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Room-Temperature Suzuki–Miyaura Couplings in Water Facilitated by Nonionic Amphiphiles[†]

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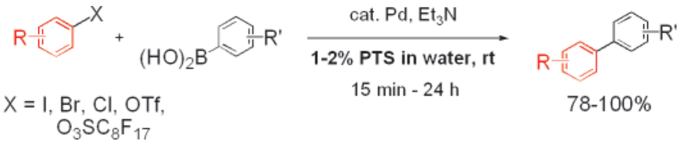
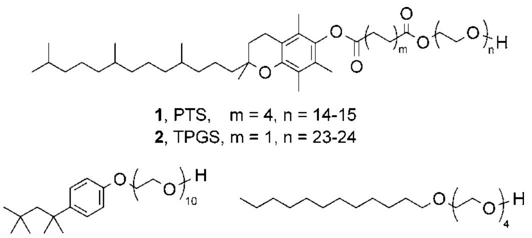
ABSTRACT



Use of a dilute aqueous solution containing a nonionic amphiphile allows efficient Suzuki–Miyaura cross-couplings of arylboronic acids with a wide array of aryl halides and pseudohalides, including sterically hindered and lipophilic substrates, in most cases at room temperature.

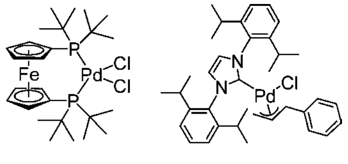
Minimization of chemical waste, of which 80% is estimated to be solvents,[1] is a constant challenge as environmental concerns are increasingly brought into focus. Much to the credit of synthetic chemists, the number of organic transformations that can be effected in an aqueous medium has blossomed over the past decade.[2] We recently disclosed that the nonionic, vitamin E-derived amphiphile PTS (*P*EG600-yl α-*T*ocopheryl *S*ebacate, **1**; Figure 1)[3] forms nanometer particles in water that can accommodate lipophilic substrates for use in Heck reactions.[4] Consequently, we have investigated the potential for aqueous solutions of **1**, as well as other nonionic surfactants (e.g., **2**−**4**), as reaction media for related palladium-catalyzed transformations. In this paper, Suzuki−Miyaura reactions are shown to proceed efficiently at room temperature, in water, without cosolvents, using only 1−2% (by mass) PTS in the presence of commercially available catalysts (Figure 2). Although such couplings[5] have traditionally been performed in the presence of water[5,6] several approaches have recently endeavored to increase percentages of this safe and economical solvent in reaction media.[1,7]



1, PTS, m = 4, n = 14-15
2, TPGS, m = 1, n = 23-24

3, Triton® X-100 **4**, Brij® 30

Figure 1. Nonionic surfactants used in this study.



5
$Pd(dtbpf)Cl_2$
(Johnson Matthey)

6
Neolyst™ CX31
(Umicore)

Figure 2. Palladium catalysts used in this study.

[†] Dedicated with greatest respect and admiration to Professor E. J. Corey, Nobel Laureate, on the occasion of his 80th birthday.

(1) Shaughnessy, K. H.; DeVasher, R. B. *Cur. Org. Chem.* **2005**, *9*, 585−604.

(2) (a) For a review, see: Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095−3165. (b) Beletskaya, I. P.; Cheprakov, A. V. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, NY, 2002; Vol. 2, pp. 2957−3006.

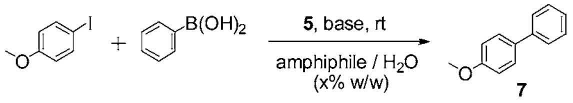
(3) Borowy-Borowski, H.; Sikorska-Walker, M.; Walker, P. R. U.S. Patent 6,045,826, Apr 2000.

(4) Lipshutz, B. H.; Taft, B. R. *Org. Lett.* **2008**, *10*, 1329−1332.

10.1021/ol702714y CCC: $40.75

Initially, reactions between 4-iodoanisole and phenylboronic acid in the presence of 2% catalyst **5**[8] (Figure 2) in 10% (w/w) aqueous PTS were investigated. While CsF (Table 1, entry 1) did not appear to be an effective base under these conditions, both K_3PO_4 and Et_3N gave promising results (entries 2 and 3). However, K_3PO_4 did not lead to the desired emulsion, making it difficult to monitor progress of the reaction. None of the reactions associated with entries 3, 4, and 7 in Table 1 showed any further conversion upon prolonged reaction times. A lower concentration of surfactant was therefore deemed favorable, although too low a concentration (entry 12) or its complete absence (entry 13) was detrimental. Consequently, 2% PTS in water (w/w) was selected for further studies. An aqueous solution of the closely related surfactant TPGS (**2**; Figure 1), which contains the 4-carbon (succinyl) linker and PEG-1000,[9] gave very similar results with this substrate (entry 9) compared to those obtained using PTS (which contains a 10-carbon, sebacyl linker with PEG-600). Complete consumption of the aryl iodide was also observed in sufficiently dilute solutions of Triton X-100 (**3**)[10] (entry 6 vs 10) and Brij 30 (**4**)[10] (entry 11), even though the latter did not result in an emulsion. Isolated yields, however, were somewhat lower using either of these two surfactants. It should also be noted that using Et_3N as solvent does result in biaryl formation, although the conversion is low (entry 14).

Table 1. Survey of Amphiphiles To Be Used in Suzuki−Miyaura Reactions in the Presence of Catalyst **5**^{a}

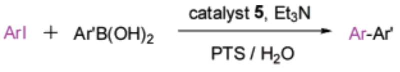


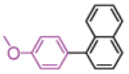
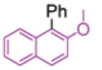
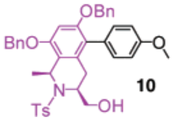
entry	x	amphiphile	base	t (h)	conv^{b} (%)	yield^{c} (%)
1	10	PTS^{d}	CsF	24	19	nd^{e}
2	10	PTS^{f}	K_3PO_4	24	80	nd
3	10	PTS^{d}	Et_3N	6	87	nd
4	15	PTS^{d}	Et_3N	6	78	nd
5	15	PEG-400^{f}	Et_3N	6	79	nd
6	15	Triton X-100^{d}	Et_3N	6	79	nd
7	5	PTS^{d}	Et_3N	6	93	nd
8	**2**	**PTS^{d}**	**Et_3N**	**6**	**96**	**96**
9	2	TPGS^{d}	Et_3N	2	100	92
10	2	Triton X-100^{d}	Et_3N	6	100	84
11	2	Brij 30^{f}	Et_3N	6	100	80
12	1	PTS^{f}	Et_3N	6	76	nd
13	0	(only water)^{f}	Et_3N	6	75	nd
14	0	(no water)^{g}	Et_3N	12	15	nd

^{a} General conditions: rt, iodoanisole (1.00 mmol), phenylboronic acid (1.50 mmol), **5** (0.02 mmol), base (3.00 mmol), aqueous amphiphile solution (2 mL). ^{b} Conversion monitored by GC. ^{c} Isolated. ^{d} Emulsion throughout the reaction. ^{e} nd = not determined. ^{f} Solids clumped. ^{g} Et_3N as solvent.

The optimized conditions from the data in Table 1 (entry 8: 2% PTS in water, 2% catalyst **5**, 3 equiv Et_3N, rt) were generally applicable to several aryl iodides (Table 2) and bromides (Table 3). One highly functionalized example (Table 2, entry 3), however, required a slightly elevated temperature (50 °C) and longer reaction time to reach completion.

Table 2. Suzuki−Miyaura Reactions of Aryl Iodides^{a}



entry	biaryl product	t (h)	yield^{b} (%)
1	 **8**	7	89
2	 **9**	9	93
3^{c}	 **10**	44	88

^{a} General conditions: rt, aryl iodide (1.00 mmol), arylboronic acid (1.50 mmol), **5** (0.02 mmol), Et_3N (3.00 mmol), aqueous PTS solution (2% w/w, 2 mL). ^{b} Isolated. ^{c} At 50 °C, aryl iodide (77 μmol), arylboronic acid (138 μmol), **5** (5 μmol), Et_3N (360 μmol), aqueous PTS solution (5% w/w, 2 mL).

Cross-couplings of sterically hindered aryl bromides (Table 3, entries 5, 6, 10, and 11) proceeded readily, although coupling between a diortho-substituted bromide and a diortho-substituted arylboronic acid could not be realized. Distinctly lipophilic aryl bromides (entries 6−12), a class of substrates noticeably absent in many other studies involving aqueous Suzuki−Miyaura reactions, also work well. Brief sonication (ca. 2 min) immediately following setup may be needed (e.g., entries 9 and 10) to enhance mixing of initially aggregated solids. Triton X-100 in some cases affords yields that are very similar to those realized with PTS, as highlighted by entries 10 and 11. Although we did not extensively investigate use of potassium aryltrifluoroborates[11] as alternatives to boronic acids, results from one case (Scheme 1) suggest that they can be used under our general conditions.

Reactions in PTS/H_2O with aryl chlorides show the expected drop in reactivity compared with that of iodides and bromides. Literature methods that offer considerable scope and mildness of reaction conditions have accrued of

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(5) For reviews, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(6) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59.

(7) For recent contributions, see: (a) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173−6177. (b) Kumar, N. S. C. R.; Raj, I. V. P.; Sudalai, A. *J. Mol. Catal. A Chem.* **2007**, *269*, 218−224.

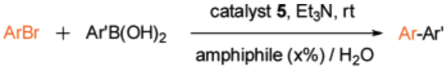
(8) Colacot, T. J.; Shea, H. A. *Org. Lett.* **2004**, *6*, 3731−3734 and references cited therein.

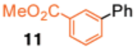
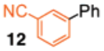
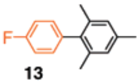
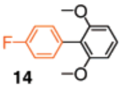
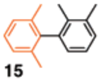
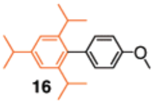
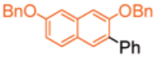
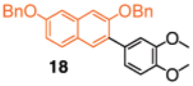
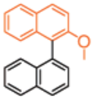
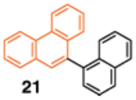
(9) PCI-102B Eastman Vitamin E TPGS NF. For applications and properties, see http://www.eastman.com/NR/rdonlyres/A2FE037B-0778-4A90-A0FC-5D07BE51064A/0/PCI102.pdf (accessed October 2007).

(10) Triton X-100: CAS no. 9002-93-1. Brij 30: CAS no. 9002-92-0.

(11) (a) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275−286 and references cited therein. (b) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288−325.

Table 3. Suzuki−Miyaura Reactions of Aryl Bromides[a]



entry	biaryl product	x	surf.	t (h)	yield[b] (%)
1	 **11**	2	**1**	0.25	95
2	 **12**	2	**1**	2	78
3	 **13**	2	**1**	2.5	96
4	 **14**	2	**1**	23	99
5	 **15**	2	**1**	5	85
6[c]	 **16**	2	**1**	24	76
7[d]	 **17**	1	**1**	24	85
8[d]	 **18**	2	**1**	20	80
9[d,e]	 **19**	2	**1**	7	83
10[e]	 **20**	2	**1**	24	99
11		2	**3**	24	100
12[c]	 **21**	2	**1**	24	78

[a] General conditions: rt, aryl bromide (0.50 or 1.00 mmol), arylboronic acid (1.50 equiv), **5** (2 mol %), Et$_3$N (3.00 equiv), aqueous amphiphile (2 mL/mmol aryl bromide). [b] Isolated. [c] 2.00 equiv of arylboronic acid. [d] 4 mL of aqueous amphiphile/mmol aryl bromide. [e] Sonicated briefly at setup.

Scheme 1. Use of a Trifluoroborate Salt in PTS/H$_2$O

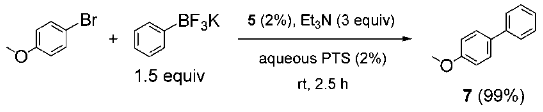
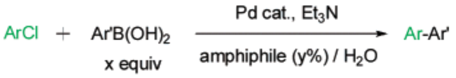
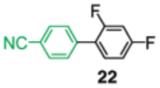
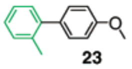
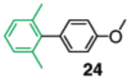
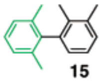
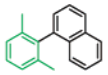
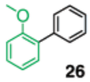
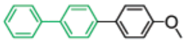


Table 4. Suzuki−Miyaura Couplings of Aryl Chlorides



entry	x	biaryl product	cat.	y	surf.	T (°C)	t (h)	yield[a] (%)
1[b]	2.0	 **22**	**5**	2	**1**	23	22	96
2[b]	2.0		**5**	2	**2**	23	22	76
3[b]	2.0		**5**	2	**3**	23	22	87
4[c]	1.5	 **23**	**5**	1	**1**	23	24	85
5[c]	2.0	 **24**	**5**	1	**1**	50	24	82
6[c]	2.0		**6**	1	**1**	23	11	99
7[c]	2.0	 **15**	**5**	1	**1**	50	24	28
8[b]	2.0		**6**	1	**1**	23	4	98
9[b]	2.0		**6**	0.1	**1**	23	24	97
10[b]	2.0	 **25**	**6**	1	**1**	23	24	90
11[b]	1.5		**6**	0.1	**1**	23	24	100
12[b]	2.0	 **26**	**6**	1	**1**	50	6	100
13[b]	1.5	 **27**	**6**	1	**1**	23	8	93
14[b]	1.5		**6**	0.1	**1**	50	24	84

[a] Isolated. [b] 2 mL of aqueous surfactant/mmol aryl chloride. [c] 4 mL of aqueous surfactant/mmol aryl chloride.

late, and today both electron-rich and sterically hindered aryl chlorides can be coupled at room temperature.[12,13] However, to the best of our knowledge, no known method has been reported for the cross-coupling of aryl chlorides, in particular hindered systems, without cosolvents in water at room temperature.

Using 4-chlorobenzonitrile as a test case, we found the more challenging, electron-poor 2,4-difluorophenylboronic acid could be coupled most effectively under the influence of 2% PTS (Table 4, entries 1−3). On the other hand, the reaction between 2-chlorotoluene and 4-methoxyphenylboronic acid (entry 4) proceeded to completion employing only 1% (w/w) aqueous PTS. Cross-coupling of 2-chloro-1,3-dimethylbenzene with 4-methoxyphenylboronic acid (entry 5) required a slightly elevated temperature to complete. With 2,3-dimethylphenylboronic acid (entry 7), neither of these adjustments were sufficient to drive the reaction with this aryl chloride to completion. Gratifyingly, it was found that switching from the phosphine-ligated catalyst **5** to the *N*-heterocyclic carbene-ligated catalyst **6**[13] (Figure 2) led to efficient cross-coupling between arylboronic acids and aryl chlorides at ambient temperatures (Table 4, entries 6, 8−11, and 13). Surprisingly, under otherwise identical conditions, catalyst **6** does not satisfactorily mediate reactions between aryl bromides and arylboronic acids.[14] While electron-rich aryl chlorides, in particular, are notoriously difficult substrates, 2-chloroanisole furnished 2-methoxybiphenyl in quantitative yield, albeit at a slightly elevated temperature (entry 12). Most substrates, nonetheless, couple efficiently

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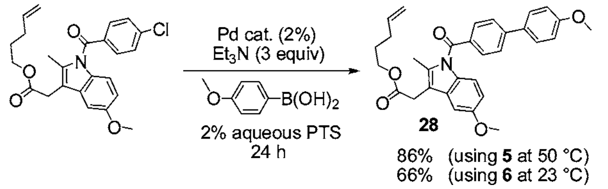
[12] (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (b) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195−15201. (c) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194−16195.

[13] Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101−4111 and references cited therein.

[14] Using catalyst **6** under otherwise identical conditions, aryl bromides showed poor conversion to the corresponding biaryl products: **13** (27%), **14** (39%), **16** (21%), and **21** (43%), as indicated by GC.

at room temperature in this aqueous medium using as low as 0.1% PTS (entries 9 and 11). More lipophilic aryl chlorides, such as the pentenyl ester of indomethacin, may require gentle heating en route to biaryl **28** (Scheme 2).

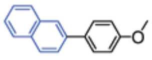
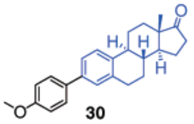
Scheme 2. Coupling of the Pentenyl Ester of Indomethacin



The option to use pseudohalides as substrates in Suzuki−Miyaura reactions has also been evaluated under these aqueous conditions. The triflate of β-naphthol was found to react readily under the same conditions (2% PTS/water, 2% catalyst **5**) used with halides (cf. Tables 1−4) to afford the corresponding biaryl product in good yield (Table 5, entry 1). Promising alternatives to triflates are the longer chain fluorosulfonates, such as nonaflates and perfluorooctylsulfonates. The latter, which have not commonly been used in this context,[15] are particularly appealing. Not only are they expected to show somewhat higher reactivity relative to aryl nonaflates,[16] but their precursor, perfluorooctylsulfonyl fluoride, is attractively priced.[17] The coupling of β-naphthyl perfluorooctylsulfonate proceeds smoothly at room temperature to afford **29** in excellent yield. Both fluorosulfonates derived from estrone, however, are totally unreactive in the presence of catalyst **5** in this aqueous medium, even at elevated temperatures. Again, switching to the NHC-containing alternative **6** readily catalyzed the cross-coupling of the triflate in good isolated yield (Table 5, entries 5 and 6).

Table 5. Suzuki−Miyaura Reactions of Aryl Fluorosulfonates[a]

$$R^FSO_3Ar + Ar'B(OH)_2 \xrightarrow[\text{amphiphile (2\%) / H}_2\text{O}]{\text{Pd cat., Et}_3\text{N}} Ar\text{-}Ar'$$

entry	R^F	biaryl product	cat.	T (°C)	t (h)	yield[b] (%)
1	CF_3	 **29**	**5**	23	2.5	81
2[c]	n-C_8F_{17}		**5**	23	2.5	95
3	CF_3	 **30**	**5**	50	24	0
4[c]	n-C_8F_{17}		**5**	50	24	0
5	CF_3		**6**	23	18	67
6	CF_3		**6**	50	24	90

[a] General conditions: aryl fluorosulfonate (0.50 mmol), arylboronic acid (0.75 mmol), Pd cat. (0.01 mmol), Et_3N (1.50 mmol), aqueous PTS solution (2% w/w, 1 mL). [b] Isolated. [c] 2 mL of aqueous PTS solution.

In summary, dilute aqueous solutions of nonionic amphiphiles have been shown to serve well in water-based media for Suzuki−Miyaura reactions at ambient temperatures. Of the various amphiphiles studied, on the basis of the data obtained to date, commercially available[18] PTS appears to offer the best opportunities for success in such cross-couplings, although other surfactants can, on occasion, be equally as effective. Reaction scope includes lipophilic aryl fluorosulfonates, aryl iodides, and aryl bromides catalyzed by the commercially available dppf analogue **5**. In the presence of **6**, likewise a commercially available catalyst, sterically hindered aryl chlorides and aryl fluorosulfonates are suitable reaction partners. Product isolation uses standard (extractive) workup procedures (see below[19] and the Supporting Information). We are currently investigating application of this technology to the synthesis of heteroaromatic biaryls; results will soon be reported.

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Supporting Information Available: Detailed experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) To the best of our knowledge, the only publication describing the use of aryl perfluorooctylsulfonates in Suzuki−Miyaura cross-couplings: Zhang, W.; Chen, C. H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473−1476.

(16) Based on the reactivity differences observed between triflates and nonaflates; see: Högermeier, J.; Reissig, H.-U. *Chem. Eur. J.* **2007**, *13*, 2410−2420 and references cited therein.

(17) n-$C_8F_{17}SO_2F$ is available for $165/mol (100 g). On that scale, $(CF_3SO_2)_2O$ sells for $237/mol and n-$C_4F_9SO_2F$ costs $256/mol. When purchasing 1 kg, the price drops to $127/mol and $145/mol, respectively, for the latter two. However, SciFinder gives no price quote for n-$C_8F_{17}SO_2F$ on that scale.

(18) Sigma-Aldrich catalog #698717; available in May, 2008.

(19) (a) **Standard procedure for Suzuki-Miyaura in PTS/water. 4-Methoxy-2′-methylbiphenyl** (**23**; Table 4, entry 4). To a 5 mL round-bottom flask was added a 15 mm long prolate spheroid magnetic stir bag. **5** (6 mg, 0.009 mmol), and 4-methoxyphenylboronic acid (114 mg, 0.75 mmol). Under a positive flow of argon while stirring were added each via syringe Et_3N (0.21 mL, 1.5 mmol), aqueous PTS (1% w/w, 2 mL), and 2-chlorotoluene (60 μL, 0.51 mmol). The reaction was stirred at rt and conversion was monitored by GC. After 24 h the contents of the flask were diluted with brine and extracted three times with ethyl acetate. The solution obtained was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The solid residue was purified by flash chromatography eluting with a gradient from 1/99 to 5/95 diethyl ether/petroleum ether to afford the product biaryl (86 mg, 85%) as a white solid; ^1H NMR (400 MHz, $CDCl_3$) matches previously reported spectral data. (b) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058−3059.