ORGANIC
LETTERS

2001
Vol. 3, No. 9
1411−1413

A Convenient Method for the Efficient Removal of Ruthenium Byproducts Generated during Olefin Metathesis Reactions

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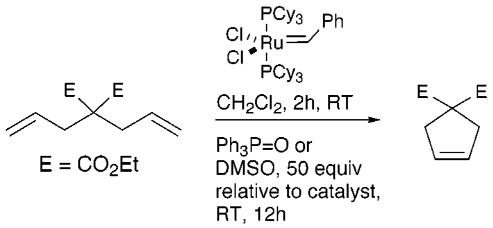
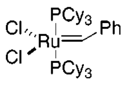
Received March 8, 2001

ABSTRACT



An efficient method for removing ruthenium byproducts generated during olefin metathesis reactions with Grubbs catalysts is described. Treatment of the crude reaction products with triphenylphosphine oxide or dimethyl sulfoxide, followed by filtration through silica gel, was found to be a practical and effective method to remove colored ruthenium byproducts.

Because of the availability of efficient ruthenium and molybdenum catalysts, the olefin metathesis reaction has emerged as a new and powerful method in organic chemistry.[1] Grubbs' ruthenium catalysts **1** and **2** have been used widely for ring-closing metathesis (RCM), cross-metathesis, and ring-opening metathesis polymerization (ROMP) reactions.[2] One drawback of this method is the formation of highly colored ruthenium byproducts during the reactions, which are difficult to remove from the reaction products, often requiring multiple chromatographic purifications. Incomplete removal of the ruthenium byproducts is known to cause complications such as double bond isomerization during distillation or decomposition of the reaction products.[3] Since metathesis reactions are expected to be used in pharmaceutical processes, efficient and convenient methods are also needed to remove potentially toxic ruthenium byproducts from the reaction products.



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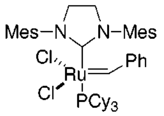

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The groups of Grubbs and Paquette have recently reported efficient methods for the removal of ruthenium byproducts from metathesis reactions.[3,4] The Grubbs method relies on removing the ruthenium byproducts as water-soluble

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10.1021/ol010045k CCC: $20.00

ruthenium tris(hydroxymethyl)phosphine complexes,[3] and the procedure from the Paquette laboratory uses oxidation with $Pb(OAc)_4$ for metal byproducts removal.[4] We herein report yet another convenient and efficient method to remove colored metal byproducts associated with RCM reactions using the inexpensive reagents triphenylphosphine oxide ($Ph_3P{=}O$) or dimethyl sulfoxide (DMSO). Our studies showed that colored ruthenium byproducts could be removed effectively by treatment of the crude reaction mixtures with $Ph_3P{=}O$ or DMSO followed by filtration through silica gel or column chromatography on silica gel.[5]

Diethyl diallylmalonate (**3**) was chosen as the substrate to examine the novel purification method (Scheme 1 and Table 1).[3] RCM of **3** using ruthenium catalyst **1** provided the crude reaction product **4**, which was subsequently treated with $Ph_3P{=}O$ or DMSO for a minimum of 12 h, followed by column chromatography to provide purified **5** as a colorless oil (Scheme 1). We examined the ruthenium levels of the purified products after adding increasing amounts of $Ph_3P{=}O$ or DMSO (5, 10, 20, 50, and 100 equiv relative to **1**) to the crude reaction mixture **4** (Table 1). The ruthenium levels in the purified RCM product **5** were analyzed by inductively coupled plasma mass spectrometry (ICP-MS).[6] As shown in Table 1, the ruthenium levels decreased with increasing amounts of the additives $Ph_3P{=}O$ and DMSO. In both cases, optimal results were observed when 50 equiv of $Ph_3P{=}O$ or DMSO relative to catalyst **1** was added to the crude product mixture (entry 5). Under those conditions, the ruthenium levels were reduced to 1.2 μg and 1.8 μg in 5.0 mg of **5**, respectively. The residual ruthenium levels achieved with this method are very similar to those reported by Grubbs (1.03 μg in 5.0 mg of **5**)[3] and Paquette (1.55 μg in 5.0 mg of product).[4]

Scheme 1

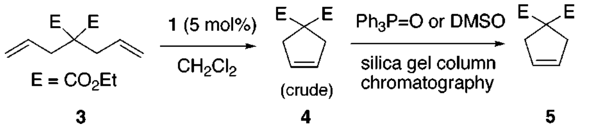


Table 1. Ruthenium Levels of **5** (μg/5 mg) after Exposure of Crude Product **4** to Different Amounts of $Ph_3P{=}O$ and DMSO for at Least 12 h at Room Temperature Followed by Column Chromatography on Silica Gel[5]

entry	Ph_3PO (equiv)[a]	ruthenium (μg/5 mg)	DMSO (equiv)[a]	ruthenium (μg/5 mg)
1	0[b]	59.7 ± 0.50	0[b]	59.7 ± 0.50
2	5[c]	2.77 ± 0.02	5[c]	6.99 ± 0.02
3	10	2.11 ± 0.02	10	5.43 ± 0.02
4	20	1.85 ± 0.02	20	2.60 ± 0.02
5	50	1.20 ± 0.01	50	1.81 ± 0.02
6	100	1.91 ± 0.01	100	1.34 ± 0.02

[a] Equivalent of Ph_3PO or DMSO relative to **1**. [b] The ruthenium content of the crude product was determined without purification by column chromatography. After digestion of the crude sample, insoluble material was filtered off, which may account for the observed decreased amount of ruthenium compared to the theoretical amount of ruthenium at 5 mol % (90 μg/5 mg of product). [c] The addition of 5 equiv did not remove all colored products.

Similar results were obtained when we used catalyst **2** in the RCM reaction of diethyl diallylmalonate (**3**).

To find the optimal reaction time needed for effective purification using the $Ph_3P{=}O$/chromatography protocol, individual reactions were examined and measurements of the ruthenium levels in purified product **5** were made (Table 2).

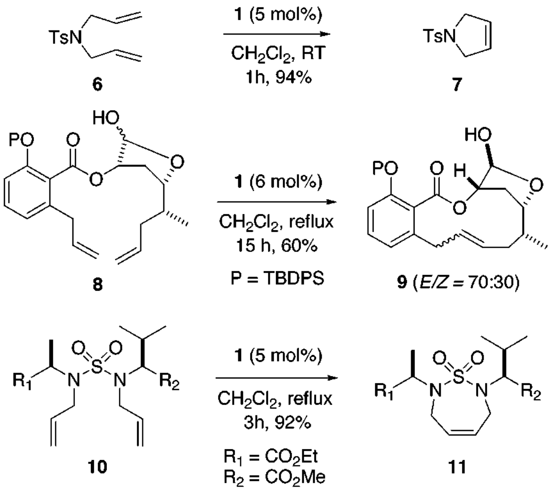
Table 2. Ruthenium Levels of **5** (μg/5 mg) after Different Exposure Times of Crude Reaction Product **4** to 50 equiv of $Ph_3P{=}O$ at Room Temperature, Followed by Column Chromatography on Silica Gel

entry	exposure time (h)	ruthenium (μg/5 mg)
1	1	16.4 ± 0.16
2	2	13.5 ± 0.21
3	4	10.2 ± 0.15
4	8	2.30 ± 0.02
5	12	1.20 ± 0.01
6	24	1.27 ± 0.01

We found that efficient removal of ruthenium byproducts was achieved with a minimum treatment time of 8 h (entry 4). However, optimum results were achieved after 12 h (entry 5).

We next examined the novel purification method with different substrates (Scheme 2) under the conditions that have been reported for the synthesis of **7**, **9**, and **11**.[7−9] The RCM transformations were carried out under argon. Once the RCM reactions were completed (monitored by TLC), $Ph_3P{=}O$ (50 equiv relative to **1**) was introduced into the reaction mixture and the solutions were stirred at room temperature overnight, while maintaining the argon atmosphere. Subsequent column

Scheme 2



chromatography on silica gel (2 g/0.01 mmol of catalyst, eluent = hexanes:ethyl acetate = 4:1) gave a clear, colorless liquid or a white solid in the reported yields (Scheme 2).[7−9] In all three cases, the colored byproducts were successfully removed from the products [ICP-MS data: **7** (0.5 μg/5 mg), **9** (1.1 μg/5 mg), and **11** (2.1 μg/5 mg)].

In summary, our results demonstrate that $Ph_3P{=}O$ and DMSO can be used effectively to remove the colored ruthenium byproducts of ruthenium catalysts **1** and **2**, which are formed after RCM, when followed by simple filtration through silica gel or column chromatography. With this method, residual ruthenium levels from metathesis reactions are lowered to approximately 1−2 μg/5 mg of product. The advantage of the method is that $Ph_3P{=}O$ and DMSO are very stable and inexpensive reagents. Both reagents have limited chemical reactivity and should therefore be compatible with a wide variety of functional groups.

Acknowledgment. We gratefully acknowledge financial support for this work by the National Institutes of Health (CA84173). We wish to thank Dr. Apurba Datta and Dr. Paul R. Hanson for helpful discussions. We also thank Dr. Paul R. Hanson for providing RCM substrate **10** in Scheme 2. We are grateful to Professor Gwendolyn L. Macpherson, Director of the Plasma Analytical Laboratory at the University of Kansas, for carrying out the ICP-MS measurements.

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(5) **Procedure for RCM of 3 and purification of crude product 4 with triphenylphosphine oxide or dimethyl sulfoxide:** A solution of diethyl diallylmalonate (**3**, 120 mg, 0.5 mmol) in CH_2Cl_2 (100 mL) was degassed with argon for 5 min and then catalyst **1** (20.5 mg, 5 mol %) was added to the solution. The reaction flask was sealed with a rubber septum. After the reaction was complete (approximately after 2 h at rt, monitored by TLC), the reaction mixture was treated with $Ph_3P{=}O$ (350 mg, 50 equiv, relative to catalyst **1**) or DMSO (90 μL, 50 equiv, relative to catalyst **1**) overnight. The solution was concentrated in vacuo and purified by column chromatography on silica gel (2 g/0.01 mmol of catalyst **1**) using hexanes:EtOAc = 8:1 as the eluent to provide the RCM product **5** in 95−98% yield.

(6) Samples (approximately 5−10 mg) were accurately weighed, digested with distilled 6 N nitric acid overnight, and diluted to a total volume of approximately 100 mL with the distilled acid and distilled deionized water to a final acid concentration of about 2%. Samples were analyzed on a PQII+XS inductively coupled plasma mass spectrometer (ICP-MS). Masses 96, 98, 99, 100, 101, 102, and 104 were monitored in all samples and standards. Drift (corrected according to the method by Cheatham, M. M.; Sangrey, W. F.; White, W. M. *Spectrochim. Acta, Part B* **1993**, *48B*, E487−E506) was usually less than 5% and always less than 10% during a single run. The reported concentration is the average of the total Ru concentration as calculated from each of the individual isotopes after drift correction. The average usually had a percent relative standard deviation (%RSD) of less than 2% and always less than 4%.

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