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Purification Technique for the Removal of Ruthenium from Olefin Metathesis Reaction Products

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Abstract: Ring-closing metathesis (RCM) products of reactions utilizing $RuCl_2(=CHPh)(PCy_3)_2$ (**1**) as a catalyst were successfully purified of unwanted ruthenium using a water-soluble coordinating phosphine, tris(hydroxymethyl)phosphine, $P(CH_2OH)_3$. Several simple and efficient purification procedures were compared for the isolation of the product of the RCM of diethyl diallylmalonate. The efficiency of this procedure was demonstrated for the isolation of crown-ether **3**.

Metal complexes are utilized in many organic transformations, including small molecule and polymer synthesis.[1] However, removal of the metal complex after completion of the reaction can pose a serious problem during product purification, especially on an industrial scale. This residual metal can be problematic in subsequent transformations, as well as for storage and use of the material. Specifically, ruthenium catalysts such as benzylidene ruthenium complex **1**,[2] are commonly utilized in olefin metathesis reactions such as RCM, cross metathesis, or ring-opening metathesis polymerization (ROMP).[3] However, it can prove very difficult to remove the highly-colored ruthenium complexes from the products of these reactions and the residual ruthenium can cause problems such as olefin isomerization during distillation of the product, decomposition over time, and increased toxicity of the final material. Herein, we describe a method to alleviate these problems by using a commercially available phosphine that facilitates the removal of ruthenium during product isolation.

Tris(hydroxymethyl)phosphine (**2**) is a moderately air stable and water soluble phosphine.[4] Because of these properties, there has been an increasing number of reports on the use of **2** as a ligand making water-soluble transition metal complexes used as catalysts[4,5] and for applications in medicinal chemistry.[6] Recently, two ruthenium complexes of **2** have been described.[7] In both cases the phosphine readily coordinated to the ruthenium resulting in a complex soluble in water. These studies prompted us to explore the use of **2** for the removal of residual ruthenium from olefin metathesis reaction products.

The RCM of diethyl diallylmalonate by ruthenium complex **1** and purification of the product using **2** was undertaken as shown in Scheme 1.[8,9] It was observed that when the crude product was added to a solution of **2**[10] and triethylamine in methylene chloride, the solution turned from a black/brown color to pale yellow within five minutes, indicating that **2** was

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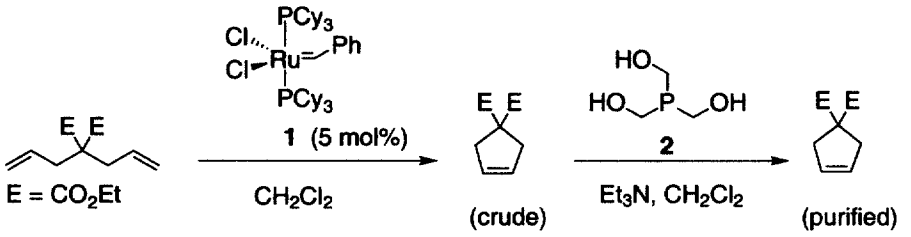
coordinating to the ruthenium. Upon the addition of water, the yellow color moved into the aqueous phase leaving the methylene chloride phase colorless. ^{1}H NMR studies indicated that all of the product remained in the methylene chloride phase and all of the phosphine moved to the aqueous phase.

Scheme 1



To quantify this observation a series of purification experiments were undertaken and the results given in Table 1. The amount of ruthenium in a 5 mg sample of the RCM product was determined by inductive-coupled plasma mass spectrometry (ICP-MS).[11] All purification methods achieved a more than 10-fold decrease in the amount of ruthenium remaining in the sample compared to the crude sample (entry 1). The results were similar whether 86 equivalents (entry 2) or 378 equivalents (entry 3) of **2** were used followed by one aqueous wash. The amount of ruthenium in the product could be decreased by adding 86 equivalents of **2** followed by 3 aqueous washes (entry 4) or adding **2** to the methylene chloride layer three times, followed by an aqueous wash each time (entry 5). Because **2** is polar and is known to graft onto silica gel,[12] a purification by stirring a solution of product, **2**, and triethylamine in methylene chloride with an excess of silica gel (entry 6) was attempted. This method gave the best result and the amount of residual ruthenium remaining in the sample was reduced to 1 μg in 5 mg of product.

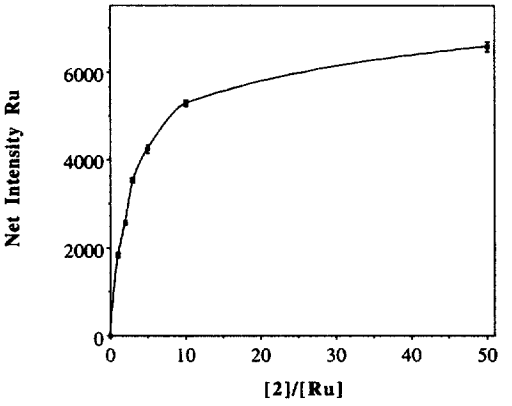
Table 1. Amount of ruthenium in 5 mg product by various purification methods*

Entry	Method	Ruthenium (μg/5 mg product)
1	crude	74.6 ± 0.8
2	86 eq. **2**, 1 H_2O wash	5.72 ± 0.07
3	378 eq. **2**, 1 H_2O wash	5.84 ± 0.07
4	86 eq. **2**, 3 H_2O washes	3.35 ± 0.07
5	86 eq. **2**, 1 H_2O wash, repeated 3 times	3.56 ± 0.07
6	86 eq. **2**, stir with silica gel, filter	1.03 ± 0.04

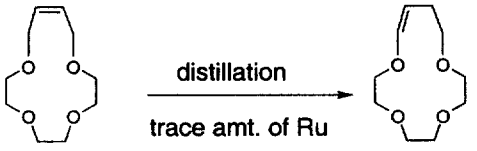
*Number of eq. of **2** based on added **1**. In each case, 2 eq. Et_3N was used.

Given that in the above experiments, the same results were obtained by adding 86 equivalents or greater of **2**, next we studied the minimum amount of **2** that would be necessary to draw ruthenium into the aqueous phase. A series of experiments were undertaken to determine the net ICP-MS intensity of ruthenium in the aqueous phase after adding a certain number of equivalents of **2** to the methylene chloride layer followed by a H_2O wash. There was a steep rise in the net intensity, and thus amount of ruthenium in the aqueous phase, between 1 and 10 equivalents of **2** (Figure 1) It appears that at least 10 equivalents of **2** is necessary to efficiently extract the ruthenium into the H_2O layer from the methylene chloride phase.

Figure 1. Ruthenium signal from aqueous phase versus equivalents of **2**



With this information, the methodology was extended to another example. The RCM of bisallyl triethylene glycol with **1** yields crown ether **3** which when polymerized by ROMP forms a polyether.[13] However, often times when **3** was purified by distillation, 2-5 % of the cyclic vinyl ether **4** formed which inhibited the ROMP of **3**.[14] Yet, when **3** was pretreated with **2** and purified with one aqueous wash, the ruthenium concentration was reduced from 80 to 8.8 μg/5 mg **3** as determined by ICP-MS. In this case, a 10-fold decrease in the ruthenium concentration was significant enough to inhibit the detrimental isomerization during distillation, thus eliminating the need for a more time-consuming purification of **3**.



3 **4**

In conclusion, removal of residual ruthenium from RCM reaction products is facilitated by the use of water-soluble phosphine **2** during the isolation process. An aqueous extraction or silica gel purification may be used. In the case of an aqueous extraction, 10 equivalents of **2** is

adequate to move the ruthenium to the H_2O phase. Further studies regarding the purification of RCM reactions in this manner and initial studies on the purification of polymers obtained through ROMP are underway.

Acknowledgements.

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9. A typical purification procedure is as follows: 3,3-Diethylester-pentene (100 mg, 0.472 mmol) in methylene chloride (0.5 mL) was added to a solution of **2** (293 mg, 2.36 mmol) and triethylamine (657 μg, 4.72 mmol) in methylene chloride (1.5 mL) and stirred for 10 minutes. Water (~2 mL) was added and the biphasic solution vigorously stirred for 15 mintues. The aqueous layer was separated and the methylene chloride removed *in vacuo* to isolate the product as a yellow oil.
10. **2** was purchased from Strem Chemicals, but may be synthesized from $[P(CH_2OH)_4]Cl$. See reference 4.
11. Samples of approximately 5 mg were precisely weighed on a microbalance, digested overnight with concentrated nitric acid, and diluted to 1% nitric acid. The samples were each measured 10 times and the intensities were obtained for ruthenium isotopes 99, 101, and 102. The intensity of pure 1% nitric acid was subtracted from the sample intensities to give the net intensities. To determine the actual concentration of ruthenium in the samples, the net intensities were compared to that of ruthenium standards. The standards were obtained by diluting a ruthenium standard of 980 μg/mL Ru in 5 wt.% HCl (obtained from Aldrich) with 1% nitric acid to get 2.04, 1.49, 0.98, 0.47, 0.1, 0.05, and 0.01 μg/mL Ru standards where each sample contained less than 0.01 wt.% HCl. The numbers given indicate the average amount of ruthenium obtained for the three isotopes measured.
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