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Olefin Cross-Metathesis Reactions at Room Temperature Using the Nonionic Amphiphile “PTS”: Just Add Water†

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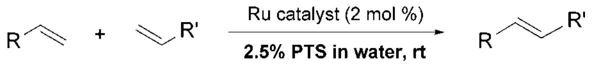
ABSTRACT



The first examples of unsymmetrical olefin cross-metathesis reactions in water, involving water-insoluble substrates, at room temperature and using commercially available catalysts are reported. The key to success is to include small percentages of the nonionic, vitamin E-based amphiphile “PTS”. The nanometer micelles formed accommodate water-insoluble substrates, along with a readily available Ru-based metathesis catalyst. Reactions proceed at ambient temperatures with high efficiency and very high *E*-selectivity, and products are easily isolated.

Reactions run in water offer several advantages: safety, economics, environmental compatibility, etc.[1] Nonetheless, there are also drawbacks, not the least of which is the limited aqueous solubility of most neutral organic substrates. In the specific case of olefin metathesis chemistry[2] also involving a water-insoluble (ruthenium-based) catalyst, these issues can present serious limitations. Partial solutions have been forthcoming,[3] where tetraalkylammonium phosphines,[4] sulfonated phosphines,[5] PEGylated NHC ligands,[6] or pendant tetralkylammonium[7] residues adorning the ruthenium carbene have been reported. Although these approaches lead to water-soluble catalysts, a sequence of steps is required in each preparation. Moreover, the solubility profile of the olefinic partners remains unaddressed. Particularly challenging are the cases involving intermolecular cross-metathesis (CM)[2e,8] of unsymmetrical lipophilic alkenes in water, for which no known technology currently exists. We now describe an especially simple protocol for effecting olefin CM at room temperature, in water, in the absence of cosolvents and without recourse to alterations in substrate or commercial catalyst design.

Screening of several amphiphiles **1−6** (Figure 1) in the CM between allylbenzene and *tert*-butyl acrylate (2 equiv)

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

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[3] (a) Clavier, H.; Grela, K.; Kirschning, A.; Mauduit, M.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6786−6801. (b) Binder, J. B.; Blank, J. J.; Raines, R. T. *Org. Lett.* **2007**, *9*, 4885−4888. (c) Mwangi, M. T.; Runge, M. B.; Bowden, N. B. *J. Am. Chem. Soc.* **2006**, *128*, 14434−14435.

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10.1021/ol800028x CCC: $40.75

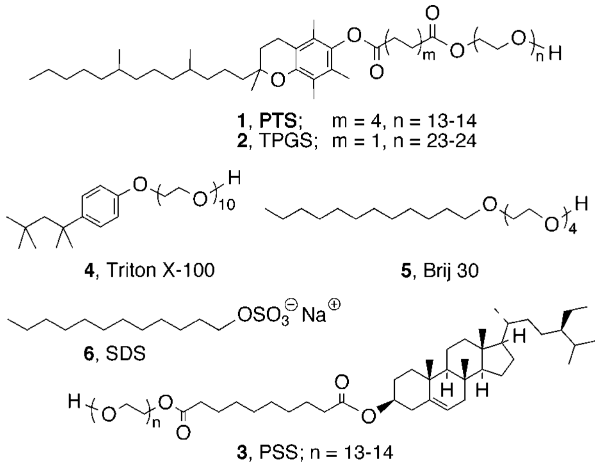


Figure 1. Structures of surfactants screened.

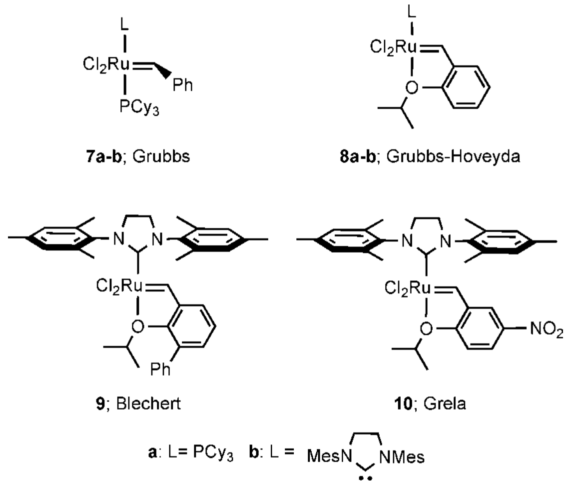
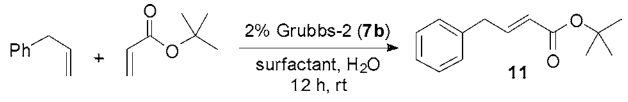


Figure 2. Structures of common Ru-based catalysts used for olefin metathesis.

Table 1. Comparison of Amphiphiles for CM in Water



entry	surfactant[a]		yield[b,c] (%)	yield[c,d] (%)
1	**PTS**	**1**	**97**	**93**
2	TPGS	**2**	67	61
3	PSS	**3**	78	70
4	Triton X-100	**4**	69	63
5	Brij 30	**5**	63	55
6	PEG-600		60	47
7	SDS	**6**	68	64
8	none		71	62

[a] 2.5% used in all cases. [b] Using 2 equiv of acrylate. [c] Isolated yields of chromatographically pure materials. [d] Using 1.3 equiv of acrylate.

using the Grubbs-2 catalyst **7b**[9] (2 mol %; Figure 2), among several possible candidates,[10] indicated that the **P**EG-600/α-**T**ocopherol-based diester of **S**ebacic acid, PTS (**1**; MW ~1200),[11] is the most effective (Table 1, entry 1). Adding a preformed, essentially water-white solution of only 2.5% (by weight) PTS in water to a 2:1 mixture of olefins and catalyst with continuous stirring overnight afforded the desired enoate **11** in high isolated yield. Switching from **7b** to the first-generation Grubbs complex **7a**[12] under otherwise identical conditions led to mainly recovered educts, along with both cis- and trans-isomers of the homocoupled unactivated alkene, and <2% of the butenoate, indicative of the importance of catalyst selection.

Other nonionic surfactants, including the structurally close yet less lipophilic analog TPGS (**2**),[13] produced more homocoupling products, and hence, lower yields of **11** (Table 1, entry 2). Replacing the vitamin E subsection of PTS with β-**S**itosterol, thereby forming the equally lipophilic "PSS" (**3**),[11] did not give competitive results (entry 3). Other neutral carriers such as Triton X-100 (**4**)[14a] and Brij 30 (**5**)[14b] afforded no improvement (entries 4 and 5, respectively). Neither PEG-600[14c] alone (entry 6) nor the common ionic surfactant sodium dodecyl sulfate (SDS) (**6**)[14d] afforded yields (entry 7) that were any higher than that from the control reaction performed "on water" (entry 8).[15]

The combination of 2% Grubbs-2 catalyst in 2.5% PTS/water forms a stable, rose-colored colloidal dispersion (Figure 3A). Although upon standing at room temperature for days the catalyst will begin to precipitate, stirring briefly restores the mixture to its original state. In the presence of reactants, the solution darkens while the CM product forms over a few hours time. Without PTS, there is no dissolution (Figure 3B).

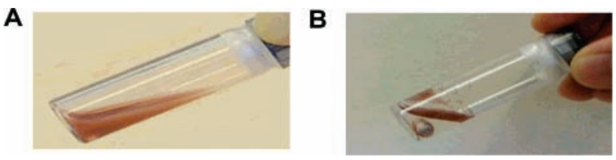


Figure 3. Appearance of Grubbs-2 catalyst in (**A**) 2.5% (w/w) PTS/water and (**B**) neat water.

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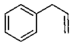
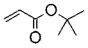
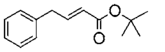
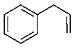
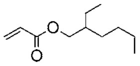
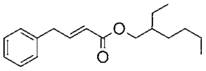
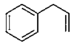
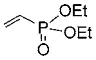
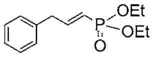
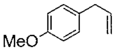
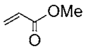
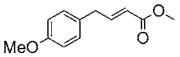
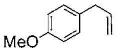
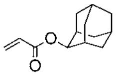
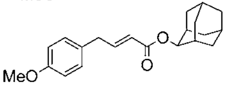
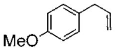
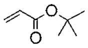
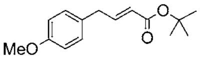
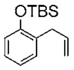
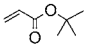
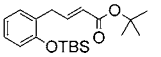
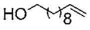
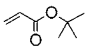
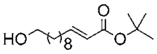
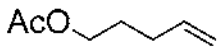
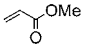
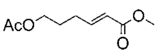
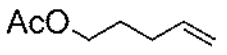
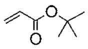
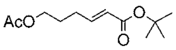
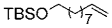
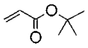
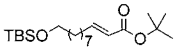
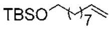
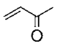
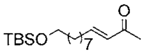
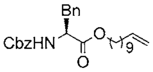
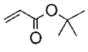
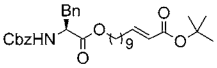
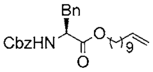
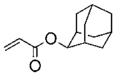
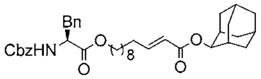
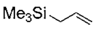
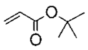
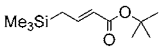
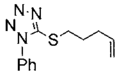
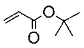
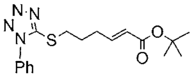
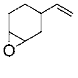
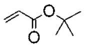
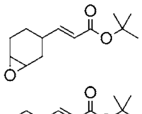
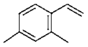
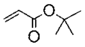
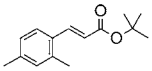
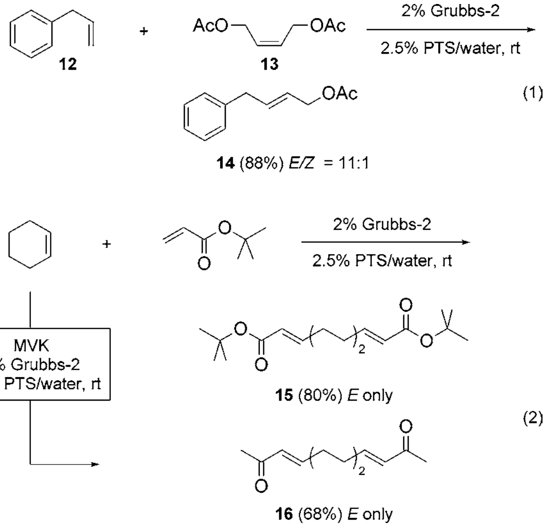
As the many successful examples in Table 2 indicate, these conditions are quite general. Particularly noteworthy features of the process include the following; (1) its simplicity; while most CM reactions are done at higher temperatures (40 °C)[8,16,17] these reactions are conducted at room temperature open in air;[10g] (2) *E*/*Z* ratios tend to be comparable to those typically observed in organic media;[8,16,17] (3) many functional groups are tolerated, such as allylic silanes, free alcohols, amino acid derivatives, and epoxides; (4) highly lipophilic partners smoothly participate; (5) product isolation is straightforward.[18] Unpredictably, the extent of homocoupling is oftentimes improved in aqueous PTS, suggesting the potential for lowering of the ratio of olefinic partners toward 1:1.[19] In fact, at a ratio of 1.3:1 there is minimal loss for the model case studied (Table 1, second column of yields), while the corresponding yields with other surfactants (or in water alone) dropped due to increased competing homocoupling. Problematic substrates included more hindered cases such as methyl methacrylate and acrylonitrile (low conversion).[10e,20] A sequence involving allylbenzene (**12**) and a symmetrical 1,2-disubstituted olefin such as diacetate **13** worked well, affording **14** (Scheme 1, eq 1).[8] Likewise, initial ring-opening reactions that subsequently converted cyclohexene (with *tert*-butyl acrylate) to all-*E* diester **15**,[16] and with methyl vinyl ketone (MVK) to diketone **16**, were successful (Scheme 1, eq 2).[21]

Table 2. Olefin CM Reactions Using 2% Catalyst in 2.5% aq PTS[a]

substrate	olefinic partner	product	yield(%)[b,c]
			96 >20:1
			92 9:1
			55 *E* only
			70 *E* only
			78 *E* only
			93 >20:1
			88 *E* only
			82 >20:1
			83[d] >20:1
			87[d] 20:1
			95 *E* only
			89 *E* only
			96 *E* only
			94 *E* only
			91 19:1
			83[e] (55)[f] 6:1
			76[d] 18:1
			72[g] 9:1

[a] Reactions were conducted at 0.5 M over 12 h at 22 °C using Grubbs-2 (**7b**). [b] Isolated yield of chromatographically pure materials. [c] *E*/*Z* ratio determined by ^{1}H NMR. [d] Using Grubbs−Hoveyda-2 (**8b**). [e] Based on recovered starting material. [f] Isolated. [g] Isolated as an inseparable mixture with styrene homocoupling product (8%); ratio determined by ^{1}H NMR.

Scheme 1. Other Examples of CM in PTS/water



12

13

14 (88%) *E/Z* = 11:1

15 (80%) *E* only

16 (68%) *E* only

The success of PTS, an amphiphile that itself forms on average 22 nm micelles in water above its critical micelle

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(11) (a) Borowy-Borowski, H.; Sikorska-Walker, M.; Walker, P. R. Water-Soluble Compositions of Bioactive Lipophilic Compounds. U.S. Patent 6,045,826, Apr 4, 2000. (b) Borowy-Borowski, H.; Sikorska-Walker, M.; Walker, P. R. Water-Soluble Compositions of Bioactive Lipophilic Compounds. U.S. Patent 6,191,172, Feb 20, 2001. (c) Borowy-Borowski, H.; Sikorska-Walker, M.; Walker, P. R. Water-Soluble Compositions of Bioactive Lipophilic Compounds. U.S. Patent 6,632,443, Oct 14, 2003.

(12) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(13) PCI-102B Eastman Vitamin E TPGS NF - Applications and Properties. http://www.eastman.com/NR/rdonlyres/A2FE037B-0778-4A90-A0FC-5D07BE51064A/0/PCI102.pdf (accessed August 2007).

(14) Sigma-Aldrich catalog nos. (a) 234729, (b) P4391, (c) 202401, (d) L3771.

(15) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolib, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275−3279. See also: Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798−3800.

concentration (0.28 mg/g),[22] may be related to its hydrophilic lipophilic balance (HLB).[23] That is, on the commonly used (albeit arbitrary) scale of 0−20 (Figure 4), PTS (HLB = 10) is less hydrophilic relative to most other common nonionic carriers. This position reflects its higher percentage of hydrocarbon (due to vitamin E + the 10-carbon sebacic acid linker) and lower content of PEG (involving only PEG-600). The HLB, however, is merely a relative index which ignores entirely the specific makeup of the amphiphile's components. Thus, based on this scale, Brij[20] 30 (**5**) has an HLB similar to that of PTS. However, the lipophilic portion of its 5−6 nm micelles formed in water[22] appears not to provide the most appropriate environment for this catalysis. These observations are in line with data on Pd-catalyzed processes in PTS/water, including Heck[22a] and Suzuki−Miyaura[22b] coupling. The key role of the α-tocopheryl subsection in **1** is further supported by direct comparison with equally lipophilic PSS (**3**), which self-aggregates into similarly sized micelles (ca. 20 nm) in water and has essentially an identical HLB. Nonetheless, results with this carrier for olefin CM are inferior to those realized using PTS. These data suggest that there is much yet to be learned about the factors controlling the interior nature of these micelles, and their abilities to "host" organometallic reactions of interest to synthetic chemists.[24]

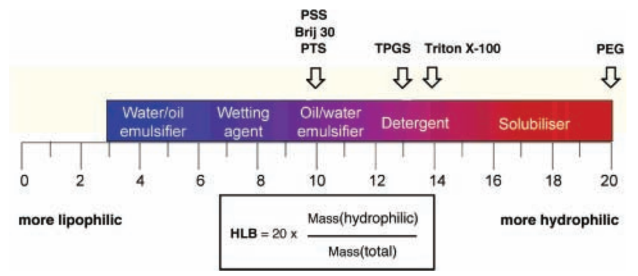

Figure 4. Hydrophilic lipophilic balance scale.

In summary, a nonionic surfactant has been identified that leads to a new, general protocol for effecting olefin metathesis in water at ambient temperatures. Intermolecular cross-couplings can be carried out in high yields and with *E*-selectivities comparable to those expected in organic media. Reactions take place under very mild and "green" conditions. No modifications of catalyst or substrate are required to enhance their water solubility, nor are there any special techniques or handling procedures of the materials involved.[25] Further successful applications to several other "name" reactions (e.g., Sonogashira couplings), in addition to the two which follow in this issue will be reported in due course.[26]

Acknowledgment. Financial support provided by Zymes, LLC is warmly acknowledged with thanks. Catalysts were generously provided by Materia, Inc. (J. Kibler and R. Pederson), for which we are most grateful. TPGS was generously provided by Eastman.

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

OL800028X

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(18) See the experimental procedure below and those in the Supporting Information.

(19) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3171−3174.

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(24) Since PEG-600 is supplied as a mixture of compounds, so therefore, PTS is a mixture of PEG monoesters, the distribution of which is readily observed by mass spectrometry. Moreover, while synthesis of PTS is straightforward (i.e., from sebacoyl chloride, racemic vitamin E, and PEG-600),[11] a complete understanding of the roles of its various ingredients, including impurities (e.g., PEG diesters, etc.) in micelle formation remains to be elucidated.

(25) Representative procedure for olefin CM (Table 2, entry 8): 10-Undecenol (94.8 mg, 0.556 mmol), *tert*-butyl acrylate (159.5 mg, 1.24 mmol), and Grubbs second-generation catalyst **7b** (9.9 mg, 0.0116 mmol) were sequentially added to a Teflon-coated, stir bar containing Biotage 2−5 mL microwave reactor vial at room temperature and sealed with a septum. An aliquot of PTS/H_2O (1.0 mL; 2.5% PTS by weight; all cross-coupling reactions were conducted at 0.5 M unless stated otherwise) was added via syringe, and the resulting emulsion was allowed to stir at rt for 12 h. The homogeneous reaction mixture was then diluted with EtOAc (5 mL) and filtered through a bed of silica gel layered over Celite, and the bed was washed (3 × 10 mL) with EtOAc. The volatiles were removed in vacuo to afford the crude material, which was subsequently purified by flash chromatography on silica gel (eluting with 10% EtOAc/hexanes) to yield the product as a colorless oil (123 mg, 82%). The reported *E*/*Z* ratios were determined by relative integrations of the olefinic resonances at 6.86 and 6.11 ppm. IR (neat): 3412, 2978, 2928, 2856, 1715, 1653, 1458, 1391, 1367, 1315, 1158, 983 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.86 (dt, $J = 15.6, 6.8$ Hz, 1H), 5.73 (dt, $J = 15.6, 1.2$ Hz, 1H), 3.64 (q, $J = 6.4$ Hz, 2H), 2.16 (qd, $J = 7.2, 1.2$ Hz, 2H), 1.56 (quintet, $J = 7.2$ Hz, 2H), 1.48 (s, 9H), 1.43 (quintet, $J = 7.2$ Hz, 2H), 1.37−1.29 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 148.4, 122.9, 80.1, 62.9, 32.8, 32.1, 29.55, 29.49, 29.4, 29.2, 28.2, 28.1, 25.8. MS (CI): *m/z* 271 (M + H, 66), 215 (100), 197 (88), 179 (15), 151 (20), 95 (29), 57 (98). HRMS (CI): calcd for $C_{16}H_{31}O_3$ $[M + H]^+ = 271.2273$, found 271.2282.

(26) Sigma-Aldrich will offer PTS/H_2O in May, 2008 (catalog #698717).