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Ruthenium-Catalyzed Olefin Metathesis in Ionic Liquids

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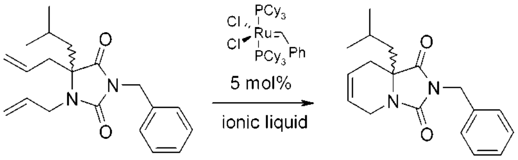
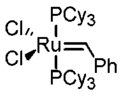
ABSTRACT

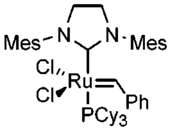


Ionic liquid 1-butyl-3-methylimidazoliumhexafluorophosphate ([bmim]PF$_6$) is described as an effective medium for ring-closing metathesis (RCM) using Grubbs catalysts. When [bmim]PF$_6$ was used as solvent, the RCM showed high conversions and a broad substrate tolerance. [bmim]PF$_6$ and the ruthenium catalyst were recycled after extraction of the product in the organic phase for at least three cycles.

Ring-closing metathesis (RCM) is widely recognized as a powerful method for creating heterocycles, constrained peptides, and complex natural products.[1] The Grubbs ruthenium catalysts **1**[2] and **2**[3] have been used most extensively in RCM because of their high reactivity, air-stability, and remarkable functional group tolerance. However, the fact that these catalysts are nonrecyclable and can only be removed from the product by repeated chromatography severely hampers their use in industrial processes. Several groups have recently identified elegant solutions for this problem. Grubbs[4] reported the removal of ruthenium complexes by exchange of their hydrophobic ligands with hydrophilic ligands followed by aqueous extraction. Other methods rely on catalyst immobilization by a solid support[5] or on removal of the catalyst by treatment with Pb(OAc)$_4$,[6] Ph$_3$PO, or DMSO.[7]



1



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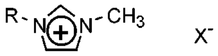

3a R=butyl, X=BF$_4$
3b R=butyl, X=PF$_6$
3c R=octyl, X=BF$_4$
3d R=octyl, X=PF$_6$
3e R=octyl, X=SbF$_6$

In this Letter we present another viable alternative by employing room temperature ionic liquids.

Ionic liquids are a new class of solvents entirely composed of ions. Their use as an environmentally friendly alternative for conventional solvents has gained much attention recently.[8] Ionic liquids are known to be nonvolatile, nontoxic, reusable, and compatible with many organic reactions.[9] Some ionic liquids are immiscible with water and organic solvents, giving triphasic ionic liquid systems, which enables easy extraction of products from the ionic liquid.[10] Our specific interest in ionic liquids was drawn by recent disclosures that

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[1] For recent reviews on olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**. *39*, 3012.

[2] Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9858.

[3] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

[4] Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137.

[5] (a) Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, P. A. *Tetrahedron Lett.* **1999**, *40*, 8657. (b) Schürer, S. C.; Gessler, S.; Buschmann, N.; Blechert, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3898. (c) Yao, Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 3896.

[6] Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Méndez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259.

[7] Ahn, Y. M.; Yang, K.-L, Georg, G. I. *Org. Lett.* **2001**, *3*, 1411.

[8] For recent reviews on ionic liquids, see: Welton, T. *Chem. Rev.* **1999**, *99*, 2071. Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772. Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 351.

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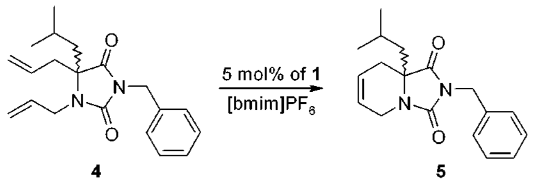
these novel solvents dissolve and stabilize many organometallic catalysts,[11] thus providing an excellent medium for recycling.

Initial studies at our laboratory were aimed at investigating the viability of performing a RCM[12] in the most frequently used ionic liquid, 1-butyl-4-methylimidazolium hexafluorophosphate [bmim]PF_6 (i.e., liquid **3b**), using compound **4**[13] as a substrate (see Scheme 1). When a temperature of 50 °C was applied, a substrate concentration of 55 mg/mL and 5 mol % of catalyst resulted in complete formation to the bicyclic hydantoin **5** after 20 h. Isolation of the product could easily be accomplished by extraction with diethyl ether. Next, recycling of the catalyst was studied using the residual solution for the next reaction cycle. Unfortunately, the RCM only showed 15% conversion after 20 h. This poor result could have been caused either by the decomposition of the catalyst or by extraction of the catalyst to the organic phase.

Scheme 1



To find the optimal ionic liquid in terms of conversion and catalyst leakage, we first studied the RCM of **4** in five different ionic liquids (**3a**−**e**) and combinations thereof (1:1, 1:2, and 1:3). Only seven of the 54 reactions gave over 69% conversion, the products of which were subsequently evaluated on their ruthenium content using ICP-AES analysis[14] (see Table 1). These studies clearly indicated that [bmim]PF_6 (entry 2) is the best solvent, giving a 98% conversion of **4** and a ruthenium contamination of 3.2 μg per mg of product. On the basis of the low ruthenium content observed in the products, it can be concluded that the catalyst remains present in the ionic liquid and the poor recycling is most probably caused by catalyst decomposition. With the objective of reducing catalyst decomposition, further efforts were aimed at optimizing the reaction time. Spectacular results were obtained by increasing the temperature to at least 80 °C (see Table 2), which reduces the reaction time 20-fold. Optimal substrate concentration and amount of catalyst were studied in a series of reactions depicted in Figure 1. From these studies it can be concluded that the substrate concentration should not exceed 30 mg/mL and that the biggest change in conversion at this concentration occurs going from 3 to 5 mol % of catalyst.[15]

Table 1. Conversions of RCM[a] in Different (Mixtures of) Ionic Liquids and Ru Contaminant Level in RCM Product **5**

entry	solvent	ratio (v:v)	convn (%)[b]	Ru residue, μg/mg
1[c]	DCM		100	1.7
2	**3b**		98	3.2
3	**3b**:**3a**	1:1	95	9.7
4	**3b**:**3d**	1:1	77	5.2
5	**3b**:**3c**	2:1	77	6.3
6	**3b**:**3e**	2:1	81	5.4
7	**3b**:**3c**	3:1	92	5.2
8	**3b**:**3e**	3:1	69	3.6

[a] All reactions were performed at 50 °C, a substrate concentration of 55 mg/mL, and 5 mol % of **1** for 24 h. [b] Conversions were measured after extraction with diethyl ether and subsequent HPLC analysis. [c] Reaction in DCM was evaporated after 1 h, and product was purified using silica column chromatography.

Table 2. Influence of Temperature on RCM in [bmim]PF_6[a]

entry	temp (°C)	convn (%)[b]
1	50	30
2	60	68
3	70	88
4	80	100
5	90	100
6	100	100

[a] Reactions were performed using **4** with a concentration of 55 mg/mL and 5 mol % of **1** for 1 h. [b] Conversions were measured after extraction with diethyl ether and subsequent HPLC analysis.

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(9) For some examples of organic reactions in ionic liquids, see the following. Alkylation: Earle, M.; McCormac, P. B.; Seddon, K. R. *Chem. Commun* **1998**, 2245. Beckmann rearrangement: Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 403. Diels−Alder reaction: Fisher, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793. Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, 23. Friedel−Crafts reactions: Adams, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R *Chem. Commun* **1998**, 2097. Oxidation of aldehydes: Howarth, J. *Tetrahedron Lett.* **2000**, *41*, 6627. Reduction of aldehydes: Kabalka, G.; Malladi, R. R. *Chem. Commun*. **2000**, 2191. Wittig reaction: Le Boulaire, V.; Gree, R. *Chem. Commun.* **2000**, 2195.

(10) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 977.

(11) For some examples of transition-metal catalyzed reactions in ionic liquids, see the following. (Asymmetric) epoxidation: Owens, G. S.; Abu-Omar, M. M. *Chem. Commun.* **2000**, 1165. Song, C. E.; Roh, E. J. *Chem. Commun*. **2000**, 837. Asymmetric hydrogenation: Brown, R. A.; Polett, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254. Asymmetric ring opening of epoxides: Song, C. E.; Rim Oh, C.; Roh, E. J.; Choo, D. J. *Chem. Commun.* **2000**, 1743. Aza-Diels−Alder reaction: Zulfiqar, F.; Kitazume, T. *Green Chem.* **2000**, 137. Coupling of aryl halides: Howarth, J.; James, P.; Dai, J. *Tetrahedron Lett.* **2000**, *41*, 10319. Suzuki cross-coupling: Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun.* **2000**, 1249. Heck arylation of vinyl ethers: Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett.* **2001**, *3*, 295. Heck reaction: Kaufmann, D. E.; Nouzoorian, M.; Henze, H. *Synlett* **1996**, *7*, 1091. Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 977. Hydrogenation/hydroformylation: Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2698. Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; De Souza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 1217. Wasserscheid, P.; Waffenschmidt, H.; Machnitzki, P.; Kottsieper, K. W.; Stelzer, O. *Chem. Commun.* **2001**, 451. Negishi cross-coupling: Sirieix, J.; Ossberger, M.; Betzemeier, B.; Knochel, P. *Synlett* **2000**, *11*, 1613. Pd-catalyzed allylation reaction: Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun.* **1999**, 1247. Stille coupling: Handy, S. T.; Zhang, X. *Org. Lett.* **2001**, *3*, 233. Trost−Tsuji reaction: Toma, S.; Gotov, B.; Kmentova, I.; Solcaniova, E. *Green Chem.* **2000**, 149.

(12) Ru-catalyzed RCM in ionic liquids has been described in a recent patent application. Gurtler, C.; Jautelat, M. EP 1035093 A2, 2000. First example of an olefin metathesis (Ni-catalyzed) in ionic liquids has been described by Chauvin, Y.; Olivier-Bourbigou, H. *CHEMTECH* **1995**, *9*, 26.

(13) Dyatkin, A. B. *Tetrahedron Lett.* **1997**, *38*, 2065.

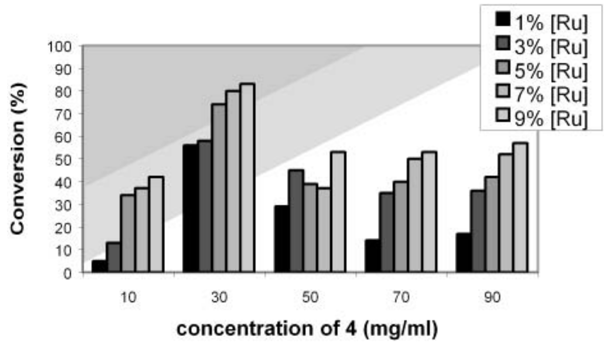


Figure 1. Influence of mol % of **1** and concentration of **4** on RCM in [bmim]PF_6. Reactions were performed at 60 °C for 30 min; conversions were measured after extraction with diethyl ether and subsequent HPLC analysis.

Having established the optimal reaction conditions, attention was focused on recycling of the catalyst in [bmim]PF_6. Interestingly, the catalyst proved to be stable in at least three consecutive runs, although the third run resulted in a markedly decreased conversion (see Table 3, entry 3). The recycling potential of the more robust dihydroimidazole catalyst **2** was also investigated. As expected, this catalyst showed an increased conversion in the third cycle. Moreover, the use of **2** resulted in products having less ruthenium contamination than that obtained with catalyst **1**. Contamination levels are now well in the range of those obtained by other methods.[4−7]

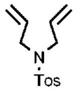
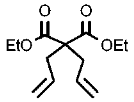
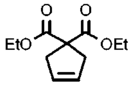
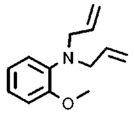
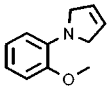
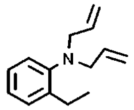
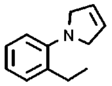
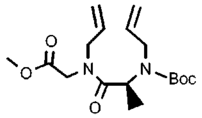
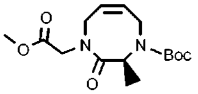
Table 3. Recycling of **1** and **2** and Ru Contaminant Level in RCM Product **5**[a]

entry	catalyst	recycling	convn (%)[b]	Ru residue, μg/mg
1	**1**		97	3.9
2	**1**	entry 1	94	4.8
3	**1**	entry 2	61	5.3
4	**2**		95	1.6
5	**2**	entry 4	88	1.6
6	**2**	entry 5	74	1.3

[a] All reactions were performed at 80 °C, a substrate concentration of 30 mg/mL, and 5 mol % of catalyst for 1 h. [b] Conversions were measured after extraction with ether and subsequent HPLC analysis.

To establish the general applicability of this method, we tested the RCM in [bmim]PF_6 on several substrates. As shown in Table 4, conversions of substrates were satisfactory and comparable to those obtained in DCM (entries 1 and 2). In some cases (entries 3−5) the conversions of the RCM were even slightly better in ionic liquid.

Table 4. RCM of Different Substrates in [bmim]PF_6[a]

entry	substrate	product	time (h)	conversion[b] (%)
1			1	100 (100)
2			1	100 (100)
3			20	75 (61)
4			20	73 (64)
5[c]			1	75 (67)

[a] All reactions were performed at 80 °C, a substrate concentration of 30 mg/mL, and 5 mol % of **1** for 1 h. [b] Conversions were measured ^1H NMR analysis of the crude reaction mixture after extraction with ether. The numbers in parentheses represent the conversion of the RCM in DCM. [c] Reaction was allowed to run for 20 h.

In summary, we have established that ionic liquid [bmim]PF_6 is an excellent solvent in which to carry out the RCM. The reaction proceeds readily with a variety of substrates, and the resulting products could be separated from the ionic liquid in a straightforward manner. Furthermore, it is possible to efficiently reuse the catalyst and ionic solvent.

Acknowledgment. The autors thank Aard Florijn (N.V. Organon) for the ICP-AES measurements. Huib Ovaa (Leiden University) is acknowledged for a sample of catalyst **2**.

Supporting Information Available: Spectroscopy data and analytical data of compounds prepared in Table 4. This material is available free of charge via the Internet at http//pubs.acs.org.

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(14) All ICP-AES (inductively coupled plasma−atomic emission spectrometer) samples were prepared first by accurately weighing the samples (~4 mg) and then adding 10 mL of 0.12 M hydrochloric acid in glacial acetic acid. To correct for matrix effects, a Pt standard was added to the sample (100 μL, 1 mg Pt/mL, Baker Instra analyzed, AAS standard). Samples were analyzed on a Perkin-Elmer Optima 3000 ICP-AE spectrometer. Intensities of spectral lines at 240.272 and 349.894 nm were measured in all samples and standards. The Ru level in the samples was determined by comparing the intensity of the spectral line with a ruthenium standard curve. Each sample was measured three times, and the average Ru contaminant level of these measurements has been reported.

(15) **General procedure for RCM in ionic liquid:** To a reaction tube was added 1,5-diallyl-3-benzyl-5-isobutylimidazolidine-2,4-dione (**4**) (9 mg, 28 μmol) which was dissolved in [bmim]PF_6 (300 μL) by heating to 80 °C for 10 min under a flow of nitrogen gas. Grubbs catalyst **1** (1.1 mg, 1.4 μmol, 5 mol %) was subsequently added to the reaction mixture. The reaction was stirred for 1 h at 80 °C, afterwhich the reaction mixture was extracted with diethyl ether (3 × 1 mL). The combined organic layers were concentrated in vacuo, which yielded a slightly colored oil (8.2 mg, 27.4 μmol, 98%). TLC analysis ($R_f = 0.40$ (heptane/EtOAc, 6/4, v/v)) indicated complete formation of **5**. ^1H NMR ($CDCl_3$): δ 7.44−7.22 (m, 5H), 5.73 (s, 2H), 4.68 (s, 2H), 4.44 (d, 1H), 3.56 (d, 1H), 2.25 (d, 2H), 1.88 (m, 2H), 1.55 (q, 1H), 0.83 (d, 3H), 0.61 (d, 3H). ESI-MS: $[M + H]^+$ 299.