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A Convenient Method for Removing All Highly-Colored Byproducts Generated during Olefin Metathesis Reactions

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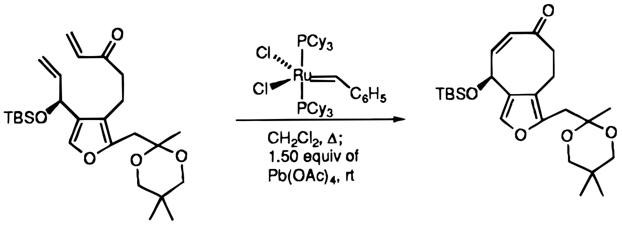
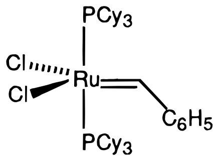
ABSTRACT



Addition of a very modest amount of lead tetraacetate (1.50 equiv relative to the amount of Grubbs catalyst) to ring-closing metathesis reaction mixtures effectively removes all colored ruthenium and phosphine impurities to deliver colorless reaction products.

The olefin metathesis reactions, in their cross-coupling, ring-opening, and particularly ring-closing modes,[1,2] have developed into processes that are of considerable value to organic synthesis.[3] The striking advances that have materialized in recent years stem largely from the availability of efficient molybdenum[4] and ruthenium[5] precatalysts having well-balanced electronic and coordinative unsaturation such that high turnover performance is manifested. Due to its increased stability, the Grubbs catalyst **1**[6] has been most widely employed, although its general ineffectiveness for producing trisubstituted alkenes is generally recognized.[7]



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Despite the major advantages offered by this group of reactions, they share the same complication. Removal of the darkly colored, metal-containing byproducts upon completion of the metathesis step is often very difficult, frequently requiring three to four chromatographic purifications to arrive at adequately metal-free final material. Failure to remove these impurities can induce later problems. These potentially include double bond migration and/or decomposition. Where drug candidates are concerned, residual toxicity is a major consideration.

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

(2) *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer: Berlin, 1998.

(3) For recent reviews, consult: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res*. **1995**, *28*, 446. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1833. (c) Fürstner, A. *Topics Catal*. **1997**, *4*, 285. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (e) Pariya, C.; Jayaprakash, K. N.; Sarkar, A. *Coord. Chem. Rev*. **1998**, *168*, 1. (f) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chem*. **1998**, *133*, 29. (g) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (h) Ivin, K. J. *J. Mol. Catal. A: Chem*. **1998**, *133*, 1. (i) Wright, D. L. *Curr. Org. Chem*. **1999**, *3*, 211.

(4) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc*. **1990**, *112*, 3875.

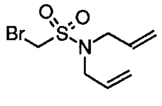
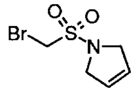
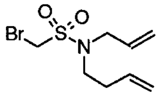
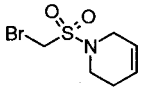
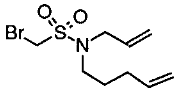
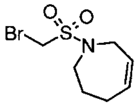
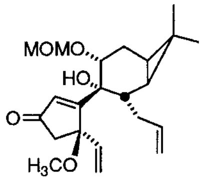
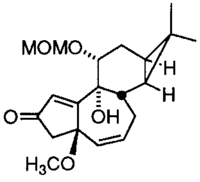
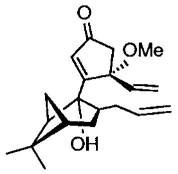
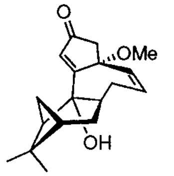
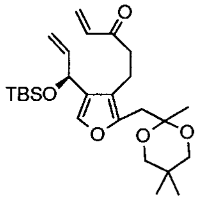
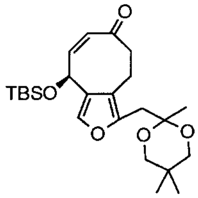
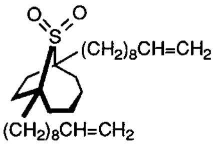
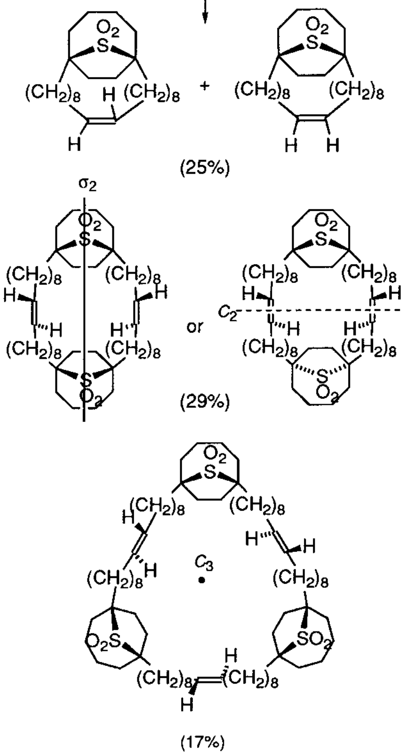
(5) (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am Chem. Soc*. **1992**, *114*, 3974. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs R. H. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2039.

(6) Fu, G.; Grubbs, R. H. *J. Am. Chem. Soc*. **1992**, *114*, 5426.

(7) (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2037. (b) Callam, C. S.; Lowary, T. L. *Org. Lett*. **2000**, *2*, 167.

10.1021/ol000036w CCC: $19.00

Table 1. Ring Closing Metathesis Results

RCM expt	Reactant	Product(s)
1		 $Pb(OAc)_4$: 0 equiv (85%) 1.25 equiv (95%) 1.50 equiv (96%)
2		 $Pb(OAc)_4$: 1.50 equiv (97%)
3		 $Pb(OAc)_4$: 1.50 equiv (96%)
4		 $Pb(OAc)_4$: 1.50 equiv (86%)
5		 $Pb(OAc)_4$: 1.50 equiv (54%)
6		 $Pb(OAc)_4$: 1.50 equiv (60%)
7		$Pb(OAc)_4$: 1.50 equiv (71%)  (25%) (29%) (17%)

To resolve such issues, Maynard and Grubbs have recently introduced the technique of adding tris(hydroxymethyl)phosphine, a water-soluble ligand, for removing unwanted ruthenium.[8] However, at least 10 equiv of this phosphine are necessary to be effective, and the reagent is extremely expensive[9] and only moderately stable.

We have investigated the feasibility of using readily available lead tetraacetate in very modest quantities for facilitating product purification after ring-closing metathesis (RCM) and here report our widespread success with this technology. $Pb(OAc)_4$ has long been recognized to be an oxidant having a broad range of uses.[10] Notwithstanding, its reactions with organometallics have largely been limited to the liberation of cyclobutadienes from their $Fe(CO)_3$ complexes.[11] Although standard electrode potentials vary considerably as a function of ligand and solvent, the magnitude of the $Pb(OAc)_4-Pb(OAc)_2$ couple (1.67 V in 1.1 N $HClO_4$)[12] is known to exceed those values recorded for various oxides of Ru (1.12−1.6 V).[13]

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[8] Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137.

[9] The prices quoted in the 1999−2001 Strem Chemical Inc. catalog for tris(hydroxymethyl)phosphine are $40/1 g and $560/25 g.

[10] (a) Criegee, R. In *Oxidation in Organic Chemistry*; Wiberg K. B., Ed.; Academic Press: New York, 1965; Part A, pp 277−366. (b) Butler, R. N. In *Synthetic Reagents*; Pizey, J. S., Ed.; Ellis Horwood Limited: Chichester, 1977; Vol. 3, pp 277−419. (c) Rubottom, G. M. In *Oxidation in Organic Chemistry*; Trahanovsky, W. S., Ed.; Academic Press: New York 1982; Part D, pp 1−145. (d) Mihailovic, M. L.; Cekovic, Z.; Lorenc, L. In *Synth. Oxid. Met. Compd.*; Mijs, W. J., DeJonge, C. R. H. I., Eds.; Plenum Press: New York, 1986; pp 741−816.

[11] (a) Barborak, J. C.; Pettit, R. *J. Am. Chem. Soc.* **1967**, *89*, 3080. (b) Merk, W.; Pettit, R. *J. Am. Chem. Soc.* **1967**, *89*, 4787. (c) Masamune, S.; Nakamura, N.; Spadaro, J. *J. Am. Chem. Soc.* **1975**, *97*, 918. (d) Brener, L.; McKennis, J. S.; Pettit, R. *Org. Synth.* **1976**, *55*, 43.

[12] Berka, A.; Dvorak, V.; Nemec, I.; Zyka, J. *J. Electroanal. Chem.* **1952**, *4*, 150.

The RCM transformations defined in Table 1 were carried out under conditions considered most effective for the particular substrate at hand. For runs 1−3, ring closure is especially facile (complete in 30 min) when performed in CH_2Cl_2 at room temperature with periodic evacuation of the flask to expedite removal of the ethylene. In contrast, runs 4 and 5 were performed in refluxing benzene for several days. The reaction times for runs 6 and 7 in refluxing CH_2Cl_2 were 36 and 12 h, respectively. Once these reaction mixtures were returned to 20 °C, $Pb(OAc)_4$ (1.5 equiv relative to **1**) was introduced with maintenance of an inert atmosphere and stirring was continued overnight at room temperature. Simple filtration of the reaction mixture through a pad of silica gel (10 g/0.05 mmol of catalyst) and washing with CH_2Cl_2 gave clear colorless filtrates that were directly evaporated to yield white solids in the reported yields.[14]

To quantify matters, the series of experiments reported in Table 2 were undertaken. The levels of ruthenium and lead in accurately weighed 5−10 mg samples were determined by inductive-coupled plasma mass spectrometry (ICPMS).[15] Since no $Pb(OAc)_4$ was used in entry A, this sample was very darkly colored. Although treatment with either 1.25 or 1.50 equiv of $Pb(OAc)_4$ strikingly reduced the levels of ruthenium, entry C was more effective at guaranteeing the absence of color and this level of $Pb(OAc)_4$ was therefore used throughout Table 1. The amount of Pb in the product samples never increased above background levels.

Table 2. Quantities of Ruthenium and Lead (μg per mg) Present in Various Samples

entry	$Pb(OAc)_4$ added, equiv	Ru level	Pb level
A	none	16.9 ± 0.1	0.007 ± 0.004
B	1.25	0.30 ± 0.01	0.005 ± 0.001
C	1.50	0.31 ± 0.04	0.001 ± 0.004

Several additional features of this useful means for removing unwanted ruthenium deserve mention. The data in Table 2 are more favorable than those provided for the purification with tris(hydroxymethyl)phosphine.[8] Yields are unaffected, the presence of sensitive functionality such as a furan ring (run 6) notwithstanding. Chromatographic purification is no longer mandated unless, of course, multiple metathesis products result (run 7).

In summary, the removal of residual ruthenium and other highly colored impurities from RCM reaction mixtures can be readily achieved by overnight stirring with 1.50 equiv of lead tetraacetate as the key workup maneuver.[16] Subsequent filtration through a pad of silica gel and solvent evaporation from the filtrate affords colorless products adequately pure for further chemical utilization.

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Supporting Information Available: General experimental procedure together with characterization data or literature citations for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Milazzo, G.; Caroli, S.; Sharma, V. K. *Tables of Standard Electrode Potentials*; John Wiley and Sons: New York, 1978; pp 350−354.

(14) Only in one or two instances was an increase in solvent polarity required to rinse off the more polar product(s). The use of ethyl acetate for this purpose did cause a very modest amount of pale yellow color to leach out.

(15) Each carefully weighed RCM product was added to 10 mL of high purity concentrated nitric acid and diluted with deionized water to a total volume of 100 mL after thorough mixing and dissolution. Two separate aliquots of each sample were prepared to assess potential inhomogeneity of the solid sample (none was found). Calibration standards (1, 5, 10, 50, 100, 500 ng/mL) of Ru and Pb were made by serial dilution of μg/mL standard solutions (CPI International, traceable to NIST standards) in 10% v/v nitric acid. A blank was made from 10% v/v nitric acid. A Perkin-Elmer Sciex ELAN 6000 Inductively Coupled Plasma-Mass Spectrometer was used for all analyses. Signals for four Ru isotopes (99, 101, 102, and 104) and three Pb isotopes (206, 207, 208) were measured. Three replicate measurements were made for each standard and sample. Samples with measured solution concentrations greater than 500 ng/mL were diluted by a factor of 20 in 10 v/v nitric acid and rerun to be certain that the results were within the range of concentrations for the calibration standards.

(16) When tri(cyclohexyl)phosphine is admixed with 1 equiv of $Pb(OAc)_4$ in CH_2Cl_2, a very insoluble solid is formed. Filtration of such solutions through silica gel according to the usual workup gives filtrates entirely devoid of phosphine, lead salt, or any other detectable residue.