Green Metathesis Reactions

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Sustainable Concepts in Olefin Metathesis

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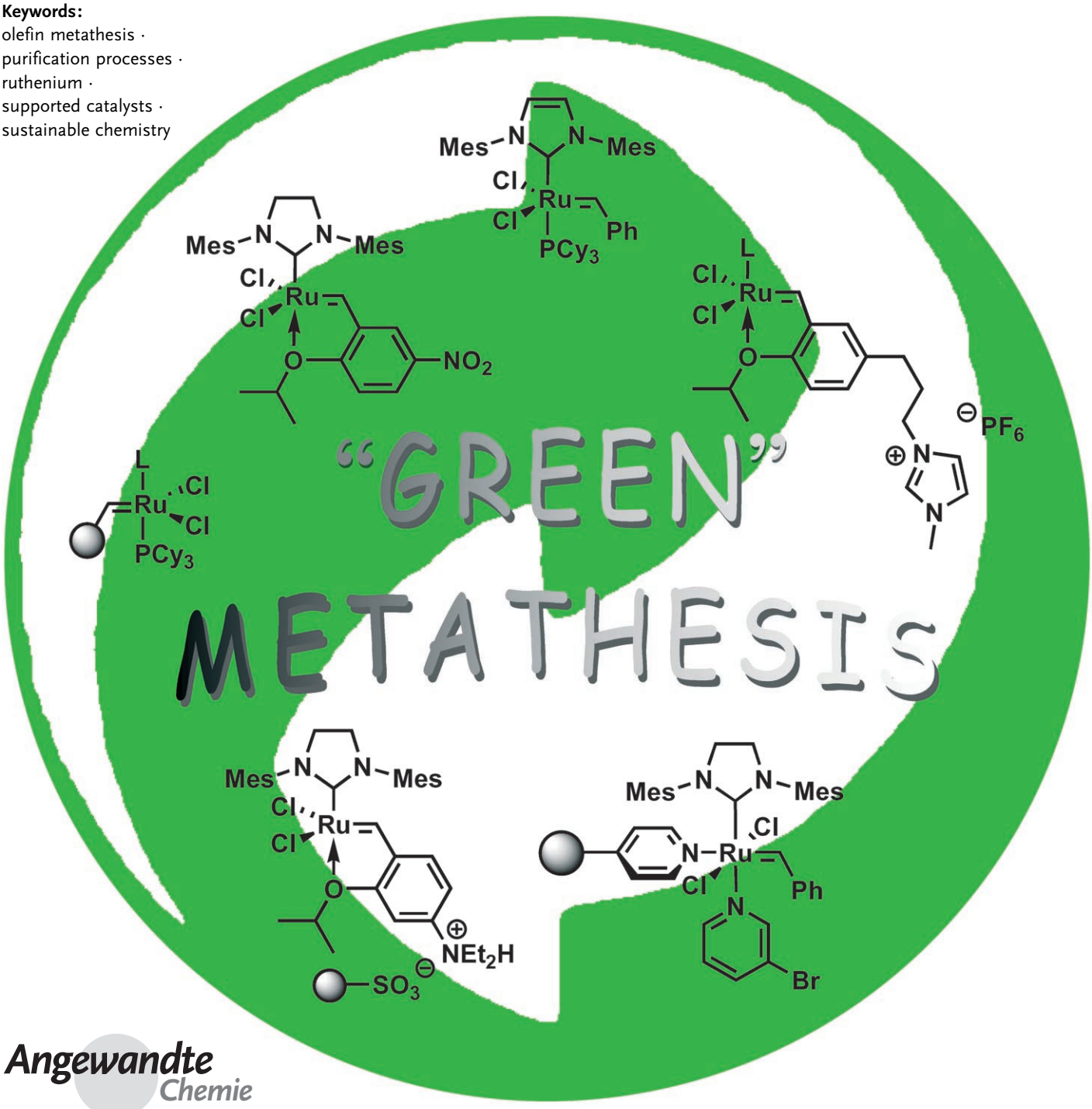

Ruthenium-catalyzed olefin metathesis reactions represent an attractive and powerful transformation for the formation of new carbon–carbon double bonds. This area is now quite familiar to most chemists as numerous catalysts are available that enable a plethora of olefin metathesis reactions. Nevertheless, with the exception of uses in polymerization reactions, only a limited number of industrial processes use olefin metathesis. This is mainly due to difficulties associated with removing ruthenium from the final products. In this context, a number of studies have been carried out to develop procedures for the removal of the catalyst or the products of catalyst decomposition, however, none are universally attractive so far. This situation has resulted in tremendous activity in the area dealing with supported or tagged versions of homogeneous catalysts. This Review summarizes the numerous studies focused on developing cleaner ruthenium-catalyzed metathesis processes.

From the Contents

1. Introduction

"What is an ideal catalyst?"—This was the key question asked by Gladysz at the beginning of this decade.[1] He proposed the following features for such an ideal catalyst: the rapid production (turnover frequency, TOF) of an infinite amount of product (turnover number, TON) preferentially at room temperature and under atmospheric pressure which implies no deactivation and poisoning under the reaction conditions. This "ideal" catalyst does not require an inert atmosphere to operate, is insensitive to reactant impurities, and affords product yields of 100%. Gladysz clearly noted that these unattainable limits can never be realized but help to focus attention on what we should strive for. The "infinite TON" limit, for example, would make catalyst recovery efforts unnecessary, a quest which is unrealistic. The design of recoverable catalysts has become a central field of catalysis research,[2] with an ideal recoverable catalyst having the following additional requirement to those listed above: it can be recovered either as the catalyst precursor or as a functionally equivalent resting state.[1] In fact, catalyst decomposition associated with leaching of the active species and decomposition itself have to be taken into account. In practice, design efforts for effective recoverable catalysts must address the removal of these catalyst impurities from solution.

Although chromatographic purification protocols have been optimized for decreasing the Ru content in the product to an almost acceptable level, the utilization of tagged reagents[3] and catalysts[4,5] is a far superior strategy. Indeed, it has seen a dramatic increase in interest. Some of the examples of this tagging approach in metathesis are illustrated in Figure 1. Different tags can be imagined, the most prominent one being a solid phase based on inorganic materials or alternatively on polymers. Polymers of choice can be either insoluble in the reaction medium, an approach that resembles the concept of heterogenization of homogeneous catalysts, or soluble therein (e.g. polyethylene glycol (PEG)), in which case they are often removed by precipitation when a second solvent is added. Other catalyst tags include ionic groups, such as ionic liquid derived groups, and perfluorinated groups. These strategies make use of the high affinity of these tags to alternative reaction media such as ionic liquids (ILs) or perfluorinated solvents that can be poorly miscible with the organic phase. The use of supported catalysts appears to be the easiest method to avoid contamination of product **C** with metal-containing catalysts (Figure 1, left). Nevertheless, if **C** (or if a by-product **D**) is formed or if one of the starting materials was employed in

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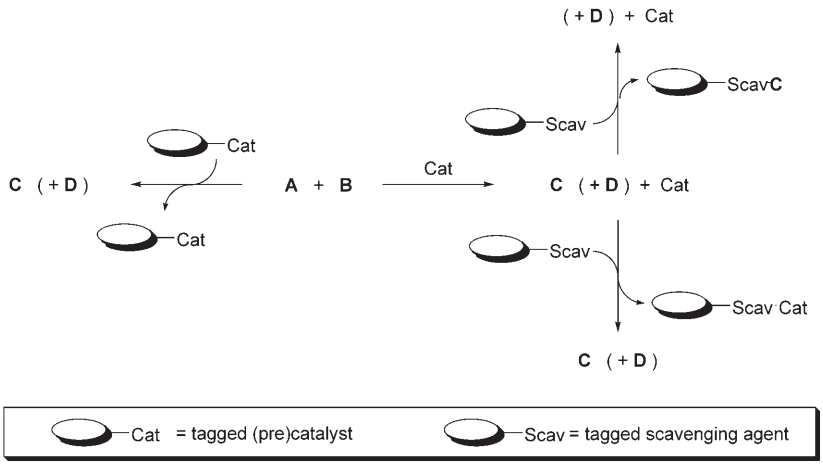

Figure 1. Concepts of purification strategies in catalysis.

excess, then the product could be isolated by using a tagged scavenging reagent for the purpose of purification (Figure 1, right).[6] Alternatively, impurities or degradation products resulting from the catalyst can also be removed by a specifically developed tagged scavenger reagent.

In this Review, we focus on strategies that have been employed to ease the recovery and reuse of Ru-based metathesis catalysts, as summarized in Figure 1.[5,6] Although the homogeneous versions of these catalysts do not fulfill the requirement of high TONs and TOFs yet, they have become very valuable catalytic tools and olefin metathesis has now become one of the most widely used methods for C–C bond formation.[7,8] Ruthenium catalysts such as those developed by Grubbs (**1**,[9] **2**,[10] and **4**[11]; Cy = cyclohexyl), Nolan (**3**[12]), Hoveyda (**5**[13] and **6**[14]; Mes = 2,4,6-trimethylphenyl), Blechert (**7**[15]), and Grela (**8**[16]) have revolutionized olefin metathesis, making it a key reaction in organic synthesis.

Unfortunately, metathesis transformations require usually large amounts of catalyst: for example, many metathesis steps in total synthesis use 20 mol% ruthenium.[8] For this reason, the development of greener metathesis processes is of great importance. In the context of facile purification protocols for metathesis catalysts, the solid-phase approach for generating recoverable Ru complexes has been employed most widely (Figure 2 A). Typically, a "covalent" attachment between the solid phase and either the ligand or the metathesis-active carbene moiety has been employed. However, for practical reasons, covalent heterogenization of homogeneous catalysts is not always beneficial as reloading of the solid phase is very difficult to achieve once the catalyst has lost its activity. In that respect, direct coordination between the solid phase and ruthenium is one way of overcoming these drawbacks. Here, the monomer already contains a group such as vinyl pyridine that can

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Andreas Kirschning completed his PhD with Prof. E. Schaumann at the University of Hamburg in 1989. Following a postdoctoral stay at the University of Washington with Prof. H. G. Floss, he joined the Clausthal University of Technology in 1991 and completed his habilitation in 1996. In 2000, he joined the University of Hannover and was soon appointed Director of the Institute of Organic Chemistry. His research interests cover natural product synthesis, glycochemistry, and synthetic technology (solid-phase-assisted synthesis, microreactors).

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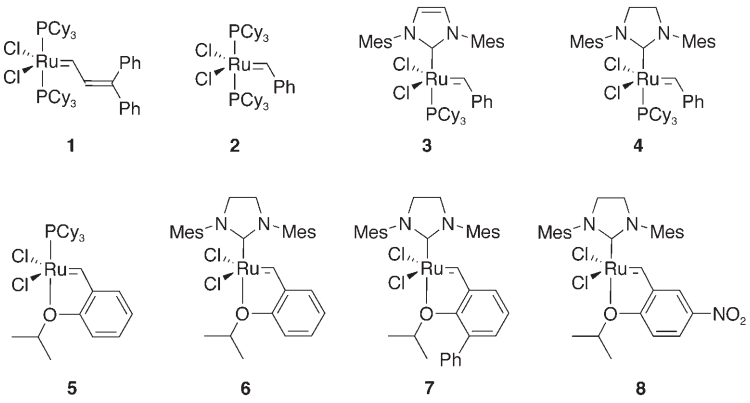


coordinate to the metal. After polymerization, a solid phase is obtained which can act as a "sea of ligands".

Nevertheless, a more general approach uses tags. The specific interactions between the tag and the other phase either allow for easy removal of the catalyst during workup (scavenging) or represent an immobilization strategy. Principal sites of tagging ruthenium complexes are summarized in structures **E** and **F** (Figure 2B). These include anionic or coordinatively bound ligands (phosphines, N-heterocyclic carbenes (NHCs), or pyridine), or carbene ligands (either in the aromatic moiety or at the alkoxy ligand).

For practical reasons, tagging of ruthenium catalysts to enhance binding to a solid phase is highly desirable. Beneficially, easy reloading of the solid phase allows for the use of solid supports that have been specially designed for the individual catalytic process without considering their costs as much as would be relevant for covalently bound catalysts. When these immobilization concepts are employed, the attachment should be strong enough to suppress leaching of the catalyst. At the same time, purification is then facilitated, for example, by filtration. After deactivation of the catalyst, the metal-containing species can be removed and the solid phase can be reactivated with fresh catalyst by simple washing protocols. In fact, this strategy can become of particular relevance to industrial applications where fixed-bed continuous-flow processes are often preferred.

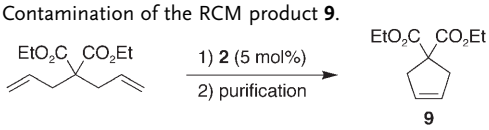
Still, it should not be forgotten that scavenger or sequestering reagents attached to solid supports which are functionalized with donor atoms (N, P, or S) have been widely employed for removing metals from homogeneous reaction mixtures (Figure 1). This approach commonly relies on the removal of the metal complexes by coordination.

This Review is intended to provide a comprehensive and critical overview on strategies that allow simple use and workup of olefin metathesis catalysts. After an overview of concepts of purification for classical solution-phase metathesis reactions, we will discuss Ru catalysts which have been specifically modified to ease purification by sequestering techniques or by immobilization to a second liquid or solid phase.

2. Problems Caused by Ruthenium Contamination in Natural or Complex Product Synthesis

The most undesirable feature of modern homogeneous metathesis catalysts is that they often form deeply colored ruthenium-[17] or molybdenum-containing[18] by-products, which are difficult to remove from the reaction products. For example, when diethyl diallylmalonate is subjected to ring-closing metathesis (RCM) using 5 mol% **2** (Table 1), the

Table 1: Contamination of the RCM product **9**.



Purification method	Residual Ru in **9** [ppm]	Ref.
none	21600–14316	[17,19]
SiO_2	1912	[19]
SiO_2 and activated charcoal	578	[19]
SiO_2 and activated charcoal, then SiO_2	60	[19]
various scavengers	2000–200	[17,24,25,34–36]

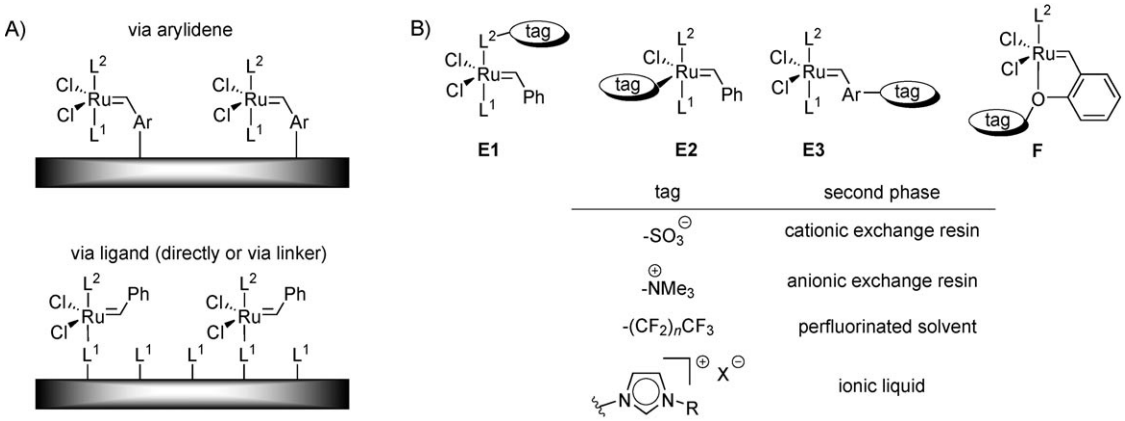
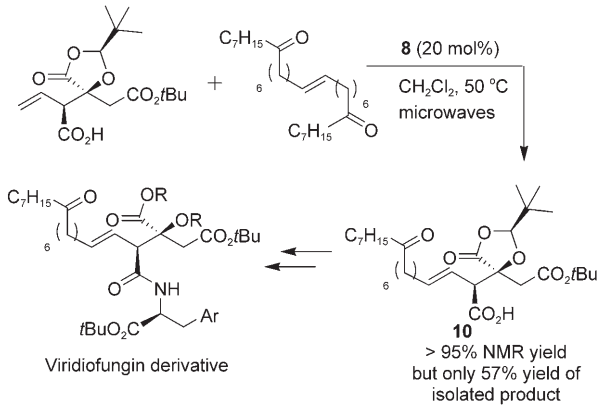


Figure 2. Purification strategies in catalysis.

resulting cyclopentene **9**[19] is found to contain 14316 ppm of Ru as measured by using inductively coupled plasma mass spectrometry (ICP-MS). Purification of such crude metathesis product using standard silica gel column chromatography reduces ruthenium levels to 1900 ppm, which is much higher than the acceptable levels for any pharmaceutical use (<10 ppm).[20]

Removal of heavy-metal impurities is a critically important task in pharmaceutical and fine chemical production, where final products must meet stringent purity requirements. In addition to the regulatory issues of metal contamination in the context of pharmaceutical synthesis, the presence of metal complexes after an olefin metathesis step can promote side reactions (often undesired) such as product isomerization,[17] or degradation[21] during workup. Therefore, the development of an efficient, economical, and practical method to remove the metal by-products is crucial for further proliferation of the metathesis methodology in industry.

A good example of the challenges related to catalyst removal after a successful metathesis step is illustrated by the total synthesis of antibiotic viridiofungin derivatives (Scheme 1), recently reported by Barrett and co-workers.[22]



Scheme 1. Preparation of viridiofungin derivatives via cross-metathesis.

The authors stated the following: "*In particular we focused on the use of the Grubbs II catalyst **4**, the Hoveyda catalyst **6**, the Blechert catalyst **7** and the Grela catalyst **8**. In our hands, neither catalyst **4** nor **6** was especially effective with slow and incomplete conversions. Both catalysts **7** and **8** were superior, with the Grela catalyst **8** the most effective. Although conversion by ^{1}H NMR was high (> 95 %), extensive chromatography was required to remove ruthenium residues from the polar acid **10**, which was isolated in 57 % yield.*" This example clearly illustrates that the reactivity problem may not be solved by higher catalyst activity alone, and that efficient ruthenium removal is equally important for the successful use of such technology in total synthesis.

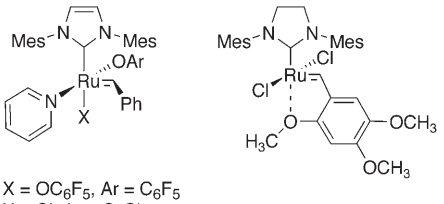
3. Procedures to Remove Homogeneous Catalysts

Several protocols have been proposed to solve the problems associated with Ru contamination that arise during pharmaceutical or fine chemical processing. Cho and Kim described a multistep method incorporating double purification on silica gel and treatment with activated carbon.[19] It was found that the initial Ru level in crude product **9** (14316 ppm, Scheme 1) was decreased to 1912 ppm after a single column chromatography on silica gel. Alternatively, the treatment of crude **9** with 100 equivalents of activated carbon for 12 h led to a reduction in the ruthenium content to 578 ppm. When the activated carbon treatment was followed by silica gel column chromatography, the ruthenium level decreased to 304 ppm. Finally, the optimized purification protocol, in which the crude product **9** adsorbed on silica gel was passed through a silica gel pad and the filtrate was treated with 50 or 100 equivalents of activated carbon for 12 h at room temperature and further purified via silica gel column chromatography, gave residual ruthenium levels of 72 and 60 ppm, respectively. This result shows that column chromatography is an effective method for ruthenium removal only if combined with pretreatment with activated carbon. Dixneuf and co-workers used carbon black to clean up the ionic liquid for the purpose of recycling it after a RCM reaction.[23] Optimized conditions allowed for the reduction of the ruthenium levels to approximately 200–400 ppm.

By using other scavengers, such as $Ph_3P{=}O$ or dimethyl sulfoxide (DMSO), and subsequently employing column chromatography, the Ru levels in **9** can be reduced to 240 and 360 ppm, respectively.[24] Similar levels of Ru were obtained by Paquette using lead tetraacetate as a scavenger.[25] The high oxidizing power and considerable toxicity of this reagent impose serious limitations to the use of the method.[26]

One of the unique properties of the Hoveyda–Grubbs complexes **5** and **6** is that up to 95 % of the catalyst can be recovered after the reaction by simple silica gel column chromatography. This is attributed to their "boomerang-like" mechanism of action:[27] Cleavage of the Ru→O bond leads to the formation of the metathesis catalytically active 14-electron species, and after the reaction is complete the Ru center again coordinates the same oxygen-containing moiety, thereby regenerating the precatalyst. This behavior could not be observed for complexes **1**–**3**. Unfortunately, the recyclability of more active analogues such as **8** and other electron-withdrawing group (EWG) activated catalysts[28] is handicapped as compared with that of **6**, and typically these catalysts can be recovered after metathesis reaction only with moderate efficiency (0–50 % of the catalyst used). Despite the theoretical possibility, the recovery of catalysts **5** and **6** has been rarely reported, most probably because of significant practical difficulties associated with separating relatively small amounts of Ru catalyst from the metathesis product by column chromatography.

Some efforts have been made to develop new homogeneous ruthenium alkylidenes that display stronger affinity to silica gel than commercially available complexes **1**–**8**. The aryloxide catalysts **11**–**13** developed by Fogg and co-workers have shown a high affinity for silica, thus enabling their efficient removal in a single chromatographic step.[29] Thus, RCM of diallyl diethyl malonate using 5 mol % **11**–**13** followed by flash chromatography affords **9** with a residual



11, X = OC_6F_5, Ar = C_6F_5
12, X = Cl, Ar = C_6Cl_5
13, X = Cl, Ar = C_6Br_5

14

Ru content that lies below the 100 ppm detection limit of inductively coupled plasma atomic emission spectroscopy (ICP-AES).[29]

Catalyst **14**, introduced by Grela and Kim,[30] exhibits catalytic activity comparable to the parent **6** but shows much higher affinity for silica gel (when dichloromethane is used as eluent), which enables its efficient removal.[31] Recently, a new efficient strategy for phase-separation and recovery of **14** was developed leading to crude products that contain approximately 400 ppm of ruthenium (Figure 3).

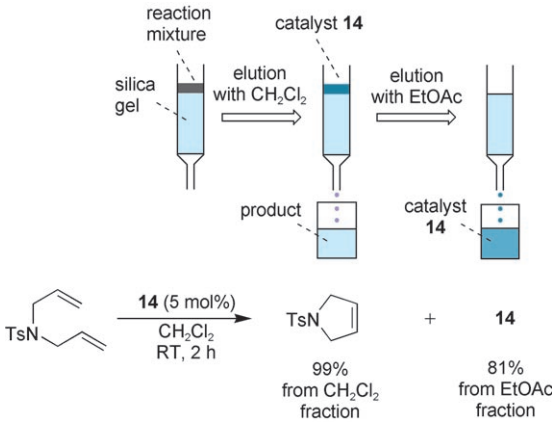
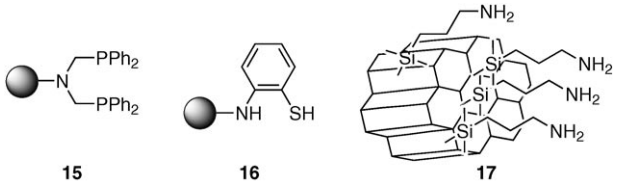


Figure 3. Phase separation and recovery of catalyst **14** using silica gel.

Although valuable, these methods do have drawbacks. Most importantly, silica gel chromatography is required in most cases to bring the ruthenium content below the 100 ppm level. In general, protocols that include silica gel column chromatography or even filtration through silica gel are relatively difficult and expensive to implement on an industrial scale. Crystallization and extraction are the preferred industrial-scale techniques for removing metal impurities, but these approaches have not always been effective.[32] The very low acceptable level of Ru in the final drug substance (<10 ppm) has made the development of an efficient yet economical and practical method critical.

Use of complex **2** with the water-soluble ligand tris(hydroxymethyl)phosphine ($P(CH_2OH)_3$) was reported by Maynard and Grubbs.[17] Simple biphasic aqueous extraction with 86–378 equivalents of $P(CH_2OH)_3$ allowed a more than 10-fold decrease in the amount of remaining ruthenium in crude **9** (to 1100 ppm). Stirring a solution of crude **9** and $P(CH_2OH)_3$ with silica gel followed by filtration gave even better results,[17] and the amount of residual Ru in the sample was reduced to 200 ppm.[33] Supported phosphine **15** was reported to reduce the ruthenium content in crude **9** from



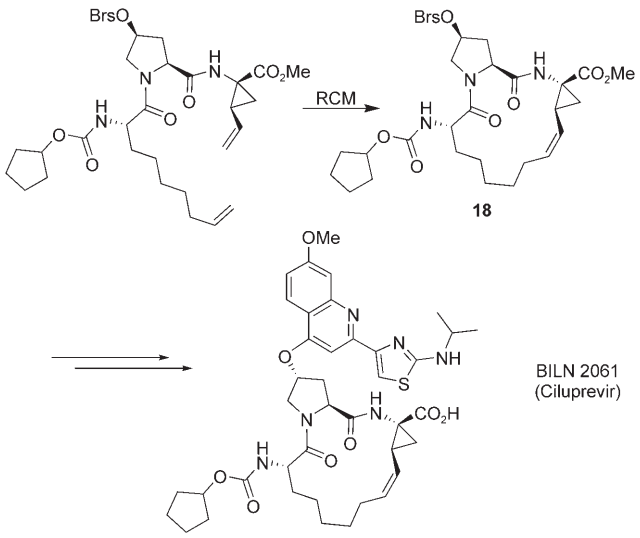
15 **16** **17**

21 600 to 2400 ppm.[34] Additional silica gel filtration or treatment with charcoal and filtration through silica gel allowed the level of Ru to be reduced further to 1660 and 1120 ppm, respectively. Recently, special functional polymers—QuadraPure resins—were developed for the removal of heavy metals (including Ru; resin **16**) in both batch and continuous processes.[35] Amine-functionalized mesoporous silicates have been used for similar purposes.[36] Scavenging of Ru after a RCM reaction catalyzed by 5 mol% of Grubbs catalyst (Figure 3) gave a product with metal concentrations of less than 2000 ppm after two treatments with amine-modified silica **17**. Most importantly, no additional chromatography step is required after treatment with scavengers **16** and **17**.[36]

3.1. Case Study: The Hepatitis C Antiviral Agent BILN 2061

An interesting application of the olefin metathesis methodology has been recently published by Boehringer Ingelheim in the synthesis of BILN 2061 (Ciluprevir), the first reported hepatitis C virus (HCV) NS3 protease inhibitor to have shown an antiviral effect in infected humans.[37] The HCV infection is a serious cause of chronic liver disease worldwide. The macrocyclic peptide, BILN 2061, is the first compound of its class to have reached clinical trials. It has shown oral bioavailability and antiviral effects in humans infected with HCV. The key step in the preparation of BILN 2061 is the RCM formation of the 15-membered macrocycle **18** (Scheme 2).[21,38]

This very challenging transformation perfectly illustrates three major problems associated with the application of metathesis methodology: 1) high catalyst loading; 2) long time needed to reach reaction completion; and 3) difficulties with catalyst removal and side reactions caused by ruthenium traces. The first two issues can be possibly overcome by using more active catalysts. While complex **2** leads to unwanted ruthenium-carbene-catalyzed epimerization of the vinylcyclopropane moiety,[39] complex **5** reacts slowly but cleanly.[21] Unfortunately, the RCM with 4–5 mol% of **5** required 20 h at reflux in CH_2Cl_2, which is an impractically long time in a manufacturing setting. The use of 2–4 mol% of **5** in toluene at 80 °C allowed the reaction to be completed within 3–4 h. In an effort to overcome the low reactivity and low TON associated with **5**, the more active second-generation catalysts **4** and **6** (2 mol%) were tested. Unfortunately, they proved to form considerable amounts of cyclic dimers in addition to the main



Scheme 2. Preparation of brosylate **18** by RCM reaction in the synthesis of BILN 2061 (Brs = *p*-$BrC_6H_4SO_2$).

product **18**.[21] Therefore, new catalysts such as **8** were investigated with the aim to shorten the reaction times and reduce catalyst loading.[20,28] Using only 0.7 mol% of **8**, the reaction is complete within 30 min under similar reaction conditions (toluene, 80 °C). It has been reported that loadings as low as 0.5 mol% of **8** lead to formation of **18** in 86% isolated yield.[40]

The large-scale purification of the crude reaction product **18** after the RCM step constitutes a serious technological challenge. Therefore, the focus of the subsequent research was to develop an effective method for purification of the crude reaction mixture and isolation of the product as a storable solid. After several aqueous extractions (water, HCl, $NaHCO_3$) and a treatment of the organic layer with activated carbon, the Ru content in the product **18**, obtained using **5** as catalyst, was between 500 and 1000 ppm.[20b] Use of P-$(CH_2OH)_3$ for aqueous extraction of the crude product has been reported[40] to lower the levels of ruthenium to below 700 ppm in some cases. Silica-based scavengers and various resins were also tested, although with less success.[41] Recently, a novel promising method based on supercritical CO_2 ($scCO_2$) extraction was used to remove a ruthenium catalyst and its derived by-products from the crude mixture.[41] Purification of cycloalkene **18** (up to 56 ppm residual Ru) was possible by taking advantage of its preferential solubility in $scCO_2$/toluene or $scCO_2/CH_2Cl_2$ mixtures, thus leaving the ruthenium by-products deposited in the autoclave. The $scCO_2$ extraction was also evaluated in a semi-continuous mode, leading to purified intermediate **18** containing 708 ppm Ru. Subsequent treatment with activated carbon reduced the ruthenium level to 100 ppm. As the RCM reaction is not the final step in the synthesis of BILN 2061, after subsequent purifications and final crystallization the active pharmaceutical ingredient had typically less than 5 ppm Ru.

Lowering the catalyst loading (as in the case of **8**) can also dramatically reduce the Ru levels. Although the first scale-up experiments were successful,[20] there is still need for improvements. For example, on a smaller scale, the crude reaction mixture after the RCM step could be evaporated safely to a small volume for further workup, whereas on a large scale, evaporation led to extensive decomposition.[21] It is not unlikely that, in some cases, an active form of the Ru catalyst is still present at the end of the reaction leading to ring opening or dimerization of **18** during the solvent evaporation. Extensive screening showed that mercaptonicotinic acid (MNA) is capable of sequestering all catalytically active Ru species, and as a result no decomposition was experienced during the concentration of MNA-treated reaction mixtures in larger scale RCM experiments.[21]

As presented in Section 5, an ultimate solution to the problems associated with removal of ruthenium complexes after the reaction can be the utilization of an immobilized catalyst. A promising noncovalent immobilization technique has been recently developed and used for this process.[42] The ionic liquid butylmethylimidazolium hexafluorophosphate ([BMI]PF_6) was used as an immobilizing matrix for **8** (5–10 mol%), and the RCM of **18** was conducted in $scCO_2$ (70 °C, 400 bar) leading to 98% conversion after 1 h. This technology can be potentially operated under batch and continuous-flow conditions.[42]

As can be seen from the BILN 2061 case, the metathesis reaction is a key step in the final product assembly but much effort is needed to develop an efficient, economical, and practical method to remove an organometallic catalyst and its decomposition products from the final desired organic molecule.[100]

4. Supported Catalysts

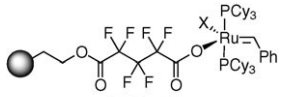
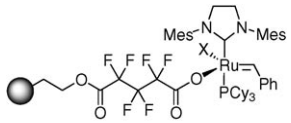
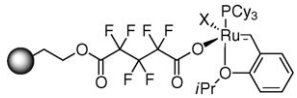
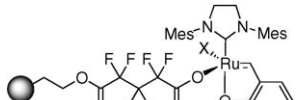
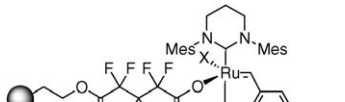
In addition to the development of new processes for the removal of ruthenium from reaction products, many immobilized catalysts have been synthesized using various anchoring sites. It is hoped that the use of such anchored catalytic species will alleviate the need for involved metal removal efforts.

4.1. Immobilization through Anionic Ligands X

Tagging or immobilization through an anionic ligand has scarcely been examined so far. Mol and co-workers exchanged one of the chloride ligands on Grubbs' precatalyst and bound this catalyst to a Merrifield-type resin with a perfluorinated linker.[43] The resulting heterogenized complex **21** (Table 2, entry 1) showed reduced reactivity compared to the homogeneous parent analogue and displayed substantial loss of activity after the second run. This should not necessarily be ascribed to a lack of tight attachment of the organometallic fragment to the support but rather reflects the inherent low stability of **2** type precatalysts that also translates into appreciable amounts of Ru contamination in the metathesis product. Boomerang-type complexes are better suited for this mode of immobilization.

Related approaches that are based on this perfluoroglutaric linker were disclosed by Buchmeiser and co-workers.[44–47] Supported catalysts **22**–**27** (Table 2, entries 2–5) are

Table 2: Catalysts immobilized through anionic ligands.

Entry	Catalyst	Cycles (yield)[a]	Residual Ru [ppm][b]
1[43]	 **21**, X = Cl	6 (23%)	156
2[47]	 **22**, X = CO_2CF_3	n.d.[c]	0.083
3[47]	 **23**, X = CO_2CF_3	n.d.[c]	0.015
4[44,46]	 **24**, X = Cl **25**, X = CO_2CF_3	n.d.[c] n.d.[c]	n.d.[c] 0.070
5[45]	 **26**, X = Cl **27**, X = CO_2CF_3	n.d.[c]	0.14

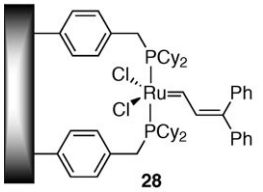
[a] Yield at the last effective cycle. [b] Determined by ICP-MS. [c] Not determined.

based on different ruthenium complexes, and monolithic systems synthesized by polymerization reactions serve as the support. The remarkable improvement of this system compared to **21** is the low degree of Ru contamination in the products (0.015 ppm; Table 2, entry 3). Unfortunately, even if these immobilized catalysts were found very active in RCM and ring-opening cross-metathesis (RO-CM), no recycling tests have been performed thus far.

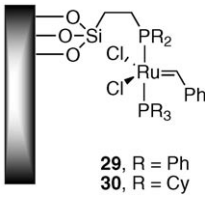
4.2. Attachment through Neutral Ligands L

4.2.1. Phosphines

The most straightforward approach to immobilize a homogenous catalyst containing a phosphine in the coordination sphere of the metal is to simply use a phosphine-containing solid support. In 1995, Grubbs and Nguyen reported the first supported olefin metathesis catalyst **28**, which makes use of polystyrene (PS)-divinylbenzene (DVB).[48] Despite a simple synthesis, catalyst **28** was found to be less reactive and selective in ring-opening metathesis polymerization (ROMP) as compared to its homogenous analogue. Complexes **29** and **30** grafted to mesoporous material were found to perform ROMP and RCM reactions efficiently; however, due to diffusion limitations their activity was reduced as compared to **2**.[49]



28



29, R = Ph
30, R = Cy

4.2.2. N-Heterocyclic Carbenes

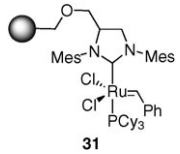
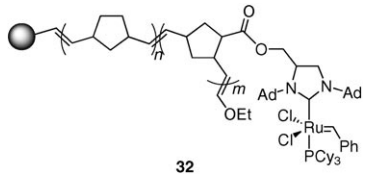
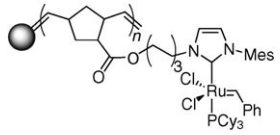
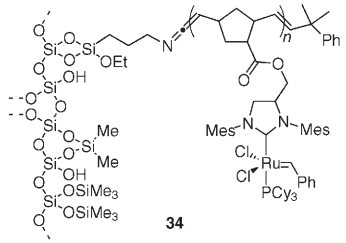
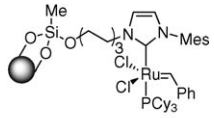
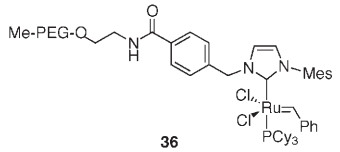
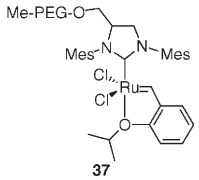
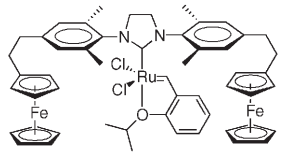
The groundbreaking introduction of N-heterocyclic carbenes (NHCs) as versatile ligands in well-defined homogeneous ruthenium-benzylidene species has extended the scope of these catalysts (reaction conditions and substrates).[11,12] The excellent coordinative properties of these ancillary ligands have led to the development of catalysts supported on solid polymers, silica, soluble polymers, and ferrocene by attachment through the backbone or the N-substituents of the NHC.

In 2000, Blechert and co-workers[50] reported the synthesis of a second-generation catalyst attached to Merrifield polystyrene (1% DVB) by an ether linkage (Table 3, entry 1). Polymer-bound complex **31** was obtained with a loading level between 0.14 and 0.40 mmol g^{-1} depending on the amount of the Merrifield resin initially used. Even if this catalyst was found to be efficient for olefin metathesis reactions, the recycling tests showed a rapid loss of activity. Only four successive cycles could be performed, and even then the reaction time was increased from 1.5 h to 2 days for the two last cycles.

Buchmeiser and co-workers reported two new catalysts anchored to monolithic materials (Table 3, entries 2 and 3). The synthesis of **32**[51] involved several steps: preparation of the monolithic structures containing the imidazolium salt, formation of the free NHC, and phosphine displacement leading to a catalyst loading of 1.4 wt%. To the best of our knowledge, complex **32** is the only example of a ruthenium-based metathesis catalyst containing one of the bulkiest NHCs, 1,3-bis(1-adamantyl)imidazol-2-ylidene (IAd).[52] The resulting immobilized catalyst promoted, in the presence of chain-transfer agents, ROMP and RCM reactions with a moderate recycling profile and with as low as 70 ppm of residual Ru in the final products. Catalyst **33**[53] anchored through a N-substituent with a loading of 0.55 wt% catalyzed RCM and enyne metathesis reactions with a moderate activity. The average Ru contamination of the products was about 70 ppm; unfortunately, no recycling was attempted using this system.

Immobilization of NHC-containing catalysts on silica has also been achieved by using the backbone and the N-substituents as anchoring points (Table 3, entries 4 and 5). Complex **34**[54] was synthesized with a catalyst loading of 0.5 wt% and displayed moderate activity in RCM depending on diffusion phenomenon associated to the use of solid supports. Catalyst **35**,[55] covalently immobilized on silica, exhibited a lower activity in RCM than its homogeneous counterpart; nevertheless, it could be reused up to three times.

Table 3: Catalysts immobilized through an NHC.

Entry	Catalyst	Cycles (yield)[a]	Residual Ru [ppm][b]
1[50]	 **31**	4 (100%)	n.d.[c]
2[51]	 **32**	3 (92%)	70
3[53]	 **33**	n.d.[c]	70
4[54]	 **34**	n.d.[c]	n.d.[c]
5[55]	 **35**	n.d.[c]	n.d.[c]
6[56]	 **36**	3 (up to 98%)	250
7[57]	 **37**	n.d.[c]	n.d.[c]
8[58]	 **38**	3 (100%)	n.d.[c]

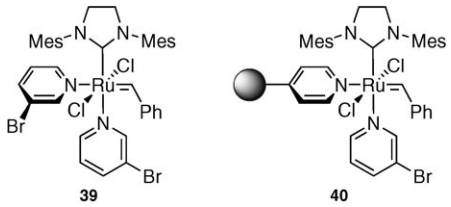
[a] Yield at the last effective cycle. [b] Determined by ICP-MS. [c] Not determined.

In an attempt to compensate for the moderate activity associated with solid supports, Grubbs and co-workers recently developed complexes anchored to soluble supports (Table 3, entries 6 and 7). Catalyst **36**[56] initiated ROMP well for cyclic olefins in both acidic water and methanol, whereas its efficiency was found to be moderate in RCM reactions carried out in methanol. Addition of diethyl ether allowed for removal of about 97% of the PEG content from the products, but the residual Ru level was not determined. The highly water-stable catalyst **37**[57] was found to be more efficient than **36** for ROMP, RCM, and CM reactions in aqueous media.[101]

In 2005, Plenio and Süßner[58] reported an interesting strategy for recycling based on redox-switchable phase tags for the separation of homogeneous catalyst **38** from the reaction products (Table 3, entry 8). The ferrocene pattern attached in **38** can be easily oxidized in situ, triggering its precipitation in the reaction media, and subsequently can be reduced, leading to the recovery of the active soluble catalyst. Complex **38** was used to perform up to three consecutive RCM reactions using this oxidation–reduction sequence.

4.2.3. Pyridines

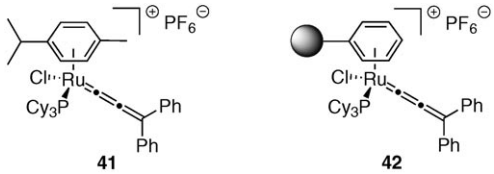
In 2002, Grubbs and co-workers reported the synthesis of substitution-labile pyridine-containing complex **39** developed


39 **40**

to shorten the initiation step, that is, to form more rapidly the 14-electron intermediate.[59] Recently, Kirschning and co-workers reported the synthesis of its supported analogue **40**.[60] The ruthenium complex can easily be immobilized through ligand exchange using polyvinylpyridine.[61] Unfortunately, the exact stereochemistry in the coordination sphere of the ruthenium center is unknown. The resulting immobilized catalyst **40** was found to be efficient in RCM and CM reactions as well as in the double-bond migration of allyl ethers. The functionalized polymer turned out to be relatively air-stable; degradation was only encountered after two weeks.[62] The authors showed that the filtered polymer **40** can be reused up to five times with a decrease in yield of 10% under fixed conditions (5 mol% **40**, toluene, 110°C, 4 h, diallylmalonate). However, analytical data on the degree of leaching were not reported.

4.2.4. η^6-Arenes

An unusual approach for immobilization through the ligand L was devised by Kobayashi and Akiyama.[63] They prepared a polymer-supported η^6-arene-ruthenium complex **42**, which served as a precursor for a soluble cationic ruthenium-allenylidene complex **41** reported by Fürstner,


41 **42**

Dixneuf, and co-workers.[64] The functionalized polymer performed in the expected manner in standard RCM reactions for at least three runs (no data on leaching were given).

4.3. Tag-Containing Alkylidenes

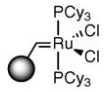
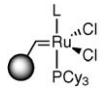
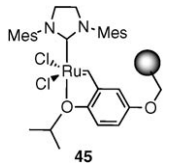
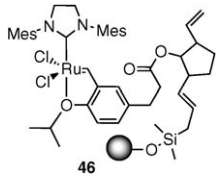
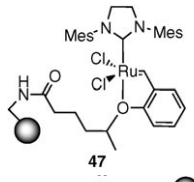
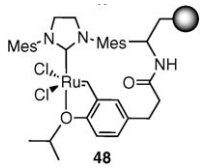
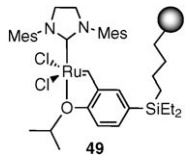
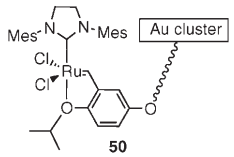
Anchoring the Ru metathesis catalyst to the support through the alkylidene moiety is the most widely used method. This concept, which has been applied to a wide range of supports (such as solid and soluble polymers, ionic liquids, and fluorous phases), is feasible mainly as a result of the release–return mechanism[27] of the metathesis reaction using this specific architecture. The release of the active species from the alkylidene-anchored moiety facilitates olefin metathesis under homogeneous conditions despite the fact that the precatalyst originates from the solid support. However, the major drawbacks of this catalyst-recycling technology is the re-anchoring of the active species to the initial support at the end of the reaction which often leads to a significant contamination of the final product by ruthenium.

4.3.1. Anchoring to a Solid Support

Barrett and co-workers were the first to apply the strategy of anchoring an alkylidene ligand to a solid support in the synthesis of a first-generation Grubbs' catalyst attached to vinyl polystyrene (Table 4, entry 1).[65] Polymer-bound complex **43** was found to be efficient for several RCM reactions but exhibited only two cycles of reusability even in the presence of additives such as 1-hexene. However, the Ru contaminant level was 500 ppm, which could be decreased to 55 ppm after chromatography. The DVB-supported complexes **44** developed by Nolan and co-workers[66] in 2000 based on the second-generation catalyst bearing a NHC displayed similar activity in RCM compared to their homogeneous parents and can be recycled up to four times without significant loss of activity (Table 4, entry 2). However, ICP-MS analyses after four cycles showed the presence of 2000 ppm Ru in the final products.

The report by Hoveyda in 1999 of the robust and efficient recyclable "boomerang" Ru catalyst **5**, bearing an isopropyl styrene ether fragment instead of the initial Grubbs' benzylidene, has contributed significantly to the development of high-performance recyclable supported catalysts. The groups of Blechert,[67] Hoveyda,[27,68] and Dowden[69] were the first to report the immobilization of this boomerang-type catalyst on different solid polymers (Table 4, entries 3–5). Whereas complexes **45** and **47** (with a loading of 5 mol%) showed similar activity and recyclability in metathesis reactions (up to five cycles), the Hoveyda version **46** supported on monolithic silica discs could be re-used in 20 cycles with 300–3000 ppm of Ru in the final products without purification or workup.[27] In 2002, Blechert and Connon[70] reported the synthesis of the phosphine-free ruthenium complex **48** anchored on a highly hydrophilic solid polymer (PEGA-NH_2; Table 4, entry 6). This heterogeneous catalyst promoted efficient RCM and CM reactions in both methanol and water. Unfortunately, no recycling test was attempted with this supported catalyst. At the same time, Grela et al.[71] described the immobilization of the Hoveyda-type catalyst on a butyldiethylsilyl polystyrene (PS-DES). This robust complex **49** could be reused five times in the RCM of a wide range of substrates with 700 ppm residual ruthenium. Finally, anchoring of the Hoveyda-type catalyst on a monolayer-protected gold cluster (Au-MPC) has been recently reported by Lee et al.[72] (Table 4, entry 8). This catalytic supported system **50** was reused up to six times to reach 80% conversion in the RCM of diallyltosylamine.

Table 4: Solid polymer-tagged catalysts.

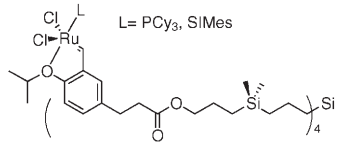
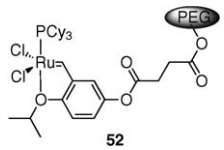
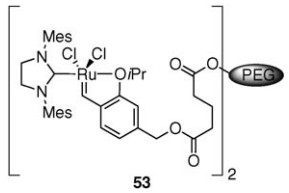
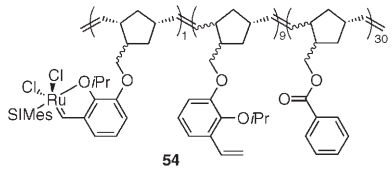
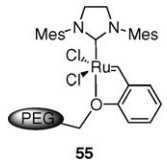
Entry	Catalyst[a]	Cycles (yield)[b]	Residual Ru [ppm][c]
1[65]	 **43**	2 (>98%)	55
2[66]	 **44** L= IMes, SIMes	4 (>98%)	2000
3[67]	 **45**	5 (>98%)	n.d.[d]
4[68]	 **46**	20 (>98%)	300–600
5[69]	 **47**	5 (63%)	n.d.[d]
6[70]	 **48**	n.d.[d,e]	n.d.[d]
7[71]	 **49**	5 (95%)	700
8[72]	 **50**	6 (80%)	n.d.[d]

[a] IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene. [b] Yield at the last effective cycle. [c] Determined by ICP-MS. [d] Not determined. [e] Used for RCM and CM in aqueous media.

4.3.2. Anchoring to a Dendritic or Soluble Support

In 2000, Hoveyda and co-workers[14a] reported the synthesis and catalytic activity of Ru-based dendrimers **51** (Table 5, entry 1). Catalytic RCM, ROM, and CM reactions

Table 5: Dentritic and soluble polymer-tagged catalysts.

Entry	Catalyst	Cycles (yield)[a]	Residual Ru [ppm][b]
1[14a]	 **51**	6 (87%)	n.d.[c]
2[73]	 **52**	8 (92%)	n.d.[c]
3[74]	 **53**	17 (94%)	n.d.[c]
4[75]	 **54**	7 (>98%)	40
5[76]	 **55**	5 (80%)	n.d.[c]

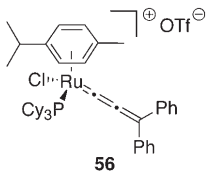
[a] Yield at the last effective cycle. [b] Determined by ICP-MS. [c] Not determined.

are efficiency promoted by these supported systems, which could be reused several times after silica gel chromatography (up to six cycles). However, isolation of the final metathesis product and recovery of the supported catalyst required silica gel chromatography. Additionally, the high solubility of these dendritic complexes in organic solvents has allowed the study of Ru leaching by ^{1}H NMR spectroscopy. During the metathesis of diallytosylamine, using 1.25 mol% of dendrimer catalyst, a loss of Ru of 13% was noted after the first cycle and reached 59% after the sixth cycle. However, the dendritic complex remains active and furnishes the desired cyclic product in 86% yield after this sixth cycle. This is a clear indication that presumably a very small quantity of the catalyst is involved in the transformation. Attempts to recycle the dendrimers **51** by precipitation to avoid chromatography proved to be unsuccessful.

Immobilization of a Hoveyda-type catalyst onto a PEG polymer was first reported by Yao[73] in 2000. The homogeneous supported complex **52** showed high activity and recyclability in the RCM of terminal olefins to reach a yield of 92% for the eighth cycle. Nevertheless, large quantities of solvent were required to recover the catalyst (by precipitation, filtration, and repeated washing). Recently, Yao and Motta[74] reported a significant improvement of his homogeneous supported catalytic system through the attachment of two Ru complexes on a PEG polymer. With a loading of 5 mol%, this new immobilized catalyst **53** proved to be highly reactive and recyclable (as it could be reused in up to 17 cycles each of 2 h duration) in the RCM of a wide variety of diene substrates including tetrasubstituted olefins. Complex **53** also promoted CM and RO-CM in high yields. Blechert and co-workers[75] reported the facile synthesis of the soluble polymeric Ru complex **54**, which proves efficient for RCM, RO-CM, and ring-rearrangement metathesis (RRM) reactions with as low a catalyst loading as 1 mol%. Interestingly, complex **54** could be reused up to eight times without significant loss of activity to yield the metathesis product with only 40 ppm of residual Ru (in the first four cycles). In 2003, Lamaty and co-workers[76] described the synthesis of catalyst **55** in which the PEG polymer was introduced through the ether fragment. However, high loadings of catalyst (10 mol%) were necessary to promote RCM reactions and a significant loss of activity was observed as yields reached 85% only after the third cycle.

4.3.3. Anchoring to an Ionic Tag

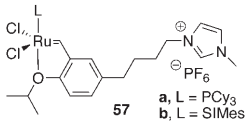
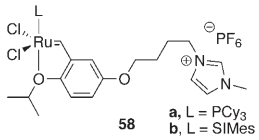
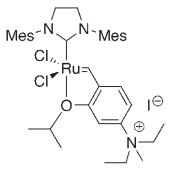
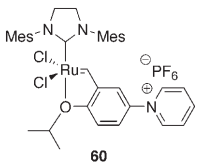
Using ionic liquids as alternative recycling media for metathesis reactions represents a remarkable alternative to polymer-supported reagents. The goal in this area is to reduce the ruthenium contamination in the metathesis products. The easy procedure required to isolate the final organic product, that is, a simple biphasic separation based on the good affinity of the catalyst for the ionic phase, highlights the beauty and ease of use of this approach. Pioneering work conducted by the groups of Chauvin,[77] then Buijsman[78] and Kiddle,[79] has shown the efficiency of several homogeneous ruthenium allenylidene salts **56** (Tf = trifluoromethanesulfonyl) in this approach (see also related complexes **41** and **42**). The efficiency of this ionic catalyst was examined only for the first two cycles in RCM, although six cycles were performed. However, important leaching of the catalyst (owing to a fast extraction from the ionic phase by the organic solvent) leads to a dramatic reduction of reactivity after a few cycles. This results in significant Ru contamination levels in the final products (1600–5300 ppm).[78] Dixneuf and co-workers[23,80] reported the use of a cationic ruthenium-allenylidene pre-catalyst for the ROMP of norbornene in a biphasic toluene-IL system.[80]


56

To solve the problem of catalyst leaching, more suitable Hoveyda-type catalysts for ionic media were independently reported in 2003 by the groups of Mauduit[81] and Yao[82]

(Table 6, entries 1 and 2). By introducing an ionic tag onto the styrenyl ether fragment, a significant improvement of reusability was observed with the first-generation ionic catalyst **57a**[81a] (2.5 mol% loading): a yield of 95% was observed for the 10th cycle in the RCM of terminal olefins in pure butylmethylimidazolium hexafluorophosphate, [BMI]PF_6 (Table 6, entry 1). Similar activity was obtained with the Yao catalyst **58a**[82a] in a dichloromethane/[BMI]PF_6 medium. However, in the case of the most challenging hindered substrates reactivity is severely reduced with these IL catalysts, which remain active only in the first two cycles. To improve the performance for these substrates, Mauduit and co-workers[81b,c] have developed a second-generation ionic catalyst **57b** (second-generation Hoveyda–Grubbs-type catalyst) that exhibits excellent reactivity in a biphasic toluene/[BMI]PF_6 medium. This system displays high recyclability (up to eight cycles in the RCM of trisubstituted olefins of equal duration (3 h) at room temperature). Moreover, extremely low Ru contamination levels were detected in the metathesis products, with an average of 7 ppm over eight cycles (1–22 ppm). Selected CM reactions were also investigated and although reasonably good conversions could be achieved, the recyclability was significantly less effective than applications in RCM (up to three cycles). Similar results are observed with the Yao second-generation catalyst **58b**,[82b] which promotes metathesis of tri- and tetrasubstituted olefins. It could be reused up to 17 times with no significant loss of activity.

Table 6: Ionic-tagged catalysts.

Entry	Catalyst	Cycles (yield)[a]	Residual Ru [ppm][b]
1[81]	 **57** **a**, L = PCy_3 **b**, L = SIMes	10 (95%)	1.2–22
2[82]	 **58** **a**, L = PCy_3 **b**, L = SIMes	17 (90%)	n.d.[c]
3[83]	 **59**	1 (>98%)	12–68
4[84]	 **60**	3 (65%)	25–138

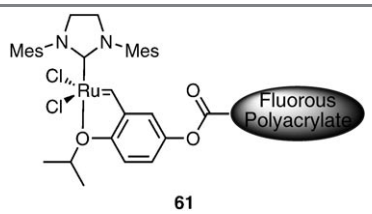
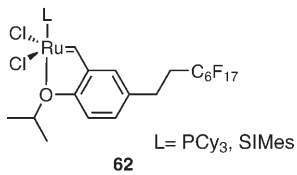
[a] Yield at the last effective cycle. [b] Determined by ICP-MS. [c] Not determined.

More recently, Grela and co-workers[83] and Mauduit and co-workers[84] have reported a novel concept in the ionic-tagged supported metathesis catalyst area. They make use of ionic tags as electron-withdrawing groups (EWGs) on the benzylidene aryl group (Table 6, entries 3 and 4). In this manner, the tag not only allows the catalyst to be kept in the ionic phase but can also lead to electronic activation of the catalyst at the same time. Ammonium-tagged catalyst **59**[83] and its pyridinium-tagged analogue **60**[84] can be efficiently used for olefin metathesis in several media including aqueous and ionic solvents leading to low levels of ruthenium contamination after a simple filtration through a pad of silica gel (12–68 ppm for **59** and 25–173 ppm for **60**). As expected, the initial rate of metathesis was significantly enhanced with 50% of the cyclized product being formed within 15–20 min instead of 9% observed in the same time period using catalyst **58b**. However, although activity in [BMI]PF_6/toluene media was efficient in the first cycle, significant loss of activity was observed in the second cycle showing that the activation process related to the ionic tag takes place at the detriment of the catalyst reuse. This clearly reflects the antinomic effect between activation of the catalyst and the recycling effort.[102]

4.3.4. *Anchoring to a Fluorous Tag*

To the best of our knowledge, only two examples related to the use of fluorous olefin metathesis catalysts in fluorous biphasic media have been reported to date. Yao and Zhang[85] were the first to develop this concept in 2004 with the synthesis of a poly(fluoroalkylacrylate)-bound ruthenium carbene complex **61** which displayed remarkable activity in RCM for a wide variety of diene substrates including tetrasubstituted olefins (Table 7). Moreover, fluorous catalyst **61** could be reused up to 20 times without significant loss of activity, but no ruthenium contamination measurements were performed in this work. Recently, Curran and Matsugi[86] have described the synthesis and catalytic activity of a light fluorous Hoveyda–Grubbs complex **62**. This catalyst exhibited high reactivity in several RCM and CM reactions of terminal olefins in dichloromethane with a loading of 5 mol% and could be reused up to seven times. Recovery of the

Table 7: Fluorous-tagged catalysts.

Entry	Catalyst	Cycles (yield)[a]	Residual Ru [ppm][b]
1[85]	 **61**	20 (94%)	n.d.[c]
2[86]	 L= PCy_3, SIMes **62**	7 (98%)	500

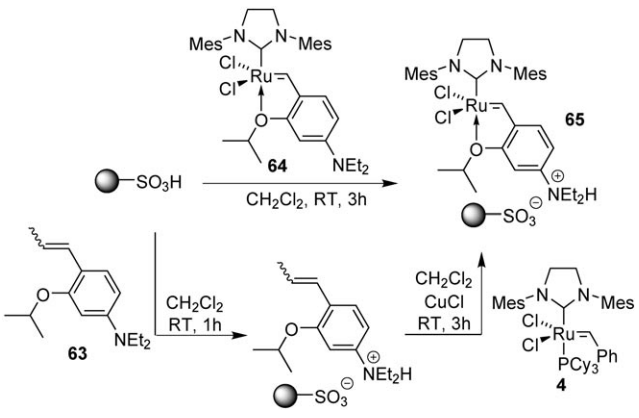
[a] Yield at the last effective cycle. [b] Determined by ICP-MS. [c] Not determined.

catalyst was achieved by a fluorous solid-phase extraction or by filtration through a pad of fluorous silica gel, but significant levels of ruthenium contamination were found in the final products (500 ppm determined by microanalysis).

4.4. Ionic Interactions between the Catalyst and a Polymeric Phase

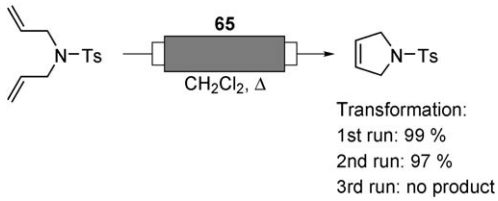
Despite the fact that many efforts of immobilization rely on covalent linkage of a ligand or carbene moieties to a solid phase, note that, in practice, this immobilization technique for homogeneous catalysts is not as efficient as was originally hoped. As the reloading of the support is very difficult or even impossible to achieve once catalyst degradation occurs, the loss of the supporting phase is irreparable. The concept of ionic attachment of transition-metal catalysts is based on tagging the complex with an additional ionic functionality that can interact specifically with another ionic phase (see also Table 6). This strategy could allow for easy removal of the catalyst during workup (scavenging) but also represents a straightforward method for recycling.[87] Considering the small difference of cost between supported catalysts and most of the anchoring phases, this strategy should find some industrial applications, particularly for fixed-bed continuous-flow processes.[88,89]

Very versatile tags are ionic in nature (such as sulfonic acids or quaternary ammonium cations) that can be either used to construct a scavenging protocol or utilized to immobilize the transition-metal complex by ion exchange to a corresponding ionic resin. An illustrative example by Kirschning, Grela et al. is depicted in Scheme 3.[90a] This specific example shows that functionalized polymer **65** is formed by direct immobilization of inactive Hoveyda-type complex **64**[90b] or indirectly by first conducting ion exchange of aniline derivative **63** followed by cross olefin metathesis in the presence of catalyst **4** and CuCl.[91] Polymer **65** is a highly active catalyst, particularly in cross-metathesis reactions, as used, for example, in the preparation of a steroidal precursor to the inhibitor of 17β-hydroxysteroid dehydrogenase type 1.[92] However, it has also proven to be useful in RCM and ene-yne metathesis in up to six runs, showing relatively low levels of Ru contamination in the products (100 ppm).[90a]



Scheme 3. Two approaches for the preparation of catalyst **65**.

The ruthenium complex was also tested under continuous-flow conditions[93] by introducing functionalized polymer **65** inside a PASSflow reactor (Scheme 4). Whereas excellent



Scheme 4. RCM under continuous-flow conditions.

conversions were obtained in the first two runs, no product was observed for the third RCM cycle, illustrating the need for catalyst reloading in the fixed bed.[94] A very important feature of this setup is the possibility of reloading and reactivating the reactor. This is simply achieved by first washing with 1N HCl, H_2O (pH 7), and dry methanol, and followed by reloading with Ru complex **65** as described above.

5. Metathesis in Supercritical Carbon Dioxide

Supercritical fluids such as carbon dioxide ($scCO_2$) have attracted much attention notably because of their higher miscibility with gases when compared to liquid solvents.[95] As an added feature, the recovery of costly transition-metal-containing complexes should be made easier by using supercritical fluids as reaction media for homogeneous catalysis.

In 1996, DeSimone and co-workers reported that $[Ru(H_2O)_6](OTs)_2$ (Ts = *para*-toluenesulfonyl) promoted the ROMP reaction of norbonene in $scCO_2$.[96] The authors noted that CO_2 did not participate in the reaction. The yield and properties of the resulting polymer were comparable to those obtained in conventional solvents. Interestingly, the addition of methanol led to complete dissolution of the catalyst and to a decrease of the *cis* olefin content of the polymer from 83 to 30%. Similar results were obtained by Blanda et al. a few years later using THF as co-solvent and the well-defined Grubbs' catalyst.[97]

Fürstner, Leitner et al.[98] later found that catalysts **1** and **2** as well as molybdenum-based Schrock catalysts are suitable for ROMP of norbornene and cyclooctene in compressed carbon monoxide. These catalysts displayed activities higher than those observed by DeSimone and co-workers. RCM was also performed efficiently using catalysts **1**–**3** on a broad range of substrates. Unfortunately, issues of residual Ru levels and catalyst recycling were not addressed.

Recently, Bannwarth and co-workers used Hoveyda-type catalysts covalently immobilized on solid support materials to carry out RCM in $scCO_2$.[99] Whereas, excellent recycling was observed with the unsupported catalysts, the immobilized versions yielded more modest performances. Nevertheless, interestingly low levels of Ru contamination were observed with this combination of supported catalysts and $scCO_2$ (≈20 ppm vs 100 ppm with both generations of Grubbs' catalysts in sCO_2).

As presented in the case study of BILN 2061 (Section 3.1),[20] a purification procedure employing $scCO_2$ has been used to reduce Ru waste levels,[41] whereas techniques involving charcoal treatments or Ru scavengers (water-soluble phosphines or thiols) were found inefficient or required long reaction times. Extraction using $scCO_2$ of the crude reaction mixture containing the solvent and 5 mol% Ru gave the product in 92% yield after 30 min and contained only 56 ppm of Ru.

6. Summary and Outlook

The development of green processes for olefin metathesis reactions is an important area that will continue to grow in the coming years. Numerous techniques have been investigated with more or less success, including systems for Ru removal, development of immobilized catalysts on various supports such as solid and soluble polymers, fluorous phases, ionic liquids, and also supercritical carbon dioxide media. Promising continuous-flow methods are emerging and will be of undeniable interest for industrial applications. Unfortunately, we clearly see that only a limited number of studies have been conducted where both recycling and ruthenium waste content are examined. Indeed, too many papers do not report on the levels of contamination in the product, which clearly is a drawback when developing olefin metathesis for industrial practice. However, several catalytic systems were found to be very efficient in terms of reusability—more than 10 consecutives runs are frequently carried out with the same catalyst batch—and with low levels of metal leaching (the 10 ppm level is often reached). We also note that of the numerous variations on metathesis, mainly polymerization reactions and RCM have been investigated, and thus far the synthetically interesting CM, RO/CM, and RRM processes have not been much explored in terms of catalyst recycling and reuse.

Because of its ease of use and versatility, and the reduction in synthetic steps leading to complex target synthesis associated with its use, olefin metathesis in its many forms continues to stimulate researchers. A bright future is undeniable for cleaner, greener, more sustainable olefin metathesis reactions because of the vital importance of the method (and of catalysis in general) and of the ever-growing need for environmentally friendly catalytic processes.

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