

Heck Couplings at Room Temperature
in Nanometer Aqueous Micelles[†]

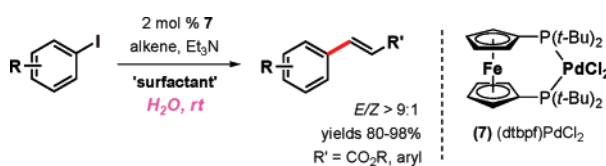
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ABSTRACT



A nonionic amphiphile such as Triton X-100 or the vitamin E-based PTS, both of which form nanomicelles in water, promotes Heck cross-couplings of non-water-soluble partners at ambient temperatures. These are the first examples of Heck reactions conducted in water (as the only solvent) at room temperature.

Ideally, organic synthesis would be performed at ambient temperature in water as the only solvent. Catalyzed reactions would allow facile product isolation using recoverable organic solvents, while the aqueous phase containing the active catalyst would be recyclable. Such concepts broadly applied to organometallic chemistry, in general, may be far from reality, although considerable efforts to identify such processes on a reaction-by-reaction basis are ongoing, and a great deal of progress has been made.¹ One approach is to consider inexpensive amphiphiles as potential additives that, upon self-assembly into micelles, accommodate otherwise insoluble organic substrates and catalysts within the lipophilic cores.² Although ostensibly a dilute solution in water, the effective concentration within the micelle could be quite high, and hence, reaction rates might be increased relative to those normally observed in organic media. While these concepts are well-grounded in micellar catalysis,² there are many parameters that must be “matched” to the reaction under study. With respect to Heck couplings in particular,³

factors such as (1) the nature of the surfactant (cationic, anionic, or nonionic), (2) palladium catalyst, and (3) base must be controlled in the search for an effective aqueous milieu. Existing methods in water require considerable heating in the absence of cosolvents.⁴ Herein we describe the use of selected nonionic micelle-forming carriers that allow, for the first time, Heck cross-couplings to be run at room temperature, in water as the only solvent.

A survey was conducted of several commercially available nonionic amphiphiles, including Triton X-100^{5a} (1), Brij-30^{5b} (2), and TPGS⁶ (3, *m* ≈ 21). Also included were known species PTS⁷ (4, *m* ≈ 13) and PSS⁷ (5), as well as the common salt SDS^{5c} (6) (Figure 1). Heck couplings between lipophilic aryl iodides and acrylates, using Et₃N as base,

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

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(5) Sigma-Aldrich catalog #'s (a) 234729, (b) P4391, (c) L3771.

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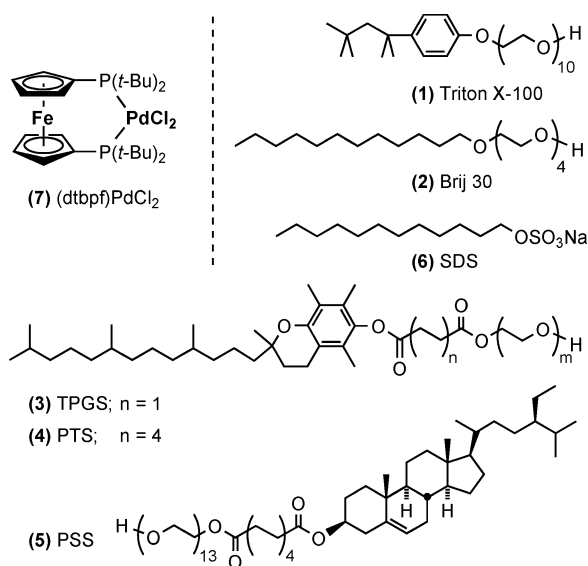
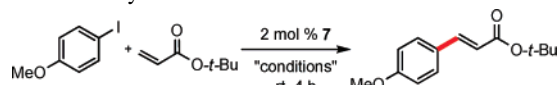


Figure 1. Various amphiphiles studied and catalyst used.

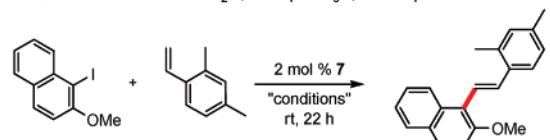
could most successfully be carried out using either Triton X-100 or more generally, PTS.

As indicated in Table 1, PTS (entry 1) was somewhat more effective than Triton X-100 (entry 2). When run “on water”⁸ (entry 7), a surprising (albeit substrate-dependent; vide infra)

Table 1. Survey of Reaction Conditions



entry	conditions	GC conversion (%)
1	15 wt % PTS/H ₂ O, 3.0 equiv Et ₃ N	91
2	15 wt % Triton X-100/H ₂ O, 3.0 equiv Et ₃ N	81
3	15 wt % PEG 400/H ₂ O, 3.0 equiv Et ₃ N	68
4	15 wt % PSS/H ₂ O, 3.0 equiv Et ₃ N	64
5	15 wt % SDS/H ₂ O, 3.0 equiv Et ₃ N	73
6	15 wt % TPGS/H ₂ O, 3.0 equiv Et ₃ N	80
7	Pure H ₂ O, 3.0 equiv Et ₃ N	84
8	3.0 equiv Et ₃ N	2
9	DMF, 3.0 equiv Et ₃ N	9
10	pH-10 Buffer	4
11	15 wt % PTS/pH-10 Buffer	12
12	2 wt % PTS/H ₂ O, 3.0 equiv Et ₃ N	25
13	2 wt % PTS/Saline, 3.0 equiv Et ₃ N	75
14	5 wt % PTS/H ₂ O, 3.0 equiv Et ₃ N, 5 % LiBF ₄	73
15	5 wt % PTS/H ₂ O, 3.0 equiv Et ₃ N, 5 % dtbpf	75



entry	conditions	GC conversion (%)
16	15 wt % PTS/H ₂ O, 3.0 equiv Et ₃ N	80
17	15 wt % TX-100/H ₂ O, 3.0 equiv Et ₃ N	99
18	15 wt % PSS/H ₂ O, 3.0 equiv Et ₃ N	34
19	15 wt % TPGS/H ₂ O, 3.0 equiv Et ₃ N	18
20	15 wt % SDS/H ₂ O, 3.0 equiv Et ₃ N	58
21	Pure H ₂ O, 3.0 equiv Et ₃ N	15

level of conversion was observed.⁹ PEG-400 in water (entry 3) was less effective. Several other control reactions served to highlight the crucial role of the surfactant. Thus, reactions run in neat Et₃N (entry 8) or in DMF with Et₃N (entry 9), indicated that the added base is not functioning as solvent and that the corresponding reaction in a purely organic medium does not occur at room temperature, as expected.^{10d} Results using pH 10 buffer alone (entry 10), or PTS/H₂O + pH 10 buffer (entry 11), suggest that an aqueous basic medium is problematic. When using 15 wt % of PTS solutions, strong, vigorous stirring is required to ensure adequate mixing. Reactions conducted in 2 wt % of PTS led to better mixing but marginal product formation (entry 12). The decrease in conversion was attributed to a lack of catalyst stability, as black and purple solids precipitated from the reaction mixture. In an attempt to increase catalyst lifetime, various additives were used (entries 13–15), but ultimately, the level of conversion was unsatisfactory.

Interestingly, when a more sterically hindered aryl iodide was employed under similar conditions, several differences were noted. In this case, Triton X-100 out-performed all other amphiphiles (entry 17), while PTS led to a somewhat slower but still effective coupling (entry 16). Most notably, the reaction conducted “on water”⁹ produced only a limited amount of the desired stilbene (entry 21). This data suggests that such reactions run in the absence of surfactant can be substrate-dependent.¹¹

Use of commercially available Johnson-Matthey catalyst (dtbpf)PdCl₂¹² (7; Figure 1) proved to be the most effective of those screened to date (Pd(OAc)₂, PdCl₂, or Pd(dba)₂ with bispophine). By simply taking a preformed solution of PTS in water (15 wt %; “stored on the benchtop”) and adding 2 mol % of (dtbpf)PdCl₂ (7), Et₃N (3 equiv), aryl iodide (1 equiv), and acrylate (2 equiv), Heck couplings take place, in general, at room temperature with reaction times ranging from 1 to 24 h. A typical reaction mixture appears heterogeneous during the first 20–30 min but becomes pseudo-homogeneous thereafter (Figure 2). Product isolation is straightforward following a standard extractive workup or filtration through a pad of silica gel (see the Supporting Information).

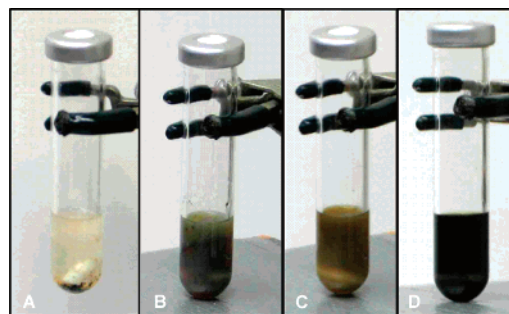
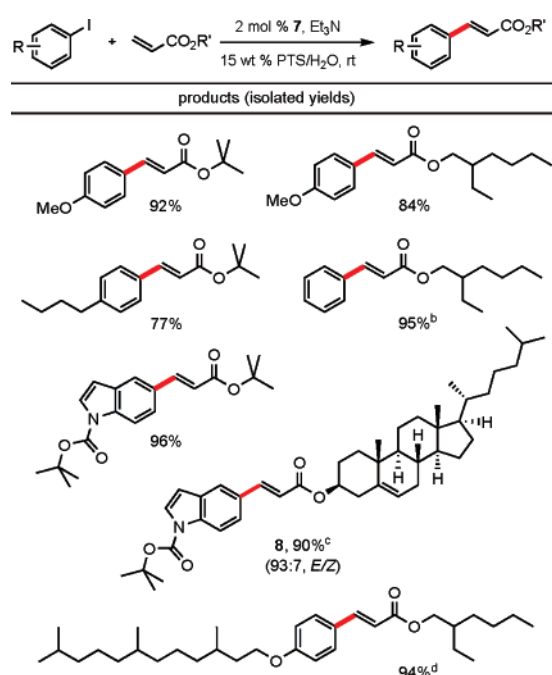


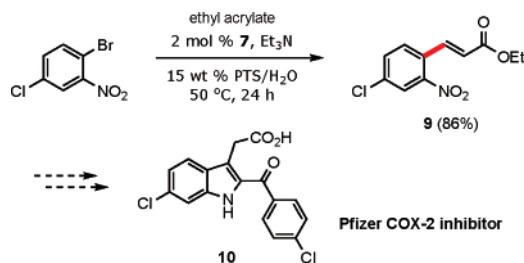
Figure 2. Appearance of a Heck coupling (Table 1, entry 1): (A) *t* = 0, note heterogeneous appearance; (B) *t* = 1 min; (C) *t* = 30 min, note pseudo-homogeneous appearance; (D) *t* = 3 h.

Table 2. Heck Couplings of Aryl Iodides with Acrylates^a

^a Reactions carried out at rt for 3–8 h using aryl iodide (1 equiv), acrylate (2 equiv), triethylamine (3 equiv), (**7**) (2 mol %), and 15 wt % of PTS/H₂O (~0.5 M). ^b Product was inseparable from excess acrylate. ^c Aryl iodide (2 equiv) and acrylate (1 equiv). ^d Run at 50 °C.

A more extensive survey of Heck couplings in 15 wt % of PTS/water¹³ is presented in Table 2, featuring isolated yields for (*E*)-cinnamates using acrylates as cross-coupling partners. Commercially available *tert*-butyl and 2-ethylhexyl acrylate appear to be more effective than less lipophilic methyl and benzyl ester analogues. “Greasy” aryl iodides and acrylates were chosen as substrates to emphasize the solubilizing power of PTS in water. Notably, highly lipophilic cholesteryl acrylate is compatible with these aqueous conditions, leading to highly functionalized indole derivative **8**.

To expand the scope of this method, initial attempts were made to couple aryl bromides¹⁰ at room temperature.¹⁴ As

Scheme 1. Heck Coupling of an Aryl Bromide¹⁵

expected, the reactions are more sluggish, likely due to the nature of substitution on the aromatic ring. Efforts to increase rates using various additives (e.g., NaCl, LiCl, NaBr, NH₄BF₄, B(OH)₃, Zn⁰, LiI, NaI, and TBAI) met with limited success. By simply warming to 50 °C, however, reactions take place. To highlight the potential for mild, aqueous Heck couplings with aryl bromides, 4-chloro-2-nitrobromobenzene was coupled to ethyl acrylate yielding cinnamate¹⁵ **9**, a known intermediate en route to Pfizer's COX-2 inhibitor¹⁶ **10** (Scheme 1).

Table 3. Heck Couplings of Aryl Iodides with Styrenes^a

entry	aryl iodide	R'	product	yield(%) ^b
1		4-F		94 (9:1, <i>E/Z</i>)
2		4-OMe		96 (9:1, <i>E/Z</i>)
3		4-OMe		97 (93:7, <i>E/Z</i>)
4		2-Cl		95 (88:12 <i>E/Z</i>)
5		2,4-Me ₂		94 (19:1, <i>E/Z</i>)
6				95 ^c (20:1, <i>E/Z</i>)
7		4-OMe		90 ^d (9:1, <i>E/Z</i>)

^a Reactions carried out at rt for 1–24 h using aryl iodide (1 equiv), styrene (2 equiv), triethylamine (3 equiv), catalyst **7** (2 mol %), and 15 wt % of PTS/H₂O (~0.5 M). ^b Isolated yield of *E/Z* mixture, ratio by GC. ^c Run at 50 °C. ^d 9:1 inseparable mixture of *E/Z* isomers.

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(12) (dtbpf)PdCl₂ (CAS no. 95408-45-0) was generously supplied by Dr. Thomas J. Colacot (E-mail: colactj@jmsa.com, Johnson-Matthey).

(13) The critical micelle concentration for PTS in water has been determined to be 0.281 mg/g at room temperature.

(14) A more detailed study will be reported shortly.

Styrenes are more reactive coupling partners relative to acrylates;^{10d} both electron-rich (Table 3, entries 1, 2, 4, 5, and 7) and electron-poor (Table 3, entry 3) aryl iodides smoothly afforded unsymmetrical (*E*)-stilbenes. Styrene-like substrates, such as water-insoluble vinyltriazole¹⁷ **12**, readily coupled with highly functionalized tetrahydroisoquinoline¹⁸ **11**, although this combination involving a relatively electron-poor precursor (**12**) required gentle heating to 50 °C (Table 3, entry 6). By contrast, related iodide **13** reacted at 25 °C with 4-methoxystyrene (Table 3, entry 7). Workup in some cases involved partitioning between 2:1 brine/H₂O and 3:1 hexanes/EtOAc, followed by extraction with 3:1 hexanes/EtOAc. This protocol leaves PTS in the aqueous phase, along with a substantial amount of the palladium catalyst. Efforts to recycle the catalyst containing aqueous phase are ongoing.

The nature of the micelles formed upon dissolution of PTS (**4**) in water was investigated using both dynamic light scattering (DLS)¹⁹ and low-temperature transmission electron microscopy (cryo-TEM).²⁰ Particle size was determined by DLS to be distributed from ca. 10–50 nm, with an average of 22 nm. Cryo-TEM data revealed a mixture of smaller spherical micelles, together with larger wormlike structures (Figure 3). Interestingly, Triton X-100 (**1**) and TPGS (**3**) in

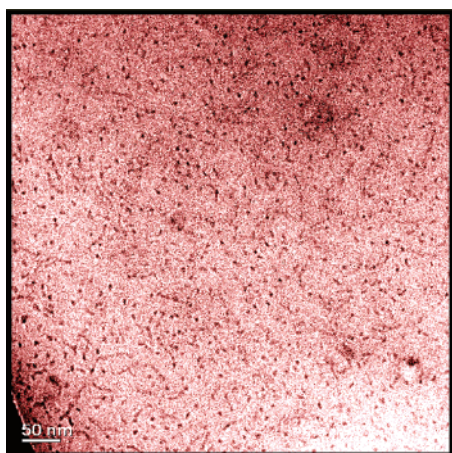


Figure 3. Cryo-TEM image of aqueous PTS (**4**).

water gave DLS data indicative of a far narrower range of smaller particles (5–6 nm). Since TPGS is structurally related to PTS, with variations only in its diacid linker length (4 vs 10 carbons) and PEG (1000 vs 600), the dramatic decrease in micellar size suggests extensive coiling in water, which may account for its lack of generality in Heck couplings. On the other hand, Triton X-100 also forms 5–6 nm micelles in water and yet can be competitive with PTS as a surfactant. Thus, micelle diameter is apparently not the sole factor affecting catalysis under these conditions. Further

studies on surfactant structure/functionality relationships are clearly needed.

In summary, an operationally simple process has been developed for carrying out traditional Heck couplings at ambient temperatures in neutral water, without resorting to cosolvents,^{21a} ionic liquids,^{21b} sonication,^{21c} electrochemistry,^{21d} or water-soluble phosphines.^{21e} Use of inexpensive PTS,²² a nonionic amphiphile, allows cross-couplings to take place under especially mild and environmentally attractive conditions.²³ Related Pd-catalyzed Suzuki–Miyaura cross-couplings are discussed in the following paper in this issue, and others (e.g., Sonogashira couplings in PTS/water) will be reported in due course.

Acknowledgment. We are most grateful to Zymes, LLC for financial support, as well as for providing PTS and PSS. We also thank Dr. Thomas J. Colacot (Johnson-Matthey) for supplying the palladium catalyst used in this study (CAS no. 95408-45-0), Dr. Jingshan Dong (University of Minnesota) and Prof. Craig Hawker (UCSB) for help with the cryo-TEM experiments, and Eastman for generously supplying TPGS.

Supporting Information Available: Experimental procedures, characterization data, and copies of ¹H and ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) Palladacycle [(*o*-tol)₃P]Pd(OAc)₂ (CAS no. 172418-32-5) was used instead of **7**, improving selectivity (GC yield 89 vs 71%).

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(22) Available from Sigma-Aldrich in May, 2008, as an aqueous solution (catalog #698717).

(23) (a) **Representative Procedure:** (*E*)-*tert*-Butyl 3-(4-methoxyphenyl)acrylate. Catalyst **7** [(dtbpf)PdCl₂, 13.0 mg, 0.02 mmol] and 4-iodoanisole (234 mg, 1.0 mmol) were added under argon to a 5.0 mL microwave vial equipped with a large stir bar and Teflon lined septum. PTS solution (2.0 mL, 15 wt%), triethylamine (416 μL, 3.0 mmol), and *t*-butyl acrylate (290 μL, 2.0 mmol) were added by syringe. The heterogeneous mixture was stirred vigorously at rt, becoming pseudo-homogeneous after 20–40 min. Reaction progress was monitored by TLC (1:10, EtOAc/hexanes). Upon consumption of aryl iodide (~5 h), the dark brown mixture was diluted with EtOAc (2.0 mL) and filtered through a pad of silica gel using EtOAc (15 mL) as eluent. The volatiles were removed on a rotary evaporator and the crude product was purified by silica gel chromatography (1:10, EtOAc/hexanes) to yield 215 mg (92%) of a light tan solid. Spectral data matched that reported in the literature. (b) Tang, Y.; Yu, Y.; Xia, W.; Song, Y. Huang, Z. *J. Org. Chem.* **2002**, *67*, 3096–3103.