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Removal of Ruthenium Using a Silica Gel Supported Reagent

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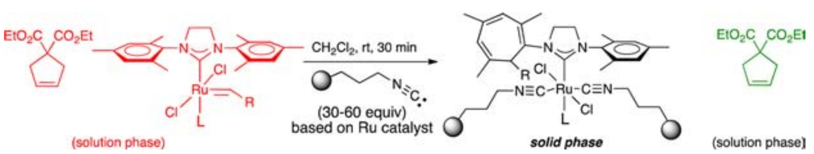
ABSTRACT

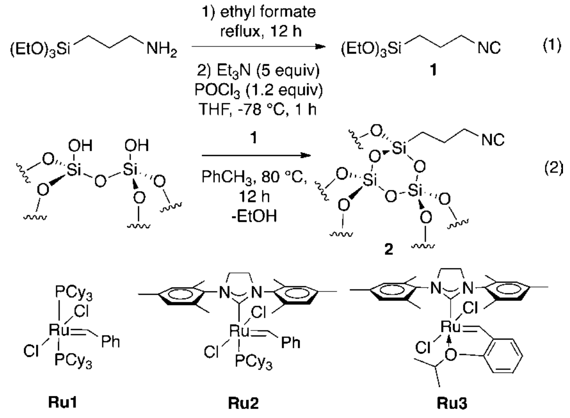


A solid-supported isocyanide ligand was developed to destroy active metathesis catalysts and to remove ruthenium byproducts from metathesis reactions. This method was able to significantly reduce the concentration of residual ruthenium from the organic products of several alkene and ene–yne metathesis reactions, under a variety of different conditions.

Metathesis promoted by ruthenium carbenes is a robust method for creating carbon–carbon double bonds in molecules with high densities of organic functionality. As a result, catalysts **Ru1**–**Ru3** have found applications in a broad range of chemistry from total synthesis[1a,b] to the synthesis of pharmaceutically relevant compounds on the industrial scale.[2] Although metatheses are fast and efficient, the removal of ruthenium during purification is a difficult problem. The removal of residual ruthenium is necessary, as it can potentially lead to decomposition or isomerization of the desired product.[3] The use of transition metal catalysis for the preparation of pharmaceuticals must be weighed against the need for a cost-effective removal method and a quality control assay. Herein we disclose a user-friendly filtration method for the rapid and efficient removal of ruthenium from a metathesis reaction. A solid-supported isocyanide reagent **2** destroys ruthenium carbene activity through a well-defined Buchner reaction and is applicable to a variety of Grubbs catalysts currently used to promote alkene and ene–yne metathesis (Scheme 1).

Currently there are several different methods used for the removal of ruthenium after the reaction is complete.[4] These methods are based on two different approaches: (1) treating the catalyst with an additive once the reaction is complete; (2) the use of a tailored catalyst with a specially designed chemical handle to assist catalyst removal.[4,5] The addition of quenching agents that facilitate the removal of ruthenium catalysts and ruthenium byproducts is attractive because they can be used with any second generation Grubbs catalyst, thereby offering a general solution to a cleanup protocol.

Scheme 1. Supported Reagent **2** and Commonly Used Grubbs Catalysts



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Although several purification protocols exist, the isocyanide-triggered Buchner reaction is advantageous over other methods. Many of the existing methods require long treatment periods and toxic metals or require expensive reagents. Examples of these include tris(hydroxymethyl)-phosphine,[6] addition of $Pb(OAc)_4$,[7] excess DMSO, or triphenylphosphine oxide,[8] or hydrogen peroxide,[9] as well as the addition of activated carbon followed by column chromatography.[10] Several of these methods require long treatment times (12 to 24 h) and operate by an undefined oxidative mechanism. A mesoporous silicate system was developed which was also found to aid in the removal of ruthenium.[11] The advantage of this system is that it works relatively quickly, but the material is expensive and tedious to prepare. Finally, a method developed previously in our group relies on the addition of KO_2CCH_2NC to the reaction mixture.[12] The isocyanide ligand is unique because it rapidly destroys the carbene and causes the ruthenium to become highly polar. Isocyanide coordination initiates the insertion of the carbene into the N-heterocyclic carbene (NHC) ligand via a Buchner reaction,[13] effectively "turning off" metathesis activity. Second, once the isocyanide is coordinated to the metal center, it produces a very polar complex which can be easily removed using standard column chromatography. The isocyanide-promoted Buchner reaction was previously shown to be effective for a wide range of Grubbs catalysts. In this study, we sought a simple filtration-based method using an isocyanide-modified silica gel.

The synthesized isocyanide-modified silica gel **2** was characterized by a distinctive IR band for the isocyanide by analogy to previously reported procedures. Grafting the isocyanide monomer **1** onto silica gel employed a literature procedure.[14] The polymer-bound isocyanide **2** (Scheme 1) was detected with reflectance-based IR microscopy. An absorption signal at 2147 cm^{-1} was found, corresponding to the surface-bound isocyanide (Figure 1). This value was in good agreement with the absorption band found for the monomer, 2150 cm^{-1}, and in agreement with previously published results.[14] Loading of the isocyanide on the silica gel was subsequently determined by titration.[15] Typically the isocyanide was titrated to be between 1.1 and 1.6 mmol/g of silica gel.

The isocyanide-grafted silica gel was able to remove the Grubbs catalyst **Ru2** and the Grubbs–Hoveyda catalyst **Ru3**. These catalysts are very efficient at promoting the ring-closing metathesis (RCM) of diethyl diallylmalonate. As a qualitative test, **Ru2** was exposed to the modified silica gel **2**. After stirring for 30 min, the color of the solution changed from red to yellow. The silica gel was then removed and the solvent was collected. To the solution was added diethyl diallylmalonate; after 2 h no reaction was observed by TLC or ^1H NMR. Identical results were obtained with **Ru3** (see Supporting Information (SI) for full experimental details).

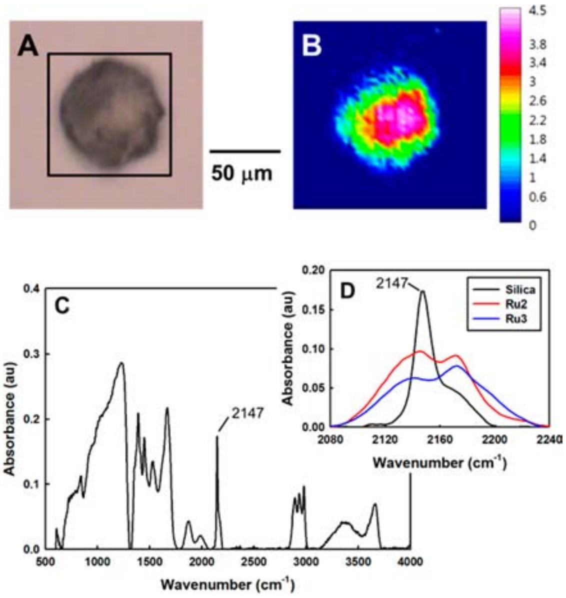

Figure 1. (A) Optical image of a single particle of silica gel **2** with aperture area (70 μm × 70 μm) marked. (B) Focal plane array (FPA) image of **2** integrated to show relative abundance of isocyanide (2135–2147 cm^{-1}). (C) Full FT-IR spectrum of **2**; the isocyanide peak (2147 cm^{-1}) is noted. (D) Isocyanide region for single beads of silica gel **2**, quench product of silica **2-Ru2**, and the quench product of silica **2-Ru3**.

The shift in the stretching frequency of the isocyanide was consistent with metal binding. The IR frequencies of the catalysts **Ru2** and **Ru3** deactivated by silica gel **2** were compared to the solution-based results of the isocyanide monomer **1** and metal-bound isocyanides (Table 1). The previous study conducted in our lab demonstrated that more than one isocyanide will coordinate to the metal center to make an 18-electron complex.[13] Catalyst deactivation with silica gel **2** resulted in two different isocyanide absorption bands indicating that more than one isocyanide may be coordinated to the metal center (Table 1, entries 3 and 5; Figure 1d). The IR frequencies of the isocyanides in the silica **2**-based and solution-based coordinated products of **Ru2** and **Ru3** were in close agreement with each other (Table 1, entry 3 vs 4; entry 5 vs 6).

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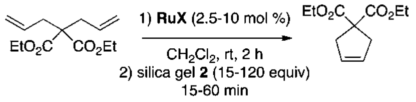
Table 1. Observed Isocyanide IR Frequencies

entry	reagent	IR frequency (cm^{-1})
1	monomer **1**	2150
2	silica grafted isocyanide **2**	2147
3	silica quenched isocyanide, **2-Ru2**	2145, 2172
4	product of **1-Ru2**	2143, 2184
5	silica quenched isocyanide, **2-Ru3**	2139, 2172
6	product of **1-Ru3**	2132, 2174

The removal of residual ruthenium was evaluated in a standard assay, the RCM of diethyl diallylmalonate (Table 2). The residual ruthenium was determined by inductively coupled plasma mass spectrometry (ICP-MS).[16] As a control, untreated silica gel only partially removed ruthenium (Table 2, entry 1). The solution treatment with soluble isocyanide KO_2CCH_2NC and passage through a silica gel plug (our previous method) gave a 10-fold reduction in ruthenium (Table 2, entry 2). Next, addition of 30 equiv and 60 equiv of isocyanide-grafted silica gel **2** was tested (Table 2, entries 3 and 4).[17] 60 equiv of **2** worked best but required at least 30 min; a longer reaction time was found to be unnecessary (Table 2, entries 5–7). During the first 30 min, a color change from red/brown to a light yellow was noted. Entry 8 demonstrated that doubling the amount of **2** to 1 g (120 equiv) further reduced the residual concentration of ruthenium. To evaluate the limits of this method, a reaction was run with an increased catalyst loading (Table 2, entry 9). This method was also found to work with the **Ru3** catalyst with similar efficiency at 2.5 and 10 mol % catalyst loadings (Table 2, entries 10 and 11). Ruthenium from **Ru1** was removed (Table 2, entry 12), but not as well as the case observed with second generation catalysts. Isocyanides react with **Ru1** by a different mechanism.[18]

When combined with silica gel purification, the ruthenium was removed to *ca.* 1 ppm. With the simple RCM reaction, purification of the cyclopentene product is trivial since the only byproduct is ethylene gas. More commonly, column chromatography is needed to purify the desired product. Entry 13 combines this method with column chromatography. The reaction was stirred with 60 equiv **2** for 30 min and then directly concentrated, and dry loaded on a pre-equilibrated 1 × 10 cm bed of silica gel. The product was eluted with 10% ethyl acetate in hexanes to afford the desired cyclopentene product in 93% yield. This result demonstrates that, in combination with column chromatography, silica gel **2** can remove over 99.99% of the original ruthenium, leaving behind 1.2 ppm Ru in the final sample.

Table 2. Optimization of Removal of Ruthenium from a Standard Metathesis Reaction



entry	RuX (mol %)	treatment **2** (equiv)	time (min)	concn [Ru][a]	concn [Ru]/ppm	Ru removed /%
1[b]	**Ru2** (2.5)	–	60	7.754	1552	88.87
2	**Ru2** (2.5)	4.4 mg (4.4) KO_2CCH_2NC	30	0.779	156	98.49
3	**Ru2** (2.5)	250 mg (30)	30	3.374	674	94.14
4	**Ru2** (2.5)	500 mg (60)	15	6.709	1342	90.98
5	**Ru2** (2.5)	500 mg (60)	30	0.659	132	99.02
6	**Ru2** (2.5)	500 mg (60)	45	0.585	118	99.01
7	**Ru2** (2.5)	500 mg (60)	120	0.551	110	99.20
8	**Ru2** (2.5)	1000 mg (120)	30	0.088	18	99.86
9	**Ru2** (5.0)	500 mg (30)	30	0.372	74	99.79
10	**Ru3** (2.5)	500 mg (60)	30	0.269	54	99.56
11	**Ru3** (10)	500 mg (15)	30	0.293	58	99.86
12	**Ru1** (2.5)	500 mg (60)	30	2.338	468	95.58
13[c]	**Ru2** (2.5)	500 mg (60)	30	0.006	1.2	99.99

[a] Concentration expressed as μg [Ru]/5 mg of crude, evaporated organic sample. [b] Using 500 mg of untreated silica gel. [c] This reaction was subsequently purified over 5.2 g (1 cm × 10 cm) of silica gel.

Next we sought to evaluate this method for catalysts under more typical reaction conditions (Table 3). Higher temperatures are often used to promote difficult ring closing and cross-metathesis reactions. Elevated reaction temperatures were screened because they can lead to catalyst decomposition and olefin isomerization.[3b] In alkene metathesis, a ruthenium methylidene is the propagating species which has been shown to thermally decompose to a dinuclear hydride species.[19] We wanted to test for "clean-up" of ill-defined decomposition products, not just active ruthenium carbenes. Depending on the application and the temperature used, ruthenium carbenes may no longer be present at the end of a metathesis reaction. Entries 1 and 2 demonstrated that this method worked equally well for high temperature reactions. It was also noticed that, during treatment with **2**, the color change from red (**Ru2**), or green (**Ru3**), to yellow took mere minutes. To be sure the effectiveness of this treatment

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(16) Residual Ru is commonly expressed as μg [Ru]/5 mg of the evaporated crude organic sample. We have included the ppm levels of Ru in the organic sample, where 0.005 μg of Ru in a 5 mg sample is equal to 1 ppm Ru. Lower ppm values are actually recorded in the ICP-MS quantitative assay, but these correspond to diluted samples and are not included here. See SI for further details.

(17) The silica gel tended to cling to the walls of the glass vessel at lower loadings. This resulted in less silica gel in contact with the homogeneous catalyst.

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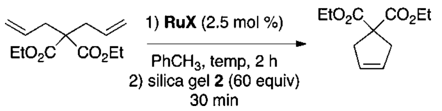
was not a product of the temperature but due to silica gel **2**; two additional experiments were run. The reaction was performed at 80 °C with a rt quench (Table 3, entry 3) and at rt with a quench performed at 80 °C (Table 3, entry 4). Similar values of residual ruthenium were obtained, indicating that the temperature of the quenching procedure is not a critical variable.

Table 3. Evaluation of Temperature as a Variable

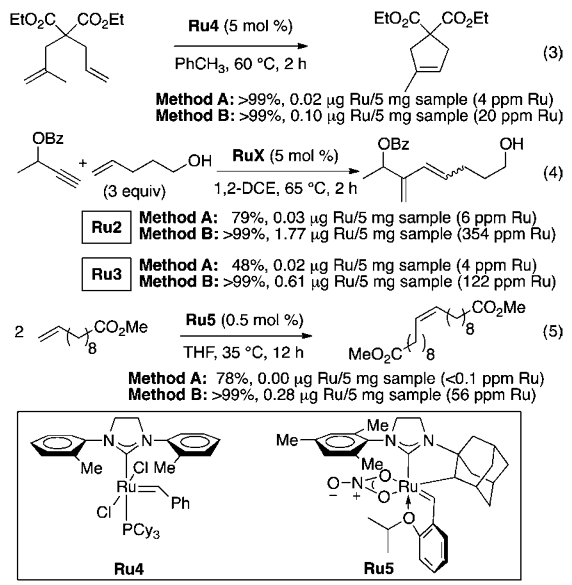


entry	**RuX**	temp (°C)	treatment temp (°C)	concn [Ru][a]	concn [Ru]/ppm	Ru removed/%
1	**Ru2**	80	80	0.59	118	99.01
2	**Ru3**	80	80	0.03	6	99.96
3	**Ru3**	80	rt	0.02	4	99.96
4	**Ru3**	rt	80	0.03	6	99.95

[a] Concentration expressed as μg [Ru]/5 mg of crude, evaporated organic sample.

Finally the effectiveness of this method was evaluated in more challenging metathesis applications (Scheme 2). The synthesis of trisubstituted alkenes requires more forcing conditions and a more active catalyst.[20] With higher temperatures, metathesis reactions that can form Ru=CH_2 intermediates and reactions done in the presence of alcohols result in greater decomposition of ruthenium carbenes.[3,19] The sterically permissive complex **Ru4** was evaluated for this RCM (eq 3). Two methods were used: (a) filtration to remove **2** followed by purification with silica gel; (b) filtration of **2** through a fritted funnel. Both samples provided low levels of ruthenium in varying chemical yields. Next an ene–yne metathesis reaction with an alkenol was evaluated using catalysts **Ru2** and **Ru3** (eq 4). This reaction is also known to cause catalyst decomposition resulting in the formation of ruthenium hydrides.[21] Even with several different ruthenium species present at the end of this reaction, quenching with silica gel **2** was effective at reducing the ruthenium content in the diene product.[22] Finally, the recently reported catalyst **Ru5**[23] was effectively quenched after the *Z*-selective homodimerization of methyl 10-undecenoate (eq 5). Catalyst **Ru5** is also known to have a unique mechanism of decomposition, different from the earlier generations of ruthenium catalysts.[24] Purification with silica gel **2** significantly reduced the levels of ruthenium.

Scheme 2. Evaluation of the Isocyanide **2** in Additional Metathesis Reactions[a]



[a] Isolated yield, and concentration of ruthenium in μg Ru/5 mg of sample, and ppm Ru in the organic sample. **Method A**: Filtration, column chromatography, and concentration of the reaction mixture prior to ICP-MS analysis. **Method B**: Filtration and concentration of the reaction mixture, and ICP-MS analysis.

In conclusion, isocyanide-grafted silica gel **2** was found to be an effective reagent for the removal of ruthenium from metathesis reactions. Metathesis activity was completely stopped in typical applications with commonly used second generation Grubbs metathesis catalysts. This method can be used as a stand alone procedure simply requiring filtration or can be used in combination with column chromatography to further reduce the levels of residual Ru. Further studies of this grafted silica gel with other metal catalysts are currently underway.

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Supporting Information Available. Experimental procedures characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) A longer reaction time (5 mol % **Ru2**, 18 h, eq 4) results in greater decomposition of the catalyst, but the silica gel **2** is still an effective purification procedure. Method A resulted in 0.058 μg/5 mg sample, or 11.7 ppm residual Ru. See SI.

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The authors declare no competing financial interest.