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An Efficient Method for Removal of Ruthenium Byproducts from Olefin Metathesis Reactions

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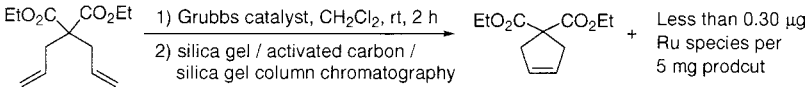
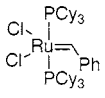
ABSTRACT



Sequential treatment of the ring-closing metathesis reaction products with silica gel, activated carbon (50 equiv wt relative to the crude products), and column chromatography on silica gel efficiently removed dark brown ruthenium byproducts from the reaction mixture. After this treatment, colorless compounds could be obtained with a ruthenium level of 0.06–0.53 μg per 5 mg of product.

Olefin metathesis has emerged as a powerful tool in the preparation of cyclic organic compounds.[1] Ruthenium catalysts **1**, **2**, and **3** have been widely used for ring-closing olefin metathesis (RCM), ring-opening metathesis polymerization (ROMP), and acyclic cross metathesis.[2−4]



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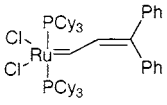

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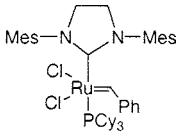

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One major concern in the use of olefin metathesis reactions especially in connection with the synthesis of biologically active compounds is the generation of colored, toxic ruthenium metal byproducts. It is extremely difficult to remove the ruthenium byproducts completely from the desired product(s) even after purification on silica gel column chromatography several times. The metal complex remaining in the product(s) may cause isomerization or decomposition during the purification of the product(s).[5] We have been involved in the synthesis of cyclic peptide analogues using the RCM[6] and we were particularly alarmed by the fact that a large amount of the ruthenium catalyst (30−50 mol % relative to substrates) was required for the optimal yields of cyclic peptide analogues. In the case where a large amount of the ruthenium catalyst was employed, a considerable portion of the ruthenium byproducts remained in the product, culminating in toxicity during bioassays.[6] This prompted us

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(4) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (b) Itoh, T.; Mitsukura, K.; Ishida, N.; Uneyama, K. *Org. Lett.* **2000**, *2*, 1413−1434. (c) Lera, M.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 2765−2786. (d) Smith, A. B., III; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984−4985.

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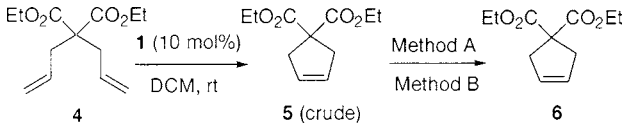
to look for an efficient method for the removal of the ruthenium byproducts.

Several groups including Grubbs,[5] Paquette,[7] and Georg[8] have recently reported methods for removing ruthenium byproducts formed from the Grubbs reagent. The Grubbs' method involves conversion of the ruthenium byproducts into water-soluble ruthenium phosphine complexes, using quite expensive tris(hydroxymethyl)phosphine, and the Paquette group utilized oxidation of the ruthenium species with $Pb(OAc)_4$. Both methods are associated with some significant drawbacks resulting from the introduction of expensive or toxic reagents to remove the ruthenium species. Georg and co-workers dealt with the ruthenium metal species by treatment with Ph_3PO or DMSO. Also Dixneuf used carbon black to clean up ionic liquid after RCM reaction for the purpose of recycling the ionic liquid.[9] Optimized conditions of these methods allowed for the reduction of the ruthenium levels down to approximately 1−2 μg per 5 mg of product(s).

During the study on the synthesis of natural cyclic pentapeptide analogues such as {*cyclo*(Phe-Leu-Pro-Ala-Ala)}[10] using Grubbs catalyst **1**, we were in search of a more effective and environment-friendly method for removal of the ruthenium byproducts. Here we wish to report such a method through a sequence involving adsorption and filtration on silica gel/activated carbon[11]/column chromatography on silica gel. This sequence was extremely efficient in reducing the ruthenium level below 1 μg per 5 mg of the reaction products.

We used diethyl diallylmalonate as a control substrate and followed the reported procedure of RCM[8] as shown in Scheme 1. The RCM of **4** was carried out by using 10 mol

Scheme 1



% of ruthenium catalyst **1** to provide dark brown crude reaction product **5**. At first the crude product was directly treated with activated carbon for 12 h. After filtration of the activated carbon, the filtrate was purified with column chromatography on silica gel to give colorless compound **6** (Method A). As summarized in Table 1, we examined the residual ruthenium levels of the purified products upon treatment with increasing amounts of activated carbon (10, 20, 50, and 100 equiv wt relative to catalyst **1**). The ruthenium levels in 5 mg of purified cyclic compound **6** were measured by inductively coupled plasma mass spectrometry (ICP-MS).[12] We found that the amount of ruthenium in the crude product **5** was 71.58 μg/5 mg without any purification (entry 1), and 9.56 μg/ 5 mg after column chromatography on silica gel only (entry 2). The number went down to 2.89 μg/5 mg after treatment of crude 5 with 100 equiv of activated carbon for 12 h (entry 3). However, when the activated carbon treatment was followed by silica gel column chromatography, the ruthenium levels decreased from 5.23 μg to 1.52 μg per 5 mg of the products after treatment with increasing amounts of activated carbon (Table 1, entries 4−7). The yields of the products were uniformly high after treatment with activated carbon and silica gel.

Table 1. Ruthenium Levels in **6** (μg/5 mg) after the Purification by Method A or B[a]

entry	activated carbon (equiv wt)	ruthenium (μg/5 mg)	method (yield %)
1	−	71.58 ± 0.33	− (95)
2	−	9.56 ± 0.05	− (95)
3	100	2.89 ± 0.01	− (93)
4	10	5.23 ± 0.03	A (92)
5	20	5.08 ± 0.02	A (90)
6	50	1.72 ± 0.02	A (92)
7	100	1.52 ± 0.02	A (90)
8	50	0.36 ± 0.01	B (94)
9	100	0.30 ± 0.01	B (91)

[a] Method A: Treatment of crude product with activated carbon (equiv wt of catalyst **1**) followed by column chromatography on silica gel. Method B: Adsorption on silica gel followed by filtration and treatment with activated carbon (equiv wt of the crude product **5**), then silica gel column chromatography.

Even though the ruthenium level in entry 7 of Table 1 was comparable to the best method available in the literature,[5,7,8] we continued our search for the conditions, aspiring toward further minimization of the ruthenium level. Indeed, insertion of one more step before the activated carbon treatment brought the ruthenium level further down. Thus after RCM the crude product **5** was adsorbed on silica gel and passed through a silica gel pad, and the filtrate was treated with activated carbon for 12 h at room temperature. The residue was purified via silica gel column chromatography to yield colorless **6** (Method B).[13] Under these conditions, the residual ruthenium level was reduced to 0.36 and 0.30 μg in 5.0 mg of **6** with use of 50 and 100 equiv of

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(11) (a) *The Merck Index*; Budavari, S., Ed.; Merk: Rahway, NJ, 1989; p 1814. Activated carbon was used chiefly for clarifying, deodorizing, decolorizing. and filtering. (b) Activated carbon used in this study was from Aldrich Chemical Co. Inc. Darco G-60, −100 mesh, powder.

(12) Reference 8 describes in detail the sampling procedure for determination of the levels of residual ruthenium in the RCM products.

(13) Procedure for RCM of **4** and purification of crude product **5** with silica gel and activated carbon (method B): To a stirred solution of 300 mg of diethyl diallylmalonate (**4**, 1.25 mmol) in degassed dichloromethane (500 mL) was added catalyst **1** (100 mg, 10 mol %) under argon atmosphere at room temperature. After the reaction mixture was stirred for 2 h, the dark solution was adsorbed on silica gel (1.0 g, 10 equiv wt, relative to catalyst **1**) and passed through a pad of silica gel (hexane:EtOAc ratio 6:1 to 2:1). The filtered solution was stirred with activated charcoal (12.0 g, 50 equiv wt of **5**) for 12 h. After the carbon was filtered, the filtrate was concentrated in vacuo and purified on a silica gel chromatographic column (hexane:EtOAc ratio 5:1) to provide product **6** as a colorless oil in 90% yield.

activated carbon, respectively (Table 1, entries 8 and 9). This result showed that Method B was slightly more effective than Method A. It is of particular note that this protocol is superior for the removal of ruthenium byproducts compared to previously reported methods[5,7,8] (ca. 1.03−1.55 μg in 5.0 mg of the product) with about a 3- to 5-fold decrease in ruthenium levels as shown in Table 2.

Table 2. Comparison of Our Method with Others' Best Results on Remaining Ruthenium Levels in RCM Products (μg/5 mg)

entry	methods[a]	equiv[b]	time	ruthenium (μg/5 mg)
1	$P(CH_2OH)_3$	86	20 min	1.03 ± 0.04
2	$Pb(OAc)_4$	1.50	overnight	1.55 ± 0.04[d]
3	DMSO	100	12 h	1.34 ± 0.02
4	Ph_3PO	50	24 h	1.27 ± 0.01
5	Method A	100[c]	12 h	1.52 ± 0.01
6	Method B	100[c]	12 h	0.30 ± 0.01

[a] Three methods are Grubbs (entry 1), Paquette (entry 2), and Georg (entries 3 and 4), respectively. [b] Equivalent of $P(CH_2OH)_3$, $Pb(OAc)_4$, DMSO, Ph_3PO, and carbon related to Grubbs catalyst. [c] Equivalent of carbon related to crude mixture (**5**). [d] The value was prorated to fit the scale with other data.

To monitor optimal activated carbon treatment time for Method B, each reaction mixture was treated with 50 equiv wt of activated carbon relative to the crude filtrates at a given time period and the remaining ruthenium in the purified RCM products was analyzed by ICP-MS as outlined in Table 3.[12]

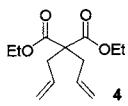
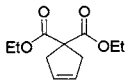
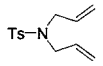
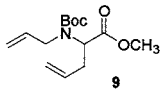
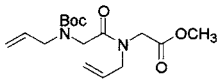
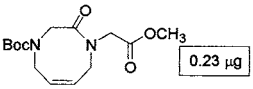
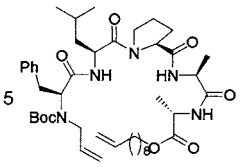
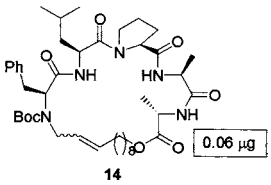
Table 3. Ruthenium Levels of **6** (μg/5 mg) According to Method B Depending upon Treatment Time of Activated Carbon (50 equiv wt to **5**)

entry	treatment time (h)	ruthenium (μg/ 5 mg)	yield (%)
1	1	7.00 ± 0.20	95
2	3	1.62 ± 0.02	94
3	6	0.82 ± 0.01	90
4	12	0.36 ± 0.01	92
5	24	0.34 ± 0.01	90

We found that the best result was obtained from the 24 h treatment (entry 5), although treatment for 12 h gave an almost equivalent result (entry 4). A ruthenium level close to that obtained via previously reported methods was achieved after a 3 h treatment (entry 2). In all cases yields of the purified product were over 90%.

With this efficient protocol for removal of the residual ruthenium in the RCM product in hand, we screened this method against conditions using an *excessive amount of catalyst* **1** with various substrates. When RCM of diethyl 2,2-diallylmalonate was carried out at room temperature for 2 h with 30 and 50 mol % of catalyst **1** and the crude product was cleaned up with 50 equiv wt of activated carbon at room temperature for 12 h, a colorless oil **6** was obtained in 94%

Table 4. Amount of Remaining Ruthenium Species (μg/5 mg of Product) Following Method B

Entry	Starting materials	Reaction Conditions Yields	Products	Remaining Ru species
1	 **4**	Catalyst **1**, DCM, rt, 2 h; 94% for 30 mol% Ru catalyst, 93% for 50 mol% Ru catalyst	 **6**	0.53 μg, 0.30 μg
2	 **7**	**1** (10 mol%), DCM, rt, 2 h, 95 %	 **8**	0.47 μg
3	 **9**	**1** (50 mol%), DCM, rt, 2 h, 97 %	**10**	0.18 μg
4	 **11**	**1** (50 mol%), DCM, rt, 6 h, 90 %	 **12**	0.23 μg
5	 **13**	**1** (50 mol%), DCM, rt, 24 h, 75 %	 **14**	0.06 μg

and 93% yields, with ruthenium levels at 0.53 and 0.30 μg/5 mg, respectively (entry 1, Table 4). In the case of *N,N*-diallyl *p*-toluenesulfonamide **7** with 10 mol % of catalyst **1**, the ruthenium level was 0.47 μg/5 mg (entry 2). When RCM of various amino acid or peptide derivatives **9**, **11**, and **13** were carried out in the presence of 50 mol % of catalyst **1**, ruthenium levels of 0.18, 0.23, and 0.06 μg in 5.0 mg of **10**, **12**, and **14**, respectively, were obtained (entries 3−5, Table 4). The ruthenium species in entry 5 (0.06 μg/5 mg of product) is by far the lowest reported level.

In summary, a most efficient protocol has been developed for removal of ruthenium byproducts generated from Grubbs catalyst **1** during RCM reaction, using a sequence of adsorption and filtration on silica gel, treatment with activated carbon, and column chromatography on silica gel. This methodology was successfully applied to the RCM with use of 10, 30, and 50 mol % of catalyst **1** on various substrates. By using the optimal conditions, the residual ruthenium levels in the RCM products were reduced to 0.06−0.53 μg/5 mg of products without detectable loss of the products. Another advantage of this protocol is that activated carbon can be easily handled and conveniently removed from the RCM products through filtration.

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