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Highly Active Water-Soluble Olefin Metathesis Catalyst

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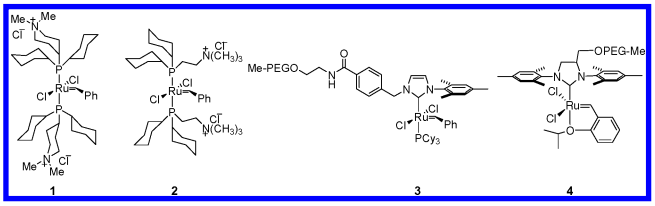
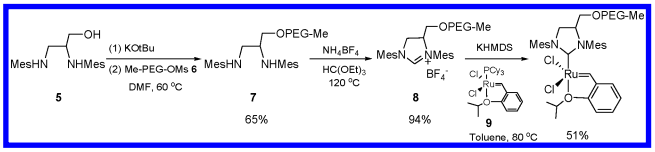
Olefin metathesis is a powerful carbon−carbon bond formation reaction in both polymer and small molecule synthesis.[1] In particular, the recent development of ruthenium olefin metathesis catalysts, which show high activity and functional group tolerance, has expanded the scope of olefin metathesis. However, performing olefin metathesis in aqueous media is still challenging due to the lack of a stable and active catalyst soluble in water. Aqueous olefin metathesis has the economic, environmental, and processing benefits of both homogeneous aqueous catalysis and aqueous two-phase catalysis.[2] Further, aqueous olefin metathesis is critical for some biological applications of olefin metathesis.



With the goal of developing a homogeneous catalyst that displays increased activity and stability, our group has reported several water-soluble catalysts, such as **1**,[3] **2**,[3] and **3**.[4] Catalysts **1**−**3** are unable to mediate the ring-closing metathesis (RCM) reaction of simple α,ω-dienes in water and show limited RCM activity in methanol. Moreover, they do not show any activity in cross-metathesis (CM) reactions in protic media. The recently developed catalyst **3** containing an *N*-heterocyclic carbene (NHC)-based ligand shows improved activity in aqueous ring-opening metathesis polymerization (ROMP) reactions.[4] Appending poly(ethylene glycol) (PEG) to the nondissociating NHC ligand allows catalyst **3** to remain in solution throughout the entire metathesis reaction. However, having the PEG−carbamoyl−benzyl group as a pendant group of NHC limited the stability of the complex **3**. Earlier studies have shown that 1,3-diaryl group of NHCs in (NHC)(L)$(Cl)_2$Ru═CHPh-type complexes are important for catalyst stability.[5] As part of the ongoing effort to use PEG as a water solubilizing moiety, we have developed the novel water soluble catalyst **4** which shows improved stability and activity in water. Appending PEG on the backbone of saturated 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene (H_2IMes) ligand renders catalyst **4** soluble in organic solvents, such as dichloromethane and toluene, as well as water, with maintaining stability and activity of well-known H_2IMes-based ruthenium metathesis catalysts.[6]

Catalyst **4** was prepared in three steps from readily available starting materials. PEG-attached diamine **7** was synthesized using an S_N2-type reaction between *N*,*N*′-dimesityl-2,3-diamino-1-propanol **5**[7] and PEG mesyl methyl ether **6**. The diamine **7** was subsequently converted to the corresponding imidazolium salt **8** through condensation with triethyl orthoformate in the presence of ammonium tetrafluoroborate. Deprotonation of **8** with potassium bis(trimethylsilyl)amide (KHMDS) followed by the addition of Ru

Scheme 1. Synthesis of Catalyst **4**



complex **9** generated the desired catalyst **4** (Scheme 1). Catalyst **4** was purified by column chromatography followed by precipitation from dichloromethane into diethyl ether. Attempts to synthesize a phosphine-containing version of this catalyst were unsuccessful.

Complex **4** is stable in water. In the ^{1}H NMR recorded in D_2O, no signal corresponding to the benzylidene proton (Ru═C*H*Ph, δ 16.4 ppm, CD_2Cl_2) was observed. Initially, this was believed to be either due to deuterium exchange of the benzylidene proton[3d] or from rapid decomposition of **4** in D_2O. However, upon extracting the catalyst with CD_2Cl_2 from the D_2O solution, the benzylidene peak reappeared. Even after 1 week in D_2O, the ^{1}H NMR spectra, after CD_2Cl_2 extraction, were not significantly altered, showing stability of this catalyst in water.[8] This type of solvent-dependent NMR behavior has been reported in micelle-type complexes.[9] We believe that catalyst **4** aggregates could form a micelle-like structure in D_2O due to the hydrophilic PEG chain and hydrophobic ruthenium center.[10]

As an activity comparison, we examined the ROMP of *endo*-norbornene monomer **10** with catalysts **2**, **3**, and **4**.[11] As shown by Figure 1, catalyst **4** showed much improved activity when compared to other water-soluble catalysts.[12] This is consistent with past results as saturated NHC-based ruthenium olefin metathesis catalysts are known to be more active than phosphine-based and unsaturated NHC-based catalysts.[5,6]

RCM reactions of water-soluble α,ω-dienes have been highly challenging due to instability toward water of the Ru methylidene species generated after the first catalytic turnover.[3b] There have been a few reports of RCM of α,ω-dienes in water.[13] However,

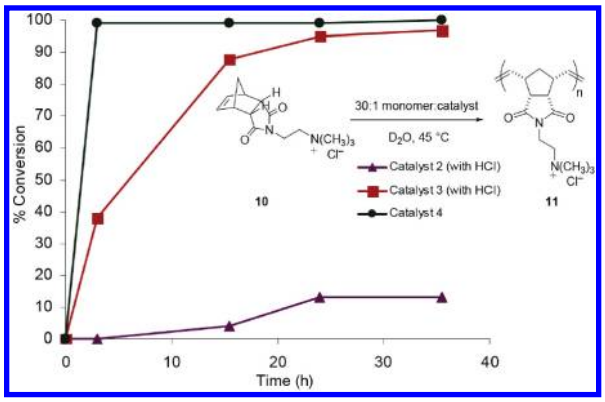


Figure 1. A comparison of the ability of water-soluble catalysts to polymerize *endo*-monomer **10** (data for catalyst **2** and **3** are obtained from ref 4).

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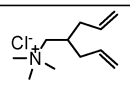
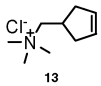
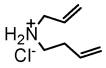
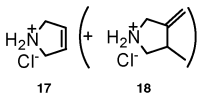
Table 1. Ring-Closing Metathesis Reactions in Aqueous Media[a]

Entry	Substrate	Time	Product	Conversion
1	 **12**	12 h	 **13**	>95%
2	 **14**	24 h	 **15**	>95%
3	 **16**	36 h	 **17** **18**	67% (+28%)
4	 **19**	24 h	 **20**	42%
5	 **21**	24 h	 **22**	<5%

[a] Reactions were carried out at room temperature with 5 mol % of catalyst **4** and an initial substrate concentration of 0.2 M in D_2O or H_2O. Conversions were determined by ^1H NMR spectroscopy.

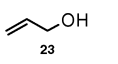
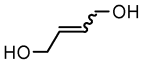
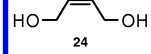
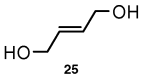
the reported reactions either involved water-insoluble substrates or water-insoluble catalysts.[13] The actual metathesis reactions in these systems are believed to occur in organic-friendly environments, such as inside solid supports, as a decrease in activity is observed with water-soluble α,ω-dienes. The best reported conversion of RCM of diallylamine hydrochloric acid salt **16** in water was just 11% at 45 °C.[13b] In homogeneous systems, there has been no report of the RCM of the α,ω-dienes in aqueous media.[14]

Catalyst **4** showed unprecedented RCM activity with water-soluble α,ω-dienes in water yielding the corresponding five- and six-membered rings in good to excellent yields (Table 1). RCM of **12** and **14** produced the corresponding five-membered and six-membered ring compounds, **13** and **15**, quantitatively (entries 1 and 2). In RCM of **16**, cycloisomerized product **18** was observed along with the major metathesis product **17** (entry 3). This type of cycloisomerization has previously been observed during olefin metathesis, presumably by ruthenium hydrides from catalyst decomposition.[13b,15] For the other substrates (entries 1, 2, 4, and 5), the corresponding cycloisomerized products were not observed. Allyl-2-methylallylamine hydrochloride **19** was cyclized to generate a trisubstituted olefin **20** with relatively lower yield (entry 4). For reasons not yet fully understood, RCM of diallyldimethylamine chloride **21** was not successful (entry 5).

Cross-metathesis is also challenging in aqueous media. To the best of our knowledge, there have been no reports of homogeneous cross-metathesis in water. The Blechert group demonstrated homodimerization of allyl alcohol **23** in D_2O up to 80% conversion using the aforementioned heterogeneous catalyst system.[13b] Catalyst **4** shows excellent activity in homodimerization of **23** and the self-metathesis of *cis*-2-butene-1,4-diol **24** in water (Table 2). However, cross-metathesis reaction with catalyst **4** is highly substrate dependent. **4** is unable to homodimerize vinylacetic acid, allylamine hydrochloride, and other water-soluble olefins derived from carboxylic acid and quaternary ammonium salts. Variations of pH using DCl or NaOD solutions did not improve the cross-metathesis activity of catalyst **4**.

A novel water-soluble catalyst which is active and stable in water has been developed. This catalyst shows unprecedented activity in ROMP, RCM, and CM in aqueous media.

Table 2. Cross-Metathesis Reactions in Aqueous Media[a]

Substrate	Time	Product	Conversion
 **23**	12 h		>95%[b]
 **24**	12 h	 **25**	94%[c]

[a] Reactions were carried out at 45 °C with 5 mol % of catalyst **4** and an initial substrate concentration of 0.2 M in D_2O or H_2O. Conversions were determined by ^1H NMR spectroscopy. [b] $E/Z \sim 15:1$. [c] 6% of **24** remains due to thermodynamic equilibrium.

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Earlier work demonstrated that *endo*-norbornene monomers are challenging ROMP substrates when compared to *exo*-norbornene monomers. See refs 1 and 4.
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