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Easily removable olefin metathesis catalysts

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A small family of olefin metathesis catalysts bearing a polar quaternary ammonium group is described. The presence of this group allows for efficient separation of ruthenium impurities after the reaction. Application of catalysts 9 and 11 10 leads to organic products of high purity, which exhibit surprisingly low ruthenium contamination levels (usually below 5 ppm) after simple and inexpensive purification step.

The development of modern Ru metathesis catalysts, such as Is Grubbs and Hoveyda–Grubbs carbenes combining high activity with an excellent tolerance to a variety of functional groups has been the key to widespread applications of olefin metathesis in synthesis of a large number of compounds.¹



Figure 1. Standard catalysts (Gru-II, Ind-I, Ind-II, Hov-II) and selected complexes 1-6 designed for simple removal of Ru from metathesis products (Mes = 2,4,6-tri-methylphenyl, Cy = cyclohexyl, TsO = *p*-toluenosulfonate)

- 20 Despite general superiority offered by this family of catalysts, they share some disadvantages. Removing of heavy-metal impurities from the reaction products becomes one of the major problems in introduction of olefin metathesis in pharmaceutical industry. The development of an efficient, economical and
- ²⁵ practical method to remove metal containing by-products might be crucial for further application of metathesis methodology in industry.² Several protocols to solve the problems associated with Ru contamination arising during pharmaceutical or fine chemical processing have been proposed.³ Use of biphasic aqueous ³⁰ extraction,⁴ various scavengers, such as lead tetraacetate,⁵
- ³⁰ extraction,⁷ various scavengers, such as lead tetradeetate,⁷ DMSO,⁶ triphenylphosphine oxide, isocyanide,⁷ functionalized mesoporous silicates,⁸ (DMSO) and supported phosphines⁹ were reported to reduce the ruthenium content to 10–1200 ppm. Alternatively, two cycles of chromatography, followed by 12 h ³⁵ incubation with activated charcoal, resulted in <100 ppm of
- residual ruthenium.¹⁰

Alternative solution to these problems can be tailored catalysts that allow for easier purification.¹¹ For example, catalysts bearing polar ammonium group in the benzylidene fragment were ⁴⁰ reported (Fig. 1).^{12,13,14} It was shown that simple filtration of the reaction mixture through silica gel results in lowering the amount of catalyst impurities in the crude products, however in the most cases the residual Ru level was still too high for pharmaceutical applications.¹² This problem is probably related to placing of the ⁴⁵ quaternary ammonium group in the benzylidene part which

dissociates during metathesis act. Ru-complexes containing quaternary ammonium groups in the NHC ligand should be better solution for removal of Ru-containing impurities after the reaction. A related approach was reported by Grubbs, who ⁵⁰ removed ruthenium from crude product by extraction with water. Poly-(ethylene glycol) (PEG) supported *N*-heterocyclic carbenebased ruthenium complex **6** migrates to water fraction, giving the product with low residual ruthenium (42 ppm).^{11c}

Recently, we elaborated a simple synthetic protocol for ⁵⁵ preparation of water soluble, quaternary ammonium chloride tagged catalysts.¹⁵ Quaternization of the preformed metal complexes allows for very simple preparation of highly polar catalysts. This method allows to obtain various Ru-complexes containing quaternary ammonium groups in the NHC ligand. ⁶⁰ Using this methodology we synthesized new complexes **9-11** (Scheme 1), according to pathway presented on Scheme 2.



Compound **13** was synthesized from commercially available *N*,N-dimethyl allylamine and was used in its crude form. Purification of **14** involved only removal of excess of 2,4,6-trimethylaniline

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and filtration of crude product through a short pad of silica gel. Salt 15 was purified by crystallization and was finally obtained in 30 % overall yield. Upon action of potassium tert-amylate, a free NHC was generated, which was reacted in situ with Ind-I to yield 5 16. This complex was then reacted with benzylidene ligand precursors 17 and 18, to give free amine-containing catalysts 7 and 8, respectively. Quaternization of these neutral complexes with methyl iodide or methyl chloride afforded catalysts 9-11 in high yields (Scheme 2). Some interesting differences in solubility 10 of complexes 9-11 were observed. Catalyst 9 is soluble only in organic solvents (such as dichloromethane) and is not soluble in water. Complex 10 showed negligible solubility in both organic solvents and water, therefore its structure was confirmed only by IR and MS analysis. However, solubility of 10 in refluxing DCM 15 is sufficient to perform homogeneous metathesis reactions. On

the other hand, catalyst 11 showed good solubility in organic solvents as well as in water.



Scheme 2. Synthesis of complexes 9-11

The catalytic activity of complexes 9-11 was determined by conducting a standard set of RCM, CM and enyne reactions in ²⁰ refluxing dichloromethane (results are summarized in Table 1).

- Catalyst 9 shows good overall efficiency, however RCM of more challenging trisubstituted dienes were accomplished only after prolonged reaction time. Although poorly defined, complex 10 proved to be more active and efficient than 9. However, due to
- 25 the above mentioned difficulties in its characterization, we think that this complex is of limited usefulness in practical applications. Fortunately, the well defined complex 11, showed a very similar application profile as 10. Therefore, complex 10 can be treated as a staging post in synthesis of catalyst 11. Although 30 dichloromethane is not an environmentally and user friendly
- solvent, we find it most suitable, since our catalysts are not soluble in toluene - the second most commonly used solvent in olefin metathesis. Nonetheless, we believe that simplicity and efficiency of ruthenium residues removal with the use of

35 complexes 9–11	outweigh	the	adverse	effects	of	the	use	of		
dichloromethane.										
Table 1 Model metathesis reactions										

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Entry	Substrate	Product	Cat.	Time (h)	Conv. ^a (%)	Yield (%)	Ru (ppm)
1 2	NTs	NTs 20	{ 9 10	2 0.25	>99 >99	98 99	4.6 ^b 1.5 ^b
3 4	NTs 21	NTs 22	{ 9 10	5.5 0.5	98 >99	96 99	4.8 ^b 2.0 ^b
5 6 7 8	CO ₂ Et CO ₂ Et	CO ₂ Et CO ₂ Et	<pre> 9 10 11 11 </pre>	4 0.5 0.3 0.3	98 >99 >99 >99	97 98 93 89	3.8 ^b 2.6 ^b 0.8 ^b <0.004 ^c
9 10 11 12	CO ₂ Et CO ₂ Et	CO ₂ Et CO ₂ Et 26	<pre>{ 9 10 10 10 11</pre>	10 2 5 2	95 95 99 >99	91 NI 97 89	0.9 ^b ND 1.0 ^b 0.9 ^c
13 14 15 16	Ph 27	Ph 28	<pre> 9 10 10 11 </pre>	1.3 0.15 0.5 0.15	98 97 99 >99	96 NI 99 86	3.8 ^b ND 2.6 ^b 8.4 ^c
17 18 19	29 3 OTBS	о	{ 9 10 11	1.3 0.5 0.3	98 >99 >99	97 98 90	1.7 ^b 0.8 ^b <0.004 ^c

Conditions: catalyst 1 mol%, DCM, 40 °C, C = 0.05 M,^a - determined by GC, ^b - filtration; ^c - extraction, NI - not isolated, ND - not determined

We checked that the optimal purification protocol for reactions in which 9-11 were applied consists of filtration of the reaction mixture through a short pad of silica gel (Figure 2A, 2B) (silica $_{40}$ gel/substrate mass ratio = 7) and product elution with additional portion of DCM (Figure 2C, 2D)



Figure 2. Filtration of the reaction mixture through silica gel

All products obtained using complexes 9 and 10 have very low 45 ruthenium contamination (below 5 ppm) as determined by ICP MS. Water solubility of 11 (2 mg/ml) gives even more interesting opportunity for ruthenium removal from crude reaction mixtures by extraction with water. In order to compare efficiency of various Ru-removal techniques, we performed two separate RCM 50 reactions of diethyl diallylmalonate (23) promoted by the same amount of catalyst 11. One of these reaction mixtures was filtered as described above, leading to the product with very low residual ruthenium level (Table 1, entry 7). To the second reaction mixture (Fig. 3A) water was added and the two phase mixture formed

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(Figure 3B) was vigorously shaken for 10 minutes.



Figure 3. Extraction of reaction mixture with water

Almost all ruthenium migrated to water phase and organic ⁵ fraction was only slightly coloured (Figure 3C). After fifth extraction (Figure 3D) both organic and water phases were colourless. As we checked, ruthenium level in the crude product was below detection limit of ICP MS method. Removal of residual ruthenium by extraction should be especially suitable in ¹⁰ industrial applications, however discharging relatively large amounts of impure water that contains heavy metal might also be problematic. Disposal of small quantities of contaminated silica gel should be much more convenient. Therefore, we decided to check if we can remove ruthenium impurities from the combined ¹⁵ water fractions (Figure 3E). To do so, we added a small amount of silica cal to the contaminated water and water it chances.

- of silica gel to the contaminated water and resulted suspension was stirred at room temperature for 10 minutes. After the black coloured solid sedimented, the water phase became colourless (Figure 3G) and ruthenium level was determined to be only 0.11
- ²⁰ ppm. It shall be noted that according to our knowledge such simple method for purification of Ru-contaminated water was never reported before. Removal of ruthenium impurities by extraction with water was previously reported by Grubbs and Hong.^{11c} However, that protocol was less efficient, and required
- ²⁵ prior evaporation of dichloromethane, dissolving of the product in diethyl ether and finally the extraction of this etheral solution with water.

Next, we decided to check the performance of **10** and **11** in metathesis of selected bio-like compounds (Table 2). RCM of *N*-Table 2. Metathesis with bio-like substrates



Condition: catalyst 1 mol%, DCM, 40 °C, C = 0.05 M, ^a - filtration, ^b - extraction

³⁰ Boc-N',N'-diallylprolinamide (32) was accomplished with very good isolated yield, however the residual ruthenium level was slightly higher than that observed for standard RCM products. Also, CM of steroid derivative 34 resulted in isolation of product with good yield. Ruthenium contamination was very low in this ³⁵ case.

Water solubility of complex 11 makes it quite universal. After proving its usefullness in metathesis in organic solvent we decided to test 11 with selected model water soluble substrates.



- ⁴⁰ Although **11** is only sparingly soluble in neat water, it effectively promoted metathesis reactions carried out in this medium. RCM of **36** and isomerisation of **38** were accomplished with very good results (Table 3).
- In conclusion, we are reporting the homogenous Hoveyda-Grubbs 45 type catalysts containing a quaternary ammonium group in the NHC ligand. Products of olefin metathesis reactions promoted by complexes 9–11, have been readily and efficiently purified from Ru-residues. Filtration of the reaction mixture through a small amount of silica gel or its extraction with water can be applied for 50 removal of Ru-containing catalyst's remains. These results may be especially interesting for pharmaceutical industry.

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Notes and references

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 † Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/
- 70 * Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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