

# A green catalyst for green chemistry: Synthesis and application of an olefin metathesis catalyst bearing a quaternary ammonium group†

Anna Michrowska,<sup>a</sup> Łukasz Gułajski,<sup>ab</sup> Zuzanna Kaczmarska,<sup>ac</sup> Klaas Mennecke,<sup>d</sup> Andreas Kirschning<sup>d</sup> and Karol Grela<sup>\*a</sup>

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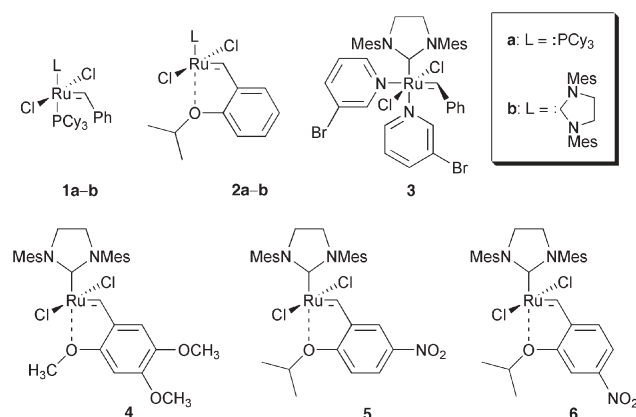
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The novel catalyst **8**, bearing a polar quaternary ammonium group, is very stable and can be easily prepared from commercially available reagents. Catalyst **8** can be efficiently used for olefin metathesis not only in traditional but also in aqueous media. Various ring closing-, cross- and enyne-metathesis reactions were conducted in water-methanol mixtures in air. The electron withdrawing quaternary ammonium group not only activates the catalyst chemically, but at the same time allows its efficient separation after reaction. Application of **8** leads to organic products of high purity, which exhibit very low ruthenium contamination levels (12–68 ppm) after filtering through a pad of silica gel.

## Introduction

Despite the general superiority offered by modern *homogeneous* Grubbs and Hoveyda–Grubbs catalysts **1–3** (Scheme 1),<sup>1</sup> they



**Scheme 1** Selected ruthenium precatalysts for alkene metathesis. Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl.

<sup>a</sup>Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, Warsaw, 01-224, Poland. E-mail: grela@icho.edu.pl

<sup>b</sup>Faculty of Chemistry, Warsaw University of Technology (Politechnika), Noakowskiego 3, Warsaw, 00-664, Poland

<sup>c</sup>Department of Chemistry, Warsaw University, Pasteura 1, Warsaw, 02-093, Poland

<sup>d</sup>Institut für Organische Chemie, Universität Hannover, Schneiderberg 1b, Hannover, 30167, Germany

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share some disadvantages. Since olefin metathesis reaction is expected to be used in pharmaceutical processes, the most undesirable feature of these complexes is that during the reaction they form ruthenium byproducts, which are difficult to remove from the reaction products.<sup>2</sup> In many cases, ruthenium levels of >2000 ppm remain after chromatography of products prepared by RCM with 5 mol% of Grubbs catalysts.<sup>3</sup> The ruthenium has to be removed prior to further processing.<sup>4</sup>

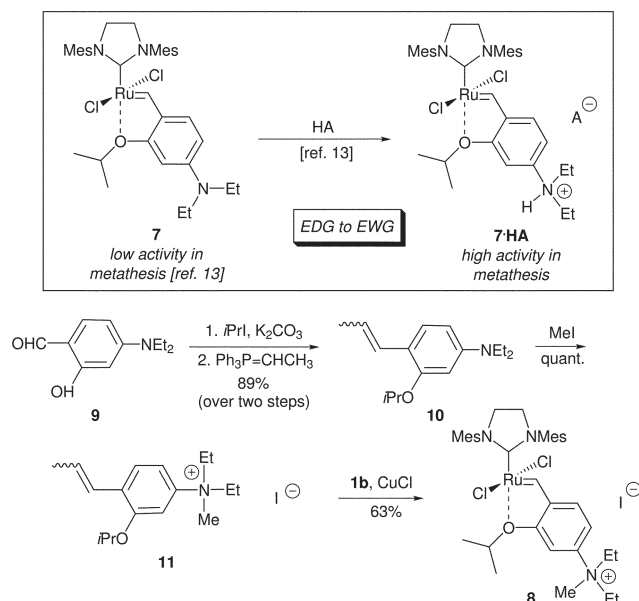
Several protocols to solve problems associated with Ru contamination arising during pharmaceutical or fine chemical processing, from R&D scale through to manufacture, have been proposed.<sup>3</sup> Use of biphasic aqueous extraction,<sup>5</sup> various scavengers, such as lead tetraacetate,<sup>6</sup> DMSO,<sup>7</sup> triphenylphosphine oxide,<sup>7</sup> and supported phosphines<sup>8</sup> were reported to reduce the ruthenium content to between 200–1200 ppm. Alternatively, two cycles of chromatography, followed by 12 h incubation with activated charcoal, resulted in <100 ppm.<sup>9</sup> Recently, special functional polymers—QuadraPure<sup>™</sup> resins—were intended for heavy metal (including Ru) removal in both batch and continuous processes.<sup>10</sup> Complex **4**, introduced by our group,<sup>11</sup> exhibits catalytic activity comparable to the parent Hoveyda–Grubbs carbene **2b**, but shows much higher affinity for silica gel when CH<sub>2</sub>Cl<sub>2</sub> is used as eluent, which enables its efficient removal. We have recently developed a new efficient strategy for phase-separation and recovery of **4**, which provides crude products containing up to 400 ppm of ruthenium.<sup>12</sup>

In continuation of our program to develop a ‘green’ metathesis catalyst,<sup>12,13</sup> herein we report on a new, airstable ruthenium homogeneous catalyst, that exhibits an increased activity in metathesis reactions and allows us to obtain crude products with low residual ruthenium levels.

## Results and discussion

### Catalyst design

We demonstrated that the 5- and 4-nitro-substituted complexes **5** and **6** initiate olefin metathesis dramatically faster than the parent Hoveyda–Grubbs catalyst **2b**.<sup>14</sup> We proposed that the electron-withdrawing (EWG) nitro-group in the benzylidene fragment of **5** and **6** weakens the O→Ru chelation and facilitates faster initiation of the catalytic cycle.<sup>14</sup> In accordance with this assumption, we observed that complex **7** (Scheme 2), bearing the electron-donating (EDG) diethylamino group shows little or no activity in olefin metathesis.<sup>13,15</sup> However, in a striking contrast, the *in situ* formed salts obtained by treatment of aniline **7** with Brønsted acids (Scheme 2) are of high activity, surpassing the parent



**Scheme 2** The concept of 'EWG-to-EDG activity switch' and preparation of complex **8**.

Hoveyda–Grubbs complex **2b** in terms of initiation speed (*electron donating to electron withdrawing activity switch*).<sup>13</sup>

Exploring further the concept of activating a catalyst using EDG to EWG activity switch, we have attempted to prepare complex **8**, bearing a quaternary ammonium group.<sup>16</sup> As illustrated on Scheme 2, we used commercially available aldehyde **10** as a starting material for the preparation of the corresponding quaternary salt **11**.<sup>17</sup> Complex **8** was obtained in the reaction of **11** (1.1 equiv.) with **1b** (1.0 equiv.) and CuCl (1.4 equiv.). Washing of the crude product with ethyl acetate and methanol afforded pure complex **8** as an air-stable, green micro-crystalline solid, soluble in acetonitrile, dichloromethane, methanol, methanol–water and ethanol–water 5 : 2 (v/v), respectively.

### Catalytic performance of **8**

To compare the relative activities of catalysts **2b**, **7** and **8**, the ring-closing metathesis of diethyl 2-allyl-2-methylmalonate (**12a**) (Table 1, entry 1) was investigated under identical conditions. The results show that the initial rate of metathesis was markedly enhanced in the case of the EWG-substituted **8**. After 20 and 40 min the yields of **13a** were 51% and 81% respectively (96% after 1.5 h), as opposed to 20% and 46% obtained with **2b** (81% after 1.5 h). This demonstrates again<sup>14,13</sup> that the activity of ruthenium metathesis catalyst **2b** can be enhanced by introduction of electron-withdrawing groups without detriment to the catalyst stability. An analogous experiment was conducted with free-amine catalyst **7**. As expected,<sup>13</sup> practically no reaction was observed during the first 2 hours (<1% conversion after 1.5 h and 8% after 24 h).

We supposed that the introduction of a polar quaternary ammonium group can be used not only to increase the catalyst activity, but also to alter its physical–chemical properties, such as affinity to silica gel, which should facilitate its separation after the reaction. To reduce this assumption to reality, a spectrum of various substrates for RCM and enyne-cycloisomerisation were tested (Table 1, entries 2–7). The data compiled in Table 1 show

that complex **8** is a superb catalyst in CH<sub>2</sub>Cl<sub>2</sub>. In addition, we observed that simple silica-gel filtration of the reaction mixture through a short pad of silica gel (20–40 × weight of the product) allows almost complete removal of ruthenium byproducts. Inductively coupled plasma mass spectrometry (ICP-MS) analysis of the selected crude products (**13**) indicated 12–68 ppm Ru, which is much lower than contamination levels obtained in reactions with catalyst **1a**<sup>3</sup> and **4**.<sup>12</sup>

Metathesis reactions are usually carried out in nonpolar organic solvents under inert and anhydrous conditions.<sup>1</sup> From an economic and environmental standpoint, water or aqueous solutions represent very attractive media for organic reactions,<sup>18</sup> and recently some efforts have been directed to the application of water or aqueous solutions in metathesis reactions.<sup>19</sup>

We were pleased to see that complex **8** efficiently catalysed the metathesis of various substrates in *non-distilled, non-degassed protic media in air* (Table 1, entries 4–5 and 8–9). Again, in one selected case we checked that the crude organic product (**13h**) contained a very low level of residual ruthenium (37 ppm).

In conclusion, we have reported the first example of a homo-genous Hoveyda–Grubbs catalyst containing a quaternary ammonium group. Catalyst **8** initiates various types of metathesis reaction in both dichloromethane and methanol–water mixtures. Furthermore, the very low levels of residual ruthenium impurities in crude organic products make **8** particularly suitable for use in pharmaceutical applications. The application of this catalyst in the synthesis of biologically important molecules in aqueous solvent mixtures is currently being pursued.

## Experimental

### Representative procedure of metathesis in CH<sub>2</sub>Cl<sub>2</sub>

A reaction tube equipped with a magnetic stirring bar was charged with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), catalyst **8** (1–5 mol%) and substrate **12** (0.2 mmol). The reaction mixture was stirred at 25 °C. After complete conversion (TLC), the reaction mixture was passed through a cartridge containing silica gel (1–2 g). The cartridge was washed with an additional portion of CH<sub>2</sub>Cl<sub>2</sub> (10–20 mL). The CH<sub>2</sub>Cl<sub>2</sub> fraction was concentrated under reduced pressure to yield crude product **13**.

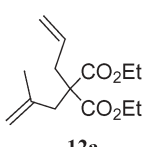
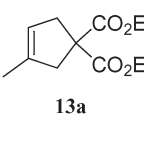
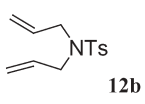
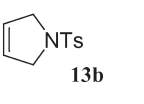
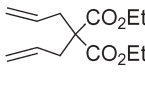
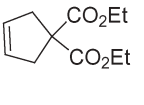
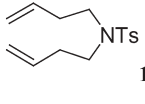
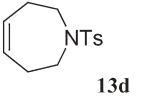
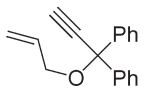
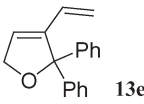
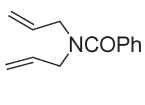
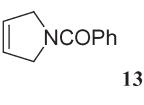
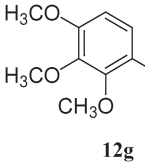
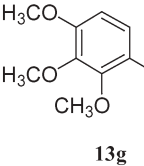
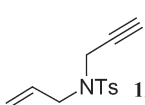
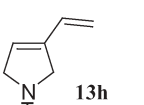
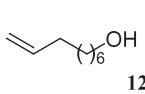
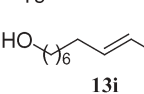
### Representative procedure of metathesis in a mixture of MeOH–H<sub>2</sub>O or EtOH–H<sub>2</sub>O, 5 : 2 v/v

A reaction tube equipped with a magnetic stirring bar was charged with catalyst **8** (6 mg, 0.007 mmol, 5 mol%) and non-degassed water (2 mL). To the resulting suspension a solution of substrate **12** (0.14 mmol) in MeOH or EtOH (5 mL) was added. The reaction mixture was stirred at 25 °C. After complete conversion (TLC), the reaction mixture was evaporated to dryness, dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and passed through a cartridge containing silica gel (1–2 g). The cartridge was washed with an additional portion of CH<sub>2</sub>Cl<sub>2</sub> (15–25 mL). The CH<sub>2</sub>Cl<sub>2</sub> fraction was concentrated under reduced pressure to yield crude product **13**.

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**Table 1** Metathesis reactions catalyzed by **8**<sup>a</sup>

Entry	Substrate <b>12</b>	Product <b>13</b>	Solvent	Catalyst (mol%)	Time/h	Conversion (%) <sup>b</sup>	Ru/ppm <sup>c</sup>
1			CH <sub>2</sub> Cl <sub>2</sub>	<b>2b</b> (5) <b>2b</b> (5) <b>2b</b> (5) <b>7</b> (5) <b>8</b> (5) <b>8</b> (5) <b>8</b> (5)	0.3 0.6 1.5 1.5 0.3 0.6 1.5	20 46 81 <1 51 81 96	
2			CH <sub>2</sub> Cl <sub>2</sub>	<b>8</b> (5)	0.5	99	68
3			CH <sub>2</sub> Cl <sub>2</sub>	<b>8</b> (5) <b>8</b> (1)	1 3.5	99 99	12
4			CH <sub>2</sub> Cl <sub>2</sub> MeOH/H <sub>2</sub> O	<b>8</b> (5) <b>8</b> (5)	1 0.5	97 99	33
5			CH <sub>2</sub> Cl <sub>2</sub> MeOH/H <sub>2</sub> O EtOH/H <sub>2</sub> O	<b>8</b> (5) <b>8</b> (5) <b>8</b> (5)	0.5 0.5 0.5	98 92 99	
6			CH <sub>2</sub> Cl <sub>2</sub>	<b>8</b> (2.5)	0.5	99	
7			CH <sub>2</sub> Cl <sub>2</sub>	<b>8</b> (3)	2	91	21
8			MeOH/H <sub>2</sub> O EtOH/H <sub>2</sub> O	<b>8</b> (5) <b>8</b> (5)	0.5 0.5	99 83	37
9			MeOH/H <sub>2</sub> O	<b>8</b> (10)	24	99 <sup>d</sup>	

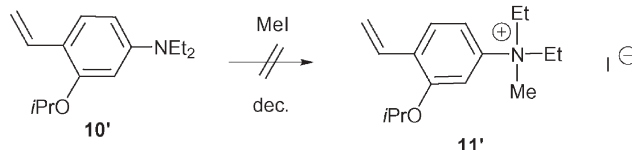
<sup>a</sup> Conditions: 1–5 mol% of catalyst, CH<sub>2</sub>Cl<sub>2</sub> or MeOH/H<sub>2</sub>O; *c* = 0.02 mol L<sup>-1</sup>, 25 °C. <sup>b</sup> Conversions were determined by analysis of <sup>1</sup>H NMR or GC-MS of the crude reaction mixture. <sup>c</sup> Level of Ru impurity in crude products determined by ICP-MS and shown as parts per million (ppm). <sup>d</sup> Reaction with 10 mol% of **8** at 40 °C.

ICP-MS analyses, and the Institute of Organic Chemistry, Polish Academy of Sciences for support (stipend for L.G.). Preparation of this manuscript would not have been possible without the help of the Alexander von Humboldt Foundation (travel allowance to K.G.), which is gratefully acknowledged.

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