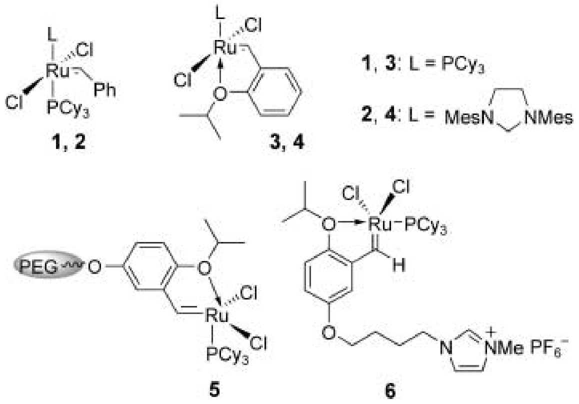
Olefin Metathesis in Ionic Liquids

Olefin Metathesis in the Ionic Liquid 1-Butyl-3-methylimidazolium Hexafluorophosphate Using a Recyclable Ru Catalyst: Remarkable Effect of a Designer Ionic Tag**

Qingwei Yao and Yiliang Zhang*

Environmental concern associated with chemical synthesis has posed stringent and compeling demands for greener processes, and the development of cost-effective and environmentally benign catalytic systems has become one of the main themes of contemporary synthetic chemistry.[1] In this context, efficient recycling and subsequent reuse of homogeneous catalysts are of prime importance.[2] The recently emerged room-temperature ionic liquids hold great potential in meeting these demands, as evidenced by their increasing popularity as innovative and environmentally benign reaction media as well as their use as new vehicles for the immobilization of transition-metal-based catalysts.[3]

The spectacular recent success of olefin metathesis[4] catalyzed by metal–carbene complexes stems largely from the availability of several well-defined catalysts, most notably, the Grubbs-type ruthenium alkylidenes **1**[5] and **2**.[6] Another major advance in this area is the discovery by Hoveyda and co-workers[7] of the recyclable Ru catalysts **3** (Cy = cyclohexyl) and **4** (Mes = mesityl = 2,4,6-trimethylphenyl). We[8] and other research groups[9] have established that various polymeric and solid supports can be used to immobilize these catalysts, as exemplified by the poly(ethylene glycol)-bound catalyst **5** (PEG = poly(ethylene glycol)). Herein, we report our success in the development of Ru complex **6** that features a designer ionic tag incorporated in catalyst **3**. This catalyst can be repeatedly recycled and reused as a highly active catalyst for the ring-closing metathesis (RCM) of various diene and enyne substrates in a minimally ionic solvent system (1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim]PF_6)[10]/CH_2Cl_2, 1:9 v/v) without significant loss of its activity.



Several Ru carbene complexes, including **1** and **2**, have been shown to be catalytically active for olefin metathesis in room-temperature ionic liquids, but their catalytic reactivity rapidly vanished in subsequent recycling runs and reuse.[11] We suspected that the rapid deactivation of the Ru catalysts might have been caused by the highly ionic nature of the solvents used, and we elected to re-examine the behavior of catalysts **1** and **3** in the RCM of the test diene **7** (Ts = toluene-4-sulfonyl) using a mixture of the ionic liquid [Bmim]PF_6 and CH_2Cl_2 (1:9 v/v) as the solvent (Table 1). Although the RCM of **7** proceeded uneventfully in the first run, as indicted by the clean and quantitative formation of the cyclized product **8** with either **1** or **3**, subsequent reuse of the catalysts recovered from the ionic liquid layer[12] resulted in a dramatic decrease in the conversion of **7**. While the poor recyclability of catalyst

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[*] Prof. Dr. Q. Yao, Y. Zhang
Department of Chemistry and Biochemistry
The Michael Faraday Laboratories
Northern Illinois University
DeKalb, IL 60115-2862 (USA)
Fax: (+1) 815-753-4802
E-mail: qyao@niu.edu

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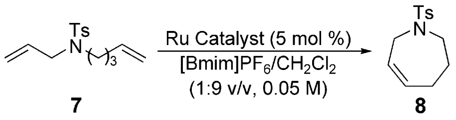
Table 1: Recycling and reuse of Ru catalysts **1** and **3** in the ring-closing metathesis of diene **7**.[a]



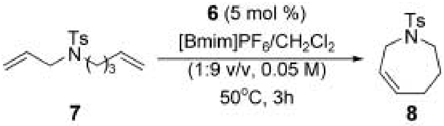
	Catalyst **1**			Catalyst **3**		
Cycle	1	2	3	1	2	3
reaction time [h]	3	3	6	3	3	6
conversion [%][b]	> 98	54	41	> 98	75	37

[a] All reactions were performed with 0.5 mmol of the substrate in the solvent system [Bmim]PF$_6$/CH$_2$Cl$_2$ (1:9 v/v, 10 mL) at 50 °C under an Ar atmosphere. [b] Determined by ^{1}H NMR spectroscopy at 500 MHz.

1 could be attributed to its known liability toward decomposition, failure to efficiently recover the more robust catalyst **3** indeed pointed to a limitation in using [Bmim]PF$_6$ as an effective means to immobilize Ru catalysts.[13]

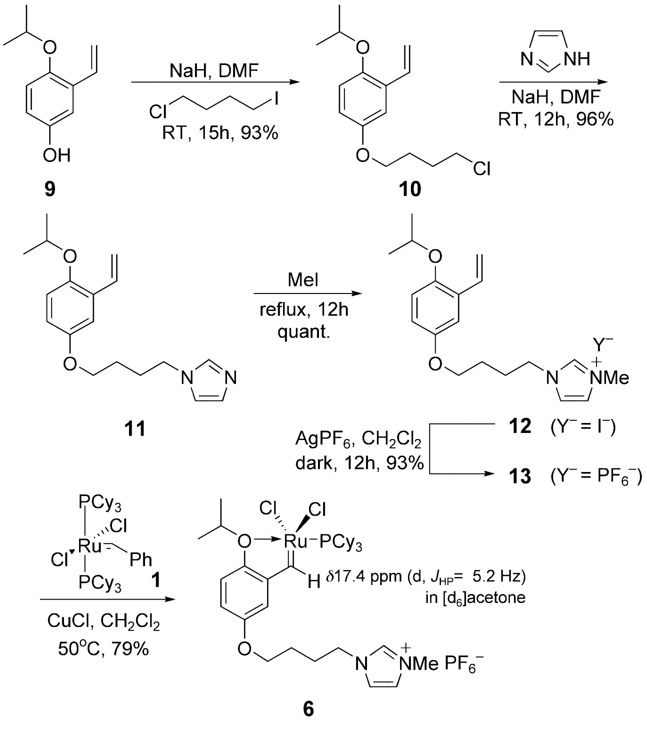
It became apparent that an enhancement in the partitioning of the Ru catalyst in the ionic liquid would ultimately be required. We further reasoned that incorporation of an ionic tag mirroring the structural motif of the ionic liquid would best meet such a requirement. To this end, ligand **13** was designed, and synthesized as shown in Scheme 1. The preparation of **13** commenced from the hydroxy-functionalized isopropoxystyrene **9**,[8] which was previously used in the synthesis of PEG-bound catalyst **5**. Alkylation of **9** with 1-chloro-4-iodobutane under standard conditions gave chloride **10**. Reaction of **10** with imidazole in the presence of NaH yielded **11** which was subsequently methylated with iodomethane to give the imidazolium iodide **12**. Anion exchange of iodide **12** with AgPF$_6$ furnished the imidazolium hexafluorophosphate **13**.[14,15] Treatment of **13** with the Grubbs catalyst **1** (first with 1.0 equiv of **1** followed by a second portion of 0.5 equiv of **1**) in the presence of CuCl in CH$_2$Cl$_2$ at 50 °C, as described by Hoveyda and co-workers,[7b] resulted in complete exchange of the styrene group to deliver the air-stable brownish powder **6**,[16] which was fully characterized by ^{1}H and ^{13}C NMR spectroscopy as well as by elemental analysis.

Table 2: Recycling and reuse of Ru catalyst **6** in the ring-closing metathesis of diene **7**.[a]



Cycle	1	2	3	4	5	6	7	8	9	10
conversion [%][b]	> 98	> 98	97	96	95	94	92	92	91	90

[a] The reactions were performed with 0.5 mmol of the substrate in the solvent system [Bmim]PF$_6$/CH$_2$Cl$_2$ (1:9 v/v, 10 mL) at 50 °C under an Ar atmosphere. [b] Determined by ^{1}H NMR spectroscopy at 500 MHz .

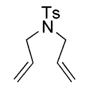
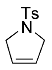
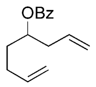
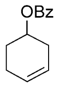
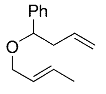
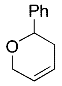
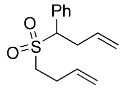
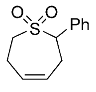
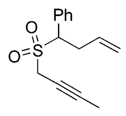
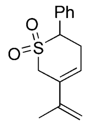
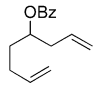
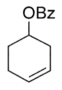


Scheme 1. Preparation of Ru carbene complex **6**.

Catalyst **6** was then evaluated for its performance toward the RCM of diene **7** under the same conditions as used for catalysts **1** and **3**. As shown in Table 2, this simple ligand modification resulted in a vast improvement over both catalysts **1** and **3**. Catalyst **6** can be recycled and reused at least 10 times with only a very slight decrease in reactivity after each run. It should be noted that the recycling of both the catalyst and the ionic liquid can simply be carried out in the air by first removing the more volatile CH$_2$Cl$_2$ under vacuum followed by extraction of the product with diethyl ether.

Having established the superior recyclability and reusability of **6**, we next examined a variety of other representative RCM substrates that lead to the formation of various carbocyclic as well as nitrogen-, oxygen-, and sulfur-containing heterocyclic compounds (Table 3). The benchmark diene substrate toluenesulfonamide **14** cyclized cleanly with high conversion under conditions similar to those used for the metathesis of **7** (entries 1 and 2). Use of a reduced amount (2.5 mol %) of the catalyst relative to the substrate also led to high conversion, even at room temperature (entry 3). The recycled catalyst/ionic liquid from the reaction of **14** was subsequently used for the metathesis of a second substrate (**16**; entry 4). The crude reaction product from **16** consists of only the cyclized product **17** and recovered **16** devoid of any detectable amount of the product from the previous reaction, thus demonstrating the practical advantage of the sequential use of a recyclable and reusable catalyst. Similarly, another batch of catalyst **6** was used to catalyze the RCM of diene **18**

Table 3: Ring-closing metathesis catalyzed by Ru complex **6** in [Bmim]PF_6/CH_2Cl_2.[a]

Entry	Substrate	(conc)	Product	Catalyst [mol %]	Conditions	Conversion [%][b] (yield [%][c])
1	 **14**	(0.05 M)	 **15**	5	50 °C, 3 h	98 (95)
2		(0.05 M)		5	50 °C, 3 h	97 (94)
3[d]		(0.1 M)		2.5	RT, 12 h	> 98 (96)
4[d]	 **16**[e]		 **17**[e]	2.5	50 °C, 4 h	95 (89)
1	 **18**[e]	(0.05 M)	 **19**[e]	5	50 °C, 3 h	98 (90)
2		(0.05 M)		5	50 °C, 3 h	96 (89)
3[g]	 **20**[f]	(0.02 M)	 **21**[f]	5	50 °C, 6 h	92 (70)
4	 **22**[f]	(0.05 M)	 **23**[f]	5	50 °C, 6 h	78 (72)
5	 **16**[e]	(0.05 M)	 **17**[e]	5	50 °C, 4 h	87 (83)

[a] Unless otherwise indicated, all reactions were performed under the following standard conditions: 0.5 mmol of substrate in the solvent system [Bmim]PF_6/CH_2Cl_2 (1:9 v/v, 10 mL) under an Ar atmosphere at the indicated temperature. [b] Determined by ^1H NMR spectroscopy at 500 MHz. [c] Yield of pure product after chromatography on silica gel. [d] Performed with 1.0 mmol of substrate. [e] Ref. [8]. [f] Ref. [17]. [g] Performed with 0.5 mmol of substrate in the solvent system [Bmim]PF_6/CH_2Cl_2 (1:24 v/v, 25 mL). Bz = benzyl.

to deliver the dihydropyran **19** for two runs with essentially equal efficacy. The recovered catalyst was then reused consecutively in the RCM of another three different substrates, each giving high yields of the respective product, without any replenishment of either the catalyst or the ionic liquid. It is noteworthy that the catalyst remained highly active (entry 5) even after being recovered from an enyne metathesis (entry 4),[17] which generates a hindered and stabilized Ru–vinylalkylidene intermediate rather than the more reactive Ru–methylidene species as in the case of the RCM of terminal dienes. Catalyst regeneration from the former intermediate would be expected to be more difficult.[18,19]

In conclusion, we have presented evidence that a task-specific modification of the bidentate ligand in **3** brings about an immense improvement in its performance as a recyclable catalyst for olefin metathesis in an ionic liquid. Given the ever-growing interest in the development of catalytic systems suitable for organic synthesis in ionic liquids, the phase-tagging strategy described here could, in principle, be applied to the immobilization of other transition-metal-based catalysts. Application of the phase-tagging ligand **13** to the immobilization of the more-powerful second-generation Grubbs catalyst **2** is currently underway in our laboratory.

Experimental Section

Ring-closing metathesis of diene **7** and general procedure for the recycling and reuse of Ru catalyst **6** and ionic liquid [Bmim]PF_6: A 25-mL oven-dried round-bottom flask equipped with a reflux condenser was charged with **6** (22.4 mg, 0.025 mmol). The flask was evacuated and filled with Ar. The ionic liquid [Bmim]PF_6 (1 mL) was then added and the flask was degassed 3 times by first evacuation and then filling with Ar. Diene **7** (140 mg, 0.50 mmol) was then added in anhydrous CH_2Cl_2 (9 mL). The flask was then heated to gentle reflux (bath temperature 45–50 °C) for 3 h. After cooling the reaction mixture to room temperature, it was concentrated under vacuum to remove the cosolvent CH_2Cl_2 and extracted with anhydrous diethyl ether (3 × 5 mL). The combined ether extracts were evaporated to give 125 mg of a crude reaction product. Examination of this crude reaction mixture by 500 MHz ^1H NMR spectroscopy revealed complete conversion of **7** and the clean formation of the cyclized product **8**. The ionic layer was dried on the vacuum line prior to its reuse in a subsequent run as described below.

A second run of the metathesis of **7** using the recycled catalyst and ionic liquid was conducted in exactly the same way as described for the first cycle, and resulted in the clean formation of **8** and complete conversion of **7**. This reaction was repeated eight more times, each time using the catalyst and ionic liquid recovered from a previous cycle. The results are listed in Table 2.

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[2] For general discussions on homogeneous catalysts and their heterogenization, see a) *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornil, W. A. Hermann)

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[12] [Bmim]PF_6 is essentially nonvolatile and almost completely insoluble in nonpolar solvents such as hexane and diethyl ether. The ionic liquid layer can be readily separated from the reaction mixture by removing the cosolvent CH_2Cl_2 under vacuum first, followed by extraction of the product and any starting material with diethyl ether.

[13] While the poor recyclability of **3** could be attributed in part to the deactivation of the catalytically active Ru–methylidene intermediate formed in the initial turnover, we believe that the diminished activity of the recovered catalyst in the ionic liquid layer is largely due to the extraction of **3** into the diethyl ether layer. To probe this possibility, a solution of *N*-tosyldiallylamine in [Bmim]PF_6/CH_2Cl_2 (1:9 v/v, 0.05 M) was treated with 5 mol% of **3** at 50°C for 2 h. After separation of the crude reaction product from the ionic liquid layer, ^1H NMR analysis revealed a complete conversion of the diene and the presence of catalyst **3** (as evidenced by its carbene signal at $\delta = 17.4$ ppm) in the crude reaction mixture. The crude reaction mixture was then dissolved in CH_2Cl_2 and recharged with another portion of the diene. After heating the reaction mixture to reflux for 2 h, it was analyzed by ^1H NMR spectroscopy, which indicated a 98% conversion of the diene. A similar reaction was performed using the recovered ionic liquid. Only 22% of the added diene was found to be converted into the cyclized product.

[14] NMR data of **13**: ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.48$ (s, 1H), 7.24 (d, $J = 17.5$ Hz, 2H), 7.03–6.98 (m, 2H), 6.82 (d, $J = 8.8$ Hz, 1H), 6.73 (dd, $J = 3.2, 8.8$ Hz, 1H), 5.72 (d, $J = 17.9$ Hz, 1H), 5.24 (d, $J = 11.4$ Hz, 1H), 4.37 (hept, $J = 6.1$ Hz, 1H), 4.20 (t, $J = 7.4$ Hz, 2H), 3.94 (t, $J = 5.9$ Hz, 2H), 3.85 (s, 3H), 2.05 (quint, $J = 7.4$ Hz, 2H), 1.74–1.80 (m, 2H), 1.30 ppm (d, $J = 6.1$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.9$, 149.6, 136.0, 131.6, 129.2, 123.5, 122.0, 117.1, 114.8, 114.4, 111.9, 72.3, 67.4, 49.8, 36.2, 27.0, 25.8, 22.2 ppm.

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[16] Data of **6**: ^1H NMR (500 MHz, $[D_6]$acetone): $\delta = 17.37$ (d, $J = 5.2$ Hz, 1H), 9.06 (s, 1H), 7.83 (s, 1H), 7.73 (s, 1H), 7.42 (d, $J = 2.7$ Hz, 2H), 7.30 (dd, $J = 2.8, 9.1$ Hz, 1H), 7.24 (d, $J = 9.1$ Hz, 1H), 5.30 (hept, $J = 6.0$ Hz, 1H), 4.51 (t, $J = 7.3$ Hz, 2H), 4.13 (t, $J = 6.0$ Hz, 2H), 4.07 (s, 3H), 2.41 (m, 3H), 2.22–1.26 (m, 34H), 1.75 ppm (d, $J = 6.2$ Hz, 6H); ^{13}C NMR (125 MHz, $[D_6]$acetone): $\delta = 154.5$, 147.1, 144.2, 137.0, 124.0, 122.6, 115.4, 113.8, 107.3, 75.2, 67.8, 49.5, 36.0, 35.4 (d, $J_{CP} = 25.3$ Hz), 29.8, 27.5 (d, $J_{CP} = 10.1$ Hz), 27.0, 26.1, 25.7, 21.5 ppm; elemental analysis (%) calcd for $C_{36}H_{58}Cl_2F_6N_2O_2P_2Ru$: C 48.11, H 6.50, N 3.12; found: C 48.09, H 6.45, N 3.05.

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