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A Solid-Supported Phosphine-Free Ruthenium Alkylidene for Olefin Metathesis in Methanol and Water

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Abstract—The synthesis and olefin metathesis activity in protic solvents of **7**, a phosphine-free ruthenium alkylidene bound to a hydrophilic solid support are reported. This heterogeneous catalyst promotes relatively efficient ring closing- and cross-metathesis reactions in both methanol and water. The potential utility of homogeneous catalyst **2** for olefin metathesis in methanol is also demonstrated. © 2002 Elsevier Science Ltd. All rights reserved.

The development of highly stable and active ruthenium alkylidenes such as **1**[1] and **2**[2] (Fig. 1) bearing *N*-heterocyclic carbene (NHC) ligands has significantly broadened the scope of the olefin metathesis reaction.[3] Consequently, ring closing metathesis (RCM) to form tetrasubstituted cycloalkenes,[1,4] selective cross metathesis (CM) with highly electron deficient alkenes[3,5] and even ring opening-cross metathesis (ROM-CM) of unstrained cycloolefins[6] are now possible. Despite its potential importance in the concise synthesis of biologically important molecules, less progress has been made with regard to the design of olefin metathesis catalysts for use in protic solvents such as methanol or water. The advantages of such a strategy are obvious; for example tedious protection/deprotection steps that are commonplace in carbohydrate metathesis chemistry[3c] could be avoided, and environmental impact could be reduced. Early examples[7] detailed the ring opening metathesis polymerisation (ROMP) of strained cycloolefins in aqueous media initiated by poorly defined ruthenium complexes such as $RuCl_3$(hydrate) or $Ru(H_2O)_6(Tos)_2$. However, these polymerisations were not living, and the water soluble initiators could not be applied to either RCM or CM. Later, the ROMP of carbohydrate functionalised monomers in aqueous/organic mixtures using the well-defined ruthenium initiator $(PCy_3)_2Cl_2Ru{=}CHPh$ were reported.[8] A breakthrough came with the preparation by Grubbs et al.[9] of water soluble metathesis catalysts **3** and **4**. These alkylidenes promoted living ROMP in acidic aqueous solution,[10] and for the first time made possible the RCM of specific diene substrates in methanol and water.[11] On the other hand, these catalysts are reported to be extremely oxygen sensitive, requiring manipulation under an inert atmosphere and rigorous degassing of solvents. In addition they did not promote the ring closure of simple α,ω-heptadienes (one terminal- and one internal-olefin component is required) and they

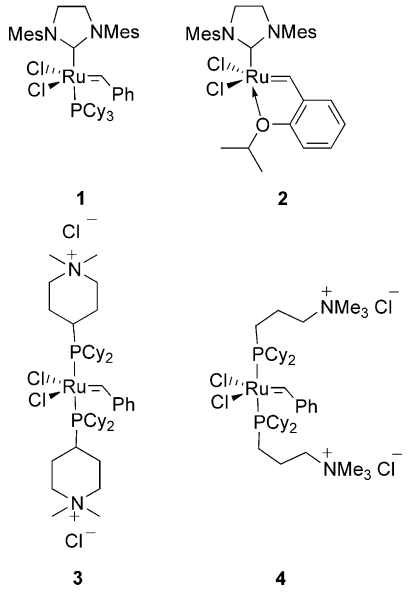

Figure 1. Ruthenium alkylidene olefin metathesis catalysts (Cy, cyclohexyl; Mes, 2,4,6-trimethylphenyl).

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possessed negligible CM activity. We therefore sought to apply the high stability of phosphine-free catalyst **2** to the problem of RCM and CM activity in methanol and water.

In contrast to **1**, phosphine-free catalyst **2** is reasonably soluble in methanol at room temperature, and readily dissolves in this solvent at 50 °C. However, **2** is completely insoluble in water or water–methanol mixtures. We have recently reported two polymer bound variants of **2** which had excellent activity and recyclability in RCM and CM processes,[12] and therefore to circumvent this solubility problem, the idea of preparing a suitably substituted analogue of **2** immobilised on a hydrophilic solid support seemed attractive. It was hoped that with such a heterogeneous species, metathesis reactions in water could occur to some extent in the resin pores, where the pre-catalyst concentration is relatively high, thereby more efficiently exposing the substrate to the hydrophobic ruthenium moiety. A similar strategy for heterogeneous catalysis in methanol has been briefly described recently by Dowden[13] with promising results.

Commercially available[14] PEGA-NH_2 resin (Fig. 2) was chosen as the hydrophilic solid support (Scheme 1). Consisting of amino functionalised dimethyl acrylamide and mono-2-acrylamidoprop-1-yl polyethyleneglycol,

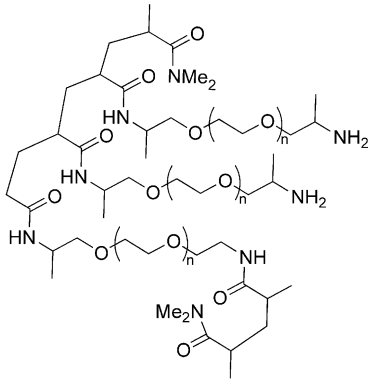
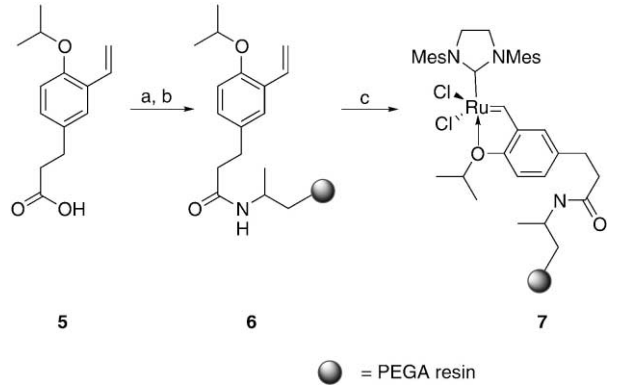


Figure 2. PEGA-NH_2 resin.



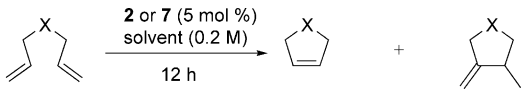
Scheme 1. Reagents and conditions: (a) DIC (5.0 equiv), HOBt (5.0 equiv), **5** (5.0 equiv), PEGA-NH_2 (1.0 equiv), DMF, 25 °C, 12 h, then repeat; (b) **6** (1.0 equiv) Ac_2O (30 equiv), TEA (35 equiv) DMAP (3.0 equiv), CH_2Cl_2, 25 °C, 5 h; (c) **6** (1.0 equiv), **1** (1.3 equiv), CuCl (1.3 equiv), CH_2Cl_2, 45 °C, 4 h.

this solid support swells 4 times more per unit mass in water than the polystyrene/polyethylene glycol-based TentaGel resins,[14] and proved perfectly stable under metathesis conditions. Isopropoxystyrene **5** was prepared according to the literature procedure[2a] and coupled to PEGA-NH_2 resin (loading 0.40 mmol g^{-1}) under standard conditions to give the immobilised ligand **6**. To ensure complete incorporation of the styrene moiety this coupling step was repeated until the resin gave a negative Kaiser test.[14] As a precautionary measure the resin was then subjected to acylation conditions. Treatment of **6** with excess **1** in the presence of CuCl as a phosphine scavenger gave the solid-supported catalyst **7** as a deep green resin[15] (Scheme 1).

The activity of both **2** and **7** in RCM was tested, using methanol and water as solvents. From the outset it was decided that for the use of these catalysts to be considered advantageous compared to **3** or **4**, they must be capable of promoting the RCM of α,ω-heptadienes (Scheme 2) in the presence of adventitious oxygen, and so no attempt was made to degas solvents and the reactions were performed under an air atmosphere. The results of these experiments are outlined in Table 1.

Gratifyingly both **2** and **7** served as active catalysts for RCM in methanol under these conditions, with **7** also exhibiting activity in water. Ammonium salt **8**, which has proven incompatible with NHC ligand-based catalysts even in CH_2Cl_2[16] could be cyclised cleanly in moderate yields with either **7** or **2** in methanol, and even underwent some reaction in water. It is noteworthy that for metathesis reactions promoted by **7**, methanol is actually a superior solvent to CH_2Cl_2.

Heptadienes **9** and **10** gave higher conversions to RCM products **13** and **14**, respectively, but were also able to undergo a competing cyclo-isomerisation pathway[17] to afford **17** and **18**. In an attempt to understand the origins of these byproducts, the RCM of **9** in CD_3OD was monitored by ^1H NMR spectroscopy at room temperature. It was found that formation of **17** was less favoured at the lower temperature, only occurring after 70% of **9** had been consumed, and coinciding with the appearance of a signal at −5.05 ppm. Interestingly, conversion to **17** continued even after the disappearance of the alkylidene signal at 16.63 ppm (ca. 130 min)[18] and ceased only after the highfield signal could no longer be observed (ca. 240 min), indicating that this catalytic isomerisation is promoted by a decomposition product of **2**, and not by **2** itself. The RCM of **11** in D_2O was



8	X = $NH_2^+Cl^-$	**12**	X = $NH_2^+Cl^-$	**16**	X = $NH_2^+Cl^-$
9	X = NTos	**13**	X = NTos	**17**	X = NTos
10	X = $C(CO_2Et)_2$	**14**	X = $C(CO_2Et)_2$	**18**	X = $C(CO_2Et)_2$
11	X = CHOH	**15**	X = CHOH	**19**	X = CHOH

Scheme 2. RCM in methanol and water.

Table 1. RCM in methanol and water promoted by **2** and **7**

Diene	Solvent	Catalyst	Temp. (°C)	Conversion (%)[a]	Product(s) (%)[a]
8	CH_2Cl_2	**7**	45	33	**12** (33)
8	H_2O	**7**	45	11	**12** (11)
8	H_2O	**7**	rt	0	None
8	MeOH	**7**	45	57	**12** (57)
8	MeOH	**2**	45	69	**12** (69)
9	CH_2Cl_2	**7**	45	100[b]	**13** (44) + **17** (9)
9	MeOH	**7**	45	100[b]	**13** (70) + **17** (24)
9	MeOH	**2**	45	100[b]	**13** (83) + **17** (10)
9	MeOH	**2**	rt	92	**13** (86) + **17** (6)
10	MeOH	**7**	45	82	**14** (38) + **18** (44)
10	MeOH	**2**	45	100	**14** (71) + **18** (29)
10	MeOH	**2**	rt	58	**14** (58)
11	MeOH	**2**	rt	73	**15** (73)
11	D_2O	**7**	rt	96	**15** (96)

[a]Relative integration of ^{1}H NMR spectrum.
[b]Acyclic isomerisation of terminal olefin also evident.

Table 2. CM in methanol and water promoted by **2** and **7**

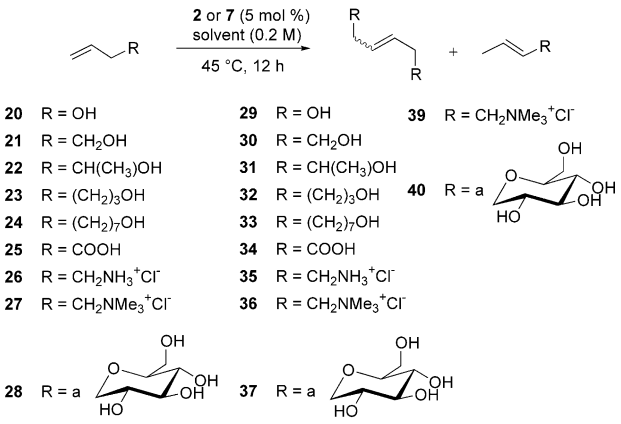
Substrate	Solvent	Catalyst	Conversion (%)[a]	Product(s) (%)[a]
20	D_2O	**7**	80	**29** (80)
20	MeOH	**2**	69	**29** (69)
21	D_2O	**7**	79	**30** (79)
22	D_2O	**7**	83	**31** (83)
23[b]	D_2O	**7**	45	**32** (45)
24	MeOH	**7**	100	**33** (100)
24	MeOH	**2**	100	**33** (100)
25	D_2O	**7**	7	**34** (7)
26	MeOH	**2**	3	**35** (3)
27	MeOH	**2**	78	**36** (5) + **39** (73)
28	D_2O	**7**	0	None
28	MeOH	**2**	65	**37** (28) + **40** (37)

[a]Relative integration of ^{1}H NMR spectrum.
[b]Not miscible with D_2O.

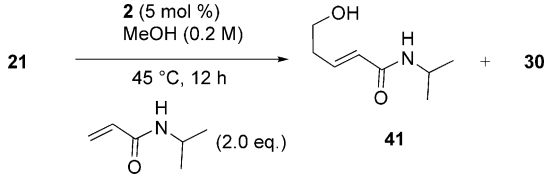
also a pleasing result. This diene is *immiscible* with D_2O at room temperature, but gives the soluble product **15** after highly efficient RCM. We would propose that **11** is of a sufficient polarity to seep into the resin pores to an environment of high catalyst concentration, aided by dissolution of the product in the solvent, which would account for the high conversion observed under mild conditions. This hydrophobic effect is currently under investigation.

Having established the activity of **2** and **7** in RCM our attention then turned to CM (Scheme 3).[19] As can be seen from the results presented in Table 2, both catalysts were active in protic solvents; the efficient formation of dimers **29**–**33** from simple hydroxy functionalised olefins **20**–**24** in D_2O was possible using heterogeneous catalyst **7**. An inverse relationship between substrate chain length and *E*/*Z* selectivity was also found; the *E*/*Z* content of homodimers **29**, **30**, and **33** were 14.6:1, 6.2:1 and 1.4:1, respectively.

Unfortunately, the high CM activity found using simple alcohol substrates did not translate to the unprotected α-C-glycoside **28**. A moderate amount of homodimer **37**



Scheme 3. CM (olefin dimerisation) promoted by **2** and **7**.



Scheme 4. Attempted selective cross-metathesis.

was formed (*E*/*Z* = 4.1:1) in MeOH using homogeneous catalyst **2**; however, a wasteful alkene isomerisation reaction was dominant. To our knowledge this is the first example of CM involving an unprotected glycoside in pure MeOH. Ammonium salts **26** and **27** either did not react or underwent a similar isomerisation process.

Recently selective cross-metathesis with acrylic acid derivatives has been reported.[3,5] Disappointingly CM between *N*-isopropyl acrylamide and **21** (Scheme 4) was unselective, affording a 52:48 mixture of CM product **41** and homodimer **30** by ^{1}H NMR (23% conversion, *E*/*Z* = 100:0). Poor results were also obtained using other electron deficient alkenes such as acrylic acid and acrylonitrile. It seems probable that the particularly electrophilic alkylidene intermediates in these reactions are of insufficient stability in nucleophilic solvents, resulting in poor conversions and unselective CM.

It is interesting to note that a heterogeneous system consisting of **1** in D_2O failed to promote either RCM or CM of **8** or **21**, respectively, under standard conditions. This indicates that metathesis reactions promoted by **7** occur mainly in the resin pores and not in the bulk solvent. In summary, these findings demonstrate that a water-insoluble ruthenium alkylidene moiety, when attached to hydrophilic solid support, can exhibit considerable metathesis activity in protic solvents. While homo- and heterogeneous catalysts **2** and **7** have some limitations, these catalysts can promote relatively efficient RCM and CM of hitherto problematic substrates in methanol and water without requiring either degassing or an inert atmosphere, and as such may have greater synthetic utility than benchmark water-soluble catalysts **3** and **4**.

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14. For infomation on swelling chacteristics and a simple Kaiser test protocol see: Novabiochem Catalogue, 2000.
15. Synthesis of catalyst **7**: PEGA-NH_2 resin (1 g, 0.40 mmol) was swollen in DMF for 1 h. In a separate flask, HOBt (307 mg, 2.0 mmol) and **5** (468 mg, 2.0 mmol) were dissolved in DMF (12 cm^3) and then DIC (252 mg, 2.0 mmol) was added. The resulting solution was allowed to stand for 10 min and then added to the resin via syringe. After gentle agitation for 12 h, the slurry was filtered and washed well with DMF (7×10 cm^3). This step was repeated until the beads gave a negative Kaiser test. Next the solvent was exchanged by repeated washing with CH_2Cl_2. A solution of TEA (1.41 g, 14 mmol) and DMAP (146 mg, 1.2 mmol) in CH_2Cl_2 (7 cm^3) was added, followed by acetic anhydride (1.22 g, 12 mmol) in CH_2Cl_2 (3 cm^3). The resulting mixture was gently agitated for 5 h at rt and then washed consecutively with CH_2Cl_2 (2×20 cm^3), DMF (2×20 cm^3), H_2O (2×20 cm^3), DMF (2×20 cm^3), CH_2Cl_2 (2×20 cm^3) and finally ether (3×20 cm^3). The resulting ligand **6** could be stored indefinitely at 4 °C under N_2. Coupling to ruthenium was carried out as follows: Ligand **6** was swollen in CH_2Cl_2 for 1 h, filtered, and then suspended in CH_2Cl_2 (4 cm^3). To this was added **1** (441 mg, 0.52 mmol) and CuCl (51.5 mg, 0.52 mmol) under N_2 and the resulting red mixture heated under reflux for 4 h. The reaction mixture was transferred to a separatory funnel and the dense phosphine salts were removed. The solvent was then removed by filtration and the resin washed with CH_2Cl_2 until the washings were colourless, and then again three times with Et_2O. The green resin was dried under high vacuum and stored at 4 °C.
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18. In a stability test, the decomposition of **2** in the absence of substrate (CD_3OD, 45 °C) was monitored by ^1H NMR. Under these conditions the alkylidene signal could still be observed after 26 h.
19. General procedures for metathesis using **7** (note: quantitative catalyst loading is assumed): Solvent (2 cm^3) was added to **7** (50 mg, 0.02 mmol), and the resulting suspension agitated gently for 10 min in air. Substrate (0.4 mmol) was then added and the mixture was stirred overnight in a closed vessel at either room temperature or 45 °C. The solvent was removed in vacuo and conversion determined by ^1H NMR. More conveniently for volatile substrates, deuterated solvents were used, making direct ^1H NMR analysis possible after filtration.