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PQS: A New Platform for Micellar Catalysis. RCM Reactions in Water, with Catalyst Recycling

Bruce H. Lipshutz* and Subir Ghorai

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106

lipshutz@chem.ucsb.edu

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ABSTRACT

The first "designer" surfactant containing a covalently bound ruthenium catalyst is reported. This species dissolves freely in water, forming nanomicelles in which ring-closing metathesis reactions on water-insoluble dienic substrates can occur in pure water at room temperature. It can also be recycled continuously without reaction workup.

Development of environmentally innocuous processes is a major theme associated with the "12 Principles of Green Chemistry".[1a] These guiding ideals, as espoused by Anastas well over a decade ago, pose a challenge to synthetic chemists worldwide: to devise chemistry that is "benign by design".[1b] Catalysis plays a huge role in furthering these goals; indeed, Sheldon, Arends, and Hanefield in their recent monograph link it prominently alongside green chemistry in their title.[2] Homogeneous catalysis, most notably in water, offers unique opportunities to minimize solvent waste, especially if a water-soluble catalyst can be reused in a single-pot continuous process. Otherwise, catalyst separation from the product can be problematic, and re-isolation is oftentimes troublesome and costly. We now disclose new technology that has been designed to accommodate all of these features using the virtues of micellar catalysis,[3] initially applied to ring-closing metathesis (RCM). This new process offers catalysis in water as the only medium, accommodation of water-insoluble substrates, reactions run at room temperature, no need for inert atmosphere or degassing, and continuous batch processing with the catalyst remaining in the water in the reaction vessel.

The three key elements of the newly designed platform, amphiphile **1** (PQS; Figure 1), include (1) a lipophilic component that serves as reaction "solvent" for *water-insoluble* organic substrates; (2) a hydrophilic portion leading to solubility in pure water; and (3) a free -OH residue within the hydrophobic core capable of covalent linkage to a pendant catalyst, in this case a Ru carbene, as in **2**. Related catalysts,

(1) (a) Anastas, P. T., Heine, L. G., Williamson T. C., Eds.; *Green Chemical Syntheses and Process*; American Chemical Society: Washington, DC, 2000. (b) Anastas, P. T., Farris, C. A., Eds.; *Benign by Design: Alternative Synthetic Design for Pollution Prevention*; ACS Symposium Series 557; American Chemical Society: Washington, DC, 1994.

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

(3) Dwars, T.; Paetzold, E.; Oehme, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7174–7199, and references therein. For examples of ligands attached to surfactants capable of micelle formation, see: (a) Goedheijt, M. S.; Hanson, B. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2000**, *122*, 1650–1657. (b) Ding, H.; Hanson, B. E.; Bakos, J. *Angew. Chem., Int. Ed.* **1995**, *34*, 1645–1647. (c) Ding, H.; Hanson, B. E.; Bartik, T.; Bartik, B. *Organometallics* **1994**, *13*, 3761–3763. (d) Bortenschlager, M.; Schöllhorn, N.; Wittmann, A.; Weberskirch, R. *Chem. Eur. J.* **2007**, *13*, 520–528.

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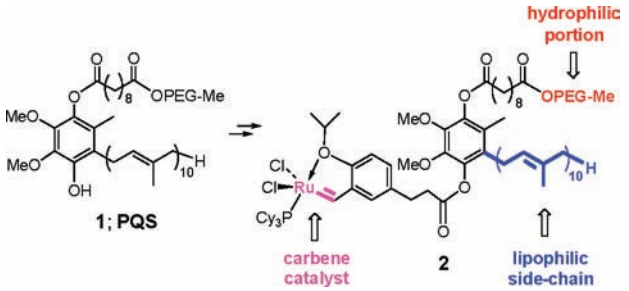
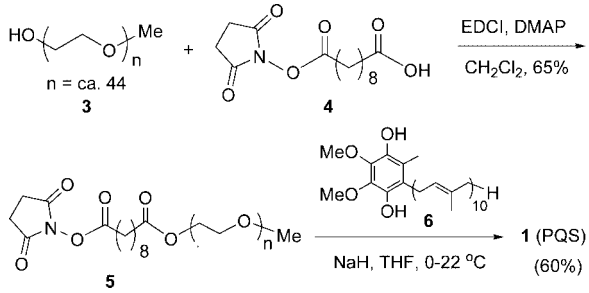


Figure 1. PQS-attached Grubbs-Hoveyda-1 metathesis catalyst for RCM reactions in water.

including those that are polymer-bound[4] (e.g., sol−gel)[5] or those bearing polar groups for achieving water solubility,[6] offer no options for effecting dissolution of water-insoluble educts and hence are used exclusively in organic media or with water-soluble substrates.

The preparation of PQS combines two readily available subsections: (1) the mixed, *O*-succinimide derivative **5**, formed by esterification using commercially available M-PEG-2000 (**3**) and monocarbonyl-activated sebacic acid **4** (Scheme 1), and (2) ubiquinol **6**, the hydroquinone form of

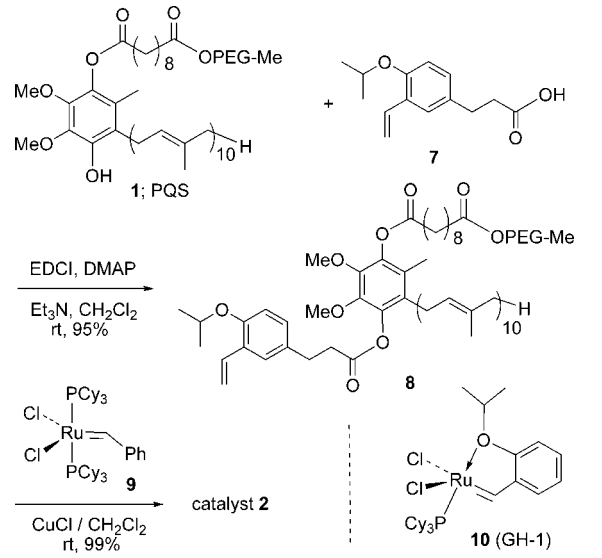
Scheme 1. Unoptimized Route to PQS (**1**)



coenzyme Q_{10}, which is formed quantitatively from its Zn/HOAc reduction.[7] Treatment of hydroquinone **6** with NaH in THF at 0 °C followed by introduction of **5** and warming to room temperature afforded PQS (**1**) in 60% isolated yield as a ca. 3:1 mix of inseparable regioisomers.[8] PQS is a colorless white solid, freely soluble in water in which it forms 9 nm micelles.[9] Its critical micelle concentration is only 0.06 mg/mL at 25 °C,[10] which corresponds to 1.97×10^{-5} M on the basis of an average molecular weight of 3046.

Esterification of the free phenolic group in **1** using Hoveyda's acid **7**[11] gave the carbene precursor **8** in high isolated yield (Scheme 2). Exposure of newly formed triester

Scheme 2. Preparation of PQS-Attached GH-1 Catalyst **2**



8 to Grubbs first generation complex **9** in the presence of CuCl[11] inserted the desired Ru carbene, thereby arriving at novel catalyst **2**.[12] Carbene **2** is a brown solid virtually identical in appearance to catalyst **10**.[13] Upon addition of **2** to water (ca. 0.1 M) a solution is formed that contains, on average, 44 nm micelles according to DLS measurements.[9] To effect RCM, the substrate need only be added, neat. Figure 2 illustrates representative examples, highlighting several noteworthy features of this remarkably simple process: (a) all cases studied to date, most of which involve water-insoluble dienic substrates, led to excellent isolated

(4) (a) Dowden, J.; Savović, J. *Chem. Commun.* **2001**, 37–38. (b) Connon, S. J.; Blechert, S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1873–1876. (c) Grela, K.; Tryznowski, M.; Bieniek, M. *Tetrahedron Lett.* **2002**, *43*, 9055–9059.

(5) Kingsbury, J. S.; Garber, S. B.; Giftos, J. M.; Gray, B. L.; Okamoto, M. M.; Farrer, R. A.; Fourkas, J. T.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4251–4256.

(6) (a) Yao, Q.; Motta, A. R. *Tetrahedron Lett.* **2004**, *45*, 2447–2451. (b) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508–3509. (c) Jordan, J. P.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5152–5155. (d) Rix, D.; Caijo, F.; Laurent, I.; GułajskiŁ.; Grela, K.; Mauduit, M. *Chem. Commun.* **2007**, 3771–3773. (e) GułajskiŁ.; Śledź, P.; Lupa, A.; Grela, K. *Green Chem.* **2008**, *10*, 279–282. (f) GułajskiŁ.; Michrowska, A.; Norażnik, J.; Kaczmarska, Z.; Rupnicki, L.; Grela, K. *Chem. Sus. Chem.* **2008**, *1*, 103–109. (g) Burtscher, D.; Grela, K. *Angew. Chem., Int. Ed.* Epub ahead of print. DOI: 10.1002/anie.200801451,

(7) Morgan, A. C.; Graves, S. S.; Woodhouse, C. S.; Sikorska, M.; Walker, R.; Wilbur, D. S.; Borowy-Borowski, H. Water Soluble Ubiquinone Compositions, Prodrugs, and Methods Relating Thereto. PCT 1996; CAN 125:123707.

(8) Acylation of ubiquinol reproducibly leads to an inseparable 3:1 mixture of regioisomers, which is uneventfully carried through to "PQS" and used as such. The ratio of regioisomers is discernible only by proton NMR. Note that PEG-2000 represents an average molecular weight, as this material is sold as a range of polyoxyethanyl-containing compounds.

(9) Determined by dynamic light scattering measurements using a Brookhaven Laser Light Scattering instrument.

(10) Determined at Augustine Scientific, Newbury, Ohio by surface tension measurements using the Wilhelmy Plate Method on a Kruss K100 Tensiometer.

(11) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(12) Catalyst **2** was characterized by its carbene signal at δ 17.39 (d, J_{PH} = 4.8 Hz), which is the only carbene peak observed, as well as the methine proton at δ 5.26 of the Ru-bound isopropoxy ligand. The structural assignment was further secured by comparison data with those of Grubbs-Hoveyda catalyst **10**[13] (δ 17.44 of Ru=C**H**Ar and 5.28 of OC**H**Me_2).

(13) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.

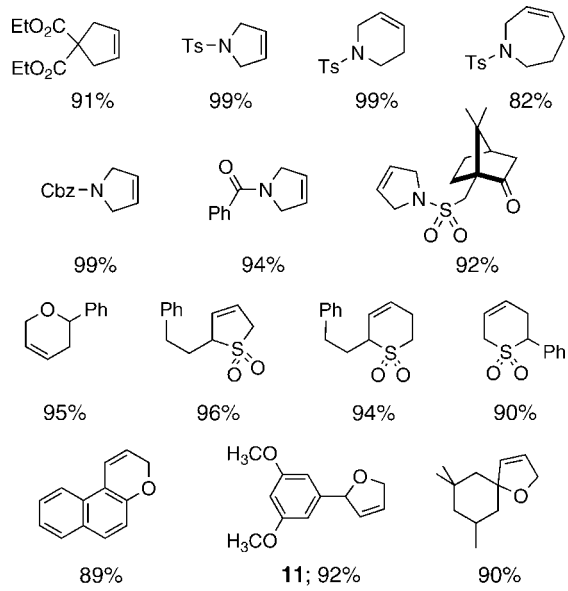
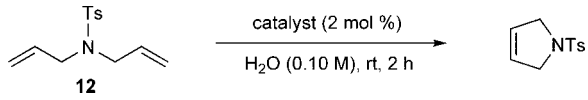


Figure 2. Products of RCM in water only, catalyzed by PQS-bound Ru catalyst **2**.

yields of the desired products; (b) the water need not be degassed prior to use; (c) these reactions can be run fully exposed to air; (d) reactions leading to five-, six-, and seven-membered rings proceed smoothly under identical conditions; (e) ring closures are fairly rapid, all taking place within 2 h at ambient temperature; (f) workup and product isolation are especially straightforward, simply involving addition of an organic solvent (e.g., Et_2O) to the reaction vessel and stirring, followed by organic solvent removal directly from the reaction vessel. Exposure of the solution obtained to charcoal followed by product purification,[14] using diene **12** (Table 1)

Table 1. Recycling of Catalyst **2** in RCM Reactions of **12**[a]

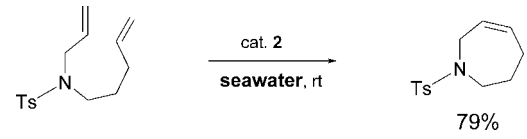


	cycle (% conversion)[b]									
catalyst	1	2	3	4	5	6	7	8	9	10
catalyst **2**	>99	>99	>99	99	98	98	97	95	94	92
Grubbs-1 (**9**)	93	79	5							
GH-1 (**10**)	94	73	<2							

[a] The reactions were performed with 0.1 mmol substrate. [b] Determined by ^{1}H NMR spectroscopy at 400 MHz.

as a representative educt, affords material containing only ca. 1.6 ppm Ru.[15] *With catalyst **2** remaining in the aqueous layer*, the process could be repeated for an additional 10 recycles. Unlike catalysts **9** and **10**, which are compromised after the first RCM in each case, PQS-derived carbene complex **2** retains ≥92% of its original activity within this (arbitrarily chosen) time frame and concentration in water.[16] Lastly, rather than using standardized HPLC-grade water, catalyst **2** was tested in seawater taken directly from the Pacific Ocean. As illustrated in Scheme 3, for the challenging case of seven-membered ring formation, essentially no differences were observed, further indicative of the robustness of this chemistry.

Scheme 3. RCM in Seawater at Room Temperature



In summary, a conceptually new platform for carrying out micellar catalysis (PQS, **1**) has been prepared, to which a Ru carbene has been covalently linked. The resulting species **2** leads to an enabling technology that uniquely offers the opportunity to effect ring-closing metathesis reactions in water, or even seawater, with water-insoluble dienes, in air, at room temperature, and with in-flask processing and

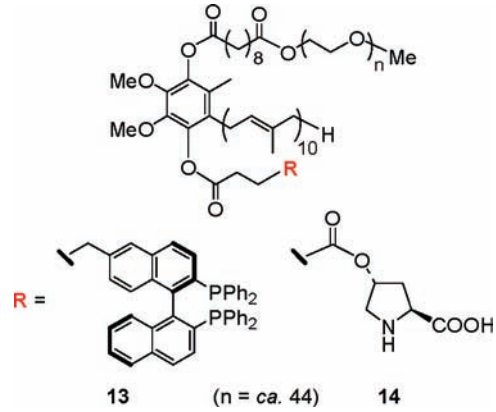


Figure 3. Designer surfactants under development for asymmetric catalysis.

recycling (i.e., under green chemistry conditions).[17] Catalysis derives from self-organization of very small amounts of PQS

(14) Hong, S. H.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1955–1957.

(15) Determined by ICP-MS measurements at the Department of Environmental Health Sciences, UCLA.

(16) It is appreciated that release and recapture (i.e., the boomerang effect) is likely involved in these reactions; see: Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8–23.

(17) (a) Clavier, H.; Grela, K.; Kirschning, A.; Mauduit, M.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6786–6801. (b) Bruckmann, A.; Krebs, A.; Bolm, C. *Green Chem.* **2008**, *10*, 1131–1141. For metathesis in ionic liquids, see: (c) Audic, N.; Clavier, H.; Mauduit, M.; Guillemin, J.-C. *J. Am. Chem. Soc.* **2003**, *125*, 9248–9249. (d) Yao, Q.; Zhang, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3395–3398. (e) Clavier, H.; Audic, N.; Mauduit, M.; Guillemin, J.-C. *Chem. Commun.* **2004**, 2282–2283.

into nanomicelles, with the lipophilic 50-carbon side chain of a readily prepared[18] ubiquinol derivative functioning as the organic "solvent". A myriad of opportunities exist for covalent attachment of other species to PQS, such as BINAP derivative **13** (e.g., for asymmetric Rh-catalyzed 1,4-additions)[19] and proline **14** (for organocatalysis)[20] as well as pharmaceuticals (e.g., pacitaxel) for inclusion within micellar environments in water (Figure 3). Results from these ongoing and related studies in catalysis will be reported in due course. Thus, in a broader sense, "designer" surfactants such as **2** have the potential to provide "green" solutions to selected problems in organic synthesis.[21]

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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.

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(18) A second generation, streamlined route to PQS has been developed; Lipshutz, B. H.; Moser, R., unpublished work.

(19) (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (b) Hayashi, T. *Synlett* **2001**, 879–887. (c) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279–1300. (d) Nurihara, K.; Sugishita, N.; Oshita, K.; Piao, D.; Yamamoto, Y.; Miyaura, N. *J. Organomet. Chem.* **2007**, *692*, 428–435.

(20) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660, and references therein.

(21) **Representative Procedure.** (Figure 2, compound **11**) Precursor diene (24 mg, 0.10 mmol) and catalyst **2** (7.5 mg, 0.002 mmol) were both added into a Biotage 2−5 mL microwave reactor vial with a Teflon-coated stir bar at room temperature and sealed with a septum. H_2O (1.0 mL; all RCM reaction were conducted at 0.1 M unless stated otherwise) was added via syringe, and the resulting solution was allowed to stir at room temperature for 3 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 further washed (2 × 10 mL) with EtOAc to collect all of the cyclized material. The volatiles were removed in vacuo to afford the crude product, which was subsequently purified by flash chromatography using silica gel (4% EtOAc/hexanes) to afford the compound as a colorless liquid (19 mg, 92%). IR (neat): 3085, 3001, 2940, 2840, 1598, 1463, 1428, 1349, 1295, 1242, 1204, 1155, 1054, 1020, 930 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.48 (d, $J = 2.4$ Hz, 2H), 6.39 (t, $J = 2.4$ Hz, 1H), 6.04−6.02 (m, 1H), 5.90−5.87 (m, 1H), 5.75−5.72 (m, 1H), 4.90−4.84 (m, 1H), 4.80−4.74 (m, 1H), 3.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 144.7, 130.0, 126.9, 104.3, 99.9, 88.0, 76.1, 55.5. EI-MS *m/z* (%): 206 (100), 177 (30), 175 (35), 165 (57), 138 (48), 137 (19). HRMS (EI) calcd for $C_{12}H_{14}O_3$ $[M]^+ = 206.0943$, found 206.0952.