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Ring-closing metathesis in biphasic BMI·PF_6 ionic liquid/toluene medium: a powerful recyclable and environmentally friendly process†

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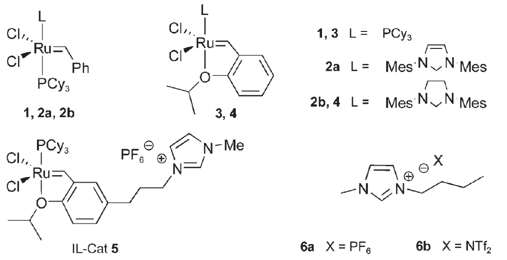
Biphasic BMI·PF_6/toluene solvent is a remarkably suitable and clean medium for performing olefin metathesis with a new 2nd generation ionic liquid supported-ruthenium catalyst: high levels of recyclability and reusability combined with a high reactivity were obtained with a variety of di- or tri-substituted and/or oxygen-containing dienes, and very low residual ruthenium levels were detected (1 to 22 ppm) in the products.

Olefin metathesis[1] has received considerable attention in synthetic organic chemistry since the development of well-defined homogeneous ruthenium carbene complexes **1**[2] and **2**,[3] which are easy to handle and extremely tolerant towards different functional groups. However, the major disadvantages of the use of these homogeneous catalysts are their poor recyclability and the difficulty of removing the ruthenium waste from the product. Hoveyda and co-workers have achieved spectacular improvements by the development of recyclable catalysts **3**[4a] and **4**[4b] based on a "release–return" olefin metathesis mechanism. This concept of recoverable and recyclable transition-metal-based catalysts has become extremely important from both an environmental and economic viewpoint and various strategies have been employed for their immobilization on different supports.[5]



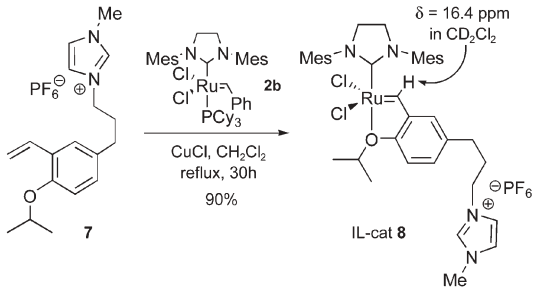
Because of their interesting properties such as ease of reuse, non-volatility and good ability to dissolve many kinds of organic and organometallic compounds, Room Temperature Ionic Liquids (RTILs) are promising candidates to replace volatile solvents traditionally used in organic chemistry.[6] In order to develop a more environmentally friendly RCM process in these new clean media, we[7] and others[8] have recently immobilised the ruthenium catalyst **3** in 1-butyl-3-methylimidazolium hexafluorophosphate (BMI·PF_6) **6a** by anchoring an imidazolium tag on the styrenyl ligand. Our first generation of ionic liquid-supported ruthenium complex **5** has been extremely suitable for performing RCM in BMI·PF_6 for various diene substrates and can be used several times. However, in the case of sterically demanding olefins **9**, because harsher conditions were necessary to complete the RCM reaction, our IL-catalyst **5** proved to be efficient only for the first two cycles. The rapid thermal decomposition of the catalyst system led us to develop a more efficient IL-catalyst, based on the well-defined ruthenium complexes **4** bearing an *N*-heterocyclic carbene (NHC) ligand, which promoted remarkable thermal stability and better general activity.[3] Herein, we report the synthesis of the IL-phosphine free *N*-heterocyclic carbene complex **8** and its use in a biphasic BMI·PF_6/toluene medium.

The ruthenium IL-catalyst **8** was easily obtained from the 2nd generation Grubbs'catalyst **2b** by a simple exchange of the styrene group following the procedure described by Hoveyda and co-workers[4] (Scheme 1). The hexafluorophosphate imidazolium styrenyl ether ligand **7**[7] was treated with a slight excess of **2b** in the presence of CuCl. After a crystallisation in a toluene/dichloromethane mixture, pure IL-catalyst **8** was isolated in 90% yield as an air stable green powder.

We have investigated the activity of IL-catalyst **8** in RTILs in the ring closing metathesis of the trisubstituted diene **9**, as shown in Table 1. Although high conversions were obtained for the first three cycles in BMI·PF_6 solvent at 60 °C, they decreased rapidly to 16% at the fifth cycle (entry 1). At 40 °C (entry 2), only 76% conversion was obtained after the first run due to the high viscosity of BMI·PF_6 at this temperature, which led to reduced catalyst mobility. Replacement of BMI·PF_6 solvent by less viscous RTILs, such as BMI·NTf_2 **6b**, increased the recyclability of the catalyst. However, because of the partial miscibility of toluene in BMI·NTf_2, product extraction proved complicated.

To overcome these problems, a volume of toluene was added in the IL medium and the RCM reaction performed under biphasic conditions. With a 50/50 (v/v) BMI·PF_6/toluene mixture, a 63% conversion was achieved after the sixth run. By increasing the volume of toluene (25/75 BMI·PF_6/toluene), we improved considerably the recycling and reuse of the catalyst. Because the IL-catalyst **8** is a recyclable catalyst based on a "release–return" olefin metathesis mechanism[4b], we assume that, during reaction, the ligand–ruthenium bond is cleaved, allowing the 14-electron ruthenium catalytic specie to reside preferentially in the toluene phase. Once the substrate has been consumed, this active complex returns to the BMI·PF_6 by reattachment to the styrenyl ether ligand **7**. In this way, the RCM reaction with IL-catalyst **8** is even feasible at room temperature in a 25/75 BMI·PF_6/toluene mixture. Thus, a higher level of recyclability (8 cycles) was obtained when the metathesis reaction was carried out at 25 °C (entry 5) and excellent conversions were obtained with an equal length of time (3 h).

Additionally, one major problem in the use of the olefin metathesis reactions (especially in the production of biologically



Scheme 1 Synthesis of the 2nd generation ionic liquid immobilised ruthenium complex **8**.

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b4/b407964g/

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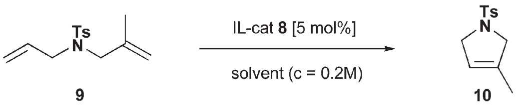
Table 1 Optimisation in the RCM of trisubstituted diene **9** with the IL-catalyst **8** and ruthenium contaminant level in cyclised product **10**



Entry	Solvent	Conditions	Cycle/conversion (%)[a] 1	2	3	4	5	6	7	8
1	$\mathrm{BMI{\cdot}PF_6}$	60 °C,3 h	>98	97	91	68	16	—	—	—
2	$\mathrm{BMI{\cdot}PF_6}$	40 °C,4 h	76	—	—	—	—	—	—	—
3	$\mathrm{BMI{\cdot}NTf_2}$	40 °C,4 h	>98	>98	91	89	74	50	—	—
4	$\mathrm{BMI{\cdot}PF_6}$ /toluene 50/50	40 °C,3 h	>98	>98	>98	96	85	63	—	—
5	$\mathrm{BMI{\cdot}PF_6}$ /toluene 25/75	25 °C,3 h	>98	>98	>98	>98	>98	>98	95	95
	Ru residue (ppm)[b]		16.9	5.4	1.6	3.3	1.2	22	5.7	2.3

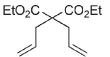
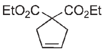
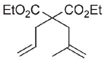
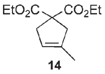
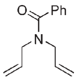
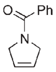
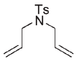
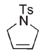
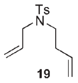
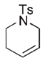
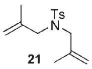
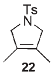
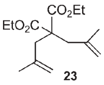
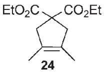
[a] Determined by ^{1}H NMR (400 MHz). [b] Determined by ICP-MS spectroscopic analysis.

active compounds) is the toxic ruthenium waste, which is very difficult to remove from the product (even after repeated purification by silica gel column chromatography). Several research groups have developed efficient methods for removal of ruthenium by-products[9] and the residual ruthenium levels have been reduced, in the best case, to 200–40 ppm of products. In our work, after each cycle using IL-catalyst **8** in the above biphasic approach, the residual ruthenium levels were determined. ICP-MS spectroscopic analysis of RCM product **10**, obtained employing optimum reaction and recycling conditions (entry 3), revealed very low residual ruthenium levels (between 1.2 to 22 ppm). The average value over eight cycles (7.3 ppm) is approximately an order of magnitude lower than the best previously reported methods.[9b–d]

Having established the recyclability and reuse of IL-catalyst **8**, we evaluated its activity in the RCM of several diene substrates at room temperature or at 40 °C (Table 2). Excellent conversions were obtained in all cases (entries 1 to 6) for up to eight cycles. As an example, we also measured the residual ruthenium level for the first run of diethyl diallylmalonate **11** and only 2.5 ppm were detected in the cyclised product **12**. Finally, to examine the scope of IL-catalyst **8**, we focused on its performance with the tetra-substituted dienes **21** and **23**, which are known to be extremely difficult substrates. The IL-catalyst proved to be efficient only for the first run for **21**, and inactive for **23** (entries 7 and 8), showing the limitation of the catalyst activity. Nevertheless, remarkably, as shown by the excellent conversions observed in successive runs with the disubstituted diene **17**, the recovered catalyst still remained highly active, attesting to the stability and the high level of recyclability of IL-cat **8** in the $\mathrm{BMI{\cdot}PF_6}$/toluene medium at higher temperature.

In summary, we have developed a powerful recyclable IL-phosphine free *N*-heterocyclic carbene ruthenium complex to perform metathesis reactions in a $\mathrm{BMI{\cdot}PF_6}$/toluene biphasic medium. High level of recyclability and reusability combined with a high reactivity were obtained for the RCM of several substrates including tri-substituted and/or oxygen-containing dienes. The low residual ruthenium levels in the RCM products promote this environmentally friendly RCM process in synthesis. A study of its use in cross-metathesis reaction is under way in our laboratory and will be reported in due course.

Table 2 Activity and recyclability of IL-catalyst **9** in the RCM of various dienes

Entry	Substrate	Product	Conditions	Cycle/conversion (%)[a]			
1	 **11**	 **12**	**[2.5 mol%]** 25 °C,3 h	1	>98	5	>98
				2	>98	6	>98
				3	>98	7	95
				4	>98	8	95
2	 **13**	 **14**	**[2.5 mol%]** 40 °C,6 h	1	>98	5	>98
				2	>98	6	>98
				3	>98	7	83
				4	>98	8	33
3	 **15**	 **16**	**[2.5 mol%]** 25 °C,3 h	1	>98	5	>98
				2	>98	6	94
				3	>98	7	81
				4	>98	8	36
5	 **17**	 **18**	**[2 mol%]** 25 °C,3 h	1	>98	5	>98
				2	>98	6	>98
				3	>98	7	96
				4	>98	8	94
6	 **19**	 **20**	**[2 mol%]** 25 °C,3 h	1	>98	5	>98
				2	>98	6	>98
				3	>98	7	94
				4	>98	8	92
7	 **21**	 **22**	**[5 mol%]** 60 °C,7 h	1	65		
				2	0		
				3[b]	**94**		
				4[b]	**90**		
8	 **23**	 **24**	**[5 mol%]** 60 °C,24 h	1	0		
				2[b]	**>98**		
				3[b]	**>98**		

[a] Determined by ^{1}H NMR spectroscopic analysis at 400 MHz. [b] Reaction performed with **17** at 25 °C for 3 h.

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