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Studies of a soluble polyethylene glycol immobilized ruthenium catalyst in aqueous media

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ABSTRACT

We have developed an air-stable soluble polyethylene glycol bound ruthenium catalyst which performs efficient ring-closing metathesis in organic solvents as well as in aqueous media.

Well-defined ruthenium-based catalysts such as **1a** and **1b** are widely used in a range of organic solvent-based olefin metathesis reactions because of their high functional group tolerance and ease of handling. While these catalysts do show some stability and activity in the presence of water,[1] their use in aqueous media is limited by a lack of solubility.[2] Various approaches have been developed to begin to overcome this shortcoming.[3]

A number of water-soluble catalysts have been reported that contain a water-solubilising ligand, for example, as in **2a** and **2b**.[4] These catalysts successfully promote ring-opening metathesis polymerization (ROMP) in aqueous media[5] and show limited ring-closing metathesis (RCM) activity of simple α,ω-dienes in methanol.[6] An improved catalyst **3** with a heterogeneous hydrophilic polymeric support, PEGA attached to the benzylidene ligand has been reported.[7] This catalyst successfully performs various RCM and cross metathesis (CM) reactions in methanol and water.[7] The hydrophilic polyethylene glycol supported NHC carbene **4** also shows good aqueous ROMP activity in water, however, its pendant PEG-carbamoyl-benzyl group limits the stability of the intermediate ruthenium alkylidene.[8] Catalyst **5**, with a PEG-soluble support appended to the NHC ligand, is reported to form aggregates in water with improved ROMP, RCM and CM activity of water-soluble substrates.[9] Other recently reported catalysts that are active in aqueous mixtures and neat water include **6** and **7**.[10] In these cases a quaternary ammonium salt is attached to the benzylidene ligand to improve aqueous solubility (Fig. 1). More recently, micellar catalysis has also been used for aqueous metathesis. Water emulsions can be stabilized by various amphiphiles[11] or supramolecular additives.[12] Another approach to overcome the low solubility of the catalyst in water is to use mixed water-organic solvent reaction media.[13]

We recently reported **8** as a soluble polyethylene glycol (PEG) immobilized catalyst with good activity in RCM of various benchmark substrates in dichloromethane in air, and with the ability to be recycled up to five times without significant loss of activity.[14] As part of our programme to develop aqueous active catalysts, we now report the results of using this catalyst to promote aqueous-based ring-closing metathesis (RCM) reactions of *N*,*N*-diethyldiallyl

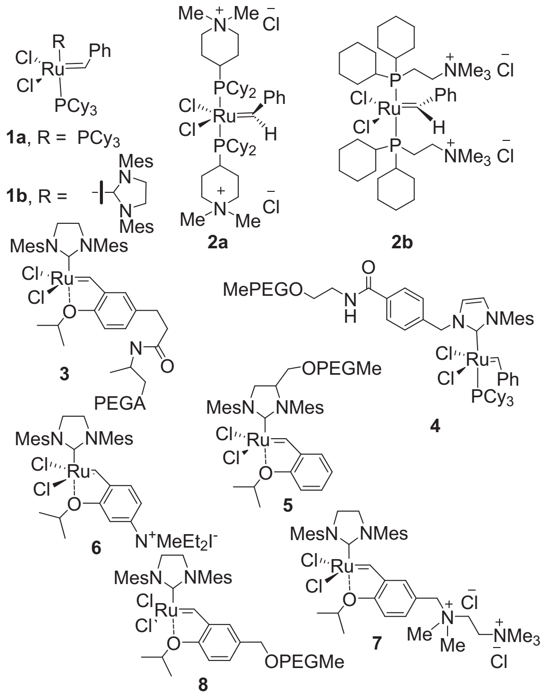

Figure 1. Ruthenium-based catalysts for olefin metathesis in aqueous media.

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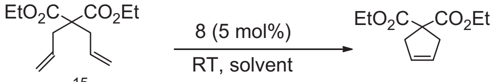
Table 1
Studies of catalyst **8** in different aqueous systems in the RCM of diene **9**[16]

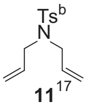
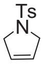
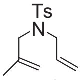
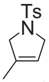
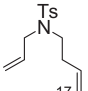
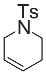
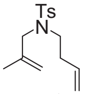
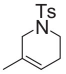
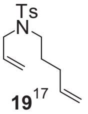
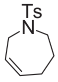
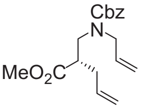
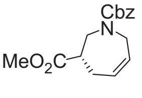
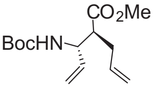
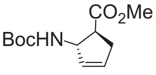
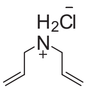
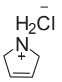


9[15] **10**[15]

Entry	Solvent	Time (h)	Conversion[a] (%)
1	EtOH/H$_2$O[b]	1	57
		16	72
2	MeOH/H$_2$O[b]	1	42
		16	50
3	Me$_2$CO/H$_2$O[b]	1	73
		16	95

[a] Determined by analysis of the ^{1}H NMR spectrum of the crude product.
[b] 2:1, v/v.

Table 2
Ring-closing metathesis of various substrates using catalyst **8**

Entry	Substrate[ref]	Product	Conversion[a] (%)	
			A	B
1	 **11**[17]	 **12**[17]	98	98
2	 **13**[17]	 **14**[17]	98	98
3	 **15**[17]	 **16**[17]	95	98
4	 **17**[17]	 **18**[18]	72	83
5	 **19**[17]	 **20**[15]	52	71
6	 **21**[19]	 **22**[21]	90	98
7	 **23**[23]	 **24**[23]	67	72
8	 **25**	 **26**	<5	35

[a] Determined by analysis of the crude ^{1}H NMR spectrum.
[b] *p*-Toluene sulfonamide A:1 h; B; 16 h.

malonate (**9**) (a metathesis benchmark substrate)[15] and a range of other dienes.

In the first instance, RCM of **9** was investigated under three separate aqueous conditions in order to establish optimum conditions and catalyst efficiency (see Table 1). The diene **9** was treated with 5 mol % of catalyst **8** at RT in the specified solvent system, with conversion into **10** being monitored after both 1 and 16 h by ^{1}H NMR spectroscopy.

The results in Table 1 reveal that acetone/water (2:1, v/v) was the optimum solvent system for RCM, with a 95% conversion of **9** into **10** after 16 h. This can be compared to ethanol/water and methanol/water systems that resulted in 72% and 50% conversion, respectively. Thus subsequent reactions, as shown in Table 2, were carried out using this acetone/water (2:1, v/v) solvent system.[16]

The efficacy of catalyst **8** was next tested in the ring-closing metathesis reactions of a series of di- and tri-substituted *N*-tosyl based-dienes (**11**, **13**, **15**, **17** and **19**), β-amino acid derived dienes (**21** and **23**) and the water-soluble ammonium chloride based diene **25**. Again the extent of cyclisation (to give **12**, **14**, **16**, **18**, **20**, **24** and **26**) was determined by ^{1}H NMR spectroscopy after both 1 and 16 h reaction times (Table 2). The reactions were run at a concentration of 0.2 M and no attempt was made to exclude air.

Catalyst **8** is particularly efficient at forming both five- and six-membered N-containing heterocycles. For example, the *N*-tosyl-diallyl dienes **11**, **13** and **15** all gave near quantitative conversion to the heterocycle after 1 h (see entries 1–3 in Table 2). Interestingly, diene **17** which contains a trisubstituted alkene, cyclised less efficiently with a 72% conversion after 1 h and a slightly improved 83% yield after 16 h (entry 4, Table 2). It is apparent that a seven-membered heterocycle is formed less efficiently, with only 52% cyclisation of diene **19** into **20** after 1 h. This only increased to 71% after the extended 16 h reaction time. It appears that introducing further substitution (not on the alkene) to the acyclic precursor diene, as in **21**,[19,20] significantly enhances conversion into the heterocycle, with 90% conversion into **22**[21] after only 1 h reaction. This observation is consistent with the well-known Thorpe–Ingold[22] effect. The diene **23**[23] lacking an amine cyclised less efficiently to give the five-membered ring product **24**[23] in only a 67% yield after 1 h (see entry 7 in Table 2). Finally, the ability of catalyst **8** to catalyse RCM in water was determined using the water-soluble diene substrate **25**. Significantly, 35% conversion into the five-membered heterocycle **26** was observed after an extended 16 h reaction time (Table 2, entry 8). RCM of diene **25** in the presence of catalysts **5**[9] and **7**[10] in neat water, however, resulted in the formation of a by-product along with **26** due to cycloisomerisation which was not observed in the presence of **8**.

In summary, these findings demonstrate that the polyethylene glycol supported ruthenium catalyst **8** exhibits good RCM activity in acetone/water (2:1, v/v) in the presence of air. The catalyst can be conveniently prepared by the reaction of Grubbs' second generation catalyst with PEG-bound olefin.[14]

Acknowledgements

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16. In a typical experiment, catalyst **8** (0.05 equiv) was added to a 1 ml vial, equipped with a magnetic stir-bar and sealed with a septa-cap. The vial was then charged with a 0.2 M solution of diene in acetone/H$_2$O (2:1, v/v). The reaction was stirred at room temperature without exclusion of air. The progress of the reaction was analysed by ^{1}H NMR after 1 h and overnight for all the reactions studied.
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19. *(S)-Methyl 2-[{(allyl(benzyloxycarbonyl)amino}methyl]pent-4-enoate* (**21**): Arndt–Eistert homologation[20] of *N*-Cbz-(*S*)-glycine followed by stereocontrolled allylation gave (*S*)-methyl 2-[{(benzyloxycarbonyl)amino}methyl]-pent-4-enoate (**27**). A solution of **27** (360 mg, 1.29 mmol) was dissolved in anhydrous THF (30 ml). This was cooled to −78 °C and P4-phosphazene (1.83 ml, 2.59 mmol) was added, and the mixture stirred at −78 °C for 1 h and then allyl bromide (219 μL, 2.59 mmol) was added. This was stirred at −78 °C for a further 2 h and then at rt for 18 h. The mixture was concentrated in vacuo and the residue partitioned between EtOAc (40 ml) and 1 M HCl (aq, 20 ml). The organic phase was washed consecutively with 1 M HCl (aq, 20 ml) and brine (30 ml) and then dried over MgSO$_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica using EtOAc and petroleum ether (30:70) to give **21** as a mixture of rotamers (0.335 g, 81%) as a colourless oil. ^{1}H NMR (CDCl$_3$, 500 MHz), δ 7.18–7.28 (m, 5H), 5.53–5.67 (m, 2H), 4.90–5.18 (m, 6H), 3.87–3.95 (m, 1H), 3.61–3.70 (m, 1H), 3.53–3.59 (m, 3H), 3.30–3.45 (m, 2H), 2.73–2.85 (m, 1H), 2.09–2.27 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.93, 174.76, 156.40, 156.24, 136.91, 136.71, 134.79, 134.68, 133.74, 133.52, 128.69, 128.57, 128.36, 128.22, 127.97, 117.48, 116.85, 67.63, 67.39, 51.95, 51.93, 50.78, 49.31, 48.14, 44.89, 44.42, 34.56; [MH]$^+$ requires: 318.1661, observed: 318.5803.
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21. The diene **21** (31 mg) and catalyst **8** (13 mg) in acetone/H$_2$O (2:1, 330 μl:165 μl) were stirred at room temperature giving **22** as a mixture of rotamers as a colourless oil. Data for the mixture: ^{1}H NMR (CDCl$_3$, 500 MHz) δ H 7.29–7.36 (m, 5H), 5.62–5.79 (m, 2H), 5.09–5.19 (m, 2H), 4.17–4.26 (m, 1H), 3.84–4.18 (m, 1H), 3.61–3.74 (m, 4H), 2.91–2.98 (m, 1H), 2.44–2.48 (m, 2H); [MH]$^+$ requires: 290.1392, observed: 290.1404.
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