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Semi-Heterogeneous Purification Protocol for the Removal of Ruthenium Impurities from Olefin Metathesis Reaction Products Using an Isocyanide Scavenger

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ABSTRACT: A low-waste, time-economical and scalable semi-heterogeneous purification protocol for the removal of ruthenium residues from olefin metathesis (OM) reactions has been developed. It is based on the noncovalent immobilization of commercially available isocyanide **QA** (**QA** = 1,4-Bis(3-isocyanopropyl)piperazine) on unmodified silica gel. The use of heterogeneous scavenger **QA@SiO$_2$** synthesized in situ during the purification process, is shown to yield OM products with metal contamination usually below 5 ppm. Furthermore, the new purification protocol was effective on a gram scale in the ring-closing OM of an intermediate in the synthesis of cathepsin K inhibitors, leading to a product with only 0.29 ppm of Ru. Finally, isocyanide QA was used in an aqueous medium reducing the metal contamination from 9977 to 21 ppm.

KEYWORDS: *olefin metathesis, ruthenium, isocyanide, metal scavenger*

INTRODUCTION

Olefin metathesis (OM) catalyzed with modern ruthenium complexes is a powerful, efficient and selective tool for creating new C(sp^2)–C(sp^2) bonds under mild conditions.[1,2] It has been used in the synthesis of complex organic molecules including natural products,[3] pharmaceutically relevant compounds,[4–6] well-defined polymers[7] and for modification of proteins.[8] However, one of the most important issues related to the use of OM is the removal of ruthenium residues after the reaction is complete. Catalyst residues can promote the decomposition or isomerization of the desired product.[9] OM is often utilized in the synthesis of active pharmaceutical ingredients (API), which are subject to strict legal limits on transition metal contamination, typically less than 10 ppm in the final API. For these reasons, the development of efficient and economical methods for the purification of OM products from metal contamination is of critical importance.[10,11]

There are several ways to address the problem of ruthenium contamination after OM: (1) using a low catalyst loading, (2) applying classic methods of purification (3) using a heterogeneous catalyst, (4) using a self-scavenging catalyst, (5) using scavengers.

OM with a ppm amount (less than 10 ppm) of catalyst is an ideal approach approach.[12] Unfortunately, it is often limited to highly pure, simple compounds and is very sensitive to trace amounts of air, moisture or solvent impurities.[13]

Conventional methods of purification are often insufficient to afford a product with low ruthenium content.[14] This is particularly true for polar products, synthesized with the use of high catalyst loadings.[15]

Anchoring of ruthenium-based catalysts on solid supports has several potential advantages, such as simpler separation from the reaction mixture by filtration.[10,16–18] However, so far none of the heterogeneous transition metal catalysts have been reported in an industrial setting. Reasons include rapid catalyst deactivation, low turnover numbers, leaching of the metal and overall complexity.[19]

Tailored self-scavenging catalysts contain tags that facilitate the removal of both the catalyst and its byproducts after the reaction is completed.[10,20–30] Similarly, to heterogeneous catalysts, the syntheses of such complexes often requires lengthy and expensive modifications.

Metal scavengers are added during workup and allow the efficient removal of metal residues through conventional methods of purification.[10,11] Their use does not require any tailored structural changes in the catalyst and they can be often used with many different transition metal complexes, offering a general solution. This approach is simpler and cheaper than using immobilized or self-scavenging catalysts. However, scavengers can contaminate the product itself and require an additional workup step.

Several homogeneous ruthenium scavengers are described in the literature,[10,11] for example, hydrogen peroxide,[31] mercaptonicotinic acid,[32] dimethyl sulfoxide or triphenylphosphine oxide,[33] $Pb(OAc)_4$[34] and water-soluble phosphine $P(CH_2OH)_3$,[35] but most of these compounds have to be used in a large excess (more than 10 equiv), require a long binding time (more than 1 h) and do not reduce ruthenium contamination below 10 ppm.

Heterogeneous scavengers can be easily separated from the solution through filtration to afford a product with a low metal content.[10,11,36–39] Therefore, they are ideally suited for applications in continuous flow mode. However, most of them have to be used in large excess with respect to the catalyst and require long treatment times. This can be caused by steric interaction with the solid support and inhibited diffusion to and from the binding sites. In addition, the heterogenization adds complexity to the system. Immobilized scavengers often require multi-step syntheses and are therefore expensive.

An alternative is the use of scavenger adsorbed on a solid support through noncovalent interactions, such as ionic or hydrogen bonding. This approach is characterized by simplicity, as such scavengers can be obtained by stirring a homogeneous scavenger with an unmodified support. However, there is always the risk of scavenger leaching and contamination of the product with metal.

Isocyanides may function both as an electrophile and as a nucleophile. This unique reactivity makes them widely used in multicomponent reactions,[40] transition-metal-catalyzed insertions,[41] synthesis of metal–organic complexes,[42] in polymerization processes[43] and in drug discovery research.[44]

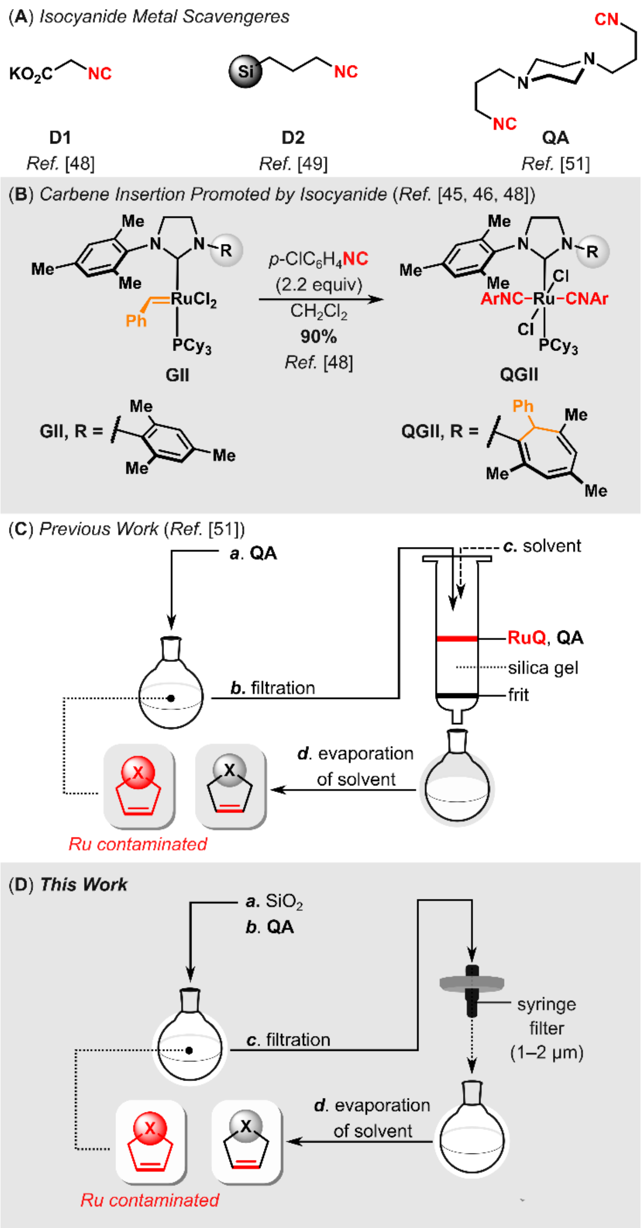


Figure 1. Isocyanide metal scavengers described in the literature (a), reactivity of isocyanides toward **GII** (b), purification of OM products using **QA** in combination with filtration through silica gel (c), new semi-heterogeneous purification protocol (d).

In 2005, the Diver group reported a novel carbene insertion reaction driven by coordination of carbon monoxide or isocyanide ligands to the Grubbs' second-generation complex (Figure 1B).[45–47] This unique ligand insertion was later used to remove ruthenium residues from OM products.[48] Coordination of the isocyanide **D1** to the ruthenium atom leads to a polar, inactive ruthenium complex which is easy to separate using standard column chromatography. This method gives OM products with ruthenium content between 120 and 2200 ppm. More recently, Diver and coworkers presented the isocyanide **D2**, supported on silica gel (Figure 1A).[49] Compared with **D1**, it was necessary to use a much larger excess of scavenger (60 equiv) and column chromatography was required to reduce the ruthenium content below 10 ppm. Furthermore, both scavengers could effectively remove palladium species at different oxidation states after palladium-catalyzed cross-coupling reactions.[50]

Recently, we reported a new bidentate ruthenium scavenger containing a piperazine ring.[51] The isocyanide **QA** is an odorless solid that is easy to handle and highly effective in removing a wide range of Ru-based catalysts. A small excess of **QA** (4.4 equiv) and a short treatment time (30–60 min) are sufficient to obtain OM products with Ru content of less than 10 ppm after a simple filtration of the post-reaction mixture through a short plug of silica gel, even for high catalyst loadings (1.0-5.0 mol%, see Figure 1C).[51] Moreover, the use of **QA** in combination with citric acid allows the simultaneous removal of Ru and Pd residues after a telescope RCM/Suzuki–Miyaura sequence.[52]

Herein, we demonstrate the use of the isocyanide **QA** noncovalently immobilized on unmodified silica gel for column chromatography (Figure 1D). This simple approach has previously been used for noncovalent anchoring of OM catalysts.[53] However, to the best of our knowledge, so far there has been no precedent for noncovalent immobilization of ruthenium scavengers on solid support. The new protocol combines the advantages of heterogeneous and homogeneous scavengers, allowing rapid and efficient removal of a wide variety of ruthenium catalysts from OM products through simple filtration.

Isocyanides easily undergo hydrolysis to formamides in the presence of acids.[54] Silica gel adsorbs water readily. Additionally, the hydroxyl groups on the surface of silica can catalyze the addition of water to isocyanide groups. Therefore, we decided to synthesize the heterogeneous scavenger **QA@SiO$_2$** *in situ*, during the purification process, which not only minimized the risk of the decomposition of the isocyanide groups over time, but also significantly simplified the purification protocol and reduced the cost of entire process.

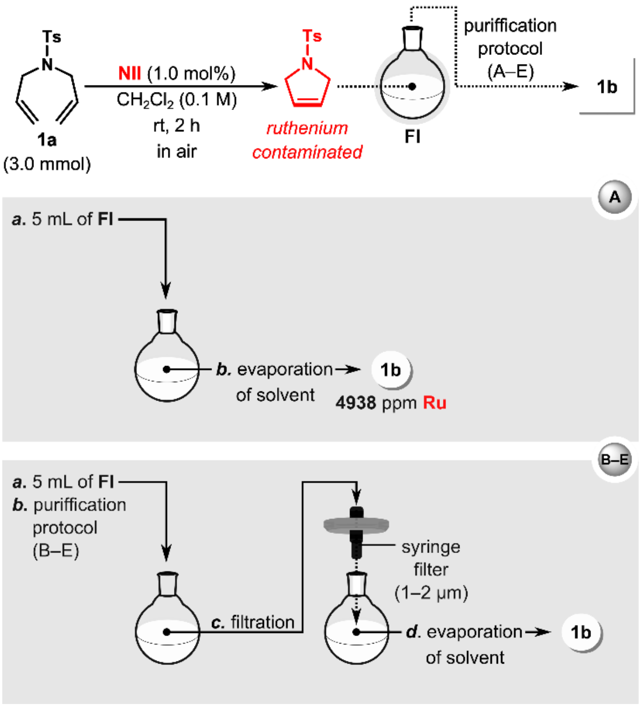
RESULTS AND DISCUSSION

To test the performance of the novel approach, several different ruthenium removal strategies were compared (Table 1). Ring closing olefin metathesis (RCM) of **1a** was performed with **NII** (1.0 mol%) in dichloromethane under ambient atmosphere. After 2 h, five samples of 5 mL each were taken from the reaction mixture and purified using methods A–E. Residual ruthenium content was determined by inductively coupled plasma mass spectrometry (ICP-MS).[52]

In a control experiment, after removing the solvent, the ruthenium content in the resulting product was 4938 ppm. Addition of silica gel (100 mg of gel for every 0.005 mmol of the Ru-catalyst) to the reaction mixture and stirring for a further 30 min at room temperature, followed by filtration through a syringe filter (1-2 μm), reduced the ruthenium level to 598 ppm (method B). The use of isocyanide **QA** (4.4 mol%, 30 min), followed by the addition of silica gel (method C) removed over 97.7% of the original ruthenium (based on the control experiment). Use of the silica gel first, followed by the isocyanide treatment (method D) gave the best result, affording a product with 82 ppm Ru, while addition of the scavenger **QA** and silica gel together and stirring for 30 min (method E) yielded a **1b** with 90 ppm

Ru. Gas chromatography (GC) analysis of the reaction mixtures showed that product **1b** was not contaminated with the scavenger after purification by methods C–D.

Table 1. Comparison of Different Ruthenium Removal Strategies



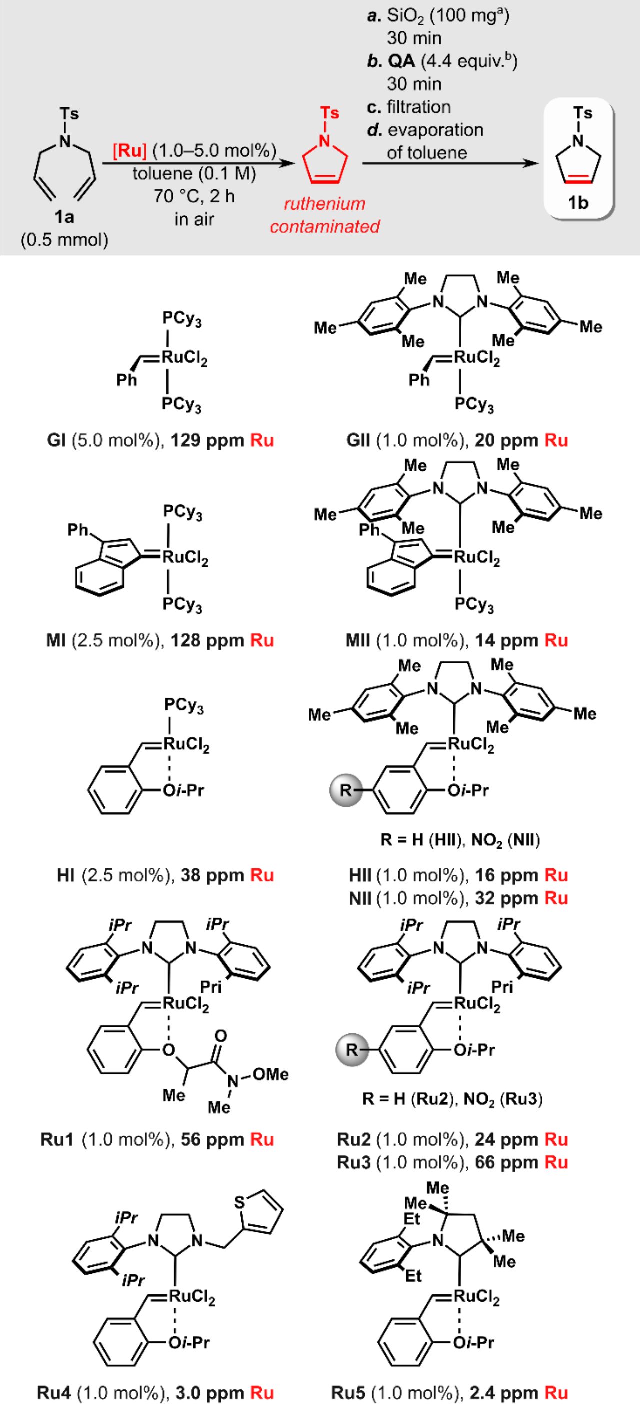
	purification protocol	Ru[a] (ppm)
A	-	4938
B	SiO_2 (100 mg) 30 min, rt	598
C	1. **QA** (4.4 mol%) 30 min, rt 2. SiO_2 (100 mg) 30 min, rt	118
D	1. SiO_2 (100 mg) 30 min, rt 2. **QA** (4.4 mol%) 30 min, rt	82
E	**QA** (4.4 mol%), SiO_2 (100 mg) 30 min, rt	90

[a] Ru content was determined by ICP-MS.

Further tests were performed with several commonly used OM catalysts.[55,56] We selected 12 structurally diverse Ru complexes. RCM reactions of **1a** were conducted at 70 °C in toluene under ambient atmosphere, using 1.0-5.0 mol% of the catalyst. The results are summarized in Table 2.

The *semi*-heterogeneous purification protocol D was effective for first generation Grubbs catalysts (**GI**, **MI**, **HI**).[57–59] The ruthenium content was only 38-129 ppm, which corresponded to the removal of 98.8% of the Ru residue from the product **1b**, despite using a significant amount of the catalyst (2.5-5.0 mol%). In the case of second generation Grubbs catalysts (**GII**, **MII**, **HII**, **NII** **Ru1-3**),[60–66] the ruthenium content in **1b** was 14-66 ppm. With increasing polarity of the Ru catalyst, the amount of ruthenium in the RCM product decreased. For the **Ru3** catalyst, the ruthenium level was 66 ppm, while for its more polar analogue **NII**, the contamination was reduced by half (32 ppm). The same trend was observed for the complexes **HII** and **Ru2**. The best results were obtained for catalysts which contained an unsymmetrical NHC ligand (**Ru4** and **Ru5** complexes).[67,68] The ruthenium level of the resulting product was below 5 ppm (3.0 and 2.4 ppm respectively). This can be explained by a different decomposition pathway for this type of ruthenium catalysts.[69] In addition, the structure of unsymmetrical NHC ligands causes the metal center to be more exposed, which can facilitate the coordination of an isocyanide ligand to the ruthenium, making **QA** more effective.

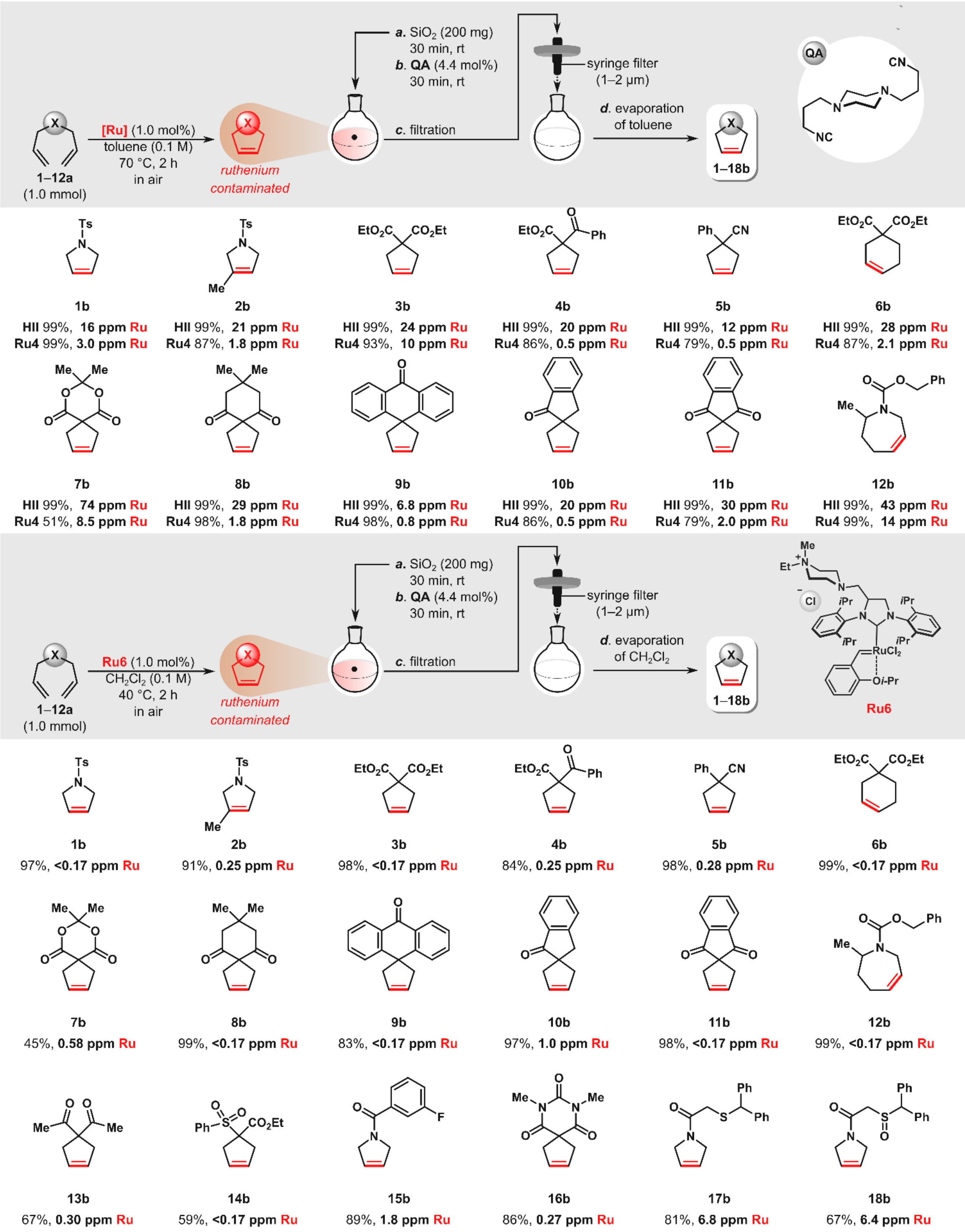
Table 2. Scope of the Optimized Purification Protocol in Removing Ru Residues of Selected OM Catalysts



GI (5.0 mol%), **129 ppm Ru**
GII (1.0 mol%), **20 ppm Ru**
MI (2.5 mol%), **128 ppm Ru**
MII (1.0 mol%), **14 ppm Ru**
HI (2.5 mol%), **38 ppm Ru**
HII (1.0 mol%), **16 ppm Ru**
NII (1.0 mol%), **32 ppm Ru**
Ru1 (1.0 mol%), **56 ppm Ru**
Ru2 (1.0 mol%), **24 ppm Ru**
Ru3 (1.0 mol%), **66 ppm Ru**
Ru4 (1.0 mol%), **3.0 ppm Ru**
Ru5 (1.0 mol%), **2.4 ppm Ru**

Conversions were determined by GC analysis and are based on the ratio of product/(product + starting material). Ru content was determined by ICP-MS. [b]Equivalents with respect to the catalyst.

Table 3. Scope of Applicability of the Semi-Heterogeneous Method in Removing Ru Residues after OM



1b	HII 99%, 16 ppm Ru	Ru4 99%, 3.0 ppm Ru
2b	HII 99%, 21 ppm Ru	Ru4 87%, 1.8 ppm Ru
3b	HII 99%, 24 ppm Ru	Ru4 93%, 10 ppm Ru
4b	HII 99%, 20 ppm Ru	Ru4 86%, 0.5 ppm Ru
5b	HII 99%, 12 ppm Ru	Ru4 79%, 0.5 ppm Ru
6b	HII 99%, 28 ppm Ru	Ru4 87%, 2.1 ppm Ru
7b	HII 99%, 74 ppm Ru	Ru4 51%, 8.5 ppm Ru
8b	HII 99%, 29 ppm Ru	Ru4 98%, 1.8 ppm Ru
9b	HII 99%, 6.8 ppm Ru	Ru4 98%, 0.8 ppm Ru
10b	HII 99%, 20 ppm Ru	Ru4 86%, 0.5 ppm Ru
11b	HII 99%, 30 ppm Ru	Ru4 79%, 2.0 ppm Ru
12b	HII 99%, 43 ppm Ru	Ru4 99%, 14 ppm Ru

1b	97%, <0.17 ppm Ru
2b	91%, 0.25 ppm Ru
3b	98%, <0.17 ppm Ru
4b	84%, 0.25 ppm Ru
5b	98%, 0.28 ppm Ru
6b	99%, <0.17 ppm Ru
7b	45%, 0.58 ppm Ru
8b	99%, <0.17 ppm Ru
9b	83%, <0.17 ppm Ru
10b	97%, 1.0 ppm Ru
11b	98%, <0.17 ppm Ru
12b	99%, <0.17 ppm Ru
13b	67%, 0.30 ppm Ru
14b	59%, <0.17 ppm Ru
15b	89%, 1.8 ppm Ru
16b	86%, 0.27 ppm Ru
17b	81%, 6.8 ppm Ru
18b	67%, 6.4 ppm Ru

Conversions were determined by GC analysis and are based on the ratio of product/(product + starting material). Ru content was determined by ICP-MS.

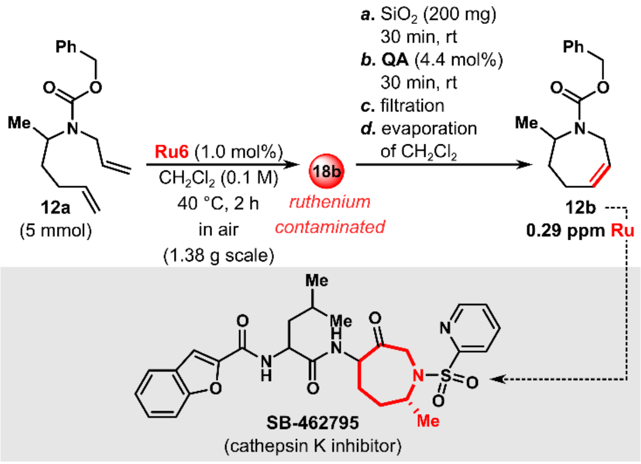
To establish the scope and applicability of the new purification method, test RCM reactions with a selection of dienes were performed (Table 3). Use of the ruthenium complex with an unsymmetrical NHC ligand (**Ru4**) usually resulted in ruthenium levels lower than 5 ppm. Only in one case (**12b**) the contamination slightly exceeded 10 ppm. The use of the second-generation Hoveyda catalyst caused an increase in ruthenium content. The RCM products synthesized with **HII** were contaminated with ruthenium at a level of 16-74 ppm. However, **HII** afforded excellent conversions (more than 99%) for all tested substrates, in contrast to the results obtained with **Ru5** (54-99%).

In the next stage of our research, the commercially available second generation Hoveyda-type complex bearing a quaternary ammonium group in the NHC ligand with a chloride counterion was used as the catalyst (**Ru6**).[70] The polar tag causes a significant increase in affinity to silica gel and thus facilitates the removal of both the catalyst and its residues.[71]

The reactions were performed at 40 °C in dichloromethane under ambient conditions, using 1.0 mol% of **Ru6** (Table 3). The new purification protocol combined with the use of self-scavenging catalyst **Ru6** gave OM products with a very low ruthenium content, in most cases below 0.25 ppm Ru, sometimes bringing the metal content below the detection limit of the used analytical method (0.17 ppm.) Only **17b** and **18b** were contaminated slightly more than 5 ppm (6.8 and 6.4 ppm, respectively).

To demonstrate that the purification protocol D is effective on a large scale, the RCM was performed with **Ru6** (1.0 mol%) using 5 mmol (1.38 g) of the dien **12a** (Scheme 1). After purification, the ruthenium content in the isolated azepine derivative **12b**, an intermediate in the synthesis of cathepsin K inhibitors,[72] was only 0.29 ppm.

Scheme 1 Removal of Ruthenium residues after RCM of 12a on a Gram Scale



Next, the possibility of applying the new methodology in cross metathesis (CM) was investigated (Scheme 2). The CM of **19a** with 4.0 equiv of *cis*-1,4-diacetoxy-2-buten (**20**) was conducted using **Ru6** (2.0 mol%). After purification, the desired bio-like product **19b** had very low ruthenium content (0.13 ppm).

Scheme 2 Removal of Ruthenium residues after CM of 19a

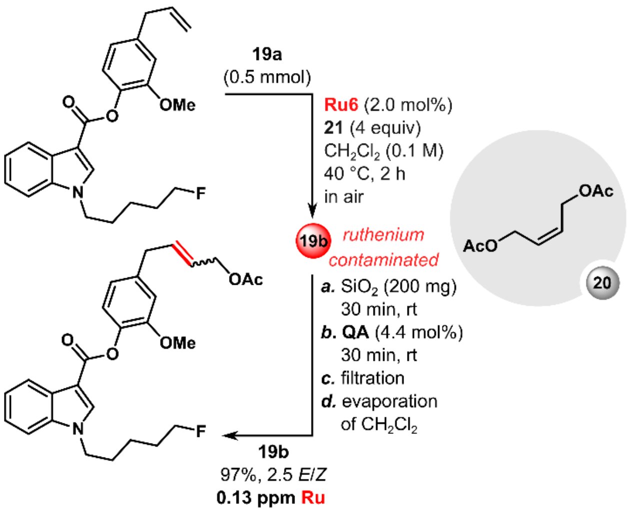
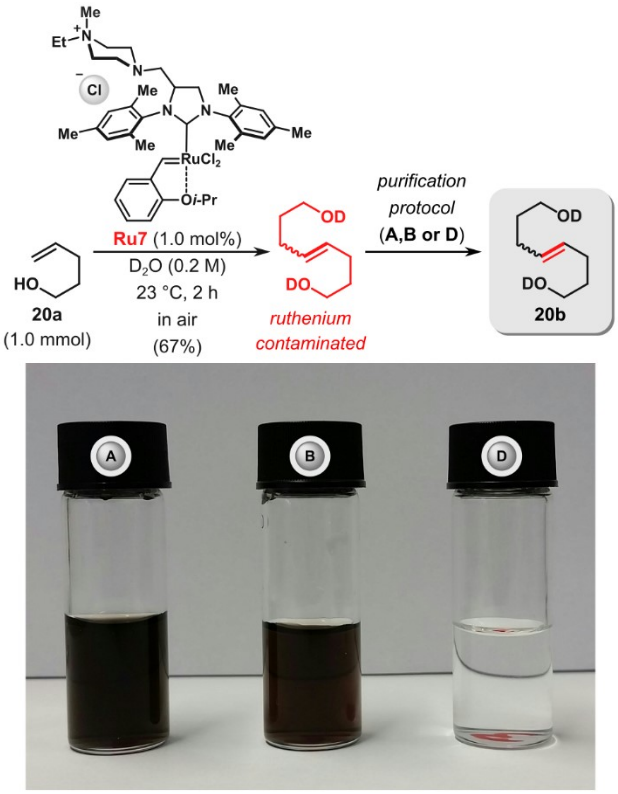


Table 4. Removal of Ruthenium Residues after OM in Water



	purification protocol	Ru^a (ppm)
A	-	17547
B	SiO₂ (200 mg) 30 min, rt	9977
D	1. SiO₂ (200 mg) 30 min, rt 2. **QA** (4.4 mol%) 30 min, rt.	33
	1. SiO₂ (200 mg) 30 min, rt 2. **QA** (8.8 mol%) 30 min, rt 2.	21

Conversion was determined by ^{1}H NMR spectroscopy and is based on the ratio of product/(product + starting material). ^{a}Ru content was determined by ICP-MS.

Traditionally, OM is carried out in dichloromethane or toluene. Due to the steric and electron-donating effects of the NHC ligands, as well as the low oxophilicity of Ru, second generation Grubbs catalysts are remarkably tolerant toward diverse functional groups, impurities and air.[73] For this reason, they can be successfully used in polar, environmentally benign solvents, including water. In the last two decades, considerable progress has been made on OM in aqueous media.[74] However, removal of ruthenium from OM reactions in water remains a substantial challenge.

In 2018, Chung and coworkers presented a water-soluble, self-scavenging catalyst bearing an adamantyl-tethered ethylene glycol oligomer in the NHC ligand. The purification protocol utilized a host–guest interaction between the catalyst and insoluble β-cyclodextrin grafted on silica.[75] After a simple filtration, the final ruthenium content in OM products ranged from 53 to 284 ppm. More recently, Olszewski and coworkers reported the isomerization of *cis*-2-butene-1,4-diol using highly water-soluble ammonium NHC-tagged Ru-catalysts with a chloride counter-ion.[21] Treatment of the post-reaction mixture with NH_4BF_4 or NH_4PF_6 resulted in counter-ion exchange and allowed the extraction of ruthenium residues to the organic phase, affording the product with 121 and 99 ppm of Ru, respectively.

Finally, we found that the new methodology is efficient in the removal of ruthenium residues from aqueous mixtures (Table 4). Self-metathesis of 4-Penten-1-ol (**20a**) was performed under ambient atmosphere using 1.0 mol% of **Ru7**.[76] To our delight, after purification, the desired product **20b** had very low ruthenium content, 33 ppm which represents a 99.8% removal of Ru from the water solution (based on the control experiment A, Table 4). Treatment of the post-reaction mixture with 8.8 mol% of **QA** enabled us to reduce the ruthenium level to 21 ppm. Purification using only silica gel led to **20b** with significantly higher ruthenium content (9977 ppm).

CONCLUSIONS

A new, simple and inexpensive semi-heterogeneous method for the removal of ruthenium residues from OM products was developed. It is based on the use of a small amount of silica gel and a small excess of commercially available isocyanide **QA**. This time-economical method is scalable, does not require chromatography and is compatible with commonly used OM catalysts. When combined with the use of a catalyst bearing a quaternary ammonium group in the NHC ligand, such as **Ru6**, it reduces Ru content in OM products usually below 0.25 ppm, even in highly challenging cases. The new purification protocol efficiently removes ruthenium residues after OM in water, affording a self-metathesis product with very low Ru content. Since isocyanides are widely used as ligands in the synthesis of organometallic complexes due to their σ-donor strength and their weak π-acidity,[42] this protocol may be used to solve the problem of transition metal contamination in pharmaceutical syntheses. These results have important implications for both laboratory and industry applications.

EXPERIMENTAL SECTION

Materials and Methods. All reactions were carried out under air. The reactions from Tables 2 and 3 were performed using Radleys Carousel. Commercially available chemicals were used as received. Ruthenium catalysts were purchased from Apeiron Synthesis S.A. Bottles with ruthenium catalysts were stored under argon, but no special precautions were taken to avoid air or atmospheric moisture exposure after extracting catalysts from the bottles. Reactions were monitored by gas chromatography with measurements done on PerkinElmer Clarus 580 with InertCap 5MS-Sil column. Purification was performed using Merck Millipore silica gel (60, particle size 0.043– 0.063 mm). Ruthenium content was determined by inductively coupled plasma mass spectrometry (NexION 300D, PerkinElmer) equipped with a traditional sample introduction system, which requires samples to be in solution in order to be analyzed, according to the previously reported procedure.[52]

Representative Procedure for Removing Ru Residues after OM (Table 3). A Radley glass tube equipped with magnetic stir bar was charged with substrate (**1**–**18a**) (1.0 mmol). Solvent (9.0 mL; toluene or CH_2Cl_2) was added. The stirrer was set to 600 rpm. The solution was heated to a predetermined temperature (40 °C or 70 °C), after which the ruthenium catalyst (**Ru4** or **Ru6**) dissolved in the reaction solvent (1.0 mL, 0.01 M, 0.01 mmol, 1.0 mol%) was added. The reaction mixture was stirred at 70 °C for 2 h under ambient atmosphere. The heating was turned off, silica gel (200 mg, 100 mg of gel for every 0.005 mmol of the Ru-catalyst) was added and the resulting mixture was stirred for 30 min. Subsequently, scavenger **QA** dissolved in the reaction solvent (1.0 mL, 0.44 M, 0.044 mmol, 4.4 equiv. with respect to the catalyst) was added and stirring continued for 30 min. Finally, the reaction mixture was filtered through a syringe filter into a 25 mL round-bottomed flask and the solvent was removed under reduced pressure to give crude **1b**–**18b**.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: Materials and methods and detailed experimental procedures (PDF).

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Notes

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Table of Contents Graphic: