in 86 % yield upon isolation (see the Supporting Information for details).

Optimization studies revealed a dependence on several variables, most notably pre-activation of the catalyst using one equivalent of MeMgBr, relative to the nickel precatalyst in THF at room temperature. Other variables included the choice of surfactant, base, and global concentration of the aqueous reaction medium. While optimum reaction conditions rely on the ligand 1,1′-bis(diisopropylphosphino)ferrocene (dippf) for aryl-aryl couplings, commercially available

---

[*] Dr. S. Handa, E. D. Slack, Prof. B. H. Lipshutz
Dept. of Chemistry and Biochemistry
University of California Santa Barbara
Santa Barbara, CA 93106 (USA)
E-mail: lipshutz@chem.ucsb.edu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201505136.



Scheme 2. Initial screening of nickel catalysts.[15] (TPGS-750-M: Aldrich catalogue #733857)

(bis)diphenylphosphinoferreocene (dppf) afforded the best results for couplings involving heteroaryl partners (see the Supporting Information for details). Also noteworthy is that only 0.35 equivalents of K_3PO_4 are needed as base, while previous reports relied on multiple equivalents.[6b,12] Moreover, the ratio of aryl boron to aryl halide could be lowered to almost stoichiometric levels (1.05:1). Among the choices between boronic acids or esters, aryl-Bpin esters exhibited greater reactivity over the corresponding boronic acids, thus allowing couplings to occur at room temperature (22 °C) in micellar nanoreactors (0.5 M), while reactions of boronic acids required mild heating to 45 °C, mainly to increase solubilization because of their highly crystalline nature. Under these reaction conditions, NMR spectroscopy revealed that the boronic acids are stable. Hence, very limited amounts of excess reagent are required. Moreover, the solubility of boronic acids was found to be far superior in aqueous TPGS-750-M as compared to that in organic solvents (see the Supporting Information). Further investigations regarding the nature of the active catalyst revealed the presence of hybrid nickel nanoparticles, and it was confirmed by cryo-TEM (Figure 1, left), SEM (Figure 1, right), and EDX experiments (see the Supporting Information). Nanoparticles were found to be either seemingly inside the micelles (black arrows) or on the surface of aggregated nanomicelles (white arrows), presumably enhancing delivery of educts from the micellar lipophilic cores.

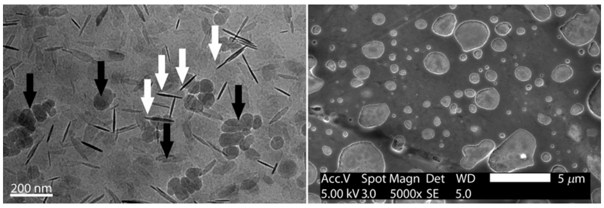
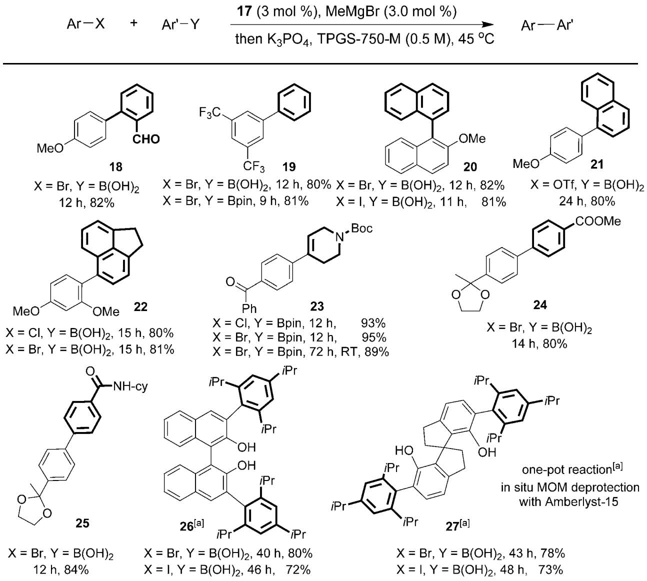


Figure 1. Cryo-TEM (left) and SEM (right) images of active catalyst in a 3 wt% aqueous solution of TPGS-750-M (see the Supporting Information for detailed elemental composition).

In establishing substrate scope, particular attention was paid to both functional-group tolerance and steric issues. As illustrated in Table 1, this technology displays remarkable generality, in contrast to most existing methods, thus leading to biaryl products independent of the halide leaving group (chlorides, bromides, and iodides). Residues such as formyl (**18**), trifluoromethyl (**19**), carbamate (**23**), ester (**24**), acetal (**24, 25**), and amide (**25**) exerted virtually no influence on these couplings. Cases of notable steric congestion can be found in products **26** and **27**. And the alkenyl boronate gave the highly functionalized styrene **23**, generated at either the typical 45 °C or at room temperature, although the latter conditions required an extended reaction time to afford a comparable yield. Cross-couplings between a bis(MOM)-protected, 3,3′-dibromo- or diiodo-BINOL and a highly hindered boronic acid led, after MOM removal, in a single pot, to the doubly derivatized biaryl **26**. Likewise, the biaryl **27** could be fashioned using the same two-step, one-pot sequence (for additional examples, see the Supporting Information).

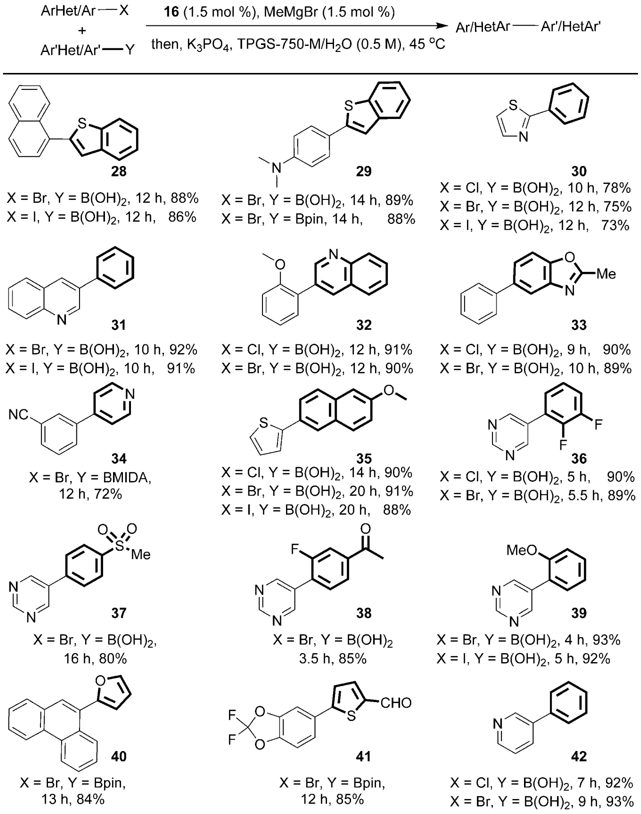
Table 1: Substrate scope for aryl–aryl cross-coupling.



Reaction conditions: Ar–X (0.5 mmol, 1.0 equiv) and Ar′–Y (0.53 mmol, 1.05 equiv). Sequence of addition: **17** was mixed with MeMgBr for 1 min at RT under Ar. Ar–X was then added and the reaction mixture stirred for 30 seconds. K_3PO_4 (0.18 mmol, 0.35 equiv) and Ar′–Y were then added sequentially. Yields are those of the isolated products. [a] Ar′–Y (1.05 mmol, 2.1 equiv), **17** (0.03 mmol, 6.0 mol%), MeMgBr (0.03 mmol, 6 mol%), K_3PO_4 (0.35 mmol, 0.70 equiv), same sequence of addition as with other Ar–X. Boc = *tert*-butoxycarbonyl, MOM = methoxymethyl, pin = pinacol.

Formation of products reflecting an aromatic/heteroaromatic combination of partners was next explored (Table 2; see the Supporting Information for additional examples). Interestingly, such systems were found to undergo cross-couplings more readily and in higher yields compared to aryl/aryl cases. No reaction was observed with non-ligated $NiCl_2$ as a catalyst, thus suggesting that the heteroaromatic is not likely

Table 2: Substrate scope for aryl–heteroaryl cross-couplings.



28
X = Br, Y = $B(OH)_2$, 12 h, 88%
X = I, Y = $B(OH)_2$, 12 h, 86%

29
X = Br, Y = $B(OH)_2$, 14 h, 89%
X = Br, Y = Bpin, 14 h, 88%

30
X = Cl, Y = $B(OH)_2$, 10 h, 78%
X = Br, Y = $B(OH)_2$, 12 h, 75%
X = I, Y = $B(OH)_2$, 12 h, 73%

31
X = Br, Y = $B(OH)_2$, 10 h, 92%
X = I, Y = $B(OH)_2$, 10 h, 91%

32
X = Cl, Y = $B(OH)_2$, 12 h, 91%
X = Br, Y = $B(OH)_2$, 12 h, 90%

33
X = Cl, Y = $B(OH)_2$, 9 h, 90%
X = Br, Y = $B(OH)_2$, 10 h, 89%

34
X = Br, Y = BMIDA,
12 h, 72%

35
X = Cl, Y = $B(OH)_2$, 14 h, 90%
X = Br, Y = $B(OH)_2$, 20 h, 91%
X = I, Y = $B(OH)_2$, 20 h, 88%

36
X = Cl, Y = $B(OH)_2$, 5 h, 90%
X = Br, Y = $B(OH)_2$, 5.5 h, 89%

37
X = Br, Y = $B(OH)_2$,
16 h, 80%

38
X = Br, Y = $B(OH)_2$
3.5 h, 85%

39
X = Br, Y = $B(OH)_2$, 4 h, 93%
X = I, Y = $B(OH)_2$, 5 h, 92%

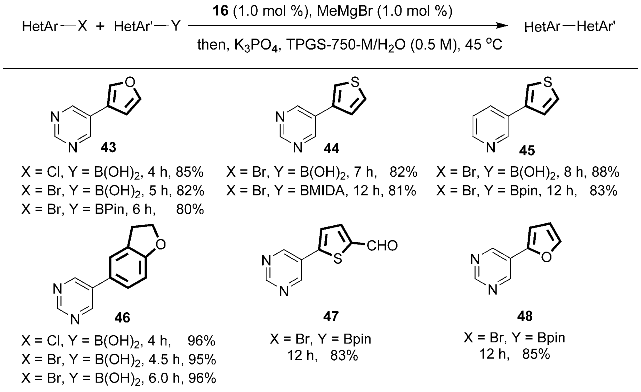
40
X = Br, Y = Bpin,
13 h, 84%

41
X = Br, Y = Bpin,
12 h, 85%

42
X = Cl, Y = $B(OH)_2$, 7 h, 92%
X = Br, Y = $B(OH)_2$, 9 h, 93%

Reaction conditions: Ar/HetAr–X (0.5 mmol, 1.0 equiv) and Ar′/HetAr′–Y (0.53 mmol, 1.05 equiv). Sequence of addition: **16** was mixed with MeMgBr for 1 min at RT under Ar. Aryl–X was then added and the reaction mixture stirred for 30 seconds. K_3PO_4 (0.18 mmol, 0.35 equiv) and Ar–Y were then added sequentially. MIDA = *N*-methyliminodiacetic acid.

Table 3: Hetero–heteroaryl cross-couplings.



43
X = Cl, Y = $B(OH)_2$, 4 h, 85%
X = Br, Y = $B(OH)_2$, 5 h, 82%
X = Br, Y = BPin, 6 h, 80%

44
X = Br, Y = $B(OH)_2$, 7 h, 82%
X = Br, Y = BMIDA, 12 h, 81%

45
X = Br, Y = $B(OH)_2$, 8 h, 88%
X = Br, Y = Bpin, 12 h, 83%

46
X = Cl, Y = $B(OH)_2$, 4 h, 96%
X = Br, Y = $B(OH)_2$, 4.5 h, 95%
X = Br, Y = $B(OH)_2$, 6.0 h, 96%

47
X = Br, Y = Bpin
12 h, 83%

48
X = Br, Y = Bpin
12 h, 85%

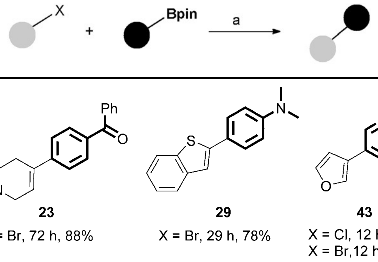
Reaction conditions: HetAr–X (0.5 mmol, 1.0 equiv) and HetAr′–Y (0.53 mmol, 1.05 equiv). Sequence of addition: **16** was mixed with MeMgBr for 1 min at RT under Ar. HetAr–X was then added and the reaction mixture stirred for 30 seconds. K_3PO_4 (0.18 mmol, 0.35 equiv) and HetAr′–Y were then added sequentially.

acting as both educt and ligand. Greater reactivity of pyrimidines as compared to that of pyridines and thiophenes was noted. Heteroaryl chlorides were typically as, or more, reactive compared to the corresponding bromides and iodides. Functional-group compatibility is equally high in these cases as well, and excellent yields were obtained for products containing dimethylamino (**29**), methoxy (**32**, **35**, and **39**), cyano (**34**), fluoro (**36, 38**, and **41**), sulfonyl (**37**), and carbonyl (**38, 41**) groups. Either catalyst **16** or **17** can be used in these transformations, but **16** is the more active and is commercially available (see the Supporting Information). Only 1.5–2.0 mol% of **16** is required in these reactions. Boronic acids were found to be slightly more reactive than the corresponding Bpin esters, the opposite to that found in the aryl/aryl couplings. In the particularly challenging case of 4-pyridylboronic acid, which is rapidly lost to protio-deborylation under SM coupling conditions, use of the corresponding MIDA boronate was successful, thus leading to the biaryl product **34**.

Cross-couplings where both partners are heteroarenes could also be effected, with an associated drop in the catalyst (**16**) loading to 1 mol% (Table 3). As seen previously with heteroaryl boronic acids, these types of educts are more reactive partners relative to their corresponding Bpin esters and MIDA boronates. Again, heteroaryl chlorides are consistently more reactive than their bromide counterparts.

Several of the examples discussed above could be arrived at with essentially equal facility by inverting the nature of the coupling partners. Thus, as illustrated in Table 4 (and in the Supporting Information), representative cases involving each of the various types of product biaryls (i.e., aryl–aryl, aryl–heteroaryl, and hetero–heteroaryl) could be prepared, thereby attesting to the inherent flexibility of this very mild and selective nickel-catalyzed coupling approach.

Table 4: Room temperature cross-couplings with reversal of polarity in coupling partners.



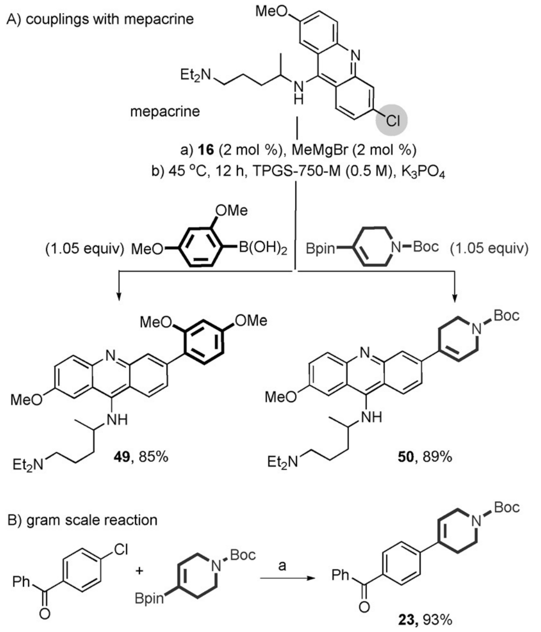
23
X = Br, 72 h, 88%

29
X = Br, 29 h, 78%

43
X = Cl, 12 h, 78%
X = Br,12 h, 80%

Reaction conditions: a) Aryl–X (0.5 mmol, 1.0 equiv) and Ar′–Bpin (0.53 mmol, 1.05 equiv). Sequence of addition: Either **16** or **17** was mixed with MeMgBr (1:1) for 1 min at RT under Ar. Aryl-X was then added and the reaction mixture stirred for 30 seconds. K_3PO_4 (0.18 mmol, 0.35 equiv) and Ar–Bpin were added sequentially. Note: For Ar–HetAr′ or HetAr–Ar′ systems 1.5 mmol of **16**, for HetAr–HetAr′ systems 1.0 mmol of **16**, and for Ar–Ar′ systems 3 mmol **17** was employed as precatalyst.

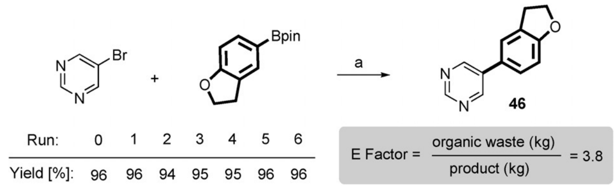
To gauge the prospects for applications to complex synthesis and/or functionalized molecule analogue formation, mepacrine, an antiprotozoal, antirheumatic, and intrapleural sclerosing agent was selected as a representative coupling partner. Introduction of both aryl and alkenyl groups by displacement from this heteroaromatic chloride took place in excellent yields affording products **49** and **50** (Scheme 3 A). The mild reaction conditions typically associated with these



Scheme 3. A) Cross-coupling with mepacrine. B) A gram-scale reaction. Reaction conditions: a) Aryl–Cl (0.5 mmol, 1.0 equiv) and vinyl-Bpin (0.53 mmol, 1.05 equiv). MeMgBr was added to **15** and stirred for 1 min at RT under Ar. Aryl–X was then added and the reaction mixture stirred for 30 seconds. Then K_3PO_4 (0.18 mmol, 0.35 equiv) and Ar–Y added sequentially.

milligram scale reactions were also applicable on a one-gram scale, affording comparable results (Scheme 3B).

Studies were also conducted to assess the potential for recycling of the reaction medium. Designer surfactants such as TPGS-750-M are engineered to remain in water, while the product undergoes in-flask extraction with minimum amounts of an organic solvent, such as MTBE. For the reaction shown in Scheme 4, **46** was obtained in consistently high yields over six consecutive recycles. Following each reaction, the product was extracted with MTBE, while the aqueous layer remained in the reaction vessel and was reused for each successive cycle. Additional nickel catalyst (1.5 mol%) was added after each recycle, given the sensitivity of nickel(0) during handling. Calculation of an E Factor,[15] based on the use of organic solvent as a measure of "greenness", led to a value of only 3.8, which is about an order of magnitude below those values typically seen for chemistry done in the fine chemicals and pharmaceuticals arenas.



Run:	0	1	2	3	4	5	6
Yield [%]:	96	96	94	95	95	96	96

$$\text{E Factor} = \frac{\text{organic waste (kg)}}{\text{product (kg)}} = 3.8$$

Scheme 4. E Factor and recycle studies. a) 5-bromopyrimidine (0.5 mmol, 1.0 equiv), Ar–Bpin (0.53 mmol, 1.05 equiv), **16** (0.0075 mmol, 1.5 mol%), MeMgBr (0.0075 mmol, 1.5 mol%), K_3PO_4 (0.18 mmol, 0.35 equiv), TPGS-750-M (3 wt%) 1 mL, 45 °C, 6 h. TPGS-750-M was recycled in all runs. In each recycle, freshly generated active catalyst (0.0075 mmol) and K_3PO_4 (0.18 mmol) were added (see the Supporting Information for details).

Another potentially important aspect of this process concerns the amount of nickel which is carried through and into the product from these cross-couplings. This amount can be a crucial factor governing not only whether, but also at which point, such couplings may be utilized, in particular when planning a sequence to an active pharmaceutical ingredient (API). Inductively coupled plasma mass spectrometry (ICP-MS) analyses of two products isolated using standard "in-flask" extraction and routine flash chromatography afforded products with each retaining less than or equal to 5 ppm nickel (see the Supporting Information).

In summary, Suzuki–Miyaura reactions can now be effected using a new procedure of considerable generality and functional-group tolerance, which relies on inexpensive nickel in nanoparticle form. The process is enabled by the proper choice of ligand on the metal, matched to the hydrophobic effect characteristic of aqueous nanomicelles. This new technology also features, unlike prior art, greater substrate scope, essentially stoichiometric levels of reaction partners, considerable flexibility in the choice of both leaving group and source of boron, very mild reaction conditions, and notably, the option for recycling of the aqueous medium containing both the surfactant and catalyst.

Acknowledgements

Financial support provided by the NIH (GM 86485) is warmly acknowledged. Assistance with physical analyses (AFM and cryo-TEM) provided by Mark Cornish and Stephan Krämer is warmly acknowledged. Technical help by Justin Smith is also much appreciated. We also warmly thank Johnson Matthey (Tom Colacot and co-workers) for providing the initial (DIPF)$NiCl_2$ used in this study, and Dr. John Reilly (Novartis, Cambridge) for obtaining the ICP data. NIH support in the form of a Shared Instrument Grant (1S10OD012077-O1A1) is greatly appreciated.

Keywords: cross-couplings · green chemistry · micelles · nanoparticles · nickel

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 11994–11998
Angew. Chem. **2015**, *127*, 12162–12166

---

[1] a) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062; *Angew. Chem.* **2012**, *124*, 5150; b) N. Wang, *Youji Huaxue* **2011**, *31*, 1319; c) B. Halford, *Chem. Eng. News* **2010**, *88*, 7; d) B. H. Lipshutz, N. A. Isley, J. C. Fennewald, E. D. Slack, *Angew. Chem. Int. Ed.* **2013**, *52*, 10952; *Angew. Chem.* **2013**, *125*, 11156; e) T. J. Colacot, *Platinum Met. Rev.* **2009**, *53*, 183; f) "New Trends in Cross-Couplings: Theory and Applications": T. Colacot, *RCS Catalysis Series* **2015**, can be found under http://pubs.rsc.org/en/content/ebook/9781849738965#!divbookcontent; g) J. Magano, S. Monfette, *ACS Catal.* **2015**, *5*, 3120.

[2] a) B. H. Lipshutz, T. B. Petersen, A. R. Abela, *Org. Lett.* **2008**, *10*, 1333; b) B. H. Lipshutz, A. R. Abela, *Org. Lett.* **2008**, *10*, 5329; c) N. A. Isley, F. Gallou, B. H. Lipshutz, *J. Am. Chem. Soc.* **2013**, *135*, 17707.

[3] For details, please see the NSF website, http://www.nsf.gov/pubs/2011/nsf11552/nsf11552.htm.
[4] a) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299; b) S. Handa, D. J. Lippincott, D. H. Aue, B. H. Lipshutz, *Angew. Chem. Int. Ed.* **2014**, *53*, 10658; *Angew. Chem.* **2014**, *126*, 10834.
[5] a) S. Saito, M. Sakai, N. Miyaura, *Tetrahedron Lett.* **1996**, *37*, 2993; b) S. Saito, S. Oh-tani, N. Miyaura, *J. Org. Chem.* **1997**, *62*, 8024; c) Review: F.-S. Han, *Chem. Soc. Rev.* **2013**, *42*, 5270.
[6] a) K. W. Quasdorf, A. Antoft-Finch, P. Liu, A. L. Silberstein, A. Komaromi, T. Blackburn, S. D. Ramgren, K. N. Houk, V. Snieckus, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 6352; b) S. D. Ramgren, L. Hie, Y. Ye, N. K. Garg, *Org. Lett.* **2013**, *15*, 3950; c) K. Huang, G. Li, W.-P. Huang, D.-G. Yu, Z.-J. Shi, *Chem. Commun.* **2011**, *47*, 7224.
[7] a) V. Percec, G. M. Golding, J. Smidrkal, O. Weichold, *J. Org. Chem.* **2004**, *69*, 3447; b) Y.-L. Zhao, Y. Li, S.-M. Li, Y.-G. Zhou, F.-Y. Sun, L.-X. Gao, F.-S. Han, *Adv. Synth. Catal.* **2011**, *353*, 1543.
[8] a) D.-G. Yu, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2011**, *50*, 7097; *Angew. Chem.* **2011**, *123*, 7235; b) M. Tobisu, T. Xu, T. Shimasaki, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 19505.
[9] R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417.
[10] M. Sera, M. Yamashita, Y. Ono, T. Tabata, E. Muto, T. Ouchi, H. Tawada, *Org. Process Res. Dev.* **2014**, *18*, 446.
[11] J.-C. Galland, M. Savignae, J.-P. Genet, *Tetrahedron Lett.* **1999**, *40*, 2323.
[12] S. Ge, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 12837; *Angew. Chem.* **2012**, *124*, 13009.
[13] N. H. Park, G. Teverovskiy, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 220.
[14] R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273.
[15] CCDC 1416412 (**17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: June 13, 2015
Revised: June 24, 2015