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A robust and recyclable ruthenium catalyst immobilised on polyethylene glycol

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ABSTRACT

A highly robust and recyclable Hoveyda-Grubbs' second generation ruthenium type catalyst immobilised on polyethylene glycol is conveniently prepared from Grubbs' second generation catalyst. The catalyst performs ring-closing metathesis of various di-and tri-substituted olefins efficiently in dichloromethane in air.

A number of well-defined and functional group-tolerant metathesis catalysts are now known, for example, the ruthenium alkylidenes **1a–c** and the more recent **2a,b**[1,2] (Fig. 1) The unique bidentate nature of the isopropoxy ether ligand of **2** results in enhanced stability in air and an ability to recycle the catalyst by chromatography on silica gel.[2c] Immobilised and supported ruthenium catalysts have also been reported that allow ease of removal of ruthenium by-products and catalyst recycling.[3] A number of catalysts of this type are known, but few display good reactivity and recyclability.[4]

Early reports on such supported catalysts employed heterogeneous polystyrene (PS) as the support.[5] However, while these catalysts can be recycled, they generally display poor catalytic activity due to limited access to the reactive site of the catalyst.[5] Catalysts based on soluble supports show improved activity with enhanced rates of diffusion relative to the heterogeneous polymers.[6–9] These catalysts can be recovered by precipitation or aqueous extraction following metathesis.[6,7] For example, the soluble-PEG-supported catalysts **3** and **4** exhibit good ring-closing metathesis (RCM) activity in dichloromethane under homogenous conditions and can be recycled to some degree.[8,9] Significantly, the NHC-immobilised catalysts **5** and **6** show some activity under aqueous conditions.[6a,b]

Here we report the synthesis of **7** (an air-stable Hoveyda-Grubbs' second generation type catalyst) and its use in RCM reactions of various di- and tri-substituted dienes to give five-, six- and seven-membered cyclic olefins (see Table 2).

Ruthenium catalyst **7** is suitable for reaction in reagent grade dichloromethane[10] without drying or degassing and can be recycled by precipitation or aqueous extraction.

The synthesis of **7** is shown in Scheme 1. Chloromethylation of **9** (itself prepared from commercially available **8**) gave the chloromethyl benzaldehyde **10**, which was reacted under standard Wittig conditions[11] to give styrene **11**. Polyethylene glycol monomethyl ether (M_n = 2000) was deprotonated with sodium hydride and **11** was added to this anion to give the PEG-tethered ligand **12**

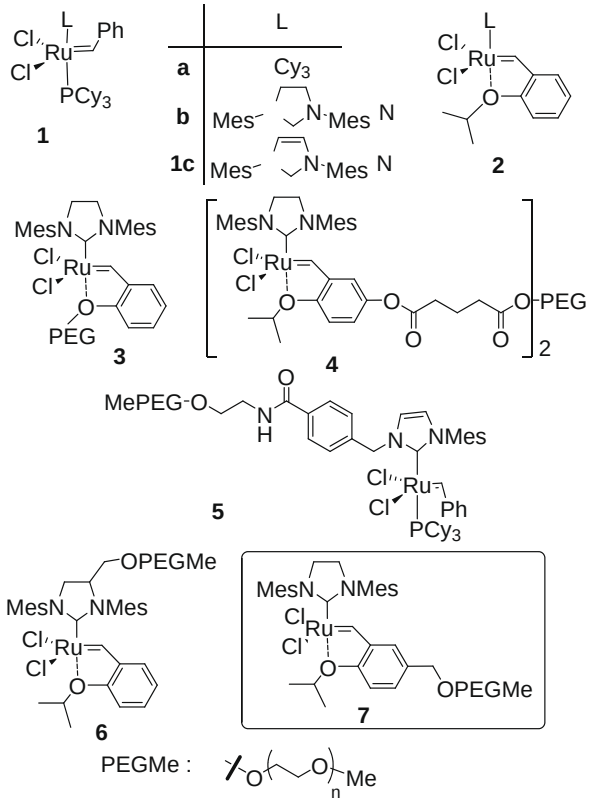

Figure 1. Ruthenium catalysts for olefin metathesis.

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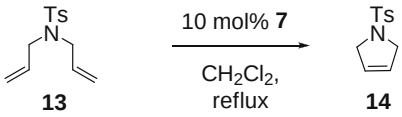
Table 1
Recyclability studies of catalyst **7** in RCM of diene **13**



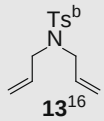
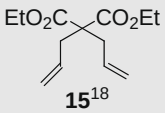
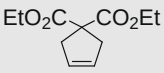
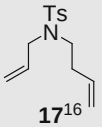
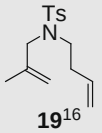
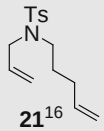
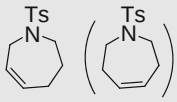
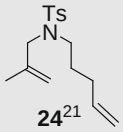
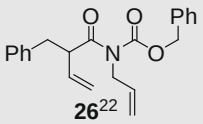
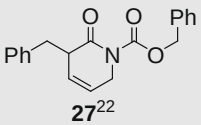
13 **14**

Cycle	Conversion[a] (%)
1	>98
2	95
3	95
4	90
5	89

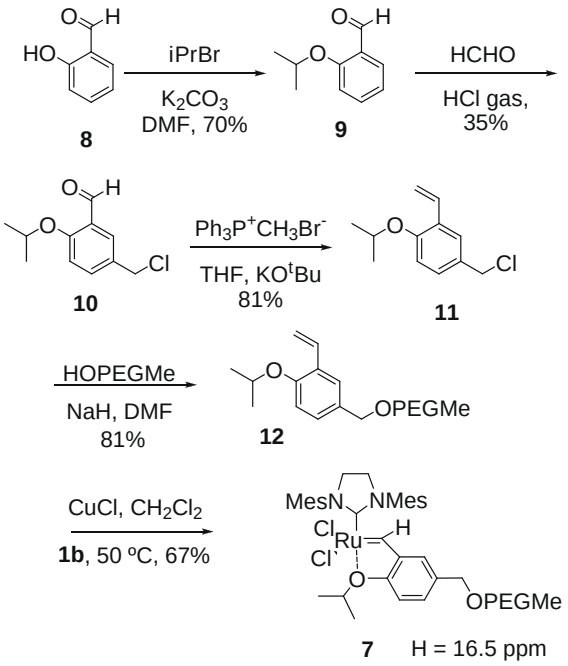
[a] Determined by analysis of the crude ^{1}H NMR spectrum.

(Scheme 1). An attempted preparation of **12**, by reaction of **10** directly with polyethylene glycol monomethyl ether, followed by Wittig olefination was problematic due to difficulties in removal of triphenylphosphine at this late stage. Treatment of **12** with Grubbs' second generation catalyst (**1b**), in the presence of CuCl to scavenge tricyclohexylphosphine, gave the PEG-immobilised catalyst **7** as a green solid in 67% yield after purification by chromatography on alumina and precipitation with ether. The structure of **7** was confirmed by ^{1}H and ^{13}C NMR, and MALDI-TOF mass spectrometry. In particular, the MALDI-TOF mass spectrum revealed an intense peak for the $[MH^+]$Na ion at 2662 Da, which is consistent with the 45 ethylene oxides (CH_2CH_2O) associated with PEG. The ^{1}H NMR spectrum ($CDCl_3$) showed a characteristic resonance for the benzylidene proton at 16.5 ppm.[12]

Table 2
Ring-closing metathesis of various di- and tri-substituted dienes

Entry	Substrate[reference]	Product	Catalyst	Time (h)	Conversion[a] (%)
1	 **13**[16]	 **14**[16]	**7** **1b**	0.5 0.5	>98 >98
2	 **15**[18]	 **16**[18]	**7** **1b**	0.5 0.5	>98 >98
3	 **17**[16]	 **18**[16]	**7** **1b**	0.5 0.5	>98 >98
4	 **19**[16]	 **20**[19]	**7** **1b**	0.5 0.5	95 98
5	 **21**[16]	 **22**[18] **23**[20]	**7** **1b**	0.5 0.5	98 98 (1:1)
6	 **24**[21]	 **25**[21]	**7** **1b**	0.5 0.5	98 98
7	 **26**[22]	 **27**[22]	**7** **1b**	2 4	94 85

[a] Determined by analysis of the crude ^{1}H NMR spectrum.
[b] 4-Toluenesulfonyl.



Scheme 1. Synthesis of catalyst **7** from 2-hydroxybenzaldehyde **8**.

The ability of **7** to catalyse RCM of *N*-tosyldiallylamine **13** (a metathesis benchmark substrate)[13] was then investigated, and the results are summarised in Table 1 for five repeated cycles. *N*-Tosyldiallylamine **13** was heated under reflux with 10 mol % of catalyst **7** for 1 h in non-degassed dichloromethane, with exposure to air. Ether was added to precipitate the catalyst and the filtrate was concentrated and analysed by ^{1}H NMR spectroscopy which showed complete conversion to **14**.[14] The filtered catalyst was reused in a further RCM reaction of **13** to give a 95% conversion to **14**. This sequence was repeated three more times without significant loss of activity (Table 1).

A comparative study of our new catalyst **7** and Grubbs' second generation catalyst **1b** was carried out with an extended set of di- and tri-substituted dienes (**13**, **15**, **17**, **19**, **21**, **24** and **26**), and the results are given in Table 2. In all cases, the reaction involved heating the substrate under reflux with 10 mol % of catalyst, with the extent of conversion to the five-, six- and seven-membered cyclic olefins **14**, **16**, **18**, **20**, **22**, **23**, **25** and **27** being determined by ^{1}H NMR analysis of the crude product (see Table 2). Catalyst **7** was removed prior to analysis by simple aqueous extraction.[14] Reactions with catalyst **1b** were carried out using dry degassed dichloromethane under inert conditions, while those with **7** were carried out with exposure to air.[15]

Reactions of **13**[16] under these conditions with either catalyst led to quantitative conversion to **14**.[17] The dienes, **15**,[18] **17**,[16] **19**[16] and **24**[21] similarly led to quantitative (or near quantitative) conversions to the corresponding five- six- and seven-membered alkenes (Table 2, entries 2–4 and 6). In the case of diene **21**,[18] significant isomerisation of the product alkene was observed with catalyst **1b** to give **22**[18] and **23**[20] in a ratio of 1:1 (Table 2, entry 5). In this case the crude product was purified by chromatography on silica gel (using 5% ethyl acetate in hexane) to give 67% of **23**[20] and 33% of **22**.[18] Some isomerisation was apparent on silica.

Treatment of **26**[22] with **1b** led to 85% conversion to **27**[22] after an extended reaction for 4 h under degassed conditions, while the reaction in the presence of **7** led to 94% conversion after only 2 h (Table 2, entry 7). The product **27** was isolated in yields of 89% (from reaction with **7**) and 80% (from reaction with **1b**), respectively, after chromatography.

In summary, we have reported a new polyethylene glycol-supported ruthenium catalyst **7** that performs RCM reactions in air using reagent grade dichloromethane. The catalyst is conveniently prepared by reaction of Grubbs' second generation catalyst with PEG-bound olefin **12**. It is stable in air for several months and performs well in RCM of a variety of dienes. The catalyst can be recycled up to five times and is easily recovered on precipitation with ether or by aqueous extraction. Catalyst **7** represents a useful addition to the growing list of supported metathesis catalysts and work is under progress to extend its activity to aqueous conditions.

Acknowledgements

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12. Synthesis of **7:** To a suspension of NaH (60 mg, 1.53 mmol) in dry DMF (80 ml) was added PEGOMe (M_n = 2000, 2.4 g, 1.22 mmol) and the mixture was stirred at rt for 30 min. A solution of **11**[8] (320 mg, 1.53 mmol) in dry DMF (5 ml) was added and the reaction mixture was stirred for 18 h. DMF was evaporated in vacuo, the residue was redissolved in CH_2Cl_2 and the mixture was filtered through a plug of Celite. The filtrate was concentrated in vacuo, dissolved in CH_2Cl_2 (3 ml) and excess ether was added to give **12** as a white precipitate (2.15 g, 81%). ^{1}H NMR ($CDCl_3$, 500 MHz), δ 1.10 (d, J = 5 Hz, 6H), 3.13 (s, 3H), 3.26–3.84 (br m, PEG), 4.24–4.29 (m, 3H), 4.98 (d, J = 10.5 Hz), 5.49 (br d, J = 17.5 Hz, 1H), 6.61 (d, J =8.0 Hz, 1H), 6.77 (dd, J = 17 Hz, 11 Hz, 1H), 6.93 (d, J = 8 Hz, 1H), 7.20 (s, 1H) ^{13}C NMR ($CDCl_3$, 126 MHz), δ 21.67, 58.46, 61.02, 68.61, 69.78, 69.95, 70.00, 70.02, 70.03 (br), 70.31, 71.37, 72.02, 72.39, 113.52, 113.58, 125.78, 127.07, 127.96, 129.66, 131.26, 154.14. To a suspension of CuCl (55 mg, 0.39 mmol) in dry CH_2Cl_2 under dry N_2 was added **12** (433 mg, 0.19 mmol) followed by **1b** (169 mg, 0.19 mmol). The mixture was heated at 50 °C for 1.5 h, then cooled to rt and passed through a plug of Celite. The solvent was removed in vacuo and the solid was passed through a column of neutral alumina (Brockmann grade III) eluting with MeOH/CH_2Cl_2 (97:3). The green band was collected, evaporated in vacuo and redissolved in minimal CH_2Cl_2. Excess ether was added to precipitate **7** as a green powder (355 mg, 67%). ^{1}H NMR ($CDCl_3$, 500 MHz), δ 1.20 (d, J = 6 Hz, 6H), 1.27–2.43 (m, 18H), 2.64 (t, J = 5.7 Hz, 2H), 3.32 (s, 3H), 3.35–3.82 (br m, PEG), 4.12 (s, 4H), 4.47 (s, 2H), 4.82–4.87 (m, 1H), 6.70 (d, J = 9 Hz, 1H), 6.80 (s, 1H), 7.01 (s, 4H), 7.43 (d, J = 8.7 Hz, 1H), 16.5 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 20.90, 20.97, 58.88, 61.54, 68.90, 70.20, 70.41, 70.46, 71.78–72.36 (br, PEG), 74.97, 112.62, 121.91, 128.36, 128.84, 129.23, 131.95, 138.63, 145.02, 151.69, 211.12, 296.17. TOF MS = $[MH]^+$ Na: 2662.763 (containing 45 CH_2CH_2O units).

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14. *Typical procedure for RCM using* **7**: To a solution of the substrate (50 mg) in reagent grade CH_2Cl_2 (5 ml) was added **7** (10 mol%) and the solution was heated under reflux for the time specified in Table 1 or 2. The solution was concentrated in vacuo, redissolved in minimal CH_2Cl_2 and excess ether was added. The catalyst was isolated by filtration. The filtrate was evaporated in vacuo and the residue was analysed by ^{1}H NMR. The catalyst was removed by aqueous extraction for the reactions shown in Table 2.
15. *Typical procedure for RCM using* **1b**: To a solution of the substrate (50 mg) in dry, degassed CH_2Cl_2 (5 ml) was added **1b** (10 mol%) and the solution was heated under reflux under an atmosphere of N_2 for the time specified in Table 2. The solution was concentrated in vacuo and the residue was analysed by ^{1}H NMR.
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17. A closer examination of the reaction of **13** with **7** revealed that the reaction was complete in 30 min, and as such, this reaction time was used throughout, with the exception of **26** which required longer reaction times.
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22. *Benzyl allyl (2-benzylbut-3-enoyl) carbamate* **26**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.79 (dd, J = 13.5 Hz, 7.5 Hz, 1H), 3.17 (dd, J = 13.5 Hz, 7.2 Hz, 1H), 4.23–4.26 (*m*, 2H), 4.68 (q, J = 7.5 Hz, 1H), 4.99–5.07 (m, 4 H), 5.18 (s, 2H), 5.64–5.71 (m, 1H), 5.88–5.95 (m, 1H), 7.14–7.17 (m, 4H), 7.21–7.24 (m, 2H) 7.26–7.39 (m, 2H), 7.32–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.00, 46.54, 51.42, 68.52, 116.76, 117.36, 126.13, 128.12, 128.19, 128.57, 128.59, 129.24, 132.74, 134.92, 136.30, 138.99, 153.97, 175.80. $[MH]^+$ $C_{22}H_{24}NO_3$ requires: 350.1711 observed: 350.1693; benzyl 5-benzyl-6-oxo-5,6-dihydropyridine-1(*2H*)-carboxylate **27**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.00 (dd, J = 13.5 Hz, 7.5 Hz, 1H), 3.17 (dd, J = 13.5 Hz, 4.5 Hz, 1H), 3.35–3.38 (m, 1H), 3.79 (d, J = 14.0 Hz, 1H), 4.14 (d, J = 14.5 Hz, 1H), 5.29 (s, 2H), 5.63–5.66 (m, 1H), 5.72–5.75 (m, 1H), 7.14–7.19 (m, 4H), 7.20–7.39 (m, 2H) 7.32–7.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.88, 45.89, 47.13, 68.51, 121.52, 125.21, 126.58, 128.03. 128.19, 128.30, 128.51, 129.27, 135.20, 137.29, 153.37, 171.00; HRMS (EI) observed: 322.1448. $[MH]^+$ $C_{20}H_{20}NO_3$ requires: 322.1443.