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Micellar Catalysis of Suzuki−Miyaura Cross-Couplings with Heteroaromatics in Water

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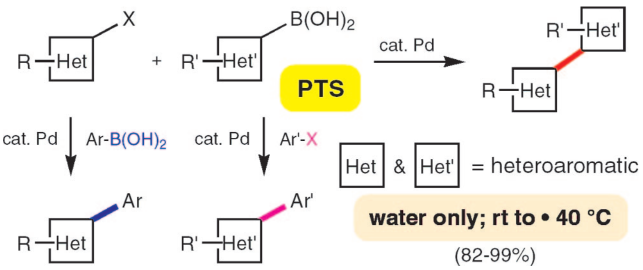
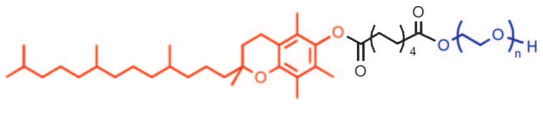
ABSTRACT



Pd-catalyzed couplings involving several heteroaromatic halides (bromides and chlorides) as well as boronic acids can be done under exceedingly mild conditions (between rt and 40 °C) in pure water using commercially available Pd catalysts and PTS, a nanomicelle-forming amphiphile.

The nanomicelle-forming, commercially available amphiphile PTS (polyoxyethanyl α-tocopheryl sebacate, **1**, Figure 1)[1] was recently introduced as a contribution to green chemistry;[2] that is, as an enabling technology that facilitates several transition-metal-catalyzed cross-coupling reactions at room temperature in water as the only solvent.[3a−c] Included among this group are Suzuki−Miyaura reactions between aryl halides or pseudohalides and arylboronic acids. The success of these Pd-catalyzed processes, which also featured biaryl syntheses from aryl chlorides, suggested that still more challenging heteroaromatic precursors as either or both reaction partners might be amenable to this micellar catalysis. Since heteroaromatic biaryls are especially valued in the pharmaceutical arena,[4] and with significant attention being paid of late to construction of such arrays,[5] a broad-based study has been conducted using aqueous PTS in the absence of cosolvents. We now present results suggestive of the scope and limitations of this technology based on



1, **PTS** (n = *ca.* 13; MW *ca.* 1200)

Figure 1. PEG-α-tocopheryl sebacate (PTS). PEG = blue; α-tocopheryl = red; sebacate = black.

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(1) Sigma Aldrich catalog no. 698717.

(2) Sheldon, R. A.; Ardens, I.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, Germany, 2007.

(3) (a) Lipshutz, B. H.; Petersen, T. B.; Abela, A. R. *Org. Lett.* **2008**, *10*, 1333–1336. (b) Lipshutz, B. H.; Taft, B. R. *Org. Lett.* **2008**, *10*, 1329–1332. (c) Lipshutz, B. H.; Chung, D. W.; Rich, B. L. *Org. Lett.* **2008**, *10*, 3793–3796. (d) Lipshutz, B. H.; Aguinaldo, G. T.; Ghorai, S.; Voigtritter, K. *Org. Lett.* **2008**, *10*, 1325–1328. (e) Lipshutz, B. H.; Ghorai, S.; Aguinaldo, G. T. *Adv. Synth. Catal.* **2008**, *350*, 953–956.

(4) (a) Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nat. Rev. Drug Discovery* **2002**, *1*, 493–502. (b) Boren, J.; Cascente, M.; Marin, S.; Comin-Anduix, B.; Centelles, J. J.; Lim, S.; Bassilian, S.; Ahmed, S.; Lee, W. N.; Boros, L. G. *J. Biol. Chem.* **2001**, *276*, 37747–37753.

(5) (a) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366. (b) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104–5112. (c) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282–1284.

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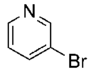
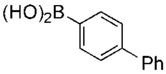
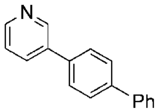
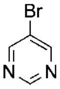
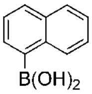
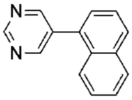
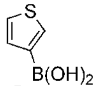
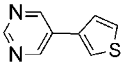
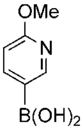
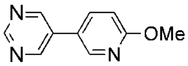
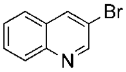
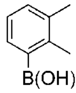
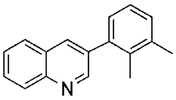
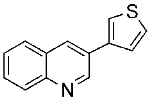
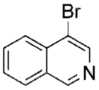
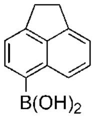
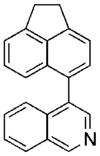
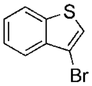
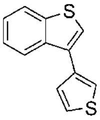
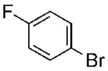
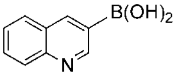
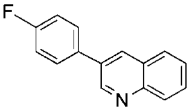
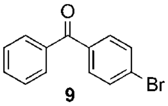
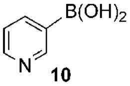
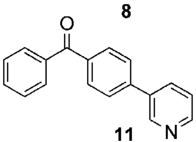
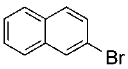
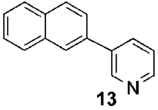
Table 1. Cross-Couplings of Aryl/Heteroaryl Bromides with Aryl/Heteroaryl Boronic Acids Using Catalyst **3** in 2% PTS/Water[a]

entry	Ar-X	Ar-B(OH)$_2$	product	temp. (°C)	time (h)	yield (%)[b]
1				rt	20	82[c]
2		(A) 		rt	6	96
		(B)  **5**		rt	6	99
		(C) 		rt	16	95
3		(A) 		rt	10	86
		(B) **5**		rt	7	97
4		 **6**		40	4	99[c]
5		**5**		rt	16	97
6	 **7**		 **8**	40	9	95
7	 **9**	 **10**	 **11**	40	6	91
8	 **12**	**10**	 **13**	40	12	90

[a] Standard conditions (unless otherwise noted): 0.5 M solution of aryl/heteroaryl bromide stirred in a 2% w/w PTS/water solution with 0.02 equiv of **3**, 3.0 equiv of Et$_3$N, and 2.0 equiv of boronic acid at the indicated temperature and time. [b] Isolated yield. [c] 1.5 equiv of boronic acid was used.

several representative heteroaromatic bromides and chlorides as well as heteroaromatic boronic acids.

Catalysts **2** and **3** (Figure 2; 2%) were chosen on the basis of their use in prior studies.[3a,5b] Typically, 1−2% PTS in pure water was sufficient; attempts at higher loading (3%) offered no advantage, and conversions were somewhat lower under otherwise identical conditions. In the absence of PTS, conversions were also lower. It has already been established that the corresponding “on water”[6] reactions do take place but to highly variable degrees and, in these cases, are seemingly not competitive.[3] Several heteroaryl bromides

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(6) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolib, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.

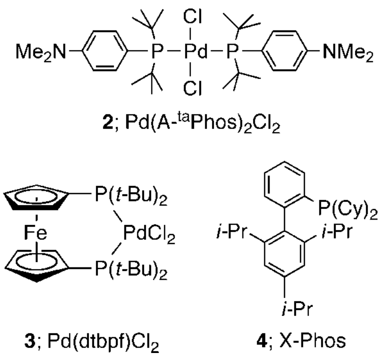


Figure 2. Catalyst complexes and ligands used in this study.

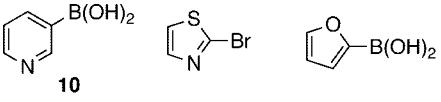
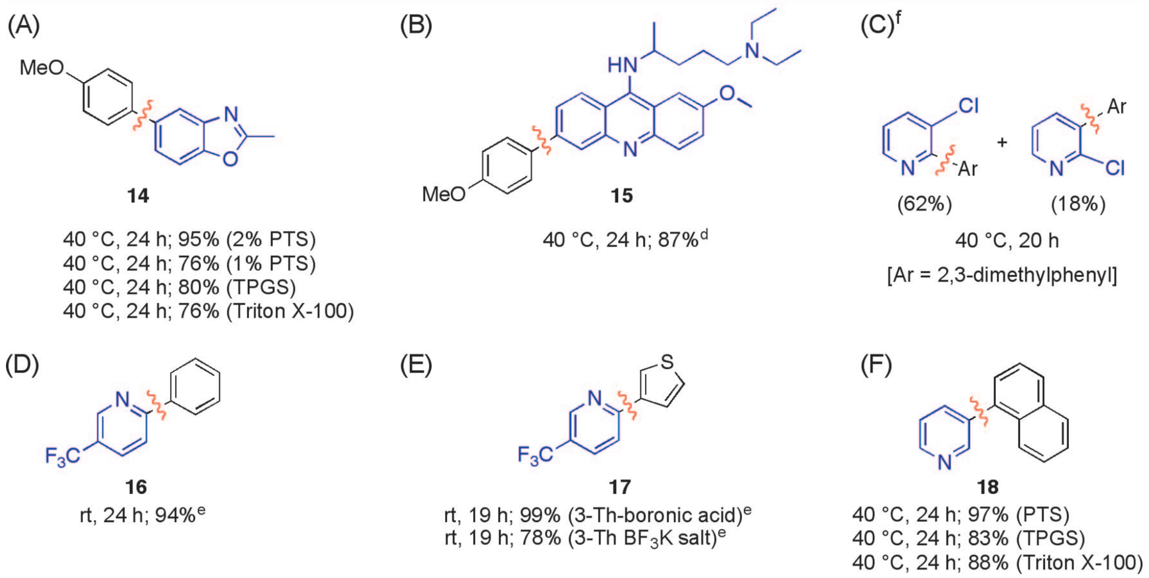


Figure 3. Coupling partners that may lead to low conversions.

were screened, as shown in Table 1, including 3-pyridyl (entry 1), 5-pyrimidyl (entry 2), 3-quinolyl (entry 3), 4-isoquinolyl (entry 4), and 3-benzothiophenyl (entry 5) derivatives. Combinations with both aryl and heteroaryl boronic acids led to high isolated yields within a 4−20 h time frame, used mainly at room temperature. Aryl bromides **7**, **9**, and **12** (entries 6−8), likewise, led to biaryls **8**, **11**, and **13**, respectively, under related conditions, although mild heating to 40 °C was needed due to the lower reactivity of these boronic acids. Overall, isolated yields can be expected to be quite good. Some combinations, however, were problematic (Figure 3), such as the case of 3-pyridylboronic acid (**10**) with heteroaryl bromides (low conversions; compare with Table 1, entries 7 and 8); 2-bromothiazole, with aromatic boronic acids (no greater than 70% conversion with various ligands, temperatures, and times), and 2-furylboronic acid (with either aromatic or heteroaromatic bromides; ≤10% conversion).

Heteroaromatic chlorides were particularly difficult to couple, even when using nonheteroaromatic boronic acids. As illustrated in Table 2, most required heating to 40 °C, a switch to ligand **2**, and reaction times approaching 1 day. Highest levels of conversion were realized, again, using 2% PTS. For example (entry A), lower conversions and consequently lower isolated yields of product biaryl **14** were observed with 1% PTS, while full conversion occurred at 40 °C in the presence of 2% PTS/H_2O. Quinacrine derivative **15** (entry B) was smoothly prepared using *p*-anisylboronic acid, but the corresponding coupling with 3-thienylboronic acid (**5**; see Table 1) or acid **6** failed under otherwise identical conditions. 2,3-Dichloropyridine selectively coupled with 2,3-dimethylboronic acid at the 2-position, but the 3-arylated was also formed (18%) in a combined yield of 80% (entry C; no bis-adduct was seen). Two biaryl products **16** and **17** resulting from cross couplings at rt with 2-chloro-5-trifluoromethylpyridine were each formed in high yield (entries D

Table 2. Couplings with Heteroaryl Chlorides (in blue) Using Catalyst **2** in PTS/Water[a−c]



[a] Standard reaction conditions (unless otherwise noted): 0.5 M solution of aryl/heteroaryl chloride in 2% w/w PTS/water with 0.02 equiv of **2**, 3.0 equiv of Et_3N, and 2.0 equiv of boronic acid at the indicated temperature and time. [b] All yields isolated. [c] All surfactants used as 2% w/w solutions in water unless otherwise noted. [d] Precursor chloride used as the commercially available $2H_2O$, 2HCl salt under the following conditions: 0.2 M solution of heteroaryl chloride in 2% PTS/water, using 5.0 equiv of Et_3N. [e] 1% w/w PTS/water solution used. [f] 1 equiv of boronic acid.

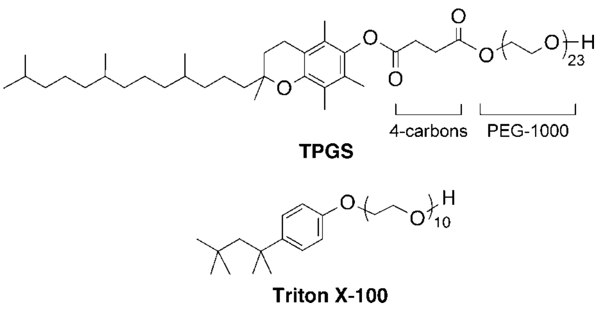


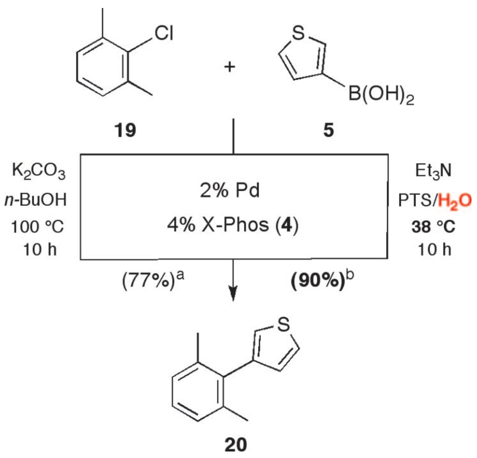
Figure 4. Other surfactants used as comparisons.

and E). Thiophene derivative **17** could be made at 25 °C from either the boronic acid or trifluoroborate salt[7] as coupling partner.

Comparisons as to the effectiveness of PTS as surfactant with two other common, nonionic amphiphiles, can be made en route to products **14** and **18**: (1) the (structurally) closely related TPGS[8] and (2) the traditional 2-component species Triton X-100[9] (Figure 4). The results show a similar trend noted previously for Pd-catalyzed (Heck[3b] and Suzuki–Miyaura[3a]) and Ru-mediated olefin metathesis (CM[3d] and RCM[3e]) reactions. That is, while other surfactants "work" to varying degrees, in general, PTS appears to provide a hydrophilic lipophilic balance (HLB)[10] and particle size that best accommodates both educts and catalysts.

The potential for these reactions to take place under green conditions is further demonstrated by direct comparison of the coupling between sterically demanding and electronically deactivated aryl chloride **19** and 3-thiophenylboronic acid **5** (Scheme 1). Thus, in lieu of an organic solvent, several equivalents of inorganic salt as base, and 100 °C heating,[5a] micellar PTS leads to the desired heterobiaryl **20** in water, using volatile triethylamine as base, and very gentle heating to only 38 °C. The isolated yield of biaryl **20** (90%) also compares favorably with the reported level of efficiency.[5a]

Scheme 1



[a] Isolated yield reported by Buchwald et al.[5a] using $Pd_2(dba)_3$ as precatalyst and 1.5 equiv of **5**. [b] Isolated yield using $Pd(OAc)_2$ as precatalyst and 2.0 equiv of **5** in 2% PTS/water.

In summary, a variety of water-insoluble heteroaromatic coupling partners are amenable to Suzuki–Miyaura cross-couplings under very mild conditions (rt up to 40 °C) using PTS technology. This approach offers an important environmentally sound alternative in our efforts toward removing organic solvents from organic reactions.

Acknowledgment. Financial support provided by Zymes, LLC is warmly acknowledged. Catalysts **2** and **3** were generously provided by Johnson Matthey.

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

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

(8) 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 June 2008).

(9) Triton X-100: CAS registry no. 9002-93-1.

(10) Pasquali, R. C.; Taurozzi, M. P.; Bregni, C. *Int. J. Pharm.* **2008**, *356.*, 44–51.