Olefin Metathesis in Homogeneous Aqueous Media Catalyzed by Conventional Ruthenium Catalysts
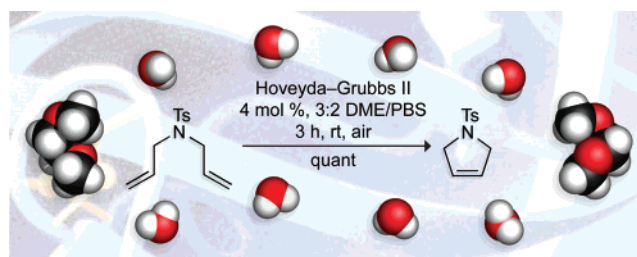
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ABSTRACT

Olefin metathesis in aqueous solvents is sought for applications in green chemistry and with the hydrophilic substrates of chemical biology, such as proteins and polysaccharides. Most demonstrations of metathesis in water, however, utilize exotic complexes. We have examined the performance of conventional catalysts in homogeneous water/organic mixtures, finding that the second-generation Hoveyda−Grubbs catalyst has extraordinary efficiency in aqueous dimethoxyethane and aqueous acetone. High (71−95%) conversions are achieved for ring-closing and cross metathesis of a variety of substrates in these solvent systems.

As a highly effective means for creating carbon−carbon bonds, olefin metathesis is a privileged reaction in the armamentarium of synthetic and polymer chemists.[1] Readily available and highly active ruthenium catalysts **1**−**4** have popularized metathesis chemistry in organic solvents (Figure 1).[2,3] On the other hand, metathesis in aqueous solvents largely remains the domain of catalysts designed expressly for use in water (Figure 2).[4−6] Despite the allure of aqueous olefin metathesis for biological applications[7] and green

chemistry,[8] the synthesis of these water-soluble ligands and complexes imposes barriers to their wider use. Developing aqueous reaction conditions suitable for catalysts such as **1**−**4** is an alternative approach. In the initial work with well-

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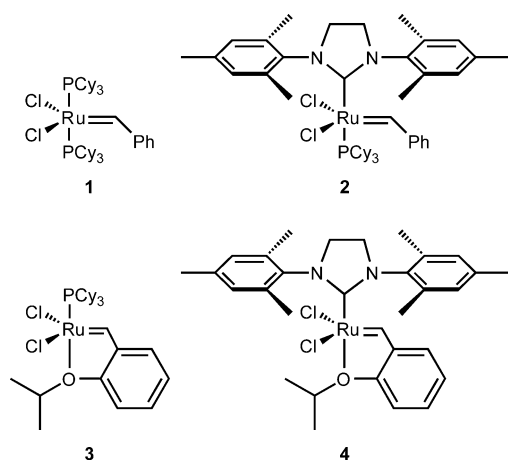
Figure 1. Conventional ruthenium olefin metathesis catalysts.

defined catalysts in aqueous systems, Grubbs and co-workers performed ring-opening metathesis polymerization (ROMP) with **1** in aqueous emulsions,[9] a method that allowed Kiessling and co-workers to synthesize biologically active glycopolymers.[10] For ring-closing metathesis (RCM) and cross metathesis (CM), Blechert and co-workers employed commercially available **2** and complex **6c**, a relative of commercially available **4**, in water/methanol and water/DMF
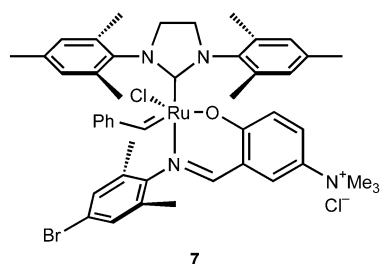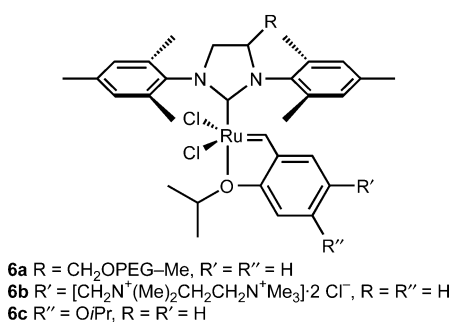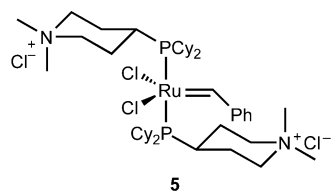

6a R = CH₂OPEG–Me, R′ = R″ = H
6b R′ = [CH₂N⁺(Me)₂CH₂CH₂N⁺Me₃]·2 Cl⁻, R = R″ = H
6c R″ = O*i*Pr, R = R′ = H

Figure 2. Metathesis catalysts adapted for aqueous solvents.

mixtures.[6] Although they achieved high conversion in the ring closure of *N*-tosyldiallylamine (**8**) in 3:1 water/methanol and 3:1 water/DMF over an extended reaction time of 12 h, these reactions were not accomplished in homogeneous systems: neither the substrate nor the catalyst was dissolved completely in the aqueous phase. In most cases detailed in their report, the ruthenium complex was only sparingly soluble in the aqueous reaction mixture.

Metathesis in homogeneous aqueous systems would likely be faster and more versatile than in these heterogeneous systems. An effective system for metathesis with commercially available catalysts in homogeneous aqueous media would not only make this chemistry more accessible but also highlight the limitations of the standard catalysts in water, informing catalyst-design efforts. Yet reports of the use of common metathesis catalysts in an aqueous context are limited. For these reasons, we chose to test the capabilities of catalysts **1**−**4** in homogeneous aqueous media, and we report the results of our exploration herein. First, we screened various organic solvents as cosolvents for RCM of **8** in homogeneous aqueous solution (Table 1). The solvents

Table 1. RCM Catalyzed by **2** in Aqueous Media
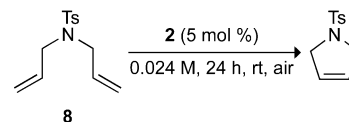
solvent[a]	conversion (%)
4:1 THF/H₂O	3
4:1 1,4-dioxane/H₂O	5
4:1 DMF/H₂O	75
4:1 (CH₃)₂CO/H₂O	>95
4:1 DME/H₂O	>95
3:1 PEG-500 dimethyl ether/H₂O	>95

[a] Mass:mass ratio.

typically used for olefin metathesis reactions, such as CH₂Cl₂, 1,2-dichloroethane, and toluene, are immiscible with water, so we resorted to water-miscible solvents. Tetrahydrofuran (THF), used previously as a solvent for ROMP and acyclic diene metathesis with varying success,[11] failed as a cosolvent for RCM. On the other hand, the ethylene glycol ether based solvents dimethoxyethane (DME or glyme) and poly(ethylene glycol) (PEG) were excellent cosolvents. Their improved results with respect to THF and dioxane could relate to their better coordinating ability.[12] Able to coordinate the tetra-coordinate ruthenium complexes of the metathesis catalytic

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cycle, these ethers could more ably protect them from detrimental coordination by water. Grubbs and co-workers suggest that decomposition of metathesis intermediates in water results from water coordination at ruthenium in the methylidene-propagating species.[13] Interestingly, these results show that the protective environment of the PEG-bearing ligand in **6a** can also be provided by ethylene glycol ethers in the bulk solvent.

Next, we studied the performance of different commercially available catalysts in the DME/water solvent system with substrate **8** (Figure 3). Phosphine-free complex
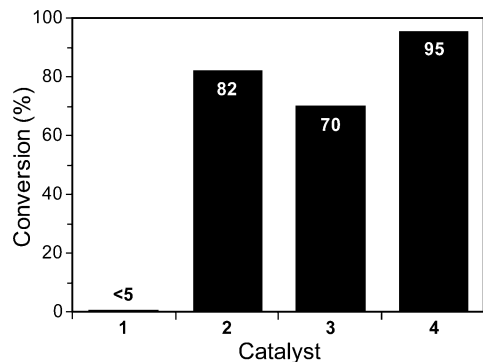

Figure 3. RCM conversion of 0.05 M substrate **8** catalyzed by complexes **1**−**4**: 1 mol % [Ru], 2:1 DME/water, 24 h, rt, under air.

4 displayed the highest turnover, with both *N*-heterocyclic carbene (NHC) complexes outperforming the first-generation catalysts. The more σ-donating NHC ligand could aid olefin coordination over attack by water, favoring metathesis with the second-generation catalysts as opposed to decomposition. The advantage of **4** over **2** is more difficult to rationalize because both complexes produce the same propagating species. The improved performance of **4** could be due to the presence of the chelating isoproxy moiety, which could potentially protect the catalyst from decomposition in water prior to entry into the catalytic cycle, as suggested by Blechert and co-workers for metathesis in organic solvents.[14] Although the ether ligand binds more loosely than does the phosphine of **2** (**4** initiates >800-fold faster at 25 °C),[15] its rebinding to ruthenium prior to metathesis is unimolecular. As a result, the ether ligand is more likely to rebind the

coordinatively unsaturated intermediate, protecting it from water to preserve the complex in solution.[14] In addition to helping select known catalysts for use in water/organic systems, these results can inform the design of water-soluble catalysts. The combination of a chelate and an NHC produces a more effective catalyst for aqueous metathesis, as borne out by complexes **6a**, **6b**, and **7**. Future catalyst designs should incorporate these features.

Following the identification of **4** as the superior catalyst in the water/DME system, the progress of RCM in acetone/water was monitored to evaluate the rate of the reaction and the lifetime of catalytically active species (Figure 4). The
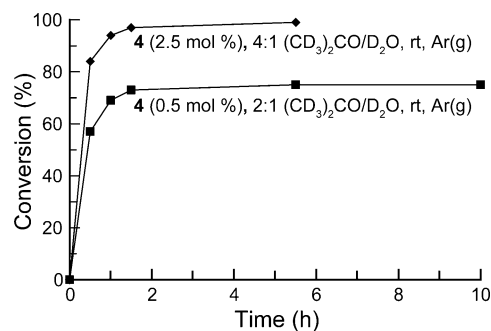

Figure 4. Kinetics of RCM of 0.05 M substrate **8** catalyzed by complex **4** in acetone/water monitored by ^{1}H NMR spectroscopy.
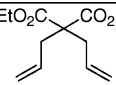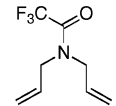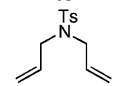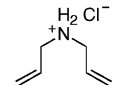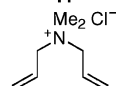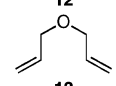
majority of RCM occurred within 90 min of the beginning of the reaction, as is typical for RCM of **8** with this catalyst and temperature.[16] Notably, this reaction is far faster than the 12-h reaction time reported by Blechert and co-workers for their heterogeneous systems.[10] Nevertheless, catalyst decomposition also proceeds quickly in the aqueous solvent, with the results of the trial with 0.5 mol % catalyst indicating that the majority of the catalytically active species is destroyed within 90 min. In organic solvents, on the other hand, complex **4** can be recovered after RCM reactions requiring several hours.[3]

With optimized reaction conditions established, we probed the RCM of a variety of dienes using complex **4** in aqueous DME and acetone solutions. Under these homogeneous conditions, substrates with a variety of substituents were metathesized to form five-, six-, and seven-membered cyclic products (Table 2). Hig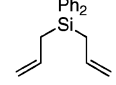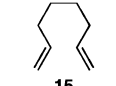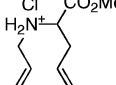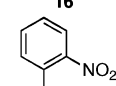h conversion was consistently achieved with traditional nonpolar substrates, except for diallyldiphenylsilane (**14**). Water-soluble substrates such as **11** and **16**, a putative model for peptide substrates, were more challenging, requiring increased catalyst loading and organic cosolvent concentrations for high conversion. As it has with many other metathesis systems, diallyldimethylammonium chloride (**12**) resisted RCM.[5,17]

Complex **4** is also capable of homodimerization of allyl alcohol (**18**) in acetone/water, achieving good conversion

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Table 2. RCM of Representative Dienes Catalyzed by **4** in Aqueous Media under Air

substrate	solvent ([substrate], M)	mol % 4	conversion (%) (time, h)
9	2:1 $(CD_3)_2CO/D_2O$ (0.05)	3	>95 (2)
	2:1 DME/H_2O (0.05)	3	85 (3)
10	2:1 $(CD_3)_2CO/D_2O$ (0.05)	3	90 (2)
	2:1 DME/H_2O (0.05)	3	>95 (3)
8	2:1 $(CD_3)_2CO/D_2O$ (0.05)	3	>95 (2)
	2:1 DME/H_2O (0.05)	1	95 (24)
11	2:1 $(CD_3)_2CO/D_2O$ (0.01)	10	>95 (48)
	4:1 DME/H_2O (0.05)	10	77 (24)
12	2:1 $(CD_3)_2CO/D_2O$ (0.05)	3	0 (2)
13	2:1 $(CD_3)_2CO/D_2O$ (0.05)	3	>95 (2)
14	2:1 $(CD_3)_2CO/D_2O$ (0.05)	3	0 (2)
	2:1 DME/H_2O (0.05)	3	0 (3)
15	2:1 $(CD_3)_2CO/D_2O$ (0.05)	3	>95 (2)
16	4:1 DME/H_2O (0.02)	40	>95 (24)
17	2:1 $(CD_3)_2CO/D_2O$ (0.05)	3	>95 (2)
	2:1 DME/H_2O (0.05)	3	75 (4)

Table 3. CM Catalyzed by **4** in an Aqueous Medium under Air

10 mol % **4**, 0.1 M substrate **18**
2:1 $(CD_3)_2CO/D_2O$, rt, air

time (h)	conversion (%)
2	71
6	75

sions can be drawn: homogeneous water/organic mixtures could be advantageous for some olefin metathesis reactions, and the principle advantage of current aqueous metathesis catalysts is merely water solubility. Conventional catalysts such as **4** are active in aqueous solvents and hence can be used for metathesis of polar molecules if the substrate is amenable to aqueous DME, PEG, or acetone. For instance, some enzymes and polysaccharides are compatible with aqueous DME,[19] suggesting that these biomolecules might be suitable for a metathesis strategy that avoids the synthesis of specialized complexes. Moreover, we have found that ribonuclease A is >90% soluble in 3:2 DME/phosphate-buffered saline (PBS). In this solution, complex **4** not only is soluble but also catalyzes the quantitative RCM of *N*-tosyldiallylamine (**8**), even in the presence of ribonuclease A.[20] Thus, apart from its insolubility in pure water, **4** is nearly as effective in the presence of water as are specialized complexes such as **6b**. Hence, additional advances in aqueous metathesis will require enhanced ligands that not only provide water solubility but also improve upon the NHC and isopropoxy chelate in protecting the complex from water.

Supporting Information Available: Procedure for the preparation of compound **16** and for performing metathesis reactions and related analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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over several hours (Table 3). Nevertheless, CM of other substrates in aqueous solvents has proven elusive for us as well as others.[5,18]

The effectiveness of **4** for RCM and CM in water/organic solution is comparable to that of complex **6b**, which is among the best catalysts for metathesis in pure water. Two conclu-

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(20) Reaction conditions: 4 mol % **4**, 0.025 M substrate **8**, 0.2 mg/mL ribonuclease A, 3:2 DME/PBS, 24 h, rt, under air. It is noteworthy that water comprises 80% of the molecules in this reaction mixture.