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A Basic Ionic Liquid as Catalyst and Reaction Medium: A Rapid and Simple Procedure for Aza-Michael Addition Reactions

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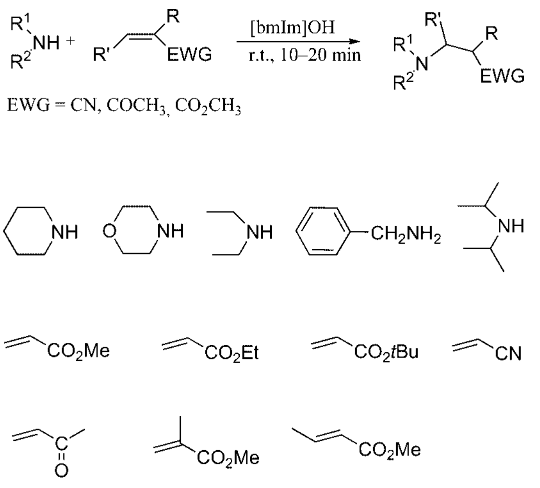
A fast, mild, and quantitative procedure for Michael addition reactions between various amines and α,β-unsaturated carbonyl compounds and nitriles in the presence of an easily accessible basic ionic liquid – 3-butyl-1-methylimidazolium hydroxide, [bmIm]OH – as both catalyst and reaction medium has been developed. For large-scale reactions the products could be directly distilled from the ionic liquid, allowing the use of organic solvents to be avoided totally. The ionic liquid could be reused at least eight times with consistent activity and was stable during the reaction process.

Introduction

The aza-Michael reaction is an important reaction in organic chemistry, especially for the synthesis of C-N heterocycles[1] containing the β-aminocarbonyl functionality, which not only constitutes a component of biologically active natural products but also serves as an essential intermediate in the synthesis of β-amino ketones, β-amino acids, and β-lactam antibiotics.[2] Such aza-Michael reactions have generally been promoted by harsh bases or strong acids, which give rise to environmentally hazardous residues and undesirable by-products.[3] With the goal of avoiding the typical disadvantages resulting from the presence of such catalysts, a large number of alternative procedures have been developed in the past few years.[4] Unfortunately, though, many of these procedures require long reaction times, rigorous reaction conditions, large excesses of reagents, and/or highly damaging chemicals. In many cases the catalyst and excess reagents have not been recoverable, which has strongly limited industrial applications. The development of an environmentally benign and simple procedure for aza-Michael addition has thus become particularly fascinating and remains a great challenge.

Room temperature ionic liquids have attracted increasing attention as the green, high-tech reaction media of the future,[5] while it has also been reported that ionic liquids containing imidazolium cations can act as powerful media in some catalytic organic reactions not only for the facilitation of catalyst recovery but also for the acceleration of the reaction rate and improvement of selectivity.[6] Since the first successful use of an ionic liquid, dialkylimidazolium chloroaluminate, as a catalyst in Friedel–Crafts acylations,[6a,6b] a number of ionic liquids containing stable acidic[7] or neutral anions[8] have been developed and successfully applied to catalyze many types of reactions. Relevant reports about ionic liquids containing stable basic anions, however, were relatively scarce: supported choline hydroxide has been used as a basic catalyst for aldol condensation reactions between several ketones and aldehydes,[9] while the basic ionic liquid [bmIm]OH has been successfully applied to catalyze Michael additions of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles.[10] We found that [bmIm]OH could also be used as an efficient catalyst for Markovnikov additions of *N*-heterocycles and vinyl esters,[11] while Ranu and co-workers have recently employed it in Knoevenagel condensations of aliphatic and aromatic carbonyl compounds.[12] In view of these elegant discoveries of catalytic activity in basic ionic liquids, we envisaged that



Scheme 1. Michael additions between amines and α,β-unsaturated carbonyl compounds.

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basic ionic liquids might also catalyze aza-Michael additions efficiently, and here we report for the first time the use of [bmIm]OH both as a novel and recyclable reaction medium and as an efficient catalyst for Michael additions between amines and α,β-unsaturated compounds to afford the corresponding 1,4-adducts in high yields at room temperature (Scheme 1).

Results and Discussion

Basic ionic liquids were synthesized by anion exchange with the corresponding imidazolium chlorides by the literature methods, with a slight modification,[13] and were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. We first compared the catalytic effects of different ionic liquids for aza-Michael addition reactions, and the results are summarized in Table 1. When the basic ionic liquid [bmIm]OH was used to catalyze the reaction between piperidine and methyl acrylate, a quantitative yield was obtained in 10 min (Table 1, Entry 1), but only moderate yields were obtained for some neutral ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmIm]PF_6) and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmIm]BF_4) (Table 1, Entries 4 and 5). The result was quite interesting, showing that ionic liquids with longer cation carbon chain lengths exhibited relatively higher Michael addition activity (Table 1, Entries 1 and 2). Some blank experiments to demonstrate the catalytic capabilities of [bmIm]OH were also carried out. When the reaction was carried out in some molecular solvents such as THF and DMSO in the absence of [bmIm]OH, it was observed that the addition reaction between piperidine and methyl acrylate produced the corresponding product in less than 30% yield in 48 h (Table 1, Entries 6 and 7). Interestingly, when a small amount (5%) of [bmIm]OH was added to neutral ionic liquids such as [bmIm]BF_4 and [bmIm]PF_6, the reaction could then also achieve 93% and 91% yields, respectively. All these results showed that the ionic liquid [bmIm]OH was playing a significant catalyst role during the reaction process, as well as serving as the reaction medium.

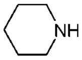
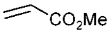
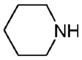
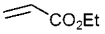
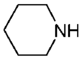
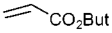
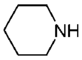
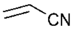
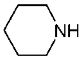
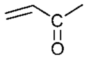
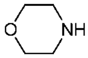
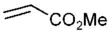
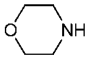
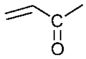
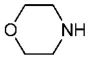
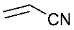
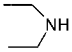
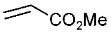
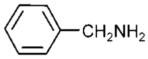
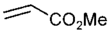
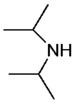
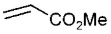
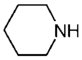
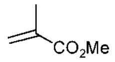
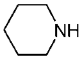
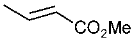
Table 1. Aza-Michael reaction between piperidine and methyl acrylate under different reaction conditions.[a]

Entry	Solvent	Time	Yield [%][b]
1	[bmIm]OH	10 min	98
2	[emIm]OH	10 min	94
3	[bdmim]OH	10 min	95
4	[bmIm]BF_4	10 min	60
5	[bmIm]PF_6	10 min	55
6	THF	2 d	15
7	DMSO	2 d	30

[a] Reaction conditions: piperidine (1.0 mmol), methyl acrylate (1.2 mmol), solvent (1 mL) at room temperature. [b] Isolated yield.

With optimal conditions to hand, we next examined the generality of this strategy for other substrates, and the results are summarized in Table 2. All the reactions proceeded smoothly in [bmIm]OH without the need for any other catalyst, to provide the corresponding 1,4 adducts in high yield. The products obtained could be isolated by simple extraction with diethyl ether, and the ionic liquid could be further washed with diethyl ether and reused several times without further purification. All the Michael adducts obtained were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Interestingly, no by-product generated from 1,2-addition, polymerization, hydrolytic reaction, or any other reaction was detected by TLC and GC-MS.

Table 2. [bmIm]OH-Catalyzed Michael reactions between amines and α,β-carbonyl compounds or nitriles.[a]

Entry	Amine	α,β-Unsaturated compounds	Time [min]	Yield [%][b]
1			10	98
2			15	97
3			20	98
4			10	98
5			10	95
6			10	97
7			10	93
8			10	98
9			10	92
10			20	80[c]
11			90	76
12			90	88
13			90	85

[a] Reaction conditions: amines (1 mmol), α,β-unsaturated compounds (1.2 mmol) in [bmIm]OH (1 mL) at 25 °C. [b] Isolated yield. [c] The bis adduct (5%) was formed.

The Michael addition between piperidine and methyl acrylate proceeded smoothly at ambient temperature and an almost quantitative yield was obtained after 10 min (Table 2, Entry 1). As the carbon chain length of the alcohol moiety increased, the reactivity decreased (Table 2, Entries 1–3). Apart from acrylate ester, acrylonitrile and methyl vinyl ketone could also provide quantitative yields in short reaction times (Table 2, Entries 4 and 5).

Sterically hindered Michael acceptors such as methyl methacrylate and methyl crotonate were tested under the same conditions (Table 2, Entries 12 and 13). Both acceptors reacted readily with piperidine to give the corresponding 1,4 adducts in high yields with relatively longer reaction times. In general, secondary amines gave higher yields than the primary amines, while in the case of benzylamines the bis adducts (5%) were also formed (Entry 10). Sterically hindered amines were found to be less active and gave only moderate yields (Table 2, Entry 11).

In order to demonstrate the scope of the practical applicability of this methodology, the Michael reaction between piperidine and methyl acrylate was carried out on a larger scale (200 mmol) in [bmIm]OH (5 mL). The reaction was complete in 15 min (TLC) and the excess methyl acrylate was evaporated off and recycled. The product was distilled directly from the reaction vessel under reduced pressure, to provide the corresponding 1,4-adduct in 99% yield, while the remaining [bmIm]OH was reused without any additional operation. The reaction was repeated eight times and the results are shown in Figure 1. It can be seen that the ionic liquid [bmIm]OH remained consistent activity during the reaction. This process totally avoided the use of organic solvents and almost quantitative yields were obtained. Consequently, it was a green synthetic method and suitable for industrial application.

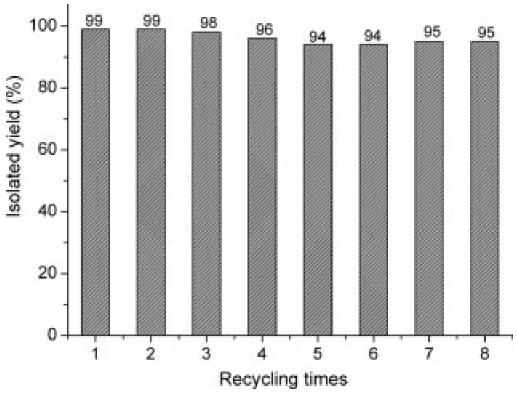


Figure 1. Recycling of [bmIm]OH in the large-scale Michael addition between piperidine and methyl acrylate. Reaction conditions: piperidine (200 mmol), methyl acrylate (240 mmol) in [bmIm]OH (5 mL) at room temperature in 15 min.

The role of [bmIm]OH in the Michael addition was worthy of exploration. It had been reported that acidic C2–H components in ionic liquids could interact with carbonyl groups and influence reaction results,[14] so in order to investigate the role of acidic C2–H in our reaction system some control experiments were performed. When the ionic liquid 1-butyl-2,3-dimethylimidazolium hydroxide ([bdmIm]OH) was used to catalyze the Michael addition between piperidine and methyl acrylate, a 95% isolated yield was obtained in 10 min (Table 1, Entry 3). This result was comparable with that obtained in [bmIm]OH, indicating that the acidic C2–H unit in [bmIm]OH was not playing a significant role in the catalysis. We thus speculated that catalysis by the basic ionic liquid [bmIm]OH may attributable to the following factors. Firstly, amines exhibited higher nucleophilicity in ionic liquids than in organic solvents.[15] On the other hand, the hydroxide anion of the ionic liquid [bmIm]OH might assist in the formation of nucleophilic anions generated from amines, which should increase the nucleophilicity of amines further, as has been demonstrated by a ^{13}C NMR experiment in our former work.[11]

The [bmIm]OH remained intact during the reaction process according to ^{1}H NMR analysis of the recovered ionic liquid. The aza-Michael addition reactions were carried out under ambient conditions and were capable of going to completion in 10–20 minutes, which might suppress side reactions due to carbene formation by imidazolium-based ionic liquids in the presence of strong bases.[16] This basic ionic liquid [bmIm]OH was thus stable under this procedure.

Conclusions

The basic ionic liquid [bmIm]OH provides a convenient, clean, efficient, and recyclable catalytic medium for Michael addition reactions between various amines and α,β-unsaturated compounds, thus substituting for volatile organic solvents and toxic catalysts. Furthermore, the products can be distilled directly from the ionic liquid in large-scale reactions, thus totally avoiding the use of any organic solvent. The ionic liquid can be reused for at least eight runs without loss of activity, thanks to which it exhibits industrial potential. Furthermore, the ionic liquid was stable during the reaction process. More applications (forming C–O, C–S, and C–C bonds) of the Michael addition reactions promoted by this task-specific ionic liquid [bmIm]OH are under development in our laboratories.

Experimental Section

Materials and General Methods: ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ with a Bruker AVANCE DMX 500 spectrometer at 500 MHz and 125 MHz, respectively. Chemical shifts are reported in ppm (δ), relative to tetramethylsilane (TMS) as the internal standard. IR spectra were measured with a Nicolet Nexus FTIR 670 spectrophotometer. All chemicals were obtained from commercial suppliers and were used without further purification. Solvents for column chromatography were distilled before use.

General Procedure for the Synthesis of Basic Ionic Liquid: [bmIm]-OH was prepared by passing the corresponding imidazolium halide ([bmIm]Cl) through a column filled with anion-exchange resin, as described in the literature.[5] The ionic liquid was characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 10.24 (s, 1 H), 7.62 (t, J = 1.7 Hz, 1 H), 7.50 (t, J = 1.7, 1 H), 4.34 (t, J = 7.4 Hz, 2 H), 4.12 (s, 3 H), 3.32–3.25 (br s, 1 H), 1.93–1.87 (m, 2 H), 1.40–1.36 (m, 2 H), 0.96 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 137.2, 123.8, 122.1, 49.7, 36.7, 32.1, 19.4, 13.4 ppm. IR (neat): $\tilde{\nu}$ = 3422, 3079, 1571, 1169 cm^{-1}. These values were in good agreement with those reported.[10] This ionic liquid is highly stable under ambient conditions and can be used in reactions without any difficulty, as recently reported.[10–12] The ionic liquid was firstly dried with anhydrous sodium sulfate, and the filtrate was then dried under vacuum at 90 °C for 24 h to eliminate the residual water.

General Procedures for Michel Additions between Amines and Conjugated Alkenes Promoted by [bmIm]OH: The amine (1 mmol) and the α,β-unsaturated carbonyl compound (1.2 mmol) were added to [bmIm]OH (1 mL) in a 10 mL conical flask and the mixture was shaken at ambient temperature for 10 min. The reaction mixture was extracted from the ionic liquid phase with ethyl ether (10.0 mL × 3), and the organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 1:1, v/v) to provide the adduct in 98% isolated yield. The ionic liquid left in the conical flask was further washed with diethyl ether, dried under vacuum at 90 °C for 2 h to eliminate any water trapped from moisture, and reused for subsequent reactions. All organic compounds are fully characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. These values were in good agreement with those reported.[4,8,17]

Synthesis of 3a on a Larger Scale (0.2 mol): Piperidine (200 mmol) and methyl acrylate (240 mmol) were added to [bmIm]OH (5 mL) in a 100 mL round flask and the mixture was stirred at ambient temperature for 15 min. The excess methyl acrylate was evaporated and recovered, and the product was distilled directly from the reaction flask under reduced pressure to provide **3a** (8.5 g). The remaining [bmIm]OH was reused without any additional operation. The reaction was repeated eight times without significant loss of activity.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures, ^{1}H NMR and ^{13}C NMR spectroscopic data.

Acknowledgments

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[1] a) Y. Hayashi, J. J. Rode, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 5502–5503; b) G. Bartoli, C. Cimarelli, E. Marcantoni, G. Palmieri, M. Petrini, *J. Org. Chem.* **1994**, *59*, 5328–5335; c) S. Hashiguchi, A. Kawada, H. Natsugari, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2435–2444; d) H. C. Liang, S. K. Das, J. R. Galvan, S. M. Sato, Y. L. Zhang, L. N. Zakharov, A. L. Rheingold, *Green Chem.* **2005**, *7*, 410–412.

[2] a) G. Cardillo, C. Tomasini, *Chem. Soc. Rev.* **1996**, *25*, 117–128; b) S. Fustero, B. Pina, E. Salavert, A. Navarro, M. C. Ramirez de Arellano, A. S. Fuentes, *J. Org. Chem.* **2002**, *67*, 4667–4679; c) *The Organic Chemistry of β-Lactams* (Ed.: G. I. George), VCH, New York, **1993**; d) E. Juaristi, H. Lopez-Ruiz, *Curr. Med. Chem.* **1999**, *6*, 983–1004; e) D. Seebach, J. L. Matthews, *Chem. Commun.* **1997**, 2015–2022.

[3] a) P. Perlmutter, *Conjugate Addition Reactions*, in: *Organic Synthesis*, Pergamon, New York, **1992**, p. 114; b) N. B. Ambhaikar, J. P. Shyger, D. C. Liotta, *J. Am. Chem. Soc.* **2003**, *125*, 3690–3691; c) M. Sani, L. Bruche, G. Chiva, S. Fustero, J. Piera, A. Volonterio, M. Zanda, *Angew. Chem. Int. Ed.* **2003**, *42*, 2060–2063; d) L. Fadini, A. Togni, *Chem. Commun.* **2003**, 30–31; e) J. C. Adrian, M. L. Snapper, *J. Org. Chem.* **2003**, *68*, 2143–2150.

[4] a) $CeCl_3$: G. Bartoli, M. Bosco, E. Marcantoni, M. Petrini, L. Sambri, E. Torregiani, *J. Org. Chem.* **2001**, *66*, 9052–9055; b) $InCl_3$: T. P. Loh, L. L. Wei, *Synlett* **1998**, 975–976; c) $Yb(OTf)_3$: D. Enders, S. F. Muller, G. Raabe, J. Runsink, *Eur. J. Org. Chem.* **2000**, *6*, 879–892; d) $Bi(OTf)_3$: R. Varala, M. M. Alam, S. R. Adapa, *Synlett* **2003**, 720–722; e) $Cu(OTf)_2$: T. C. Wabnitz, J. B. Spencer, *Tetrahedron Lett.* **2002**, *43*, 3891–3894; f) $LiClO_4$: N. Azizi, M. R. Saidi, *Tetrahedron* **2004**, *60*, 383–387; g) β-Cyclodextrin: K. Surendra, N. S. Krishnaveni, R. Sridhar, K. R. Rao, *Tetrahedron Lett.* **2006**, *47*, 2125–2127; h) Polyethylene glycol: R. Kumar, P. Chaudhary, S. Nimesh, R. Chandra, *Green Chem.* **2006**, *8*, 356–358; i) Heterogeneous solid acids: N. S. Shaikh, V. H. Deshpande, A. V. Bedekar, *Tetrahedron* **2001**, *57*, 9045–9048; j) $Cu(acac)_2$ immobilized in ionic liquids: M. L. Kantam, V. Neeraja, B. Kavita, B. Neelima, M. K. Chaudhuri, S. Hussain, *Adv. Synth. Catal.* **2005**, *347*, 763–766.

[5] a) Z. C. Zhang, *Adv. Catal.* **2006**, *49*, 153–237; b) P. J. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed.* **2000**, *39*, 3772–3789; c) T. Welton, *Chem. Rev.* **1999**, *99*, 2071–2083; d) T. Welton, *Coord. Chem. Rev.* **2004**, *248*, 2459–2477; e) H. Olivier-Bourbigou, L. Magna, *J. Mol. Catal. A: Chem.* **2002**, *182*, 419–437; f) L. A. Blanchard, D. Hancu, E. J. Beckman, J. F. Brennecke, *Nature* **1999**, *399*, 28–29; g) R. A. Brown, P. Pollet, E. Mckoon, C. A. Eckert, C. L. Liotta, P. G. Jessop, *J. Am. Chem. Soc.* **2001**, *123*, 1254–1255; h) W. Leitner, *Nature* **2003**, *423*, 930–931; i) X. F. Yang, M. W. Wang, C. J. Li, *Org. Lett.* **2003**, *5*, 657–660; j) A. Kumar, S. S. Pawar, *J. Org. Chem.* **2004**, *69*, 1419–1420.

[6] a) J. A. Boon, J. A. Levinsky, J. L. Pflug, J. S. Wilkes, *J. Org. Chem.* **1986**, *51*, 480–483; b) Y. Chauvin, H. Olivier-Bourbigou, *Chemtech* **1995**, *25*, 26–30; c) C. E. Song, D. U. Jung, S. Y. Choung, E. J. Roh, S. G. Lee, *Angew. Chem. Int. Ed.* **2004**, *43*, 6183–9185; d) R. Sheldon, *Chem. Commun.* **2001**, 2399–2407; e) Y. J. Kim, R. S. Varma, *Tetrahedron Lett.* **2005**, *46*, 7447–7449; f) B. C. Ranu, R. Jana, *J. Org. Chem.* **2005**, *70*, 8621–8624; g) A. L. Zhu, T. Jiang, D. Wang, B. X. Han, L. Liu, J. Huang, J. C. Zhang, D. H. Sun, *Green Chem.* **2005**, *7*, 514–517.

[7] a) J. Z. Gui, X. H. Cong, D. Liu, X. T. Zhang, Z. D. Hu, Z. L. Sun, *Catal. Commun.* **2004**, *5*, 473–477; b) T. Joseph, S. Sahoo, S. B. Halligudi, *J. Mol. Catal. A: Chem.* **2005**, *234*, 107–110; c) H. P. Zhu, F. Yang, J. Tang, M. Y. He, *Green Chem.* **2003**, *5*, 38–39; d) G. Driver, K. E. Johnson, *Green Chem.* **2003**, *5*, 163–169; e) G. J. Kemperman, T. A. Roeters, P. W. Hilberink, *Eur. J. Org. Chem.* **2003**, *9*, 1681–1686.

[8] a) J. McNulty, S. Cheekoori, J. J. Nair, V. Larichev, A. Capretta, A. J. Robertson, *Tetrahedron Lett.* **2005**, *46*, 3641–3644; b) Y. R. Jorapur, C. H. Lee, D. Y. Chi, *Org. Lett.* **2005**, *7*, 1231–1234; c) H. Y. Shen, Z. M. A. Judeh, C. B. Ching, *Tetrahedron Lett.* **2003**, *44*, 981–983; d) E. J. Corey, Y. Bo, J. Busch-Petersen, *J. Am. Chem. Soc.* **1998**, *120*, 13000–13001; e) M. Horikawa, J. Busch-Peterson, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 3843–3846; f) E. J. Corey, F. Y. Zhang, *Org. Lett.* **1999**, *1*, 1287–1290; g) J. S. Yadav, B. V. S. Reddy, G. Baishya, *J. Org. Chem.* **2003**, *68*, 7098–7100; h) B. C. Ranu, S. S. Dey, *Tetrahedron* **2004**, *60*, 4183–4188; i) L. W. Xu, J. W. Li, S. L. Zhou, C. G. Xia, *New J. Chem.* **2004**, *28*, 183–184.

[9] S. Abello, F. Medina, X. Rodriguez, Y. Cesteros, P. Salagre, J. E. Sueiras, D. Tichit, B. Coq, *Chem. Commun.* **2004**, 1096–1097.

[10] B. C. Ranu, S. Banerjee, *Org. Lett.* **2005**, *7*, 3049–3052.

[11] J. M. Xu, B. K. Liu, W. B. Wu, C. Qian, Q. Wu, X. F. Lin, *J. Org. Chem.* **2006**, *71*, 3991–3993.

[12] B. C. Ranu, R. Jana, *Eur. J. Org. Chem.* **2006**, *16*, 3767–3770.

[13] a) S. K. Poole, P. H. Shetty, C. F. Poole, *Anal. Chim. Acta* **1989**, *218*, 241–263; b) K. Fukumoto, M. Yoshizawa, H. Ohno, *J. Am. Chem. Soc.* **2005**, *127*, 2398–2399.

[14] a) A. Aggarwal, N. L. Lancaster, A. R. Sethi, T. Welton, *Green Chem.* **2002**, *4*, 517–520; b) J. Ross, J. L. Xiao, *Chem. Eur. J.* **2003**, *9*, 4900–4906.

[15] a) L. Crowhurst, N. L. Lancaster, J. M. P. Arlandis, T. Welton, *J. Am. Chem. Soc.* **2004**, *126*, 11549–11555; b) M. Meciarova, S. Toma, P. Kotrusz, *Org. Biomol. Chem.* **2006**, *4*, 1420–1424; c) N. L. Lancaster, *J. Chem. Res. (S)* **2005**, 413–417.
[16] a) V. Jurcik, R. Wilhelm, *Green Chem.* **2005**, *7*, 844–848; b) J. Dupont, J. Spencer, *Angew. Chem. Int. Ed.* **2004**, *43*, 5296–5297.
[17] a) H. X. Zhang, Y. H. Zhang, L. F. Liu, H. L. Xu, Y. G. Wang, *Synthesis* **2005**, *13*, 2129–2136; b) K. L. Li, P. Horton, M. B. Hursthouse, K. K. Hii, *J. Organomet. Chem.* **2003**, *665*, 250–257.

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