

Purification of Olefin Metathesis Reaction Products via Straightforward and Low-Cost Protocols

Eleftherios K Pefkianakis¹ and Georgios C Vougioukalakis^{1,2*}

¹Department of Physical Chemistry, IAMPPNM, NCSR Demokritos, Agia Paraskevi 15310, Greece

²Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis Zografou, Athens 15771, Greece

Abstract

From the point of view of an organic chemist, the discovery of novel and efficient carbon-carbon bond forming reactions is a continuous scientific quest. Olefin metathesis, a metal-catalyzed reaction, can be considered as one of the most robust tools in this respect. As a result, metathesis has been widely used over various chemistry and materials science fields. The increased popularity of this powerful transformation is mostly due to the development of highly efficient, functional group tolerant, and air- and moisture-stable ruthenium catalysts. However, the complete removal of ruthenium from the reaction products, in order to avoid undesired side-reactions, isomerization, or even the decomposition of products, is very often a highly challenging task. The present article focuses on the most straightforward and efficient methodologies for the removal of ruthenium residues from olefin metathesis post reaction mixtures. These purification protocols can be easily carried out in any common organic synthesis laboratory, needless of specialized reagents and experimental setup.

Keywords: Olefin metathesis; Homogeneous catalysis; Organic synthesis; Ring-closing metathesis; Cross metathesis; Ruthenium; Catalysts; Purification

Introduction

Over the past fifteen years, olefin metathesis [1-3] has been sophisticatedly used by scientists working in a variety of research fields to develop new synthetic routes, as well as a plethora of novel materials and industrial processes [4-8]. The huge impact of metathesis to chemical synthesis led to the awarding of the 2005 Nobel Prize in Chemistry to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock.

The most commonly utilized olefin metathesis transformations in an organic synthesis laboratory, i.e. ring-closing metathesis (RCM) and cross metathesis (CM), are shown in scheme 1. RCM is primarily driven by entropic factors as one substrate molecule affords two molecules of products. Lacking the entropic driving force of RCM, CM is more challenging and can lead to relatively low yields of the desired cross-product [9,10].

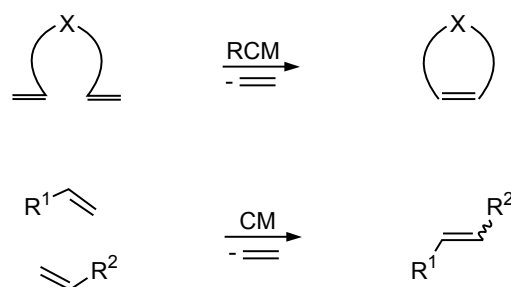
The widespread use of olefin metathesis has been mainly triggered by the development of well-defined ruthenium catalysts with high air and moisture stability and functional group tolerance [1-3]. Unfortunately, however, the complete removal of residual ruthenium after the end of the reaction is a major problem, very often even after several consecutive SiO₂ column chromatographic purifications [11]. This is especially true when increased catalyst loadings are necessary, given that high catalyst loadings usually increase the residual ruthenium impurities in the metathesized product.

Purity is an issue of utmost importance during the synthesis of biologically-active compounds due to the relatively low acceptable transition metal content in pharmaceutical applications (the allowed levels for oral administration of ruthenium are 5 ppm or below). Moreover, residual ruthenium species may cause isomerization, decomposition, or other undesired side-reactions in subsequent synthetic steps or even during the purification of the metathesized compounds.

Discussion

Two simple general strategies have been thus far developed for

the removal of the residual ruthenium in homogeneous reactions utilizing common, commercially-available catalysts (complexes 1-4, Figure 1). These two approaches include either the purification of the products on SiO₂ in conjunction with treatment with activated carbon, or the use of common ruthenium scavengers, such as dimethyl sulfoxide, in combination with column chromatography [11]. The purification protocols based on these strategies do not require structural modifications on the catalyst in order to remove ruthenium residues. Note that these purification techniques also have weaknesses, including: i) the usually high required loading of the scavenger; ii) long processing times; and/or iii) numerous washings and extractions.



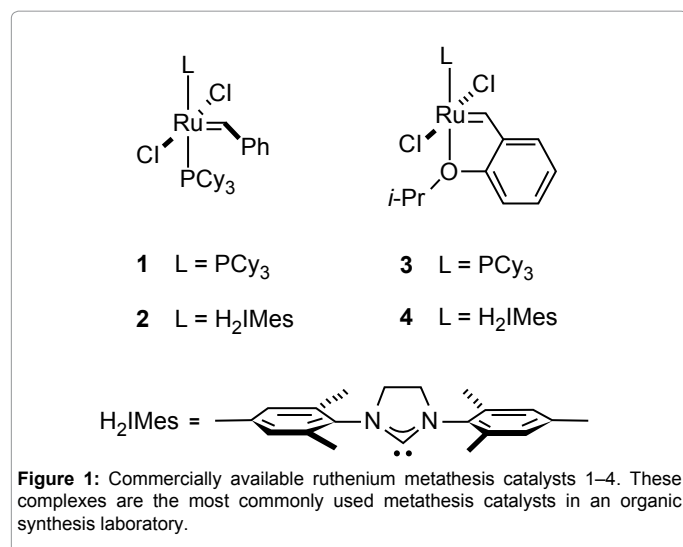
Scheme 1: Ring-closing metathesis (RCM) and cross metathesis (CM). The most frequently utilized metathesis transformations in organic synthesis.

***Corresponding author:** Vougioukalakis GC, Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis Zografou, Athens 15771, Greece, Tel: +30-2106503634; Fax: +30-2106511766; E-mail: vougiouk@chem.uoa.gr, vougiouk@chem.demokritos.gr

Received January 16, 2013; **Accepted** January 18, 2013; **Published** January 18, 2013

Citation: Pefkianakis EK, Vougioukalakis GC (2013) Purification of Olefin Metathesis Reaction Products via Straightforward and Low-Cost Protocols. *Organic Chem Curr Res* 2: e118. doi:10.4172/2161-0401.1000e118

Copyright: © 2013 Pefkianakis EK, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



The first series of ruthenium sequestration methods by-passing the need to introduce specialized reagents in order to remove the residual ruthenium were published in 2003 [12]. The most efficient approach in that work had to do with the removal of catalyst 1 (Figure 1) from a series of RCM reactions mixtures and uses three consecutive purification steps: i) stirring of the crude reaction mixture with 10 equivalents (wt) SiO₂ relative to catalyst 1, followed by filtration through a pad of SiO₂; ii) stirring of this filtrate with 50 equivalents (wt) activated charcoal relative to the crude metathesized product for 12 hours at r.t., followed by filtration; and iii) SiO₂ column chromatographic purification. Under these conditions, the residual ruthenium levels in the RCM products were found to be between 12 and 106 ppm, without detectable loss of the products.

The second general method for deactivating and sequestering all types of homogeneous ruthenium metathesis catalysts was published in 2009 [13]. Commercially-available 2-[2-(vinylxy)ethoxy]ethanol (5) or the easily-synthesized amine-containing vinyl ether derivatives N,N-diethyl-2-[2-(vinylxy)ethoxy]ethanamine (6) and N¹,N¹,N³-trimethyl-N³-[2-(vinylxy)ethyl]propane-1,3-diamine (7) were utilized. More specifically, 4 molar equivalents of the sequestering compound in relation to the catalyst used are added to the metathesis mixture, following the end of the metathesis reaction. The resulting mixtures are stirred for an additional 30 min at room temperature, in the case of 5, or 2 hours at 50°C in the case of 6 and 7. SiO₂ column chromatographic purification (5), a simple pass through a SiO₂ plug (6), or three consecutive washes with 2N aqueous HCl (7), afford metathesized products with ruthenium levels as low as 2 ppm, <43 ppm, or <15 ppm, respectively.

Another successful strategy for the removal of the catalyst from the metathesized products, involving the simple immobilization of catalyst 4 (Figure 1) on commercial SiO₂ both in pellet and powder form, was reported in 2008. The adsorption of 4 was proposed to occur via the direct attachment of ruthenium species to the surface silanols via ligand exchange [14]. According to this method, SiO₂ is suspended in a toluene solution of catalyst 4 and stirred at room temperature for 2 hours. Filtration, washing with hexane and subsequent drying affords the final heterogeneous solid catalyst. This supported catalyst, stable for up to at least 4000TON, was successfully utilized in a series of RCM and CM transformations. The powdered catalyst is separated from the products by filtration, while the workup with pellets is carried out by

simple decantation of the reaction mixture. Metathesis transformations carried out in hexane gave reaction mixtures with ruthenium content below the detection limit of ICP-MS (0.04 ppm); nevertheless, the use of more polar solvents such as diethyl ether led to ruthenium leaching in the reaction mixture. For the same reason, the use of highly polar substrates such as alcohols and acids with this catalytic system has to be avoided.

According to a similar protocol, catalysts 1, 2, and 4 (Figure 1) can be easily immobilized in the pores of amorphous Al₂O₃ with the aid of ionic liquids [15]. To obtain the supported catalysts, amorphous Al₂O₃ is suspended in a solution of the respective ruthenium complex and ionic liquid in tetrahydrofuran and stirred at room temperature for 4 hours. Tetrahydrofuran is then evaporated under vacuum and the resulting material is rinsed with anhydrous diethyl ether twice before evacuated again to afford the final free-flowing powder. The as-obtained immobilized catalysts were successfully utilized in a variety of RCM and macrocyclic RCM reactions, with benzene and toluene being the reaction solvents of choice. Ruthenium leaching from this kind of immobilized catalysts was reported to be 0 ppm, as measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES).

Finally, an even simpler and highly efficient methodology was reported in 2005 for the removal of catalyst 1 from the reaction mixture, achieving very low ruthenium levels in the purified organic products [16]. This can be performed by treating the crude reaction mixture with SiO₂ (4 g per 0.01 mmol catalyst) and DMSO (50 molar equivalents relative to the catalyst) at room temperature for 12 hours. Ruthenium levels can thus be easily reduced to 8 ppm in the metathesized products.

Summary

The sequestration of ruthenium catalyst residues from olefin metathesis reaction products is quite often problematic. However, pharmaceutical chemistry applications demand final products of very high purity, while unsuccessful removal of ruthenium impurities during the production of fine chemicals may catalyze undesired side-reactions in subsequent steps. The goal of the present article is to briefly summarize the most efficient, straightforward, and inexpensive protocols for the quenching of ruthenium impurities from olefin metathesis post-reaction mixtures. All these strategies can be easily performed in any common organic synthesis laboratory.

The Importance of Open Access Journals

The term “Open Access Journals” has recently evolved from a simple fact into an academic movement across the globe. Open access can be defined as an ideal for the common “public good”, a tool not only for the scientists but also for science-concerned people not affiliated with a research institution or a university. Along with the financial globalization of our time comes the need for free access in scientific knowledge and its benefits for educational and other purposes. Open access journals such as the journal “Organic Chemistry: Current Research” allow researchers to maximize their access to scientific data. Simultaneously, scientists become broader acknowledged themselves by being cited more often, thus achieving one of their scientific goals. The authors of this article recognize the fundamental importance of the existence of journals like “Organic Chemistry: Current Research” and encourage the continuation of the good work and the publication of high-quality research articles in the field of organic chemistry.

Acknowledgements

GC Vougioukalakis thankfully acknowledges funding from a Foundation for Education and European Culture scholarship.

References

1. Ivin KJ, Mol JC (1997) *Olefin metathesis and metathesis polymerization*. Academic Press, San Diego.
2. Grubbs RH (2003) *Handbook of metathesis*. WILEY-VCH, Weinheim.
3. Vougioukalakis GC, Grubbs RH (2010) Ruthenium-based heterocyclic carbene-coordinated olefin metathesis catalysts. *Chem Rev* 110: 1746-1787.
4. Fürstner A (2000) Olefin metathesis and beyond A list of abbreviations can be found at the end of this article. *Angew Chem Int Ed Engl* 39: 3012-3043.
5. Trnka TM, Grubbs RH (2001) The development of L2X2Ru=CHR olefin metathesis catalysts: an organometallic success story. *Acc Chem Rzes* 34: 18-29.
6. Schrock RR, Hoveyda AH (2003) Molybdenum and tungsten imido alkylidene complexes as efficient olefin-metathesis catalysts. *Angew Chem Int Ed Engl* 42: 4592-4633.
7. Grubbs RH (2004) Olefin metathesis. *Tetrahedron* 60: 7117-7140.
8. Kress S, Blechert S (2012) Asymmetric catalysts for stereocontrolled olefin metathesis reactions. *Chem Soc Rev* 41: 4389-4408.
9. Vougioukalakis GC, Grubbs RH (2008) Synthesis and activity of ruthenium olefin metathesis catalysts coordinated with thiazol-2-ylidene ligands. *J Am Chem Soc* 130: 2234-2245.
10. Vougioukalakis GC, Grubbs RH (2008) Ruthenium-based olefin metathesis catalysts coordinated with unsymmetrical N-heterocyclic carbene ligands: synthesis, structure, and catalytic activity. *Chemistry J* 14: 7545-7556.
11. Vougioukalakis GC (2012) Removing ruthenium residues from olefin metathesis reaction products. *Chemistry J* 18: 8868-8880.
12. Cho JH, Kim BM (2003) An efficient method for removal of ruthenium byproducts from olefin metathesis reactions. *Org Lett* 5: 531-533.
13. Liu W, Nichols PJ, Smith N (2009) Di(ethylene glycol) vinyl ether: a highly efficient deactivating reagent for olefin metathesis catalysts. *Tetrahedron Lett* 50: 6103-6105.
14. Berlo BV, Houthoofd K, Sels BF, Jacobs PA (2008) Silica immobilized second generation Hoveyda-Grubbs: a convenient, recyclable and storageable heterogeneous solid catalyst. *Adv Synth Catal* 350: 1949-1953.
15. Hagiwara H, Okunaka N, Hoshi T, Suzuki T (2008) Immobilization of Grubbs catalyst as supported ionic liquid catalyst (Ru-SILC). *Synlett* 12: 1813-1816.
16. Haack K, Ahn YM, Georg GI (2005) A convenient method to remove ruthenium byproducts from olefin metathesis reactions using polymer-bound triphenylphosphine oxide (TPPO). *Mol Divers* 9: 301-303.