Olefin-Metathesis Catalysts

DOI: 10.1002/ange.200701258

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

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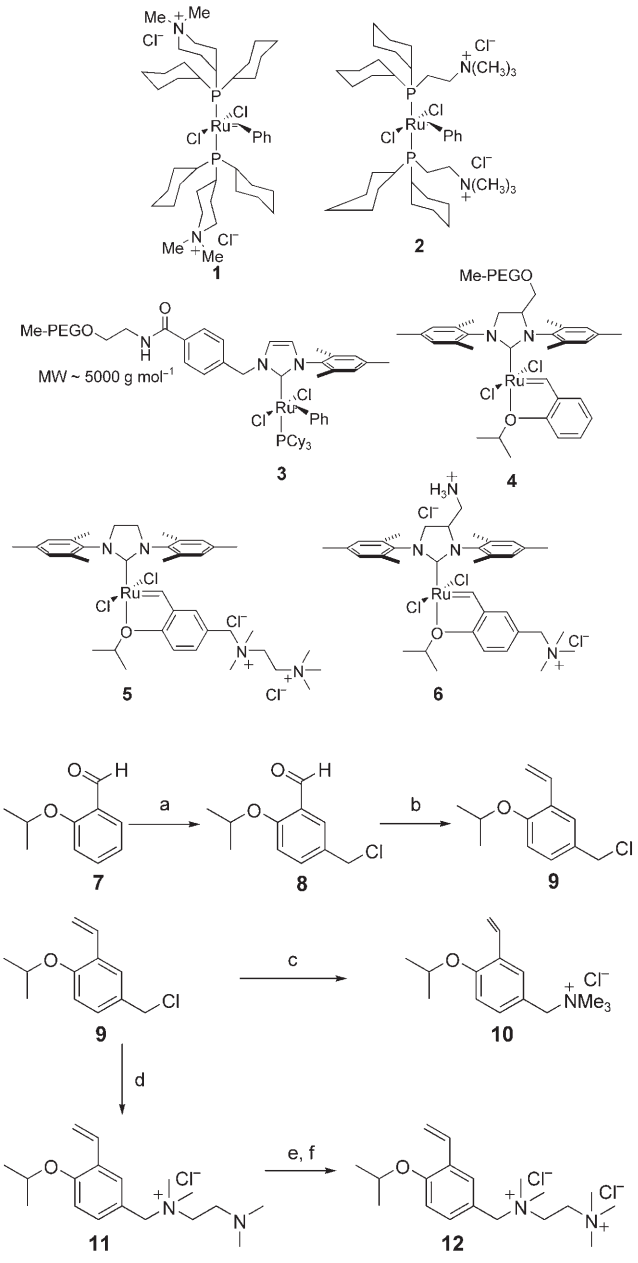
Olefin metathesis is a powerful transformation in modern chemistry.[1] By mediating the exchange of olefin substituents, metathesis catalysts enable such reactions as ring-closing metathesis (RCM), cross-metathesis, and ring-opening metathesis polymerization (ROMP) reactions useful for small-molecule,[1,2] 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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[**] We thank Soon H. Hong for the generous donation of substrates **23** and **25** and for helpful discussions, and Dr. Mona Shahgholi for mass spectroscopic analysis. The National Institutes of Health (5R01M068647) is acknowledged for funding.

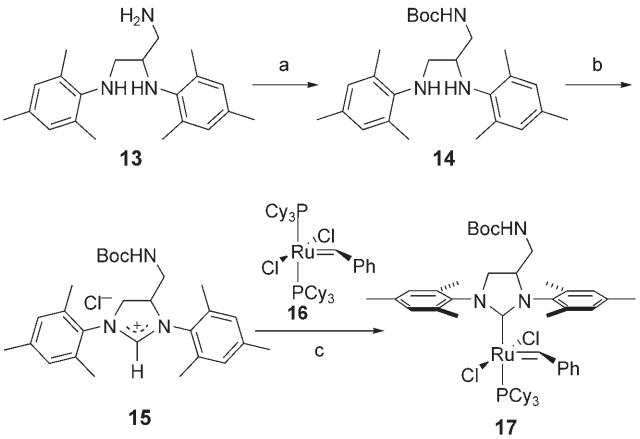
Supporting information for this article, including full experimental details and ^1H and ^{13}C NMR spectra, is available on the WWW under http://www.angewandte.org or from the author.

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]

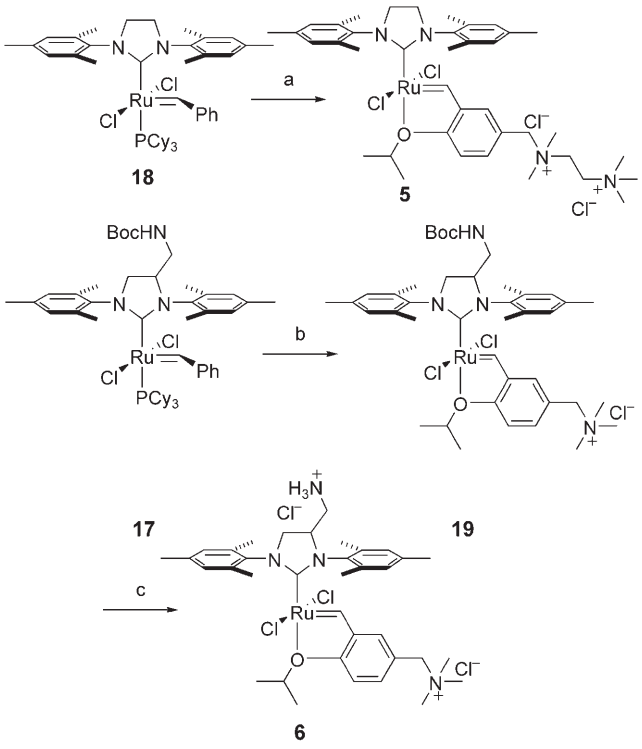
Catalysts **5** and **6** can be synthesized by reacting the appropriate ruthenium benzylidene with styrenes **10** and **12** (Scheme 3). Mixing **10** and **12** with complexes **17** and **18** in the presence of copper(I) chloride gives Boc-protected complex **19** and catalyst **5**, respectively.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

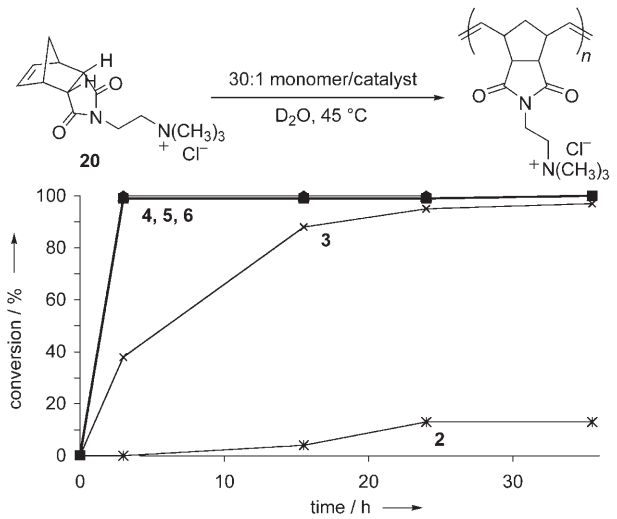
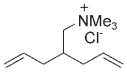
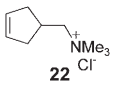
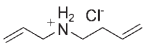
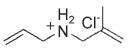
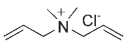
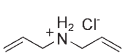
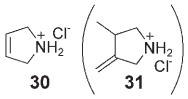


Figure 1. Conversion versus time profile for polymerization of monomer **20** by catalysts **2**–**6** as measured by ^{1}H NMR spectroscopy. For catalysts **2** and **3**, the polymerization was run in the presence of one equivalent of DCl (versus catalyst) for increased activity. (The results for catalysts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

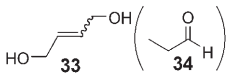
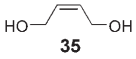
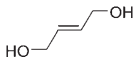
Catalysts **5** and **6** also mediate the RCM of α,ω-dienes in water. This is a challenging transformation in water that, to date, has only been catalyzed by catalyst **4**.[6d] Table 1 lists the results of the RCM reactions of five different substrates with catalysts **5** and **6** and provides the 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	**21**	0.5	**22**	>95
4		24		>95
5	**23**	24	**24**	>95
6		4		84
4[b]		24		42
5		24		70
6	**25**	6	**26**	26
4[b]		24		<5
5		24		<5
6	**27**	24	**28**	<5
4[b]		36		67 (+28)
5		24		>95
6	**29**	4	**30** **31**	36 (+59)

[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	**32**	6	**33** **34**	69 (+12)	19:1
4[b]		12		94	–
5[c]		24		92	–
6[c]	**35**	2		94	–

[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.

Received: March 21, 2007
Published online: June 5, 2007

Keywords: metathesis · N-heterocyclic carbenes · polymerization · ruthenium · water

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