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A simple oxidative procedure for the removal of ruthenium residues from metathesis reaction products

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ABSTRACT

Ruthenium residues can be easily and rapidly removed from Grubbs metathesis products by washing with 15% aqueous hydrogen peroxide, which converts any ruthenium complexes into highly insoluble ruthenium dioxide, which then catalyzes the conversion of excess peroxide into water and oxygen. Ruthenium levels lower than 2 ppm can be routinely obtained; an additional advantage is that any phosphines are also rapidly oxidized to the corresponding, more polar phosphine oxides thereby facilitating their removal as well in many cases.

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Amongst the many spectacular developments in synthetic organic methodology in recent times, the various forms of metathesis chemistry represent one of the most significant, representing a true paradigm shift in synthetic thinking. In particular, the development of the two Grubbs catalysts, Mark I and Mark II, and the later addition of the Grubbs–Hoveyda complex have rendered this methodology readily available to all.[1] The breadth of applications has already made these essential tools in many synthetic endeavours. Such ubiquitous chemistry is, however perhaps inevitably, not without some drawbacks. When compared with the magnificence of the method, one of these seems almost trivial: it is often very difficult to separate the desired product(s) from the ruthenium catalysts **1–3**, despite these being used in small quantities, typically 1–5 mol %.

Unfortunately, it turns out that it is often very difficult to completely remove ruthenium residues by the usual silica gel-based chromatographic methods. While this can often be addressed by crystallization or distillation, or even by gradual loss during subsequent steps or repeated chromatography, it is not only an annoying and tedious feature of this otherwise generally superb methodology, it also presents serious problems in pharmaceutical synthesis, wherein permitted levels of such metallic contaminants are very low. For example, the allowed levels for oral administration amongst members of the platinum group [Pt, Pd, Ir, Rh, Ru and Os] are only 5 ppm or below a total of 20 ppm if two or more are present.[2]

It is therefore hardly surprising that a number of methods for the removal of ruthenium residues from completed metathesis reactions have been reported during the past few years. The first contribution was, unsurprisingly, from the Grubbs group who suggested using some 86 equiv of tris-(hydroxymethyl)phosphine to complex the ruthenium contaminants.[3] Other complexation methods include the addition of either 50 equiv of triphenylphosphine oxide or 100 equiv of dimethyl sulfoxide followed by filtration through silica gel,[4] later extrapolated to the use of a polymer-bound phosphine.[5] Such methods remove the ruthenium down to the 200 ppm level at best. However, filtration through an alternative immobilized species, aminopropyltriethoxysilane on silica or related solid supports, can take these levels down as low as 35 ppm.[6] Related methods include filtration through activated carbon,[7] supercritical fluid[8] and the use of a modified catalyst.[9] More recently, two methods have been reported wherein the ruthenium is removed as a water-soluble species, either by the addition of a polar isocyanate[10] or by using a modified Mark II catalyst (cf. structure **2**) having a polyethyleneglycol (PEG) chain incorporated into the carbene ligand.[11] With the exception of the silane method,[6] none of these methods look to be especially efficient and/or practical and often require the use of relatively large amounts of complexing agents. Perhaps curiously, there has been only one report of an overtly chemical method for ruthenium removal. This features oxidation by the addition of 1.5 equiv of lead (IV) acetate relative to the catalyst to a completed metathesis reaction followed by stirring at ambient temperature overnight and filtration through silica gel, reported by the Paquette group.[12] This reduces ruthenium levels to around 300 ppm, arguably a surprisingly high

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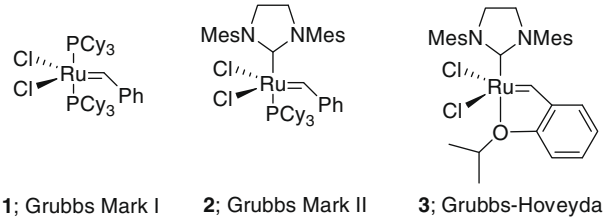
level for such a chemical method. It would therefore seem that there is still a need for the development of practical, cheap and potentially large-scale purification methodology in this area. All of this chemistry has recently been summarized by Nolan and co-workers.[13]

We have recently reported that a straightforward hydrogen peroxide wash can obviate the requirement for extensive chromatography in the separation of Mitsunobu products from excess and spent reagents.[14] No doubt, a significant role associated with such peroxide washes is the rapid oxidation of any phosphines to the corresponding, much more polar and hence more easily removed phosphine oxides. It occurred to us that a similar oxidative procedure could be effective for the decomposition and eventual removal of ruthenium catalyst residues from metathesis reaction products. Herein, we report that this is indeed a successful and simple method, which could find widespread application (Scheme 1).

We first came across the ruthenium removal problem when preparing samples of the (*E*,*E*)-dienyl diesters **5** using the remarkably efficient cross metathesis reaction between a cycloalkene [e.g., **4**] and an acrylate (Scheme 2).[15] We used the Mark II catalyst **2** at levels as low as 0.37 mol % but could still not remove the ruthenium completely. We observed that simply stirring the completed reaction mixture under air for 48 h converted all the ruthenium into insoluble ruthenium dioxide without a significant reduction in product yield. However, this is clearly not an attractive or even viable procedure, except perhaps in relatively exceptional cases.

The idea of using oxidative ruthenium removal was then translated into an application of our chromatography-free Mitsunobu work-up procedure.[14] The crude reaction product containing the diester **5** was simply vigorously stirred with a large excess of 15% v/v aqueous hydrogen peroxide at ambient temperature.[16] During the next fifteen minutes or so, the mixture began to effervesce with increasing vigour and there was a mild exotherm, both of which subsided after this time as a blue–black solid was precipitated. A subsequent starch–iodine test showed the absence of peroxide. After a very simple aqueous work-up, the dienyl diesters **5** were isolated in over 80% yields as pure clear oils, which showed spectroscopic and analytical data identical to those previously reported.[15]

A second example and one which has served as a standard test of previous purification methods[2,11,13] was used to determine the efficacy of the present method for the removal of the Mark I catalyst **1** (Scheme 3). This entailed the ring-closure metathesis of the diallyl malonate **6**[17] to give the cyclopentene diester **7**.[1,18] Following completion of the rapid RCM, the reaction mixture was worked

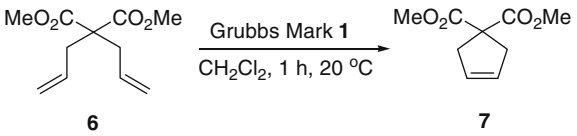


1; Grubbs Mark I **2**; Grubbs Mark II **3**; Grubbs-Hoveyda

Scheme 1. Grubbs metathesis catalysts.

4 **5**

Scheme 2. A useful cross metathesis reaction.[15]



6 **7**

Scheme 3. A representative RCM reaction.[17]

up[16,19] in a similar fashion to the foregoing cross metathesis shown in Scheme 2.

Samples of the two products **5** and **7** were then analyzed for their ruthenium content, along with additional samples, prepared using higher levels of catalyst, to provide a sterner test of the present removal procedure. In addition, one of the runs was left to stir open to the air for a prolonged period, with no addition of peroxide. Each sample was analyzed using ICPMS,[20] in line with most previous reports. The results are collected in Table 1.

Presumably because of the much higher catalyst loading, a single wash of the reaction mixture containing 5 mol % of Grubbs Mark 1 catalyst **1** only removed around 85% of the ruthenium; however, a second treatment with hydrogen peroxide (entry 2) reduced the ruthenium level to around 15 ppm.

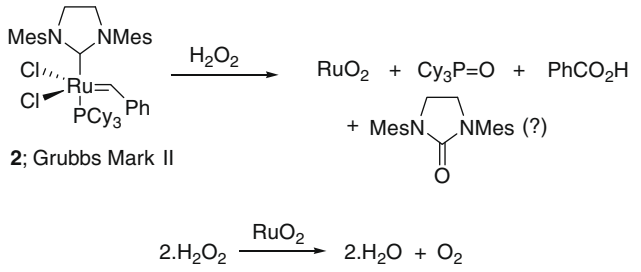
Interestingly, as mentioned above, simply stirring a reaction mixture containing a relatively low level of the Mark II catalyst **2** under air for 48 h resulted in oxidation of the bulk of the ruthenium, the level of which was reduced to 132 ppm (entry 3). Although attractive in some ways, many final products may not respond well to such a lengthy exposure to the atmosphere. In contrast, a single exposure to hydrogen peroxide in examples with this low level of catalyst loading led to almost complete removal of ruthenium (entries 4 and 5) and one certainly acceptable for pharmaceutical synthesis.[2] At higher catalyst loadings above 1 mol % (entries 6 and 7), two washes were necessary to reach similar levels although a single treatment (entry 6) achieved a ruthenium level of around 12 ppm. These ruthenium levels are significantly lower than most previously reported.

An additional benefit of the present oxidation procedure is that it will assist in the removal of the other catalyst components. Thus, from our previous work,[14] no doubt the phosphine ligands will be rapidly oxidized to the much more polar oxides, which should be removed during the filtration through silica gel. The released benzaldehyde might also be oxidized but to benzoic acid and similarly removed. The fate of the carbene ligand is uncertain, but a distinct possibility is oxidation to the corresponding cyclic urea, again a very polar material (Scheme 4). Although not examined, we assume that the related Grubbs–Hoveyda catalyst **3** would undergo comparable decomposition at a similar rate.

The one drawback of the present method is the requirement for a considerable excess of hydrogen peroxide by reason of its rapid decomposition by the ruthenium dioxide produced as the metathesis catalyst is destroyed (Scheme 4).[21] While it is certainly possible to carry out the oxidation in a separating funnel, this requires great care and manual dexterity as the oxygen is released quite rapidly. The method described in Ref. 16 is therefore recommended. It is also possible to carry out the oxidation by adding the aqueous peroxide

Table 1
Ruthenium content after oxidation

Entry	Catalyst (mol %)	Work-up	[Ru] ppm	% removal
1	Mk 1 (5.0)	H_2O_2	2116	84.90
2	Mk 1 (5.0)	H_2O_2 (2×)	15.10	99.45
3	Mk 2 (0.37)	Air (48 h)	132	85.76
4	Mk 2 (0.37)	H_2O_2	1.33	99.95
5	Mk 2 (0.37)	H_2O_2	2.05	99.55
6	Mk 2 (1.37)	H_2O_2	12.46	99.28
7	Mk 2 (1.37)	H_2O_2 (2×)	2.53	99.88



Scheme 4. A proposed overall reaction scheme for the decomposition of Grubbs metathesis catalysts.

as a slow stream. In our view, this should be an easily scalable method, given due attention to the formation of oxygen, which surely can be readily controlled at a perfectly safe level.

Given the cheapness of hydrogen peroxide, together with the fact that no by-products are produced during the oxidation which require any separation, we contend that this method should find many applications on both small scale and large scale, the latter after some further development. Indeed, given that it is easy to separate the ruthenium dioxide, which is produced most likely as a hydrate, this might be regarded as a 'green' method and will certainly be amenable to the easy isolation and re-use of the ruthenium dioxide, which is not a particularly cheap reagent.

In terms of group and compound compatibility, dilute aqueous hydrogen peroxide is a relatively innocuous reagent and will not attack many functionalities, especially during the brief exposure under these neutral conditions required here. In our earlier work,[14] we showed that 1,3-dithiane was not oxidized by exposure to 15% aqueous hydrogen peroxide during around 10–15 min at ambient temperature, approximately the conditions used here. No doubt there will be some incompatibilities but we anticipate that these will be very few.

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20. A sample of both treated and untreated reaction product was accurately weighed and added to a volumetric flask. Each sample was digested overnight in aqua regia (20 ml) and the resulting solution diluted to 100 ml with distilled water. The solution was then analyzed by ICPMS, which had been standardized using a ruthenium solution of known concentration. Each run was duplicated as a check. Typical results were as follows: The total ruthenium content [^{99}Ru and ^{101}Ru] of an untreated sample according to ICPMS was 1542.8 ppb, equivalent to 1.5428 ppm or 1.5428 μg ml^{-1}. The 100 ml total volume of solution thus contained 154.28 μg of Ru. The original untreated product sample weighed 58.00 mg, which therefore contained 154.28 μg of ruthenium, equivalent to 2660 μg g^{-1} or 2660 ppm of ruthenium. A typical equivalent figure for a treated sample weighing 74.00 mg was [Ru] = 0.984 ppb. This equates to 0.0984 μg in 100 ml of solution and hence in the 74 mg sample. This finally equates to 1.33 μg g^{-1} or 1.33 ppm of ruthenium. The values quoted in Table 1 are the average of two runs.
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