Olefin-Metathesis Catalysts

Small-Molecule N-Heterocyclic-Carbene-Containing Olefin-Metathesis Catalysts for Use in Water**

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Olefin metathesis is a powerful transformation in modern chemistry.^[1] By mediating the exchange of olefin substituents, metathesis catalysts enable such reactions as ring-closing metathesis (RCM), cross-metathesis, and ring-opening metathesis polymerization (ROMP) reactions useful for smallmolecule,^[1,2] macromolecular,^[3] and even supramolecular chemistry.^[4] Because they are stable towards air and moisture and tolerant of a broad range of functional groups, ruthenium complexes are particularly useful catalysts for this transformation.^[1,5] While olefin metathesis in traditional organic solvents is now ubiquitous, its potential utility in water is largely untapped.

Hindering the implementation of aqueous metathesis is a lack of suitable catalysts. To address this need, our group has developed water-soluble catalysts 1-4 (PEG: poly(ethylene glycol)).^[6] Other groups have also developed catalysts for use in aqueous environments though these catalysts require cosolvents or perform metathesis in the organic pores of a polymer resin.^[7] Catalysts 1, 2, and 3 are quite unstable in water and only show limited activity for aqueous metathesis reactions other than ROMP.^[6b-c,8] Phosphine-free catalyst 4 demonstrates a greater ability to mediate ring-closing metathesis in an aqueous environment.^[6d] However, 4 is a macromolecular, polydisperse catalyst that appears to form aggregates in water. Therefore, we describe herein the synthesis of small-molecule, N-heterocyclic carbene (NHC)-containing ruthenium complexes 5 and 6 and their activity in aqueous metathesis.

The syntheses of styrenes 10 and 12 used to produce catalysts 5 and 6 are shown in Scheme 1. Chloromethylation followed by Wittig olefination of readily synthesized benzaldehyde 7 provides benzyl chloride 9 in moderate yield. Amination with trimethylamine then yields isopropoxystyrene 10. Amination of 9 with N,N,N',N'-tetramethylethylenediamine followed by methylation and ion exchange gives isopropoxystyrene 12.

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Scheme 1. Reagents and conditions: a) formaldehyde, HCl(aq), HCl(g), 50 °C, 3 h (66%); b) BrCH₃PPh₃, KOtBu, THF, $-60 \rightarrow 15$ °C, 2 h (78%); c) NMe₃, MeCN, 0 °C \rightarrow RT, 12 h (81%); d) Me₂N(CH₂)₂NMe₂, MeCN, RT, 24 h, 90%; e) Mel, CH₂Cl₂, RT, 7 h; f) Amberlite IRA-400(Cl), H₂O, RT, 12 h (performed three times; 81%, three steps).

The synthesis of the ruthenium complex that displays an appropriately substituted NHC ligand for the production of 6 is straightforward (Scheme 2). Selective protection of the



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primary amine of readily prepared triamine **13** followed by cyclization gives dihydroimidazolium salt **15**. Deprotonation and ligand exchange with complex **16** yields the desired ruthenium compound **17**, which appears as a mixture of rotational isomers by ¹H and ³¹P NMR spectroscopy, even at high temperatures, owing to slow rotation about the ruthenium–NHC bond.^[9]

Catalysts **5** and **6** can be synthesized by reacting the appropriate ruthenium benzylidene with styrenes **10** and **12** (Scheme 3). Mixing **10** and **12** with complexes **17** and **18** in the presence of copper(I) chloride gives Boc-protected complex **19** and catalyst **5**, respectively. Deprotection of **19** with freshly prepared HCl/benzene solution then produces catalyst **6**.

Catalyst **5** is only soluble in water at low concentrations (<0.01 M) though it is sufficiently soluble to be detected by ¹H NMR spectroscopy in deuterium oxide. In contrast, catalyst **6** readily dissolves in water. Moreover, catalyst **6** is relatively stable in water with a decomposition half-life of over a week at ambient temperature under inert conditions.

As reported for other water-soluble catalysts,^[6c-d] the ROMP of challenging *endo*-norbornene monomer $20^{[6c,10]}$ was performed to compare the activities of catalysts 2-6 (Figure 1). Both catalysts 5 and 6 rapidly transform monomer 20 into product polymer. Hence, catalysts 5 and 6 are highly competent ROMP catalysts, which show activities similar to 4 for this reaction.



Scheme 2. Reagents and conditions: a) Boc₂O, DMAP, CH₂Cl₂, RT, 2 h (86%); b) HC(OEt)₃, NH₄Cl, 120 °C, 16 h (90%); c) *t*BuOK, **16**, THF, RT, 17 h (61%). Boc: *tert*-butyloxycarbonyl; Cy: cyclohexyl.

Catalysts **5** and **6** also mediate the RCM of α, ω -dienes in water. This is a challenging transformation in water that, to date, has only been catalyzed by catalyst **4**.^[6d] Table 1 lists the results of the RCM reactions of five different substrates with catalysts **5** and **6** and provides the reported results with catalyst **4** for comparison.^[6d] The ring-closing of substrates **21** and **23** is readily accomplished by all three catalysts though a lower conversion of **23** is observed with catalyst **6**. However, the ring-closing of **25** to form a trisubstituted olefin proceeds in good conversion for catalyst **5** and poor conversion for catalyst **6**—a difference ascribed to the relative stabilities of the two catalysts under the reaction conditions. Like catalyst



Scheme 3. Reagents and conditions: a) **12**, CuCl, CH_2Cl_2 , 45 °C, 1 h (46%); b) **10**, CuCl, CH_2Cl_2 , 45 °C, 1 h; c) HCl, C_6H_6 , RT, 45 min (67%, two steps).



Figure 1. Conversion versus time profile for polymerization of monomer **20** by catalysts **2–6** as measured by ¹H NMR spectroscopy. For catalysts **2** and **3**, the polymerization was run in the presence of one equivalent of DCI (versus catalyst) for increased activity. (The results for catalysts **4**, **5**, and **6** overlap. Data for catalysts **2**, **3**, and **4** were obtained from references [6c] and [6d].)

4,^[6d] neither **5** nor **6** successfully ring-closed substrate **27**. The RCM of challenging substrate **29** can yield significant amounts of cycloisomerized side product **31**, which is believed to be produced by ruthenium hydrides generated during catalyst decomposition.^[6d,7c,11] Interestingly, catalyst **5** fully

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Table 1: RCM reactions in water.[a]

Catalyst	Substrate	<i>t</i> [h]	Product	Conversion [%]
4 ^[b]	NMe ₃	12		> 95
5		24	NMe ₃	>95
6	21	0.5	22 ^{CI°°}	> 95
4		24		> 95
5		24		> 95
6	23	4	24	84
4 ^[b]	$+ \frac{H_2}{C}$	24	+	42
5	∧ [™] N [™]	24		70
6	25	6	26	26
4 ^[b]		24		< 5
5		24		< 5
6	27	24	28	< 5
4 ^[b]	H ₂ Cr	36		67 (+28)
5	/ ⁺ N ² / ⁻ /	24	H_2^+ Cr H_2^+ NH ₂	> 95
6	29	4		36 (+59)

[a] Reactions were performed at 30 °C with 5 mol% catalyst and an initial substrate concentration of 0.2 μ in D₂O. Reaction times are not optimized. Conversions were determined by ¹H NMR spectroscopy and represent the average of two trials. [b] Reactions were performed at room temperature with 5 mol% catalyst and an initial substrate concentration of 0.2 μ in D₂O or H₂O. These data were obtained from reference [6d].

Table 2: Cross-metathesis reactions in water.[a]

Catalyst	Substrate	<i>t</i> [h]	Product	Conversion [%]	E/Z
4 ^[b] 5 6	он 32	12 24 6	HO-33 OH O 34 H	>95 82 (+4) 69 (+12)	15:1 13:1 19:1
4 ^[b] 5 ^[c] 6 ^[c]	ноон 35	12 24 2	HOOH	94 92 94	- - -

[a] Reactions were performed at 45 °C with 5 mol% catalyst and an initial substrate concentration of 0.2 μ in D₂O. Conversions were determined by ¹H NMR spectroscopy and represent the average of two trials. Reaction times were not optimized. [b] Reactions were performed at 45 °C with 5 mol% catalyst and an initial substrate concentration of 0.2 μ in D₂O or H₂O. These data were obtained from reference [6d]. [c] Reactions were performed at 30 °C.

ring-closes substrate 29 to the desired product 30 while both 4 and 6 yield significant amounts of 31. While this result is poorly understood, it is speculated to be related to the moderate aqueous solubility of 5 and/or its ruthenium hydrides. These solubility properties may make catalyst 5 more stable than catalysts 4 and 6 and/or its hydrides less active than those formed from catalysts 4 and 6.

While catalysts **5** and **6** show reasonable activity for aqueous RCM, they are poor catalysts for aqueous crossmetathesis. Even so, both **5** and **6** can homodimerize allyl alcohol in moderate conversions and mediate the *cis–trans* isomerization of *cis*-butenediol **35** (Table 2). The activities of catalysts **5** and **6** are quite similar for these two reactions, though both give lower conversions for allyl alcohol homodimerization than catalyst **4**.^[6d] Also, some isomerization of allyl alcohol to propionaldehyde is observed for both catalysts **5** and **6** which is not observed with **4**. These results reflect an apparent lower stability for catalysts **5** and **6** relative to **4** under these reaction conditions. Attempts to dimerize other substrates, including those based on amino acids, carbohydrates, and ammonium salts, failed. Therefore, while catalysts **5** and **6** are unable to make many aqueous cross-metathesis reactions practical, along with catalyst **4** they do represent progress in this area.

In conclusion, the synthesis of two small-molecule aqueous metathesis catalysts has been described. Both catalysts mediate ROMP and RCM reactions in aqueous media. While neither catalyst is sufficiently stable for the practical aqueous cross-metathesis of many substrates, they do homodimerize allyl alcohol.

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