Olefin-Metathesis Catalysts

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

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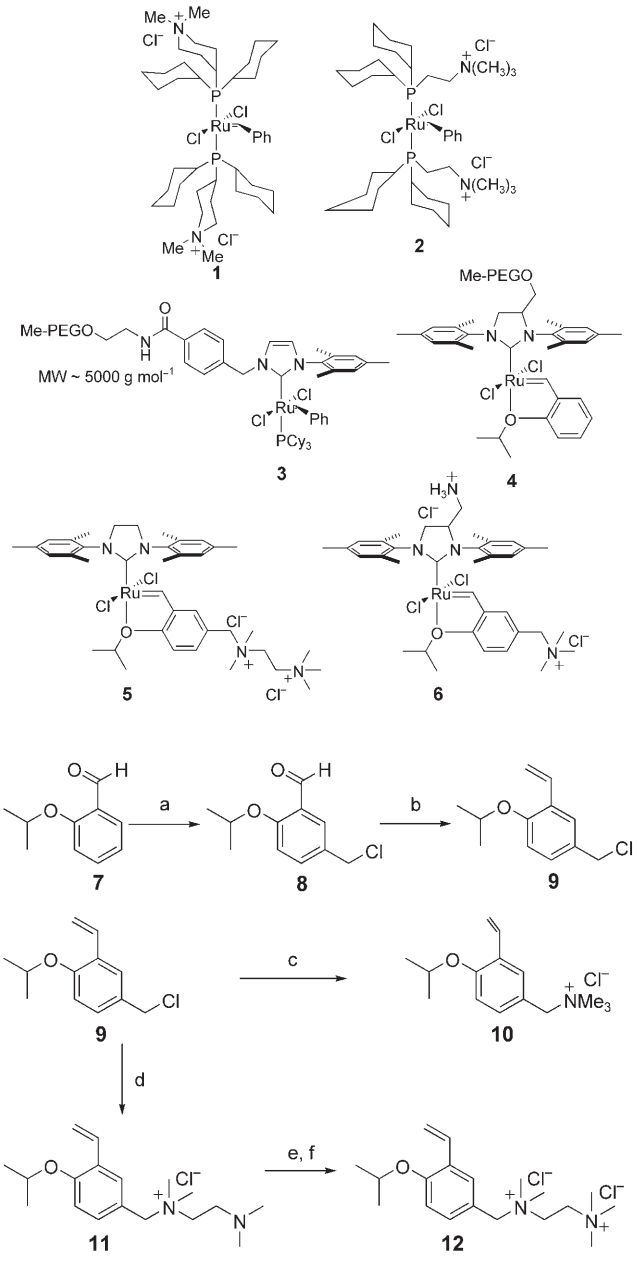
Olefin metathesis is a powerful transformation in modern chemistry.[1] By mediating the exchange of olefin substituents, metathesis catalysts enable such reactions as ring-closing metathesis (RCM), cross-metathesis, and ring-opening metathesis polymerization (ROMP) reactions useful for small-molecule,[1,2] 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**.



Scheme 1. Reagents and conditions: a) formaldehyde, HCl(aq), HCl(g), 50 °C, 3 h (66%); b) $BrCH_3PPh_3$, KO*t*Bu, THF, −60→15 °C, 2 h (78%); c) NMe_3, MeCN, 0 °C→RT, 12 h (81%); d) $Me_2N(CH_2)_2NMe_2$, MeCN, RT, 24 h, 90%; e) MeI, CH_2Cl_2, RT, 7 h; f) Amberlite IRA-400(Cl), H_2O, 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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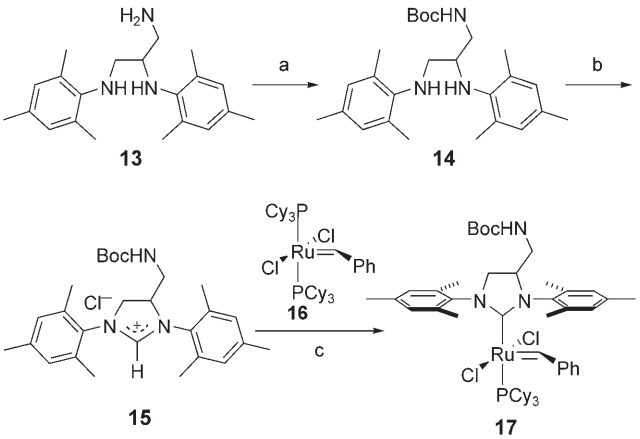
primary amine of readily prepared triamine **13** followed by cyclization gives dihydroimidazolium salt **15**. Deprotonation and ligand exchange with complex **16** yields the desired ruthenium compound **17**, which appears as a mixture of rotational isomers by ^{1}H and ^{31}P NMR spectroscopy, even at high temperatures, owing to slow rotation about the ruthenium–NHC bond.[9]

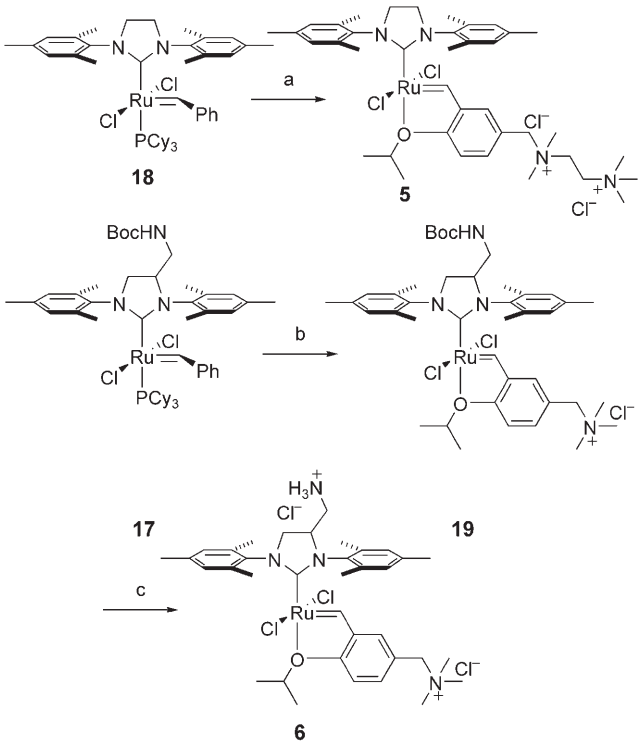
Catalysts **5** and **6** can be synthesized by reacting the appropriate ruthenium benzylidene with styrenes **10** and **12** (Scheme 3). Mixing **10** and **12** with complexes **17** and **18** in the presence of copper(I) chloride gives Boc-protected complex **19** and catalyst **5**, respectively. 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 ^{1}H 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) Boc_2O, DMAP, CH_2Cl_2, RT, 2 h (86%); b) $HC(OEt)_3$, NH_4Cl, 120 °C, 16 h (90%); c) *t*BuOK, **16**, THF, RT, 17 h (61%). Boc: *tert*-butyloxycarbonyl; Cy: cyclohexyl.



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).

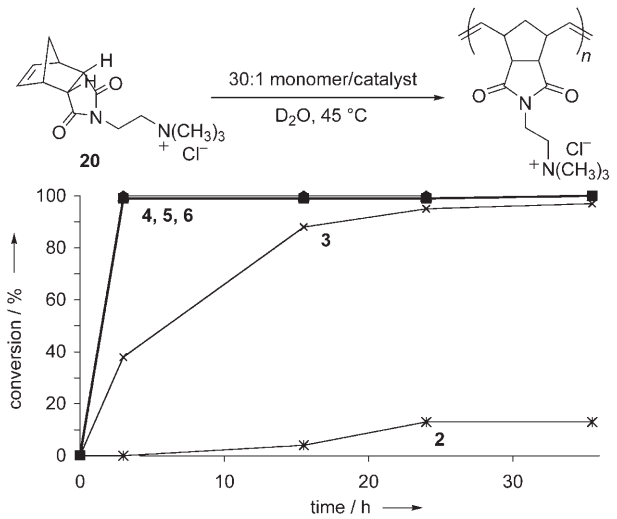
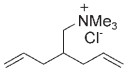
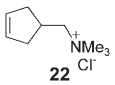
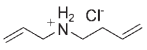
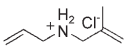
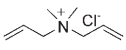
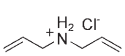
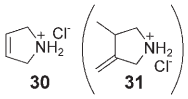


Figure 1. Conversion versus time profile for polymerization of monomer **20** by catalysts **2**–**6** as measured by ^{1}H NMR spectroscopy. For catalysts **2** and **3**, the polymerization was run in the presence of one equivalent of DCl (versus catalyst) for increased activity. (The results for catalysts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

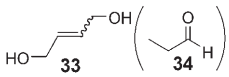
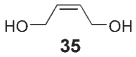
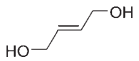
Catalysts **5** and **6** also mediate the RCM of α,ω-dienes in water. This is a challenging transformation in water that, to date, has only been catalyzed by catalyst **4**.[6d] Table 1 lists the results of the RCM reactions of five different substrates with catalysts **5** and **6** and provides the 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 **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

Table 1: RCM reactions in water.[a]

Catalyst	Substrate	*t* [h]	Product	Conversion [%]
4[b]		12		>95
5		24		>95
6		0.5		>95
	21		**22**	
4		24		>95
5		24		>95
6		4		84
	23		**24**	
4[b]		24		42
5		24		70
6		6		26
	25		**26**	
4[b]		24		<5
5		24		<5
6		24		<5
	27		**28**	
4[b]		36		67 (+28)
5		24		>95
6		4		36 (+59)
	29		**30** **31**	

[a] Reactions were performed at 30 °C with 5 mol% catalyst and an initial substrate concentration of 0.2 M in D_2O. 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 M in D_2O or H_2O. These data were obtained from reference [6d].

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

Catalyst	Substrate	*t* [h]	Product	Conversion [%]	*E*/*Z*
4[b]		12		>95	15:1
5		24		82 (+4)	13:1
6		6		69 (+12)	19:1
	32		**33** **34**		
4[b]		12		94	–
5[c]		24		92	–
6[c]		2		94	–
	35				

[a] Reactions were performed at 45 °C with 5 mol% catalyst and an initial substrate concentration of 0.2 M in D_2O. 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 M in D_2O or H_2O. 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 cross-metathesis. 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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