Ring-Closing Metathesis at Room Temperature within Nanometer Micelles using Water as the Only Solvent

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Dedicated to Professor Andreas Pfaltz on the occasion of his 60th birthday.

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Abstract: Simply mixing a water-insoluble diolefinic substrate and Grubbs second generation catalyst in pure water containing small amounts of the amphiphile polyoxyethanyl α -tocopheryl sebacate (PTS) leads to efficient ring-closing metathesis.

Keywords: amphiphiles; nanomicellar catalysis; polyoxyethanyl α -tocopheryl sebacate (PTS); ringclosing metathesis; surfactants

Although there are arguments as to the pros and cons of water as a solvent for organic reactions,^[1] the situation is made all the more confusing given the options 'with water,'^[2] 'in water,'^[3] and 'on water.'^[4,5] The simplest approach would be to rely on water alone; i.e., with no co-solvents involved whatsoever. Of course, depending upon reaction type, substrates, additives, catalysts and other possible parameters, solubility issues can overshadow opportunities for the exclusive use of water as solvent. One remarkably simple potential solution relies on the presence of an amphiphile that "dissolves" otherwise water-insoluble reaction components within its micellar lipophilic core that has self-assembled in aqueous media.^[6] If an appropriate surfactant is identified, reactions may benefit not only in terms of ease of handling, but also with respect to rates accelerated by micellar catalysis.^[7] In 2002, Davis and Sinou studied the effect of several phase-transfer catalysts and both ionic (e.g., SDS; sodium dodecyl sulfate) and nonionic surfactants (e.g., Brij 35; decaoxyethylene dodecyl ether), on ring-closing metathesis (RCM) reactions in water with the Grubbs-1 catalyst under very carefully controlled conditions (Schlenk techniques, distilled, deionized, and degassed water, etc.).^[8] Their conclusion was that such reactions may not require any surfactant; that water alone could in many cases afford cyclized products in high yields. Recently, the 3-component amphiphile PTS (1, (polyoxyethanyl α -tocopheryl sebacate) has been introduced as a "general pur-



pose" nonionic amphiphile, allowing for Heck,^[9] Suzuki,^[10] and olefin cross-metathesis (CM) reactions^[11] to occur with lipophilic substrates also in pure water at room temperature. Unsymmetrical CM reactions were shown to proceed far better under the influence of PTS than 'on water',^[4,5,8] reactions presumably taking place within the *ca.* 25 nanometer micelles formed. In this report RCM reactions^[12,13] are described, using minimal amounts of PTS in water at ambient temperatures, along with a far more reactive yet commercially available ruthenium catalyst (Scheme 1).

Aqueous solutions containing only 1.5-2.5% PTS (by weight) served admirably as reaction media for a variety of diolefinic educts, as illustrated in Table 1. The Grubbs second generation catalyst^[14] (2%) could be used as received from commercial sources.^[15] Addition of both starting material and catalyst to PTS in water can be carried out in air.^[14d] Likewise, these RCM reactions do not require inert atmosphere conditions. Efficient stirring at room temperature over a few hours at concentrations of *ca*. 0.1 M usually leads to complete consumption of starting materials and very clean, high yielding cyclizations. Ring sizes composed of 5- (entries A, B, E, F), 6- (entry C), and 7-





Scheme 1. Ring-closing metathesis affording di-, tri- or tetra-substituted cycloalkenes.

Table 1. Ring-closing metathesis reactions in 2.5% PTS/ water.^[a]



 [a] 2 mol% Grubbs 2nd generation catalyst at 0.1 M at 22 °C for 3 h.

^[b] Isolated yield of chromatographically purified material.

members (entry D) are smoothly formed. Both heteroatom (entries B–F) and non-heteroatom rings (entry A) can be realized. Amine-derivatized precursors include *N*-arylsulfonyl (entries B–D, F) or benzoyl examples (entry E). Remarkably, on increasing the overall reaction concentration from 0.1 M to 0.3 M in water, thus decreasing the amount of PTS to 0.8% (by weight), the reaction rate and efficiency remained unchanged (e.g., in the case of entry B).

2,5-Dihydropyrroles can result from *N*-allylated sulfonamides of varying substitution patterns on one or both of the double bonds. Thus, in addition to a symmetrically substituted diallylamine (2), methyl- and dimethylated analogues 3 and 4, respectively (Scheme 2), gave the expected identical product 5 in comparable yields. Use of prenylated amine 4 is particularly noteworthy, and is suggestive that such terminally disubstituted olefins can also be used in (previously unprecedented) RCM reactions. Reaction work-up and product isolation free of any PTS is very straightforward, a general observation as noted in earlier uses of this amphiphile^[9-11] (also, see procedure below).

Formation of trisubstituted alkene derivatives within both 5- and 6-membered rings, products unavailable previously due to reliance on the less reactive Grubbs-1 catalyst,^[8] took place uneventfully in very high yields (Scheme 3). In the case of metathesis of methallylated amine **6** (in 2.5% PTS/H₂O, 97% yield), the corresponding reaction 'on water' (i.e., in



Scheme 2. Ring-closing metathesis on variously substituted allylic amines.



Scheme 3. RCM forming trisubstituted olefins in PTS/water.

water but in the absence of PTS)^[4] led to an 80% yield of product 7 under otherwise identical conditions. The homologue of 6, sulfonamide 8, efficiently closed to 9 essentially quantitatively.

One case of a tetrasubstituted olefin was studied, focused on educt **10**. As expected, metathesis was far slower, requiring heating to 60 °C over 24 h to afford **11** in a modest 66% isolated yield. Most of the remaining mass was starting material.



In summary, an especially simple methodology has been uncovered that allows for ring-closing metathesis reactions involving lipophilic substrates and a highly active, water-insoluble ruthenium catalyst to be effected at room temperature in water as the only medium. The virtues of this technology include (1) less catalyst is required than that used in a related study;^[8] (2) tri- and tetra-substituted olefins can be fashioned; (3) higher levels of conversion, usually approaching 100%, and high yields of products, are to be expected; (4) simple and quick work-ups are involved; (5) unlike prior work on RCM reactions in water,^[8] no special handling is required; no Schlenk techniques, no water degassing, no inert atmosphere; (6) PTS/H₂O will soon be commercially available.^[16] Additional applications of PTS/H₂O as a medium for organometallic chemistry (e.g., asymmetric hydrosilylations with CuH, and Sonogashira couplings) are under study and will be reported in due course.

Experimental Section

Representative Procedure for Olefin RCM (Table 1, entry F).

Diallylsulfonamide (47 mg, 0.15 mmol) and Grubbs second generation catalyst (2.6 mg, 0.003 mmol) were both added into a Teflon-coated stir-bar-containing Biotage 2–5 mL microwave reactor vial at room temperature, and sealed with a septum. An aliquot of 2.5% (by weight) PTS/H₂O (1.5 mL; all RCM reactions were conducted at 0.1 m unless stated otherwise) was added, *via* syringe, and the resulting emulsion was allowed to stir vigorously at room temperature for 3 h. The homogeneous reaction mixture was then diluted with EtOAc (5 mL), filtered through a bed of silica gel layered over Celite, and the bed further washed (3×10 mL) with EtOAc to collect the cyclized material. The volatiles were removed under vacuum to afford the crude material

which was subsequently purified by flash chromatography on silica gel (12% EtOAc/hexanes) to furnish the product as a white solid; yield: 41 mg (96%); mp 86-88°C; IR (thin film): $\nu = 2971$, 2912, 2876, 1744, 1483, 1470, 1415, 1403, 1379, 1331, 1217, 1146, 1111, 1051, 982, 966, 945 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): $\delta = 5.78$ (t, J = 4.0 Hz, 2H), 4.26–4.17 (m, 4H), 3.38 (d, J=14.8 Hz, 1H), 2.81 (d, J=14.8 Hz, 1 H), 2.52 (ddd, J=14.4, 11.5, 4.0 Hz, 1 H), 2.37 (dt, J = 18.4, 4.0 Hz, 1 H), 2.09 (t, J = 4.8 Hz, 1 H), 2.07–1.99 (m, 1H), 1.92 (d, J=18.4 Hz, 1H), 1.64 (ddd, J=14.4, 9.6, 4.8 Hz, 1H), 1.41 (ddd, J=12.4, 9.2, 4.0 Hz, 1H), 1.12 (s, 3H), 0.88 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 215.8$, 125.8, 58.4, 55.0, 48.1, 44.7, 42.92, 42.76, 27.1, 25.3, 20.1, 19.9; MS (CI): m/z (%)=284 (M + H, 21), 215 (18), 151 (11), 123 (12), 109 (20), 68 (100); HR-MS (CI): m/z =284.1322, calcd. for $C_{14}H_{22}NO_3S [M + H]^+$: 284.1320.

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