Onium-tagged Ru complexes as universal catalysts for olefin metathesis reactions in various media*

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Abstract: Polar olefin metathesis catalysts bearing a pendant electron-withdrawing (EWG) onium group are reviewed. The presence of this group not only activates the catalysts electronically, but renders them more hydrophilic. Catalysts can, therefore, be efficiently used not only in traditional media such as methylene chloride and toluene, but also in technical-grade alcohols, alcohol–water mixtures, and in neat water. In addition, some onium-tagged catalysts can act as inisurfs (initiator + surfactant molecules), promoting metathesis under heterogeneous aqueous conditions. Finally, some of these catalysts can be used in ionic liquids. Various ring-closing-, cross- and enyne metathesis reactions were conducted with these catalysts.

Keywords: aqueous media; catalysis; ionic liquids; olefin metathesis; ruthenium; sustainable chemistry.

INTRODUCTION

Ru-based olefin metathesis reactions represent an attractive and powerful transformation enabling the formation of new C–C double bonds (Fig. 1) [1].

The development of modern Ru metathesis catalysts, such as Grubbs (**1a,b**) and Hoveyda–Grubbs carbenes (**3a,b**, Fig. 1) combining high activity with an excellent tolerance to a variety of functional groups has been the key to widespread applications of olefin metathesis in organic synthesis and polymer chemistry [1]. Despite the general superiority offered by this family of catalysts, they share some disadvantages. Since olefin metathesis reactions are expected to be used in pharmaceutical processes, the most undesirable feature of these complexes is that during the reaction they form Ru by-products, which are difficult to remove from the reaction products [2]. In many cases, Ru levels of >2000 ppm remain after chromatography of products prepared by ring-closing metathesis (RCM) with 5 mol % of Grubbs catalysts [3]. The Ru has to be removed prior to further processing [4]. Several protocols to solve problems associated with Ru contamination have been proposed but none are universally attractive so far [3,5].
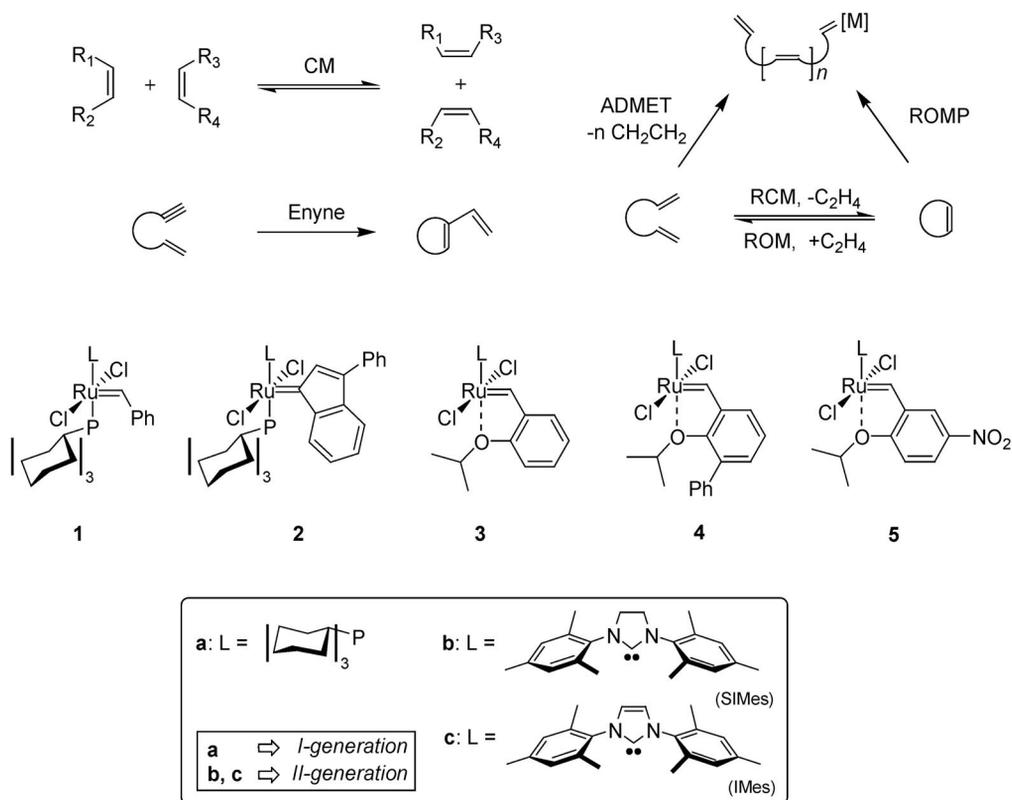
Fig. 1 Selected modern catalysts for olefin metathesis and the transformation itself: RCM = ring-closing metathesis, ROM = ring-opening metathesis, ADMET = acyclic diene metathesis polymerization, ROMP = ring-opening metathesis polymerization, CM = cross-metathesis.

In addition, due to environmental problems, there is a need to use water as a safer, benign, and cheap solvent [6,7]. Furthermore, aqueous media can be critical for some biological applications of olefin metathesis [8]. Classical Ru initiators were used in ring-opening metathesis polymerization (ROMP) in mixed water/organic solvent systems in the presence of dodecyltrimethylammonium bromide or sodium dodecylsulfate (SDS) [9]. RCM in water has been a challenge for a long time because of the instability of the formed carbene in water [10a]. However, the notion of "green chemistry" [7] has encouraged some groups to test precatalysts **1a,b** in methanol or water in the presence of surfactants, polydimethylsiloxane, or without additives [10]. Unfortunately, in addition to low solubility of **1a,b** in these media, a decrease of reaction rate is often observed, and, therefore, increase of catalyst loading or reaction temperature is usually needed.

Onium-tagged catalysts offer an alternative solution to the problem of product purification following metathesis in aqueous mixtures.

APPLICATION OF ONIUM-TAGGED CATALYST IN TRADITIONAL MEDIA

We demonstrated that the 5- and 4-nitro-substituted Hoveyda–Grubbs catalysts initiate olefin metathesis dramatically faster than the parent complex **3b** [11]. It was proposed that the electron-withdrawing (EWG) nitro group decreases the electron density on the chelating oxygen of the isopropoxy group and weakens the O → Ru coordination, facilitating faster initiation of the metathesis catalytic cycle [11,12]. In accordance with this assumption, it was observed that complex **6** (Fig. 2), bearing the electron-do-

nating (EDG) diethylamino group shows little or no activity in olefin metathesis [13]. However, in a striking contrast, the in situ formed salts **7**, obtained by treatment of complex **6** with with Brønsted acids HA, are of high activity, surpassing the parent Hoveyda–Grubbs complex **3b** in terms of initiation speed [13]. The formation of a polar salt not only activates the catalyst but also changes its physical properties, such as solubility in polar media and was used to create a site for noncovalent immobilization on a solid phase [14,15].
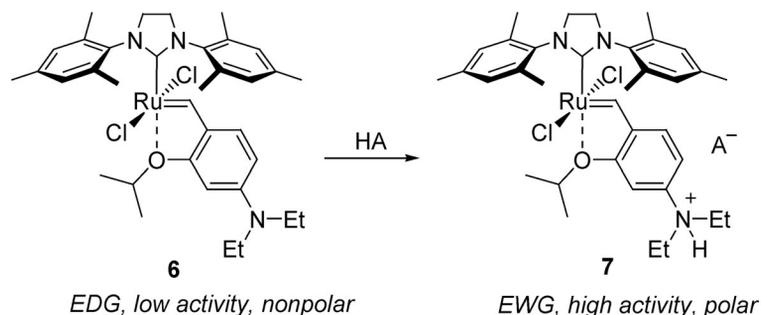
Fig. 2 Concept of "electron-donating to electron-withdrawing activity switch".

The concept of "electron-donating to electron-withdrawing activity switch" [12] (Fig. 2) was later extended by Grela to prepare complex **8** (Fig. 3), bearing a quaternary ammonium group [16–19]. After this preliminary report, other catalysts bearing polar quaternary ammonium groups in the ben-
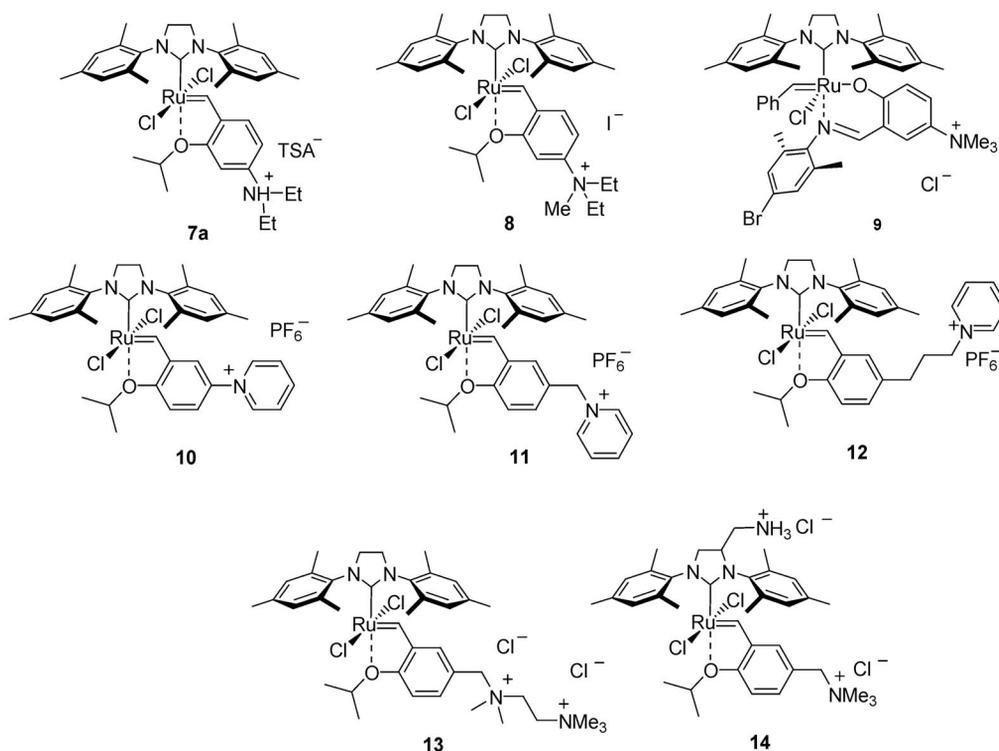
Fig. 3 Ru quaternary ammonium-tagged catalysts (TSA = *p*-CH$_3$C$_6$H$_4$SO$_3$).

zylidene fragment were reported by Raines (**9**) [20], Mauduit and Grela (**10–12**) [21], and Grubbs (**13**, **14**) [22].

All these precatalysts show high activity in traditional media, such as methylene chloride (Table 1) in various versions of metathesis reactions, including applications in natural product synthesis (Table 2). Importantly, as it was shown in the case of **7a**, **8**, and **10**, a simple purification step results in very low levels of residual Ru impurities in the crude products.

Table 1 RCM of substrate by using catalysts **7a**, **8**, **10**, **11** in methylene chloride at room temperature.

entry	substrate	product	cat. (mol %), time (min)	yield (%)	Ru (ppm)
1			**7a** (5), 15	92	-
			8 (5), 30	99	68
			10 (5), 30	99	138
			11 (5), 45	97	-
2			**8** (5), 60	99	12
			10 (5), 120	78	113
			11 (5), 60	99	-
3			**8** (5), 60	97	33
			10 (5), 30	99	173
			11 (5), 30	98	-
4			**7a** (5), 5	99	14
			8 (5), 30	99	-
			10 (5), 30	99	25
			11 (5), 15	99	-
5			**8** (2.5), 30	99	-
			10 (2.5), 30	99	-
			11 (2.5), 30	99	-
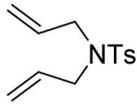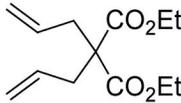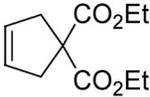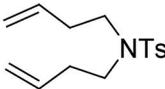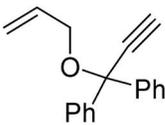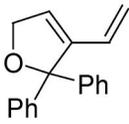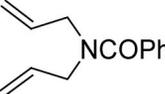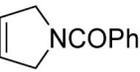
Table 2 RCM of complex natural product intermediates by using **7a** in refluxing methylene chloride.

entry	substrate	product	**7a** (mol %), *t* (h),	conv. (%)
1		(*E:Z* ~ 1:1)	(9), 1	99
2		(*E:Z* ~ 4:1)	(13), 0.3	65
3			(13), 12	69
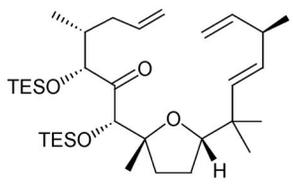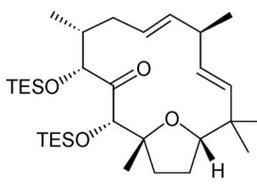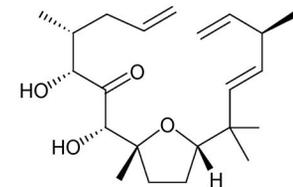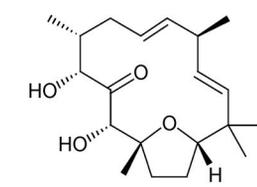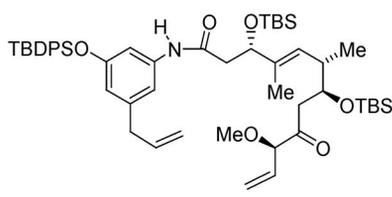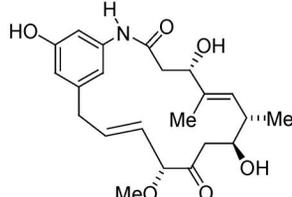
Catalyst **7** can be activated by using *p*-toluenosulfonic acid [23]. Precatalyst **7a** shows high activity in various variants of metathesis reactions, including applications in natural product synthesis. Importantly, a simple purification procedure results in very low levels of residual Ru impurities in the crude products. Thus, tagged Ru complexes like **7a** are particularly suitable for metathesis reactions for pharmaceutical applications [15].

SOLID-PHASE METATHESIS

Polar ammonium tags can be also used as attachment points to immobilize the metathesis catalyst on a solid support. In this novel strategy for Ru-based metathesis catalyst immobilization, the amino group plays a twofold role, being first an active anchor for immobilization and secondly, after protonation, activating the catalysts [14].

This catalyst immobilized on glass polymer composite Raschig rings (Fig. 4) can be used for combinatorial chemistry and high-throughput screening [14]. Recyclability studies showed that the same ring containing catalyst **7b** can be used for up to 6 cycles of metathesis, however, with gradual loss of activity. Importantly, the solid phase can easily be reactivated by a washing protocol (1 M HCl, H_2O, methanol, then addition of fresh **6**).
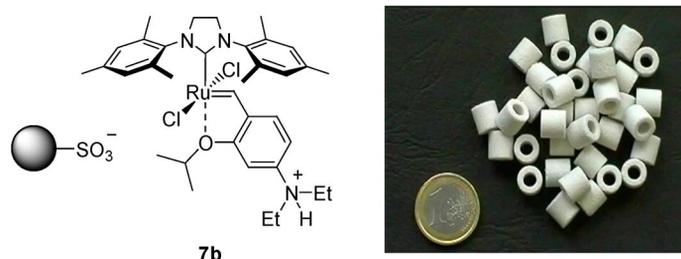
Fig. 4 Catalyst immobilized on Rashig rings.

The typical Ru contamination level of RCM and cross-metathesis (CM) products was around 100 ppm [14]. This is significantly lower than the Ru contamination reported for Hoveyda's catalyst on sol-gel pellets [24]. Polymer-bound catalyst **7b** is highly active in CM reactions, as exemplified by the preparation of a steroidal precursor to the inhibitor of 17β-hydroxysteroid dehydrogenase type 1, useful in the treatment of estradiol-dependent diseases like breast cancer or endometriosis (Table 3). Unfortunately, in the case of CM with acrylates, the Ru contamination level of the crude products was significantly higher (<3500 ppm) [15], which is not an excellent value but still is lower than Ru levels typically determined for standard homogeneous Ru catalysts (up to 20 000 ppm) [3,7].

Table 3 Application of catalyst immobilized on Rashig rings.

entry	substrate	product	temp. (^{o}C), time (h)	conv. (%)	Ru (ppm)
1			22 (18)	95 $E\!:\!Z$ = 1.2:1	21
2			45 (16)	99	30
3			40 (8)	99 only E-izomer	<3500

High-throughput synthesis and isolation techniques are of great interest for the pharmaceutical industry. Such techniques facilitate the preparation of large libraries of potentially biologically active products in a very short time. In this context, we became interested in new techniques for high-throughput synthesis and isolation of some natural product-like scaffolds, using olefin metathesis as the key step for the generation of advanced structures. We have found that tagged Ru catalyst **8** can be immobilized on standard analytical and preparative thin-layer chromatography (TLC) plates (Fig. 5) [25]. Substrates (dienes, enynes) migrate through the catalyst's zone during plate development where they undergo olefin metathesis (Table 4). This technique allows olefin metathesis reactions whilst simulta-

neously purifying the resulted products. This new 2D technique should overcome the difficulty of removing dark-colored residues of the spent metathesis catalyst, and offers scope for application in high-throughput preparation of products libraries in the pharmaceutical industry.
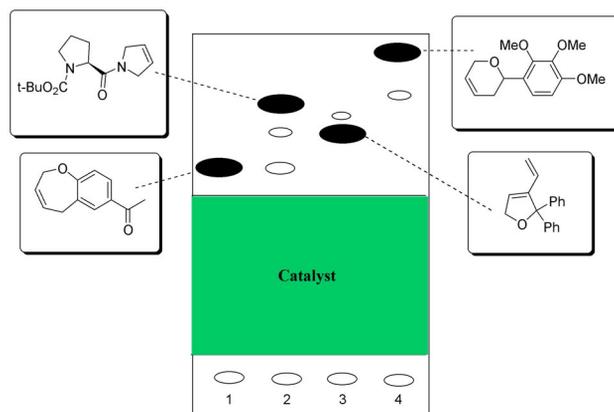
Fig. 5 Four simultaneous olefin metathesis-purification sequences using **8** on a TLC plate.

Table 4 Selected products obtained by metathesis on a TLC plate.

entry	substrate	product	yield (%)
1			97
2			91
3			61
4			95
5			94
6			55

APPLICATION OF ONIUM CATALYSTS IN WATER MIXTURES AND IN NEAT WATER

A comparison of results obtained in some model RCM and CM reactions leads to the conclusion that while the application profiles of all these catalyst are in general quite similar, some interesting differences can be noted. Grela's quaternary ammonium catalyst **8** is only slightly soluble in neat water (0.002 M), however, a number of metathesis reactions of water-soluble substrates have recently been conducted successfully in this medium [17,19]. Raines' complex **9** was tested only in methanol and methanol–water mixtures. Catalysts **10** and **11** were initially designed for applications in room-temperature ionic liquids (RTILs) [21,26] and are not soluble in neat water. On the contrary, Grubbs' **14** readily dissolves in water (**13** is soluble in low concentrations: <0.01 M). Moreover, **14** is relatively stable in this solvent, with a decomposition half-life of over one week at room temperature. While **13** and **14** are very active in RCM of charged dienes and in CM of allylic alcohol, sometimes an unwanted isomerization reaction appeared, which was not observed with **8** (Table 5). However, reactions with ionic catalysts in water are highly substrate-dependent. The RCM of diene **15a**, bearing a charged ammonium center in allylic position, witnesses a significant decrease of catalytic activity of **8**, as compared with complexes **13** and **14** (Table 6). Interestingly, despite the rather forcing conditions required to promote this transformation (110 °C, in a microwave oven), and in contrast to the results reported for **13**, the by-product **15c** was not detected. It should be noted that diallylamine hydrochloride **15a** is smoothly cyclized by **8** in methylene chloride [19].

Table 5 Selected reactions mediated by quaternary ammonium-tagged catalysts **8**, **13**, and **14** in neat water. [a]By-product **15c** formed. [b]By-product **16** formed.

entry	substrate	product	cat (mol %)	t (h)	temp (°C)	conv. (%)
1	Me₃N⁺ Cl⁻ (diene)	Me₃N⁺ Cl⁻ (cyclopentene)	**8** (5)	5	25	99
			13 (5)	0.5	30	>95
			14 (5)	24	30	>95
2	H₂N⁺ Cl⁻ **15a**	H₂N⁺ Cl⁻ **15b**	**8** (5)	0.12	110	44
			13 (5)	24	30	>95[a]
			14 (5)	6	30	36 (+59)[a]
3	HO (allyl alcohol)	HO⌒⌒OH	**8** (2.5)	3.5	25	>99
			13 (5)	24	45	82 (+4)[b]
			14 (5)	6	45	69 (+12)[b]
4	HO⌒⌒OH (cis-butenediol)	HO⌒⌒OH	**8** (2.5)	8	25	>99
			13 (5)	24	45	92
			14 (5)	2	45	94
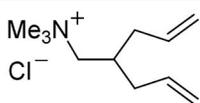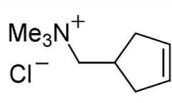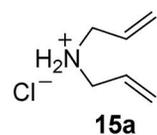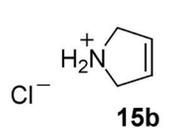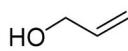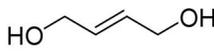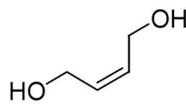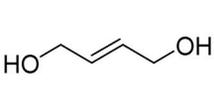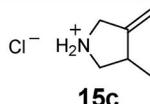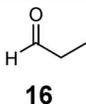
Cl⁻ H₂N⁺ **15c**   O **16**

While catalysts **8**, **13**, and **14** are able to make many aqueous RCM and CM reactions practical, attempts to convert other substrates, including those based on amino acids, carbohydrates, and ammonium salts, failed [19,22]. Undoubtedly, further progress in this field is necessary.

Table 6 Selected reactions mediated by quaternary ammonium-tagged catalysts **8–11** in aqueous media.

entry	substrate	product	solvent	cat. (mol %), time (h), temp.(^{o}C)	yield (%)
1	![structure] NTs	![structure] NTs	EtOH/H$_2$O (5:2)	**8** (5), 24, 25	83
			CD$_3$OD	**9** (5), 9, 55	>95
			EtOH/H$_2$O (5:2)	**10** (5),24, 25	50
			EtOH/H$_2$O (5:2)	**11** (5),2, 25	75
2	![structure] O Ph Ph	![structure] O Ph Ph	EtOH/H2O (5:2)	**8** (5), 0.5, 25	99
			CD3OD/D2O (5:2)	**9** (10), 6, 55	>95
			EtOH/H2O (5:2)	**10** (5), 0.5, 25	99
			EtOH/H2O (5:2)	**11** (5), 0.25, 25	97

APPLICATION OF ONIUM CATALYST IN RTILs

Activity studies of catalysts **6** and **8** in RTILs were performed. Although activity was good in the first cycle, recyclability was poor and significant loss in activity was observed even after the first cycle (Table 7). The surprisingly high activity of **6** in [bmim]PF$_6$ remains unclear at present.

Table 7 Amino- and ammonium-bearing catalysts tested in ionic liquids.
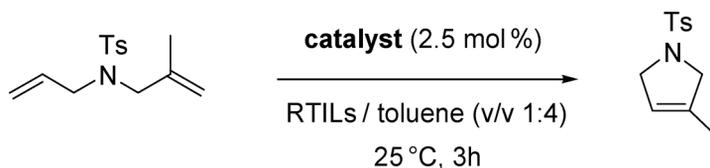
entry	catalyst	RTILs	cycle/conv.(%)		
			1	2	3
1	**6**	BMI.PF$_6$	>98	38	1
2	**8**	BMI.PF$_6$	>98	33	2

Catalysts **10–12** were tested both in imidazolium- and pyridinium-based ionic liquids. Activated pyridinium catalyst **10**, although being the fastest RTIL-metathesis catalyst reported so far, could not be recovered well (Table 8). This is probably due to the aforementioned electronic activation—re-anchoring of the benzylidene ligand is not a favored process in this case, which results in the migration of the 14-electron species into organic layer and their loss. Nonactivated pyridinium catalyst **12** could be recovered much more efficiently than activated catalyst **10**. Catalyst activity achieved through electronic activation stands in conflict with properties like stability and recyclability. The proper balance of these antinomic properties could be reached by adjusting the length of the hydrocarbon linker between pyridinium and benzylidene moieties. Catalyst **11** bearing a methylene linker was shown to be the perfect compromise of activity and recyclability, making this development interesting from the practical point of view [26].

Table 8 Pyridinium-tagged catalyst performance.
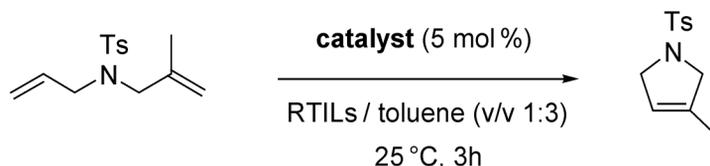
entry	catalyst	RTILs	cycle/conv.(%)					
			1	2	3	4	5	6
1	**10**	BMI.PF$_6$	>98	95	65	6	-	-
2	**11**	BMI.PF$_6$	**>98**	**>98**	**>98**	**>98**	**>98**	**>98**
3	**12**	BMI.PF$_6$	>98	>98	>98	>98	93	91

SUMMARY AND OUTLOOK

Onium groups, attached to the benzylidene part of Hoveyda-type complexes, not only activate the catalysts electronically, but at the same time make them more polar. These catalysts can, therefore, be efficiently used not only in traditional media such as methylene chloride and toluene, but also in technical-grade alcohols, alcohol–water mixtures, and in neat water. In addition, such complexes can act as inisurfs (initiator+surfactant molecules), promoting metathesis under heterogeneous aqueous conditions. Finally, some of these catalysts can be used in RTILs.

ACKNOWLEDGMENTS

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