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A neutral, water-soluble olefin metathesis catalyst based on an *N*-heterocyclic carbene ligand

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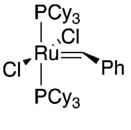
Abstract—A water-soluble ruthenium-based olefin metathesis catalyst supported by a poly(ethylene glycol) conjugated *N*-heterocyclic carbene ligand is reported. The catalyst displays greater activity in aqueous ring-opening metathesis polymerization (ROMP) reactions than previously reported water-soluble metathesis catalysts.

The olefin metathesis reaction is a powerful method for carbon–carbon bond formation in both polymer and small molecule synthesis.[1,2] In particular, ruthenium-based olefin metathesis catalysts are well suited for applications in organic synthesis because they are remarkably tolerant of air, moisture, and a large variety of functional groups.[3–5] The high tolerance of **1** toward water inspired the development of water-soluble analogs **2** and **3** that catalyze olefin metathesis reactions in water and protic organic solvents.[6–10] Ruthenium-based olefin metathesis catalysts incorporating *N*-heterocyclic carbene ligands (**4** and **5**) display increased metathesis activity relative to **1** and retain the functional group tolerance that is a hallmark of **1**.[11–13] With the goal of developing a homogenous aqueous catalyst that displays increased activity relative to bis(phosphine) analogs **2** and **3** we synthesized the poly(ethylene glycol) (PEG) conjugated *N*-heterocyclic carbene-containing ruthenium benzylidene catalyst **8** as shown in Scheme 1. We anticipated that inclusion of the PEG group would not only render the catalyst soluble in water and some organic solvents, such as toluene and dichloromethane, but also insoluble in diethyl ether. This solubility profile could prove useful in the separation of catalyst **8** from organic products. For example, the catalyst could be removed from organic-soluble material by precipitation from diethyl ether. Additionally, in contrast to other polymer displayed metathesis catalysts,[14–20] appending PEG to the non-dissociating *N*-heterocyclic carbene ligand allows catalyst **8** to remain in solution throughout the entire metathesis reaction.

The ring-opening metathesis polymerization (ROMP) of *exo*-monomer **9** was investigated to examine the reactivity of catalyst **8** in water (Scheme 2). In D_2O at 45 °C,



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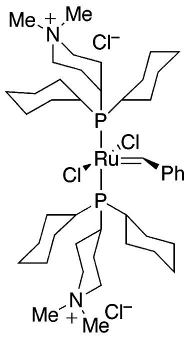

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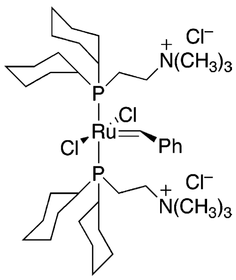

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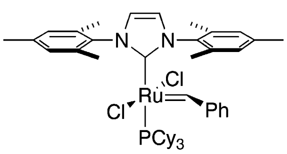

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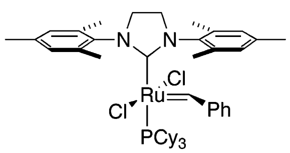

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Keywords: Olefin metathesis; Aqueous metathesis; Ruthenium; *N*-Heterocyclic carbene; Ring-opening metathesis polymerization.

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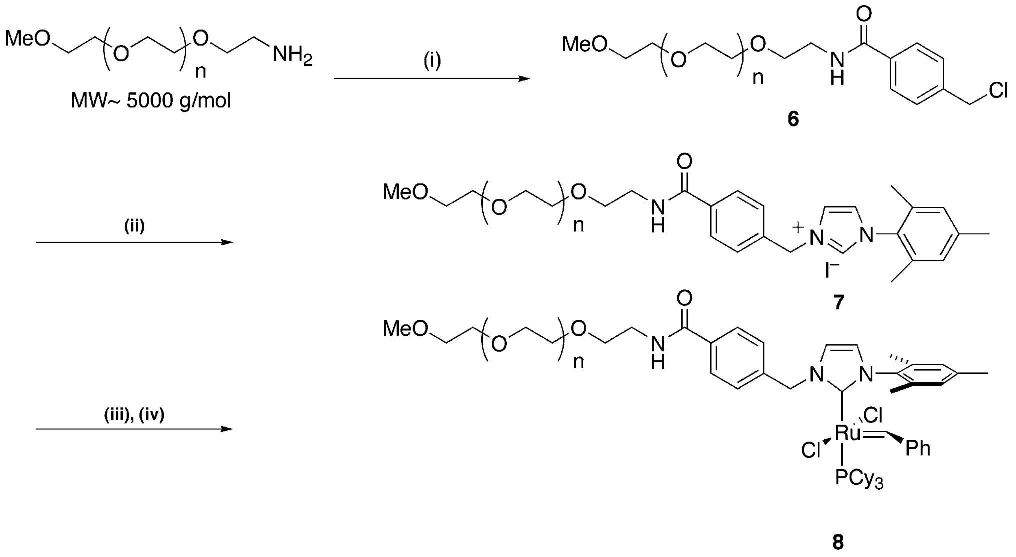
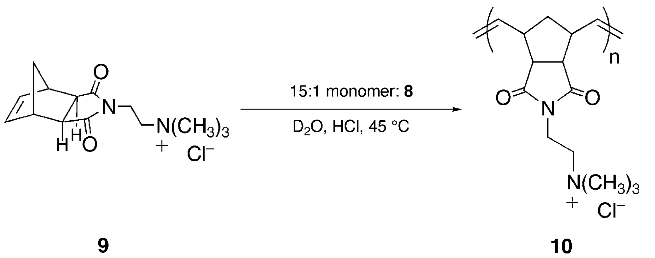


Scheme 1. Reagents and conditions: (i) 4-(chloromethyl)benzoyl chloride, DMAP, pyr, CH_2Cl_2, 25 °C, 4 h (87 %), (ii) mesityl imidazole, NaI, acetone, 60 °C, 14 h (98%), (iii) KO^{t}Bu, tol, 25 °C, 15 min, (iv) **1**, tol, 25 °C, 20 min (58%).



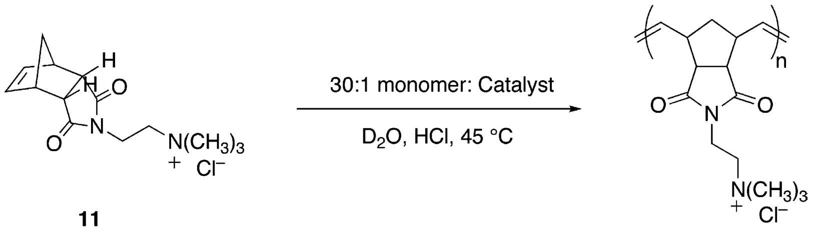
Scheme 2.

catalyst **8** initiated the ROMP of **9** to give polynorbornene **10** in 73% conversion after 24 h, as measured by ^{1}H NMR spectroscopy. Further conversion was not observed even after an additional 12 h at 45 °C. However, in the presence of 1 equiv of HCl, relative to **8**, the catalyst polymerized monomer **9** to 95% conversion within 15 min. This observation is consistent with mechanistic studies which have shown that phosphine dissociation from catalysts **1**, **4**, and **5** is required for entry into the catalytic cycle.[21] Dissociation of phosphine from catalyst **8** may be disfavored in water due to the energetic cost of solvating two neutral molecules. Thus, protonation of free phosphine by HCl inhibits re-association of the phosphine ligand thereby increasing catalyst activity. This is consistent with studies of water-soluble bis(phosphine) catalysts **2** and **3**, which showed that the addition of 0.3–1.0 equiv of HCl, relative to catalyst, increased catalyst activity with the concomitant observation of protonated phosphine.[6]

Earlier work has demonstrated that *endo*-norbornene monomers are challenging ROMP substrates.[1,22,23] For this reason, the ROMP of *endo*-monomer **11** was studied to compare the activities of catalyst **8** and the bis(phosphine) catalyst **3**. Gratifyingly, under acidic conditions, catalyst **8** was able to effect the ROMP of hindered norbornene **11**, and the polymerization proceeded to 95% conversion within 24 h as judged by ^{1}H NMR spectroscopy. The ROMP of **11** with catalyst **3** was slower and proceeded to only 13% conversion after 24 h in acidic water (Fig. 1). These results suggest that, in aqueous media, the *N*-heterocyclic carbene-containing catalyst **8** is significantly more active for the polymerization of hindered norbornenes than the previous generation of bis(phosphine) catalysts.

Although an active catalyst species was not detected spectroscopically, the relatively long reaction times required to completely polymerize **11** suggest that some potentially active species must be present in solution beyond 24 h. To further investigate the lifetime of **8** in solution, upon completion of the reaction detailed in Figure 1, the catalyst **8** reaction mixture was allowed to stand at room temperature for 56 h. Then, 10 equiv of *exo*-monomer **9** were added, and after an additional 24 h at 45 °C, ^{1}H NMR showed that 87% of the newly added monomer had been converted to polymer. In contrast, addition of 10 equiv of monomer **9** to a solution of benzylidene **8** in acidic D_2O that had undergone the same schedule of heating and standing in the absence of monomer gave only 4% polymer after 24 h at 45 °C. This suggests that the metathesis-active ruthenium alkylidene generated during ROMP of **8** with monomer **11** is more stable in acidic water than the parent benzylidene.

Finally, to determine the activity of **8** in polar, protic organic solvents, cyclooctene was polymerized in methanol. Benzylidene **8** catalyzes the ROMP of cyclooctene to give polycyclooctene in 86% conversion within 14 h at 45 °C. To further examine the activity of **8** in polar organic solvents, several ring-closing metathesis reactions were attempted in methanol (Table 1). As an initial test, the ring closing of diethyl diallylmalonate (**12**) was attempted. Although the conversion for this transformation was low (40%), it represented a significant improvement over previous results with methanol-soluble bis(phosphine) catalysts **2** and **3**.[24] The low yields for the bis(phosphine) catalysts were attributed to the



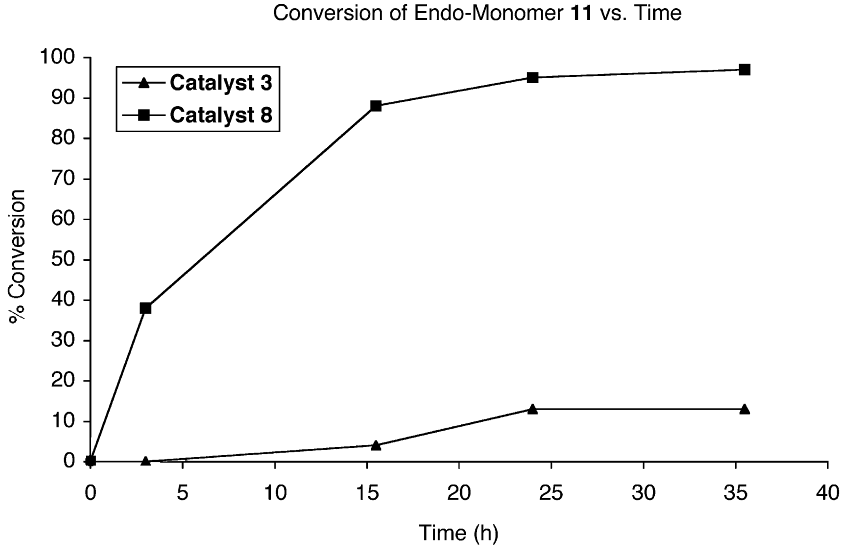
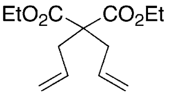
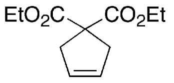
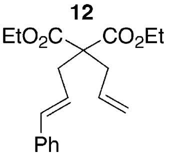
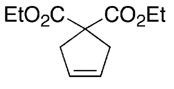
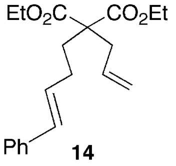
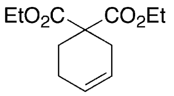


Figure 1. A comparison of the ability of catalysts **3** and **8** to polymerize challenging, *endo*-monomer **11**.

Table 1. Ring-closing metathesis reactions in methanol with catalysts **8**, **2**, and **3**

Substrate	Product	% Conversion with catalyst		
		8[a]	**2**[b]	**3**[b]
 **12**		40	<5	0
 **13**		62	80	95
 **14**		82	45	55

[a] Reactions were carried out at 45 °C with 5 mol % catalyst with an initial substrate concentration of 0.2 M in methanol-d_4. Conversions were determined by ^{1}H NMR spectroscopy.

[b] Data from Ref. 24.

instability of the ruthenium methylidene intermediate [Ru]=CH_2 produced after a single turnover.[24] Consistent with this hypothesis, ring-closing reactions using the phenyl-substituted substrates **13** and **14** that do not produce a methylidene intermediates gave higher yields of cyclized product with bis(phosphine) catalysts **2** and **3**.[24] Similarly, catalyst **8** also generated higher cyclized yields with substrate **13** than with **12** which suggests that the methylidene derivative of **8** is also unstable or less active in methanol. Consistent with these observations, the cross-metathesis of terminal olefins, which proceeds through a methylidene intermediate,[25,26] has currently been unsuccessful in protic media.

Catalyst **8** is insoluble in ether. Therefore, precipitation of a reaction mixture followed by filtration might provide a simple way to remove **8** from organic products. This is an attractive feature as ruthenium by-products are often difficult to remove from metathesis reactions.[27,28] Gratifyingly, precipitation of the reaction mixture from the ring closing of **14** with catalyst **8** from ether followed by filtration reduces the mixture's PEG content by nearly 97% (as judged by ^{1}H NMR spectroscopy, data not shown).[‡]

In conclusion, PEG was incorporated into the first example of a homogenous aqueous olefin metathesis catalyst coordinated with a *N*-heterocyclic carbene ligand. Catalyst **8** initiates the ring-opening metathesis polymerization of strained cyclic olefins in both water and methanol. Furthermore, direct comparison of the

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[‡] While diminution of the mixture's PEG content does not guarantee a reduction of its ruthenium content, this is a promising result for the proposed strategy of ruthenium extraction.

activity of **8** relative to a previously reported water-soluble bis(phosphine) catalyst reveals that catalyst **8** is more active for the polymerization of hindered monomers in water. In addition to ROMP, **8** also catalyzes the ring-closing metathesis of organic substrates in methanol. These results show that ruthenium olefin metathesis catalysts containing a *N*-heterocyclic carbene ligand are quite active in water.

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Supplementary data

Experimental procedures for ring-closing and ROMP experiments along with ligand, catalyst, and substrate syntheses, including characterization data, are available upon request from rhg@caltech.edu. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.096.

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