

Quest for the ideal olefin metathesis catalyst^{*,**}

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Abstract: Attempts were made to create a catalyst that approaches Gladysz's vision of an "ideal catalyst". Modifications of the Hoveyda–Grubbs catalyst were carried out with the aim to increase its activity and broaden the scope of its applicability to challenging metathesis reactions. This was done by introduction of an electron-withdrawing substituent on the isopropoxybenzylidene group in order to diminish the donor properties of the oxygen atom. The resulting stable and easily accessible nitro-substituted Hoveyda–Grubbs catalyst has found a number of successful applications in various research and industrial laboratories. Also, a new concept for noncovalent immobilization of a ruthenium olefin metathesis catalyst is presented. The 2-isopropoxybenzylidene ligand of Hoveyda–Grubbs carbene is further modified by an additional amino group, and immobilization is achieved by treatment with sulfonated polystyrene, forming the corresponding ammonium salt. In this novel strategy for the immobilization of ruthenium-based metathesis catalysts, the amino group plays a dual role, being first an active anchor for immobilization and secondly, after protonation, activating the catalysts by electron-donating to -withdrawing switch. The same concept has been used in the preparation of a quaternary ammonium catalyst for aqueous olefin metathesis.

Keywords: olefin metathesis; catalysis; immobilization; ruthenium; carbenes; green chemistry.

INTRODUCTION

Catalysis has widely recognized benefits—thermodynamically favorable reactions that have no low-energy kinetic pathways can be rendered possible under mild conditions. At the beginning of this decade, Gladysz asked whether one can really make an "ideal catalyst" [1]. He proposed that such a catalyst [2] is one that

1. produces an infinite amount of product from a single catalyst molecule (or heterogeneous equivalent), a criterion that implies: no deactivation under reaction conditions and no poisoning under reaction conditions;
2. effects a rapid reaction (high turnover frequency or TOF) without the need for external cooling or heating;
3. effects a rapid reaction under atmospheric pressures of gaseous reactants;
4. has no intrinsic inert atmosphere requirement;
5. is insensitive to reactant impurities; and
6. gives a product yield of 100 %.

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**Dedicated to Prof. John A. Gladysz on the occasion of his 55th birthday.

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The first requirement is the most important and implies a turnover number (TON) of infinity. The TON describes the degree of activity of a catalyst; and the catalyst efficiency is described through its TOF (in h^{-1}). TON represents the average number of substrate molecules converted into the product per molecule of the catalyst [3]. Certain omissions from the above list should be highlighted. For example, a catalyst that

7. is readily available and inexpensive,
8. is nontoxic and nonhazardous, and
9. requires no activation or initiation step

is obviously preferable. However, since the “infinite TON” limit is under discussion, requirements 7 and 8 asymptotically approach being negligible (zero). In real-life process chemistry, they are not. Requirement 9 would imply a “living” catalyst that directly reacts with substrates. Gladysz clearly noted that these unattainable limits can never be realized, but they help focus attention on what we should strive for.

Finding a subtle balance between the stability of the catalyst (and its insensitivity to impurities), and its high activity has been called one of the “Holy Grails” of catalysis. This is especially visible in the field of olefin metathesis—a fairly old reaction that has long remained a laboratory curiosity without significance for advanced organic chemistry (Fig. 1) [4]. New molybdenum (**3**) and ruthenium (**1**) catalysts [2] (Fig. 1), which for the first time combined high catalytic activity with fairly good stability, however, have revolutionized the field [5,6]. As a result, recent decades have seen a burgeoning of interest in olefin metathesis, as witnessed by a rapidly growing number of elegant applications [7]. Using this tool, chemists can now efficiently synthesize an impressive range of molecules that only a decade ago required significantly longer and tedious routes (Fig. 1). The development of efficient and selective ruthenium catalysts **1a–c** has especially been the key to the widespread application of olefin metathesis in organic synthesis [2].

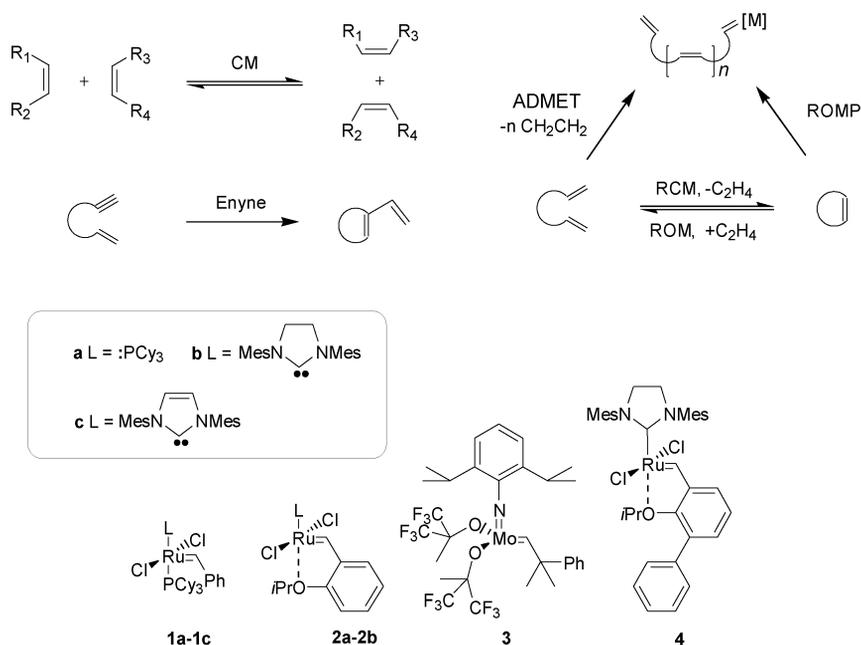


Fig. 1 Olefin metathesis: RCM = ring-closing metathesis; ROM = ring-opening metathesis; ADMET = acyclic diene metathesis polymerization; ROMP = ring-opening metathesis polymerization; CM = cross metathesis. Modern catalysts for olefin metathesis. *i*Pr = isopropyl; Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl.

metathesis (CM), and enyne metathesis reactions (Fig. 1) [13]. Interestingly, 4-nitro isomer **5** also exhibits high activity in model metathesis reactions [14a]. These complexes can be prepared in a few steps from commercially available reagents (Fig. 2).

Catalyst **6** was also tested in a number of CM reactions with challenging partners [14], such as vinyl sulfones [14a], vinyl phosphine oxides [14b] (including a homo-metathesis variant [14c]), and vinyl azulenes [14d], leading to valuable building blocks (Fig. 3). Also, CM reaction between olefinic partners and *E*- or *Z*-1,2-dichloroethene used as a solvent is possible using **6** (Fig. 3) [15]. Functionalized vinyl chlorides are useful substrates in Pd-catalyzed C–C couplings and other transformations.

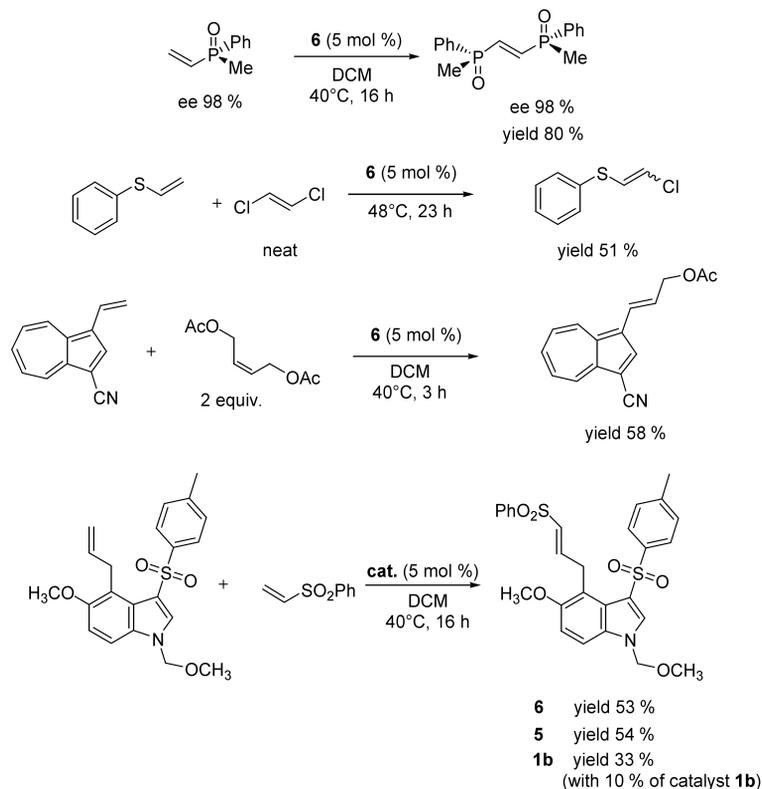


Fig. 3 CM with some challenging substrates using catalysts **5** and **6**.

Also, 4-nitro isomer **5** (see Fig. 2) was found to exhibit high activity in certain metathesis reactions [13a]. Schmidt observed that using this complex allowed complete conversion of the triene **7** into its metathesis products **8** and **9** even at $-30\text{ }^{\circ}\text{C}$ (Fig. 5) [16]. This observation is indicative of the extraordinarily high activity of nitro-substituted catalysts [17]. It is noteworthy that neither air stability nor thermodynamic stability of **5** and **6** are reduced as compared with those of the parent complex **2b** [12,13].

As a result, this stable and easily accessible catalyst has found a number of successful applications in various research and industrial laboratories (Fig. 4) [18]. For example, nitro-catalyst **6** has been applied by Honda (Tokyo, Japan) as a key step in total syntheses of cytotoxic alkaloids (–)-securinine, (+)-viroallosecurinine, and (+)-*N*-Boc-norpandamarilactonine A [18a,b,i] and by Kalesse (Hannover, Germany) en route to antitumor hexacyclinic acid and (–)-FR182877 [18c]. Frelek (Warszawa, Poland) applied **6** in preparation of some cepham analogs [19]. Another impressive CM application of **6** was

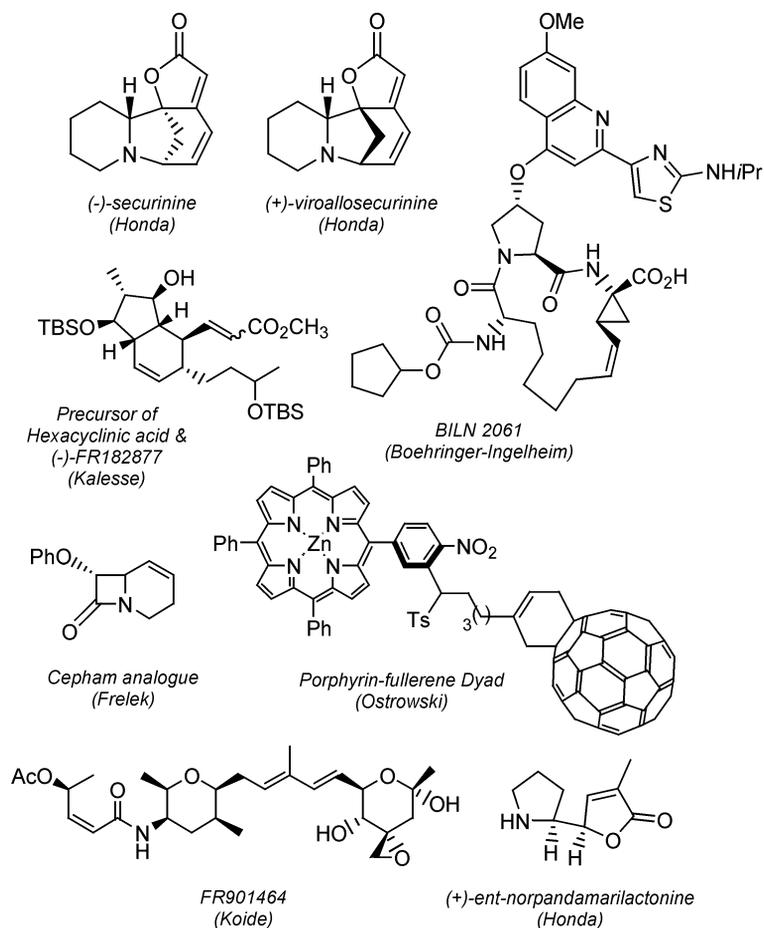


Fig. 4 Selected products prepared with **6**. Ts = 4-CH₃C₆H₄SO₂; TBS = *tert*-butyl(dimethyl)silyl; Ac = CH₃CO.

published by Koide et al. (Pittsburgh, USA) in total synthesis of *(+)*-FR901464, an antitumor agent that regulates the transcription of oncogenes and tumor suppressor genes (Fig. 4) [18d,e]. The final connection of two fragments of this antitumor agent via diene-ene CM was especially challenging. The fragile nature of alkene fragment B (thermal decomposition at +47 °C) precluded more forcing reaction conditions. Gratifyingly, despite the absence of *any protecting groups* [20], application of the highly active catalyst **6** at room temperature furnished FR901464 in 40 % yield (51 % based on recovered diene) [18d]. Similarly, in a synthesis of some viridifungin derivatives, Barrett (Imperial College, UK) found the nitro-catalyst being the most effective [18h]. Ostrowski (Siedlce, Poland) applied **6** in preparation of some porphyrin building blocks, including a porphyrin-fullerene dyad, being a new artificial photosynthetic model (Fig. 4) [18f,g]. An interesting application of the nitro-catalyst **6** has been recently published by Boehringer Ingelheim Ltd. in synthesis of BILN 2061 (Ciluprevir™), the first reported hepatitis C virus (HCV) NS3 protease inhibitor to have shown an antiviral effect in infected humans [21,22]. The HCV infection is a serious cause of chronic liver disease worldwide. The macrocyclic peptide, BILN 2061 (Fig. 4), is the first compound of its class to have reached clinical trials [22]. The key step in the preparation of BILN 2061 is the RCM formation of a 15-membered ring. Among several ruthenium catalysts used in this reaction, 5-nitro-substituted proved to be the most active one [22]. Loadings as low as 0.5 mol % of **6** give good results in the cyclization of the macrocyclic ring of BILN 2061, making this step highly effective in larger-scale preparations [22b,c]. A potentially very promising con-

dition for RCM with nitro-catalyst **6** has been recently disclosed by the same company [23]. Ionic liquids (ILs) were used as an immobilizing matrix for catalyst **6**, and the metathesis reaction was conducted in supercritical carbon dioxide. This technology can now be operated under continuous-flow conditions and used for the macrocyclization of BILN 2061 [23].

Both of the nitro complexes, according to Gladysz's concept, can be considered as a step toward the preparation of a "ideal catalyst". They effect a rapid reaction (TOF even at $-30\text{ }^{\circ}\text{C}$!), are prepared from commercially available substrates and exhibit excellent stability to air and moisture and thermal stability up to $110\text{ }^{\circ}\text{C}$. One of the observed drawbacks is that catalysts **5** and **6** may be deactivated under the reaction conditions (they are only partially recyclable after the reaction), breaking the first requirement of a TON of infinity.

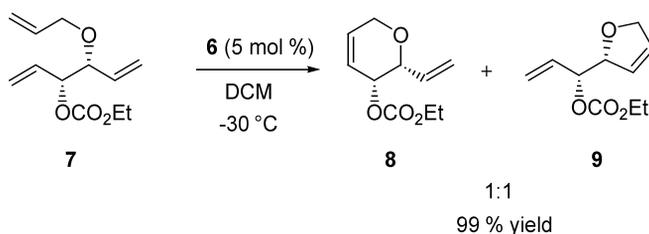
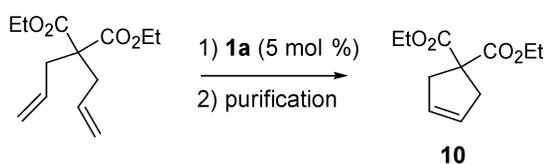


Fig. 5 Conversion of the triene **7** into its metathesis products **8** and **9**.

In our quest for "ideal catalysts", we followed Gladysz's statement that "In the 'infinite TON' limit, recoverability is no longer an issue. Nonetheless, everyone would agree that an 'ideal catalyst' that is recoverable in single-molecule form is preferable to one that is eventually lost in a product stream. Thus, recoverable catalysts are a very important field for research. An 'ideal recoverable catalyst' is one that can be recovered quantitatively (e.g., every molecule for a homogeneous species), either as the catalyst precursor or a functionally equivalent rest state. The other attributes of the ideal catalyst remain—particularly the high TON and TOF values" [1]. We decided to focus our efforts on designing a new catalyst that would not only be highly active but also recoverable.

Despite general superiority offered by modern homogeneous Grubbs and Hoveyda–Grubbs catalysts **1–2**, they share some disadvantages. The most undesirable feature of these complexes is the formation of ruthenium by-products which are difficult to remove from the reaction products, presenting a problem when the olefin metathesis reaction is used in pharmaceutical processes [11,24]. In many cases, ruthenium levels of >2000 ppm remain after chromatography of products prepared by RCM with 5 mol % of Grubbs catalysts (see Fig. 6) [25]. Several protocols to remove toxic ruthenium impurities have been proposed [25]. The use of biphasic extraction, various scavengers, such as lead tetraacetate, dimethylsulfoxide (DMSO), or phosphine additives (including supported phosphines) were reported to reduce the ruthenium content between 200–1200 ppm [24]. Alternatively, two cycles of chromatography, followed by 12 h incubation with activated charcoal, resulted in <100 ppm [25]. Recently, a novel promising method based on supercritical CO_2 extraction was used to remove a ruthenium catalyst and its derived by-products from the crude mixture [23].



| Purification method | Residual Ru in 10 [ppm] |
|---|--------------------------------|
| none | 21600 - 14316 |
| SiO ₂ | 1912 |
| SiO ₂ and activated charcoal | 578 |
| SiO ₂ and activated charcoal, than SiO ₂ | 60 |
| various scavengers | 2000 - 200 |

Fig. 6 Contamination of the RCM product **10** [24].

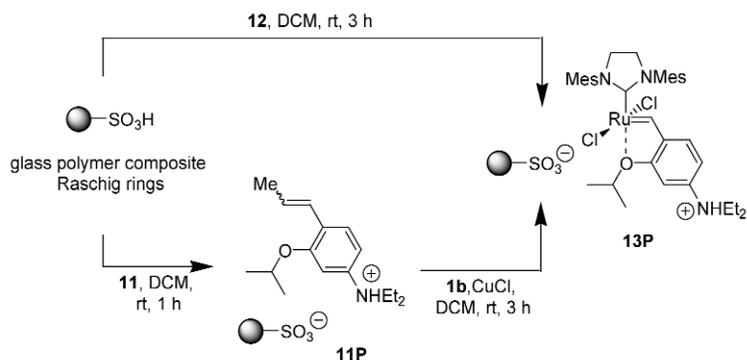
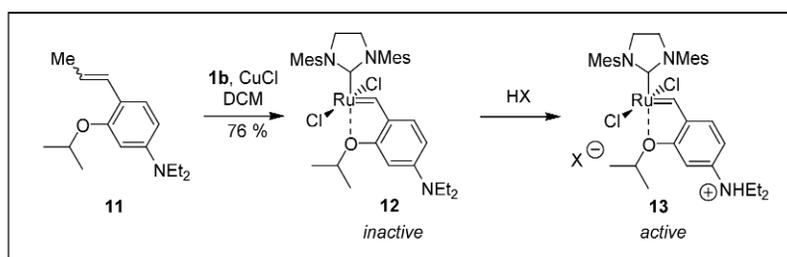
NEW CONCEPTS OF IMMOBILIZATION: NONCOVALENT BINDING OF HOVEYDA–GRUBBS CATALYST TO POLYMERIC PHASES. PREPARATION OF A CATALYST ON RASCHIG RINGS

Several attempts have been made to immobilize Grubbs-type carbenes **1** on solid or soluble supports either via ligand L (Fig. 1) or via the carbene moiety [26]. Recently, various Hoveyda–Grubbs carbenes **2** were attached to different resins or soluble supports preferentially via the 2-alkoxybenzylidene fragment [26].

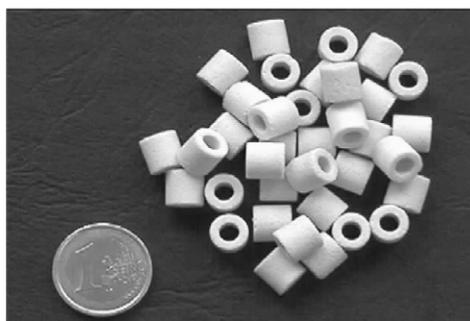
However, for practical reasons, *noncovalent attachment* of catalysts to a solid phase is highly desirable. The possibility of reloading the solid phase opens the door for utilizing solid supports which have been specially designed for the individual catalytic process without considering their costs as much as would be relevant for covalently bound catalysts. Indeed, this concept should be of particular relevance in continuous-flow processes [27] using reactors filled with heterogeneous or immobilized homogeneous catalysts [28]. The attachment ought to be strong enough to suppress leaching of the catalyst. However, after inactivation of the catalyst, it is beneficial if it can be removed and the solid phase can be reactivated with fresh catalyst. Some techniques for the noncovalent attachment of chemical catalysts to solid supports have been developed [29]. Recently, Kirschning's group (Hannover, Germany) has successfully tested this concept in the preparation of a Grubbs-type catalyst *coordinatively bound* to polyvinyl pyridine resin [30].

In accordance with our finding that EWGs activate Hoveyda-type catalysts via weakening the *i*PrO–Ru chelation, we observed that complex **12**, bearing the electron-donating (EDG) diethylamino group [31], shows no or very little activity in olefin metathesis of model substrates. However, in a striking contrast, the in situ formed salts obtained by treatment of aniline **12** with Brønsted acids are of high activity, surpassing the parent Hoveyda–Grubbs complex **2b** in terms of initiation speed (*electron-donating to -withdrawing activity switch*, Fig. 7a) [32]. We envisaged that after reaction with polymer-supported acids, the new cationic ruthenium complex can be conveniently immobilized by ion exchange to form **13P** (Fig. 7a). In this novel strategy for ruthenium-based metathesis catalysts immobilization, the amino group plays a dual role, being first an active anchor for immobilization and secondly, after protonation, activating the catalysts [33].

Using the above-described strategy of noncovalent immobilization, we prepared, in cooperation with Kirschning's group, catalyst **13P** immobilized on glass polymer composite Raschig rings (Fig. 7b), which can be used for combinatorial chemistry and high-throughput screening [33]. Recyclability studies showed that the same ring-containing catalyst **13P** can be used for up to six cycles of metathesis,



a)



b)

Fig. 7 (a) Two approaches for the preparation of catalyst **13P**. The principle of catalyst **12** activation. (b) Megaporous glass Raschig rings used for immobilization of **12**.

however, with gradual loss of activity. Importantly, the solid phase can easily be reactivated by a washing protocol (1 N HCl, H₂O, methanol then addition of fresh **12**). The contamination level of products with ruthenium was around 100 ppm. This is significantly lower than the ruthenium contamination reported for Hoveyda's catalyst on sol-gel pellets [34]. Polymer bound catalyst **13P** is highly active in CM reactions, as exemplified by the preparation of a steroidal precursor to the inhibitor of 17 β -hydroxysteroid dehydrogenase type 1, useful in treatment of estradiol-dependent diseases such as breast cancer or endometriosis [35].

The practicability of Raschig rings loaded with the Ru-complex **13P** (3 μ mol Ru/ring; 5 mol %) in high-throughput synthesis was demonstrated [33,36]. Ring-closing and enyne metathesis of representative substrates proceeds cleanly, with typically high conversion leading to various carbo- and heterocycles (Fig. 8). At the end of the reaction, the catalyst **13P** can be simply removed with a pair of tweezers and rinsed with minimal amounts of dichloromethane, producing minimal solvent waste [33]. Although, as shown above, this catalyst possesses good application profile, it does not fulfill all the re-

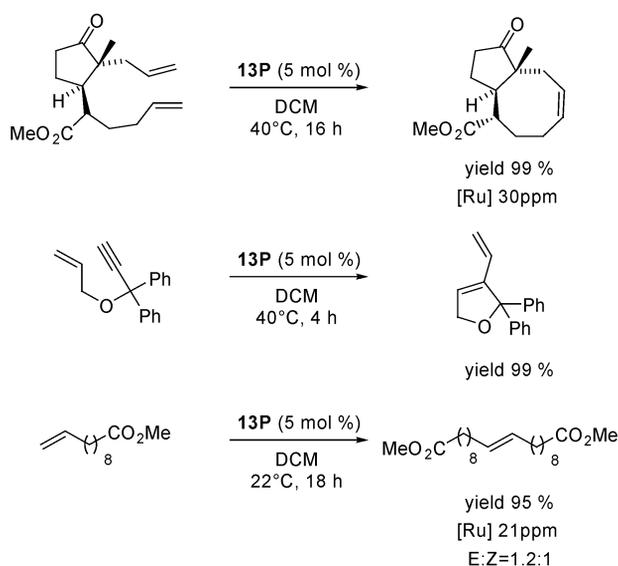


Fig. 8 Selected examples of metathesis reaction with catalyst **13P** bound to Raschig rings. One Raschig ring **13P** per reaction was used (5 mol % Ru).

quirements of Gladysz's definition of an "ideal catalyst". It has rather low TOF and TON (loadings of 5 mol % of Ru were typically used), and does not yet possess perfect recyclability, which can be clearly seen by its gradual loss of activity.

SYNTHESIS OF A HOVEYDA–GRUBBS CATALYST BEARING A QUATERNARY AMMONIUM GROUP: APPLICATION IN AQUEOUS METATHESIS

Exploring further our concept of activating a catalyst via electron-donating to -withdrawing activity switch, we have obtained complex **14** bearing a quaternary ammonium group (Fig. 9) [31,36]. This catalyst exhibits higher activity than the parent Hoveyda complex **2b** and has a high affinity for silica, enabling its efficient removal in a single chromatographic pass [31,36].

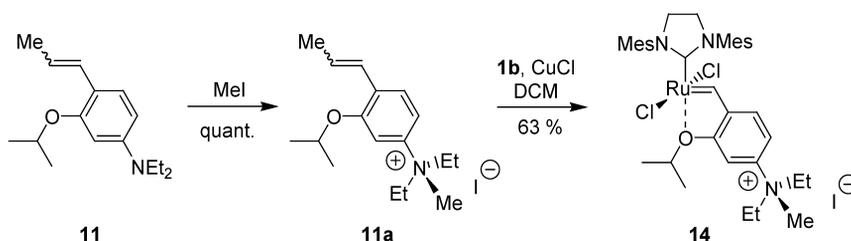


Fig. 9 Synthesis of complex **14** bearing a quaternary ammonium group.

Thus, RCM of various dienes using **14** (Fig. 10), followed by passing the reaction mixture through a short column of silica, affords products in which the residual Ru content is typically below 100 ppm.

Due to environmental problems associated with the use of large volumes of organic solvents, there is much interest in the use of water as a more safe, benign, and cheap solvent. The aqueous olefin metathesis [37] is critical for some biological applications. Interestingly, we found that iodide **14** is sol-

uble in water at low concentrations (<0.002 M) and can promote with excellent yields even such a challenging transformation as CM (e.g., reaction of homoallylic alcohol shown in Fig. 10) [36b]. Complex **14** can, therefore, find applications as a universal catalyst for metathesis reactions not only in neat water, but also in protic organic solvents (such as alcohols) as well as in traditional nonpolar solvents. Moreover, its facile removal from organic products can be expected to offer new opportunities in green applications of olefin metathesis [36a].

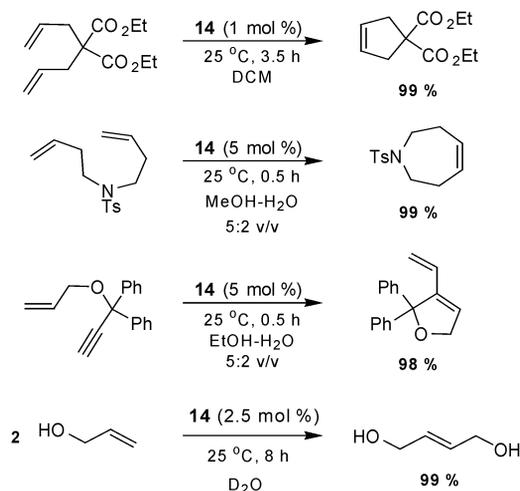


Fig. 10 Applications of **14** in selected RCM reactions. Conversions were determined by analysis of ¹H NMR or GC/MS of crude reaction mixture.

SUMMARY AND OUTLOOK

Olefin metathesis still stimulates researchers because of its ease of use and versatility and the reduction in synthetic steps required to achieve complex target molecules. Continuous investigation over the past decades has led to the development of highly active olefin metathesis catalysts for sophisticated synthetic tasks and for polymer production. We have systematically searched for improved ruthenium complexes, which could enable us to create an “ideal catalyst” as proposed by Gladysz. Isopropoxy benzylidene derivatives **2**, pioneered by Hoveyda, exhibit high activity and possess excellent functional group tolerance. Catalyst **2b** has been successfully fine-tuned in order to increase its activity and applicability by the introduction of EWGs to diminish the donor properties of the oxygen atom. As a result, the stable and easily accessible nitro-substituted catalysts **5** and **6** have found a number of successful applications in various research and industrial laboratories. The results described herein demonstrate that the activity of ruthenium metathesis catalysts can be enhanced by introduction of EWGs without detriment to catalyst stability. This principle can be used not only to increase the catalyst activity, but also to alter its physicochemical properties, such as solubility in a given medium or affinity to silica gel. An example of novel immobilization strategy, based on this concept, is presented. In fact, the possibility of reversibly binding catalysts to a solid phase is of major importance for industrial applications, particularly when continuous-flow processes with immobilized homogeneous catalysts are pursued. A bright future is undeniable for cleaner, greener, more sustainable olefin metathesis reactions, due to the vital importance of the method (and of catalysis in general) and of the ever-growing need for environmentally friendly catalytic processes.

ACKNOWLEDGMENTS

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