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Efficient Removal of Ruthenium Byproducts from Olefin Metathesis Products by Simple Aqueous Extraction

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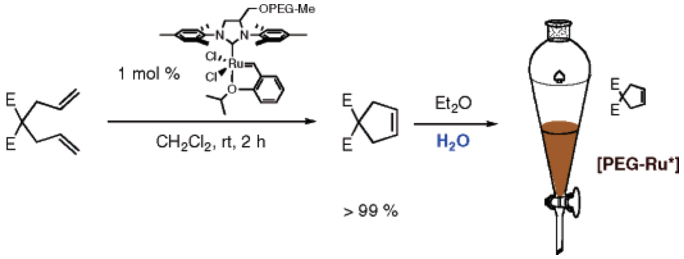
ABSTRACT



Simple aqueous extraction removed ruthenium byproducts efficiently from ring-closing metathesis (RCM) reactions catalyzed by a poly(ethylene glycol) (PEG) supported N-heterocyclic carbene-based ruthenium complex.

Olefin metathesis is a powerful carbon−carbon bond formation reaction in both polymer and small molecule synthesis.[1,2] In particular, the recent development of ruthenium olefin metathesis catalysts such as **1**−**3** (Figure 1), which show high activity and functional group tolerance, has expanded the scope of this reaction.[3] However, it has proved very difficult to remove the highly colored ruthenium complexes completely from the desired product even after purification by silica gel column chromatography. The residual ruthenium complexes can cause problems such as olefin isomerization,[4−6] decomposition over time,[7,8] and increased toxicity of the final product which is critical especially in connection with the synthesis of biologically active materials.[9]

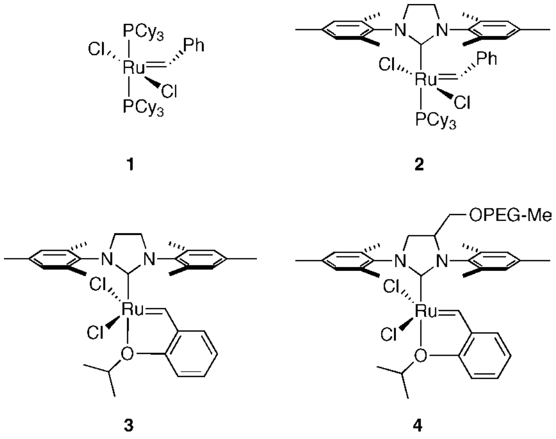


Figure 1. Ruthenium-based olefin metathesis catalysts.

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(1) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997.

(2) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vols. 1−3.

(3) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140.

(4) Courchay, F. C.; Sworen, J. C.; Ghiviriga, I.; Abboud, K. A.; Wagener, K. B. *Organometallics* **2006**, *25*, 6074−6086.

(5) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160−17161.

(6) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865−1880.

(7) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414−7415.

(8) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202−7207.

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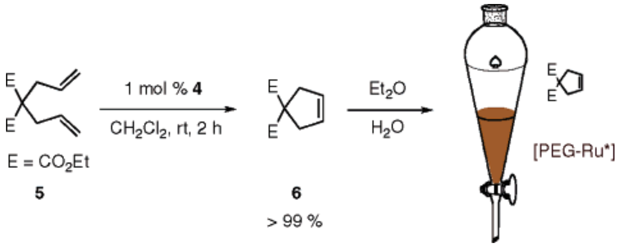
Several protocols have been reported to remove the ruthenium byproducts. The use of tris(hydroxymethyl)phosphine (THMP),[9] $Pb(OAc)_4$,[10] DMSO (or $Ph_3P{=}O$),[11] activated carbon,[12] supported phosphines,[13] supercritical fluid,[14] a modified catalyst,[15] mesoporous silicates,[16] and a polar isocyanide ($CNCH_2CO_2K$)[17] has been reported to reduce the ruthenium content from homogeneous olefin metathesis reactions. Although these purification methods afford low levels of residual ruthenium, they also have drawbacks, such as high loadings of expensive, toxic, and/or unstable ruthenium scavengers, long processing times, the requirement of silica gel column chromatography, or numerous washings and extractions, which are not practical and economical in many cases.[14] Furthermore, most methods do not actually reduce the ruthenium contamination below the 10 ppm level, which is necessary for pharmaceutical applications.[18,19]

Recently, we reported poly(ethylene glycol) (PEG) supported catalyst **4** ($M_n \sim 2639$, M_n = number average molecular weight) which is active and stable in aqueous media (Figure 1).[20] The unique solubility profile of PEG renders **4** soluble in some organic solvents such as dichloromethane and toluene, which are typical solvents for olefin metathesis, as well as aqueous media. The catalyst is not soluble in other organic solvents such as diethyl ether, isopropyl alcohol, and hexanes, following the solubility profile of PEG. This extraordinary solubility of **4** prompted us to develop a simple aqueous extraction method to remove the ruthenium byproducts after olefin metathesis reactions. The idea is simple: to extract PEG-bound ruthenium complexes with water from a diethyl ether solution containing the desired organic products, after performing the olefin metathesis reaction homogeneously in CH_2Cl_2 or toluene (Scheme 1).

Scheme 1. Removal of Ruthenium Byproducts by Simple Aqueous Extraction



The activity of catalyst **4** in CH_2Cl_2 was compared with catalysts **2** and **3** in the ring-closing metathesis (RCM) reaction of diethyl diallylmalonate (**5**).[21] As shown in Figure 2, the attachment of a PEG chain to the N-heterocyclic carbene (NHC) does not significantly affect the catalyst activity.

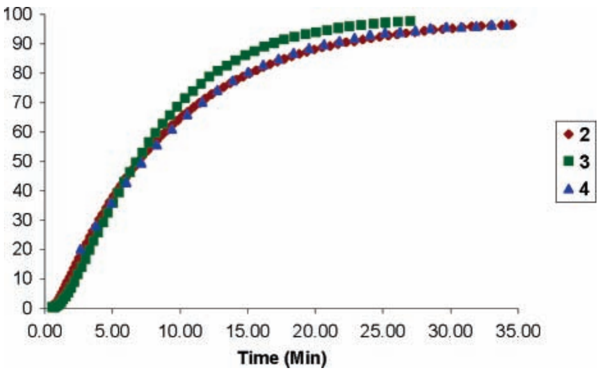


Figure 2. RCM of diethyl diallylmalonate (conditions: 1 mol % of Ru catalyst, 0.1 M, CD_2Cl_2, 30 °C).[21]

The RCM of substrate **5** by catalyst **3** followed by purification using several reported methods was undertaken to collect reference data (Table 1). Silica gel chromatography, which is not practical and efficient on an industrial scale, was avoided in all cases. Simple extraction reduced the ruthenium content by approximately half (entry 1). Treatment

Table 1. Ruthenium Level in **6** (ppm) after Purification

entry	catalyst[a]	purification method	[Ru][b] (ppm)
1	**3**	5 H_2O washes	1779
2	**3**	THMP (50 equiv[c]) and 5 H_2O washes	91
3	**3**	DMSO (50 equiv[c]) and 5 H_2O washes	786
4	**3**	5 H_2O washes and activated carbon[d]	82
5	**4**	5 H_2O washes	41[e]
6	**4**	THMP (50 equiv[c]) and 5 H_2O washes	2
7	**4**	5 H_2O washes and activated carbon[d]	<0.04
8	**3**	PEG ($M_n \sim 10000$, 50 equiv[c]) and 5 H_2O washes	562
9	**3**	PEG ($M_n \sim 550$, 50 equiv[c]) and 5 H_2O washes	1165

[a] 1 mol %. [b] Analyzed by ICP−MS, crude [Ru] ~ 4400 ppm (22 μg/5 mg) for both **3** and **4**, 1 μg/5 mg = 200 ppm. [c] Based on the ruthenium catalyst. [d] 1.3 wt equiv of the crude product **6**. [e] Three H_2O washes do not increase the measured ruthenium level.

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(9) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137−4140.

(10) Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Mendez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259−1261.

(11) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411−1413.

(12) Cho, J. H.; Kim, B. M. *Org. Lett.* **2003**, *5*, 531−533.

(13) Westhus, M.; Gonthier, E.; Brohm, D.; Breinbauer, R. *Tetrahedron Lett.* **2004**, *45*, 3141−3142.

(14) Gallou, F.; Saim, S.; Koenig, K. J.; Bochniak, D.; Horhota, S. T.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2006**, *10*, 937−940.

(15) Michrowska, A.; Gulajski, L.; Kaczmarska, Z.; Mennecke, K.; Kirschning, A.; Grela, K. *Green Chem.* **2006**, *8*, 685−688.

(16) McEleney, K.; Allen, D. P.; Holliday, A. E.; Crudden, C. M. *Org. Lett.* **2006**, *8*, 2663−2666.

(17) Galan, B. R.; Kalbarczyk, K. P.; Szczepankiewicz, S.; Keister, J. B.; Diver, S. T. *Org. Lett.* **2007**, *9*, 1203−1206.

(18) Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X. D.; Wang, T. B. *Org. Process Res. Dev.* **2005**, *9*, 198−205.

(19) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889−900.

(20) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508−3509.

(21) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740−5745.

with DMSO, in the absence of silica gel chromatography, is not as effective as ruthenium removal employing THMP or activated carbon.[11] THMP[9] or activated carbon[12] treatment with an aqueous workup effectively reduced the ruthenium level below 100 ppm; however, this ruthenium level is still too high for practical use.

In contrast, simple aqueous extraction reduced the ruthenium level to 41 ppm following RCM with catalyst **4**, which is lower than the level achieved by THMP or activated carbon treatment with catalyst **3** (entry 5).[22] Clear diethyl ether and brown aqueous phases were observed during the extraction. Employing the aqueous extraction protocol with catalyst **4** in combination with THMP or activated carbon reduced the ruthenium level below 10 ppm, which is suitable for pharmaceutical applications (entries 6 and 7).[14] The activated carbon treatment after aqueous extraction was extremely efficient, reducing the ruthenium level below the detection limit of our analysis, <0.04 ppm.

PEGs themselves were next tested for removing residual ruthenium from the RCM by **3**. The tested PEGs ($M_n \sim$ 10 000 and $M_n \sim 550$) did not show effective removal of the ruthenium byproducts (entries 8 and 9). These results indicate that the PEG-supported NHC ligand remains bound to the ruthenium byproducts or scavenges them after olefin metathesis reactions. The NHC-bound decomposition products isolated from reactions with catalyst **2** have been reported in both organic solvents and aqueous media.[7,23,24]

In conclusion, we have demonstrated a convenient and efficient method for removing ruthenium-containing byproducts from olefin metathesis reactions by simple aqueous workup. This practical, economical, and environmentally friendly method reduced the ruthenium contamination level down to the useful range for biologically active material applications.

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[22] A typical purification procedure is as follows: Crude 3,3-diethyl-ester-pentene (**6**, 100 mg, 0.472 mmol) in diethyl ether (∼30 mL) was transferred to a separatory funnel. The diethyl ether solution was washed three or five times by water (∼30 mL), dried over $MgSO_4$, and concentrated. Approximately 20∼30 mg of the resulting clear oil was accurately weighed by a microbalance and digested with concentrated nitric acid overnight for ICP−MS analysis. For activated carbon purification, the activated carbon (1.3 wt equiv of the crude product **6**) was added to the diethyl ether solution after the extraction and stirred for 24 h. After the carbon was filtered, the filtrate was concentrated in vacuo to provide **6** as clear oil. THMP and DMSO methods were carried out following the literature procedures except avoiding silica gel treatment or column chromatography.

[23] Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827−2833.

[24] Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T. L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546−2558.