

Stetter Reaction in Room Temperature Ionic Liquids and Application to the Synthesis of Haloperidol

Siddam Anjaiah,^a Srivari Chandrasekhar,^b René Grée^{a, c, *}

^a ENSCR, Laboratoire de Synthèse et Activation de Biomolécules, CNRS UMR 6052, Avenue du Général Leclerc, 35700 Rennes Beaulieu, France

^b Indian Institute of Chemical Technology, Hyderabad – 500007, India

^c Present address: Université de Rennes 1, Laboratoire de Synthèse et Electrosynthèse Organiques, CNRS UMR 6510, Avenue du Général Leclerc, 35042 Rennes Cedex, France
Fax : (+33)-223-236-955; e-mail: rene.gree@univ-rennes1.fr

Received: April 29, 2004; Accepted: July 23, 2004

Abstract: Imidazolium-type room temperature ionic liquids (RTILs) have been used for the Stetter reaction, affording the desired 1,4-dicarbonyl compounds in good yields. Thiazolium salts and Et₃N are efficient catalysts for this reaction performed in ionic liquid. The possibility to recycle and reuse the solvent has

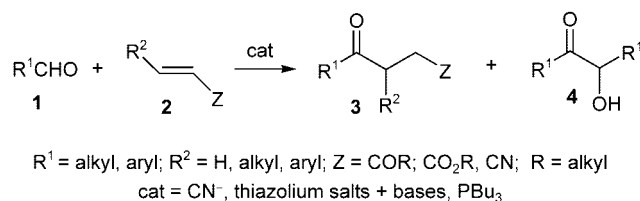
been demonstrated, although it was not possible to recycle the thiazolium catalyst. This method was used in the total synthesis of haloperidol.

Keywords: 1,4-dicarbonyls; haloperidol; ionic liquids; organic catalysis; Stetter reaction; thiazolium salts

Introduction

“Room temperature ionic liquids” (RTILs) are the subject of much current interest as novel reaction media and one of the possible alternatives to “volatile organic solvents” (VOS).^[1] This recent development is mainly due to their unique physical properties which make them attractive solvents for organic synthesis,^[2] organometallic catalysis^[3] as well as for biotransformations.^[4] Furthermore, the combination of RTILs with supercritical CO₂ offers very exciting new possibilities.^[5] It is known that the nature of the ionic liquid has a strong influence on the reactivity of dissolved molecules and on the stereoselectivity of the reactions performed in such solvents. Furthermore, it has been demonstrated recently that the outcome of reactions can even be controlled by the nature of the RTILs.^[6] In recent years, many organic reactions have been successfully performed in imidazolium-type RTILs. However limitations have been established in the use of basic conditions: this is due to the abstraction of the acidic H-2 proton of the imidazolium by soluble bases^[7] and trapping of the corresponding heterocyclic carbenes.^[8]

As part of our ongoing studies on the use of ionic liquids in synthesis,^[9] we became interested in the Stetter reaction: this is a very simple and useful method to prepare 1,4-dicarbonyl compounds, which are key intermediates in organic synthesis.^[10] This reaction involves the catalyzed addition of aldehydes to electron-deficient alkenes and is in competition with the formation of benzoin (Scheme 1).



Scheme 1. The Stetter reaction.

As catalysts, CN[−] or PBu₃^[11] can be used but thiazolium salts in the presence of bases have a much broader scope. The addition of the catalyst to the aldehyde affords a stabilized carbanion which then reacts either with the electrophilic olefin to give the expected 1,4-adduct or with a second aldehyde molecule affording the benzoin product. This Stetter reaction has been already widely used in organic synthesis to prepare, for instance, cyclopentenones^[12] and heterocycles.^[13] More recently, it has been extended to electrophilic olefins anchored either on solid support^[14] or onto “task specific ionic liquids”.^[15] Finally, in the intramolecular version, excellent results in terms of asymmetric synthesis have also been reported recently.^[16]

The Stetter reaction is performed in protic solvents like alcohol or in aprotic ones such as DMF, dioxane, acetonitrile and even without solvent. However, alternative solutions appear also to be of much interest and therefore the purpose of this publication is:

- To demonstrate, for the first time, that imidazolium-type RTILs can be employed with success as solvents for this Stetter reaction, in spite of their known sensi-

tivity to basic conditions. The desired 1,4-dicarbonyl compounds have been isolated usually in good yields and we have further established that it is possible to recycle and reuse these solvents, although it is not yet possible to recycle the catalyst.

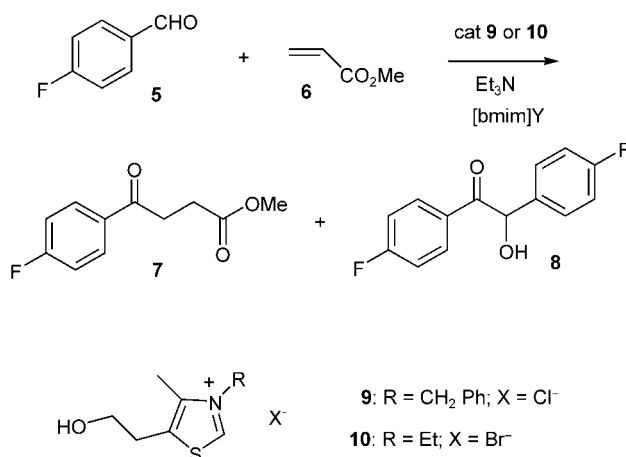
- To study the scope and limitations of this reaction with different type of aldehydes and electrophilic alkenes.
- To use this method as a key step in the preparation of haloperidol, an antipsychotic agent.^[17]

Results and Discussion

Optimization of the Reaction Conditions for the Stetter Reaction in Imidazolium-Type RTILs

The condensation of *p*-fluorobenzaldehyde with methyl acrylate was selected as a model to optimize the reaction conditions, using butylmethylimidazolium tetrafluoroborate [bmim][BF₄] as the solvent (Scheme 2).

The commercially available, and commonly used thiazolium salt **9** was chosen as a catalyst and we first opti-



Scheme 2. Our model reaction.

mized its concentration (Table 1). Without catalyst the reaction afforded already a small amount (15%) of the 1,4-addition product **7**, together with the benzoin **8** (34%) (entry 1). These compounds are easily separated by flash chromatography on SiO₂ and their spectral data are in agreement with literature values. The formation of **7** was not unexpected since it is known that salts of various heterocycles, including imidazoliums, can also be used as catalysts.^[18] Therefore, the solvent is also able to react as a catalyst, even if the latter salts are less active than usual thiazolium salts, and the yields of the desired product **7** are poor in that case.

Then we made a systematic increase in the quantity of thiazolium salt **9** from 5 to 20 mol % resulting in a concomitant increase in the yield of the 1,4-adduct **7** to 63% (entries 2 to 4). The use of 40 mol % catalyst did not give further improvement in the yield (entry 5) and therefore we selected 20 mol % for the next experiments. It has been established that, under classical conditions (cat. **9** in DMF), α,β -unsaturated esters are relatively poor substrates in the Stetter reaction, affording low yields (*ca.* 30%) of 1,4-adducts.^[10] It must be noted that significantly better yields were obtained here by using the ionic liquid as the solvent. Changing the nature of the catalyst to **10** did not improve the yield of **7** (entry 6). The use of a larger excess of acrylate (10 equivalents) also gave a similar yield in **7**. In [bmim][BF₄], the cyanide anion was a poor catalyst: under the same reaction conditions it afforded **7** in only 28% yield (entry 7). Then we checked the nature of the ionic liquid: changing the counterion to [PF₆] (entry 8) or to [NTf₂] (entry 9) gave similar yields in adduct **7**. The abstraction of the H-2 proton of imidazolium salts by bases and trapping of the corresponding carbenes is known to be responsible for the difficulties encountered in using this type of RTIL under basic conditions.^[8] Therefore, the 1,2-dimethylimidazolium salt [bdmim][BF₄] was also studied but afforded a similar good yield in **7** (entry 10). This result demonstrates that, in the case of this Stetter reaction catalyzed by thiazolium salts, the presence of the H-2 proton is no longer a limiting factor. A tentative explanation

Table 1. Optimization of reaction conditions

Exp.	Solvent	Catalyst (%)	Alkene	7 Yield [%]	8 Yield [%]
1	[bmim][BF ₄]	9 (0)	6	15	34
2	[bmim][BF ₄]	9 (5)	6	19	32
3	[bmim][BF ₄]	9 (10)	6	53	29
4	[bmim][BF ₄]	9 (20)	6	63	31
5	[bmim][BF ₄]	9 (40)	6	60	32
6	[bmim][BF ₄]	10 (20)	6	57	30
7	[bmim][BF ₄]	CN ⁻ (20)	6	28	35
8	[bmim][PF ₆]	9 (20)	6	67	31
9	[bmim][NTf ₂]	9 (20)	6	62	32
10	[bdmim][BF ₄]	9 (20)	6	60	25
11	[bmim][BF ₄]	9 (20)	2 (R ² = H; Z = COMe)	65	28
12	[bmim][BF ₄]	9 (20)	2 (R ² = H, Z = CN)	61	27

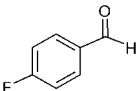
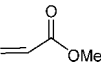
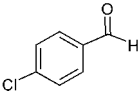
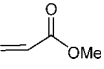
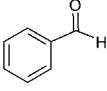
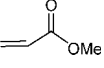
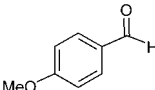
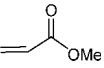
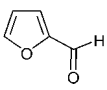
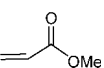
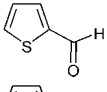
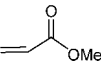
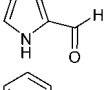
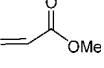
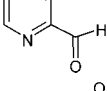
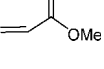
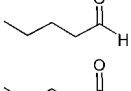
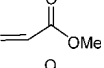
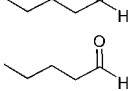
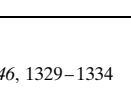
is that the thiazolium salt reacts faster with the base, affording the corresponding carbene which is the catalyst in the Stetter reaction and in the benzoin condensation. Therefore, such a higher reactivity towards the catalyst would limit the effect of the base added to the imidazolium solvent. This is in good agreement with literature data on the benzoin condensation.^[18] Finally, it was shown that the same conditions could be applied with success to other electrophilic alkenes (methyl vinyl ketone, entry 11) and acrylonitrile (entry 12). It is known that, under classical conditions, the formation of benzoin is reversible and kinetically controlled and therefore, in DMF, benzoin could be used also as starting material.^[10] This is no longer the case in bmimPF₆: a reaction, performed under the same conditions but using **8** instead of **5** as starting material, gave no trace of **7** in the crude reaction mixture and the starting compound **8** was quantitatively recovered.

Extension of the Stetter Reaction in RTILs to Other Aromatic and Aliphatic Aldehydes

In a next step we have studied the extension of these reaction conditions to other aldehydes (Table 2).

Starting from aromatic aldehydes with different types of substituents the reaction proceeded also in moderate to good yields (50–68%) of the desired 1,4-adducts (entries 1 to 4). In each case, small amounts of benzoin derivatives were also formed in these reactions. As far as 5-membered heterocyclic aldehydes are concerned, furfural (entry 5) or thiophene carboxaldehyde (entry 6) gave good yields (60–70%) in corresponding adducts, while no reaction was observed in the case of the pyrrole derivative (entry 7). In contrast, pyridine proved to be very reactive since the reaction was completed in 3 hours (instead of 10–14 h for benzaldehyde and substituted benzaldehydes) affording the 1,4-adduct in 70% yield (entry 8). Aliphatic aldehydes can also be used and the catalyst **10** is recommended for the latter aldehydes.^[10] Valeraldehyde was selected as a model and the desired 1,4-adducts were obtained in good yields

Table 2. Extension to various aldehydes.

Entry	Aldehyde	Alkene	Cat. [%]	Time [h]	7 Yield [%]
1			9 (20)	10	60
2			9 (20)	12	50
3			9 (20)	12	56
4			9 (20)	14	68
5			9 (20)	12	60
6			9 (20)	10	70
7			9 (20)	0	0
8			9 (20)	3	70 (1 st run) 66 (2 nd run) 60 (3 rd run)
9			10 (20)	10	67
10			10 (20)	10	78
11			10 (20)	10	65

(65–78%) for the three representative alkenes (entries 9–11).

One of the key aspects of the use of RTILs in organic synthesis is the possibility to recycle and to reuse such solvents. The highly reactive pyridine-2-carboxaldehyde appeared as a good substrate to study this recycling problem. At the end of the first run of the reaction with methyl acrylate the products were extracted with ether. The ionic liquid solvent was washed with H₂O, dried under vacuum and then reused for a second run to give a similar yield in 1,4-adduct. A third cycle was also performed, with only a slight decrease in yield (60%, entry 8). However, it must be noted that the catalyst must be added again after each run otherwise the yield drops dramatically (only 10% yield for **7**). This result may be due to some decomposition of the catalyst under these reaction conditions but further mechanistic studies will be necessary in order to clarify this aspect.

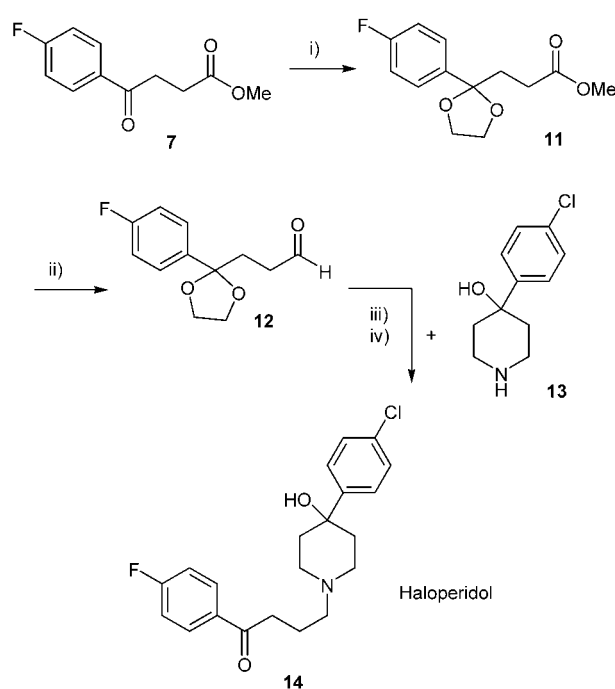
The reuse of the solvent to perform the Stetter reaction with another substrate was also demonstrated: after a first reaction with *p*-fluorobenzaldehyde, the same [bmim][PF₆] solvent was used to perform a reaction with pyridinecarboxaldehyde. Careful study by high field NMR established that only traces (<5%) of the first 1,4-adduct are present in the crude reaction mixture of the second reaction. Therefore, it is possible to recycle and reuse the imidazolium solvents in this Stetter reaction.

Haloperidol is a widely used antipsychotic drug, in spite of some undesirable side effects.^[17]

The 1,4-adduct of *p*-fluorobenzaldehyde and methyl acrylate **7**, prepared as described previously, was used as the starting material for a short synthesis of haloperidol (Scheme 3). After protection of the carbonyl as a ketal group affording **11**, the ester was reduced to the aldehyde **12** in good yield using DIBAL-H at low temperature. A reductive amination process, using the commercially available piperidinol **13**, followed by the deprotection of the ketone afforded the target haloperidol. The spectral data of **14** are in full agreement with literature and this compound was obtained in 55% overall yield from **7** and 30% yield from *p*-fluorobenzaldehyde.

Conclusion

The Stetter reaction can be performed in imidazolium-type RTILs as solvents, with thiazolium salts and Et₃N as catalysts. In these conditions the 4-oxocarboxylic esters were isolated in good yields, usually higher than those obtained in classical organic solvents. Furthermore, it was possible to recycle and reuse the ionic liquid but not the catalyst. This method was employed as a key step in the total synthesis of haloperidol.



Reagents and conditions: i) ethylene glycol, *p*-TsOH, benzene, reflux, 18 h, 83%; ii) Dibal-H, -78 °C, 1 h, 93%; iii) NaBH₃CN, AcOH, MeOH, rt, 36 h; iv) conc. HCl, MeOH, reflux, 2 h, 70% (two steps).

Scheme 3. Total synthesis of haloperidol.

Experimental Section

Some typical procedures for the Stetter reaction in [bmim][PF₆] are given below.

4-(4-Fluorophenyl)-4-oxobutyric Acid Methyl Ester (**7**)

To a stirred suspension of catalyst (2.17 g, 20 mol %) in [bmim][PF₆] (5 mL) were added Et₃N (2.44 g, 24.17 mmol) methyl acrylate (6.92 g, 80.57 mmol) and *p*-fluorobenzaldehyde (5 g, 40.28 mmol) at room temperature. The temperature was raised to 80 °C and the reaction mixture stirred for 12 h. After completion of the reaction, as indicated by TLC, the product was extracted with Et₂O (3 × 25 mL). The organic phase was dried and the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO₂ to afford **7**; yield: 5.07 g (60%) and benzoin **8** (30%). Data for **7**: ¹H NMR (400 MHz, CDCl₃): δ = 2.78 (t, *J* = 6.5 Hz, 2H), 3.31 (t, *J* = 6.5 Hz, 2H), 3.72 (s, 3H), 7.11–7.19 (m, 2H), 8.00–8.07 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 28.36, 33.67, 52.25, 116.12 (d, *J*_{CF} = 22 Hz), 131.11 (d, *J*_{CF} = 9 Hz), 133.38 (d, *J*_{CF} = 3 Hz), 166.22 (d, *J*_{CF} = 255 Hz) 173.69, 196.87.

3-[2-(4-Fluorophenyl)-[1,3]dioxolan-2-yl]propionic Acid Methyl Ester (**11**)

To a stirred solution of **7** (5 g, 23.79 mmol) in benzene (60 mL) were added ethylene glycol (2.95 g, 47.60 mmol) and PTSA (0.226 g, 5 mol %) at room temperature, and the reaction mix-

ture was refluxed for 20 h, using a Dean–Stark trap. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature and successively washed with saturated aqueous NaHCO_3 solution, brine and dried over MgSO_4 . It was concentrated under reduced pressure, and the residue was purified by chromatography on SiO_2 to afford ketal **11**; yield: 5.10 g (83%); ^1H NMR (400 MHz, CDCl_3): δ = 2.21 (t, J = 7.1 Hz, 2H), 2.40 (t, J = 7.1 Hz, 2H), 3.72 (s, 3H), 3.70–3.77 (m, 2H), 3.95–3.99 (m, 2H), 6.94–7.03 (m, 2H), 7.37–7.45 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 28.94, 35.88, 51.85, 65.03, 109.55, 115.32 (d, J_{CF} = 21 Hz), 127.92 (d, J_{CF} = 8 Hz), 138.48 (d, J_{CF} = 3 Hz), 162.92 (d, J_{CF} = 245 Hz), 174.08.

3-[2-(4-Fluorophenyl)-[1,3]dioxolan-2-yl]-propionaldehyde (**12**)

To a stirred solution of ketal **11** (2 g, 7.87 mmol) in CH_2Cl_2 (40 mL) was added DIBAL-H (1.11 g, 7.87 mmol, 1 M solution in THF) at -78°C and the reaction mixture was stirred for 1 h at the same temperature. The reaction was quenched by adding aqueous NH_4Cl solution and extracted with CH_2Cl_2 (2×25 mL). The organic layer was dried over MgSO_4 , concentrated under reduced pressure, to give aldehyde **12** which was found to be pure enough for the next step; yield: 1.64 g (93%); ^1H NMR (400 MHz, CDCl_3): δ = 2.24 (t, J = 7.0 Hz, 2H), 2.51 (td, J = 7.0 Hz, J = 2.0 Hz, 2H), 3.70–3.77 (m, 2H), 3.96–4.05 (m, 2H), 6.99–7.10 (m, 2H), 7.40–7.50 (m, 2H), 9.75 (t, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ = 35.45, 39.15, 62.87, 109.88, 115.26 (d, J_{CF} = 21 Hz), 127.84 (d, J_{CF} = 8 Hz), 136.29 (d, J_{CF} = 3 Hz), 166.04 (d, J_{CF} = 245 Hz), 200.62.

4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-1,1-ethylenedioxy-1-(4-fluorophenyl)butane

To a stirred solution of **12** (0.5 g, 2.23 mmol) and **13** (0.94 g, 4.46 mmol) in methanol (5 mL) were added acetic acid (0.13 g, 2.23 mmol) and NaCNBH_3 (0.14 g, 2.23 mmol) at room temperature and the solution was stirred for 30 h at the same temperature. The reaction mixture was neutralized by addition of aqueous NaHCO_3 solution and extracted with CH_2Cl_2 (2×25 mL). The organic phase was dried over MgSO_4 and the solvents were removed under reduced pressure. Chromatography on SiO_2 afforded haloperidol ethylene ketal; yield: 0.728 g (78%); ^1H NMR (400 MHz, CDCl_3): δ = 1.55–1.75 (m, 4H), 1.85–1.95 (m, 2H), 2.05–2.18 (m, 2H), 2.35–2.47 (m, 4H), 2.75–2.85 (m, 2H), 3.73–3.76 (m, 2H), 3.99–4.02 (m, 2H), 6.98–7.02 (m, 2H), 7.27–7.30 (m, 2H), 7.41–7.43 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ = 20.63, 37.89, 38.10, 48.99, 58.15, 64.23, 70.63, 109.67, 114.98 (d, J_{CF} = 21.5 Hz), 125.82, 127.22 (d, J_{CF} = 8 Hz), 128.09, 132.44, 138.04 (d, J_{CF} = 3.1 Hz), 146.53, 162.15 (d, J_{CF} = 244.2 Hz).

Haloperidol (**14**)

A solution of haloperidol ketal (0.5 g, 1.18 mmol) and concentrated HCl (0.5 mL) in methanol (5 mL) was refluxed for 2 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and successively washed with 5% aqueous ammonia and water. The solution was dried over MgSO_4 and the solvent was removed

by evaporation under reduced pressure. The residue was eluted through a silica gel column using a mobile phase of (CH_2Cl_2 :MeOH, 9:1) to afford haloperidol (**14**); yield: 0.291 g (65%); ^1H NMR (400 MHz, acetone- d_6): δ = 1.52–1.60 (m, 2H), 1.80–1.96 (m, 5H), 2.44–2.49 (m, 5H), 2.69–2.72 (m, 2H), 7.26–7.31 (m, 4H), 7.41–7.44 (m, 2H), 8.10–8.14 (m, 2H); ^{13}C NMR (100 MHz, acetone- d_6): δ = 23.46, 36.96, 39.56, 50.43, 58.79, 71.43, 116.63 (d, J_{CF} = 20.7 Hz), 127.03, 127.18, 132.13 (d, J_{CF} = 8.7 Hz), 136.56 (d, J_{CF} = 3.3 Hz), 139.94, 154.60, 172.20 (d, J_{CF} = 250 Hz), 199.08; MS: m/e = 376 (M^+).

Acknowledgements

We thank P. Guénot (CRMPO Rennes) for the mass spectral analysis. This work was supported by the Ministère des Affaires Étrangères (fellowship to S. A.) as part of CEFISO/IFCOS. S. C. thanks the CEFIPRA/IFCPAR (2305–1) for supporting the visits to Rennes.

References and Notes

- [1] P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, **2003**.
- [2] a) T. Welton, *Chem. Rev.* **1999**, 99, 2071–2084; b) M. J. Earle, K. R. Seddon, *Pure Appl. Chem.* **2000**, 72, 1391–1398.
- [3] a) P. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed.* **2000**, 39, 3772–3789; b) R. Sheldon, *Chem. Commun.* **2001**, 2399–2400.
- [4] a) S. H. Schoefer, N. Kaftzik, P. Wasserscheid, U. Kragl, *Chem. Commun.* **2001**, 425–426; b) P. Lozano, T. Diego, D. Carrié, M. Vaultier, J. L. Iborra, *Chem. Commun.* **2002**, 692–693; c) F. van Rantwijk, R. M. Lau, R. A. Sheldon, *Trends Biotechnology* **2003**, 21, 131–138.
- [5] S. V. Dzyuba, R. A. Bartsch, *Angew. Chem. Int. Ed.* **2003**, 42, 148–150.
- [6] M. J. Earle, S. P. Katdare, K. R. Seddon, *Org. Lett.* **2004**, 6, 707–710.
- [7] For examples of the use of KOH as a base in imidazolium solvents, see: a) M. J. Earle, K. R. Seddon, P. B. McCormac, *Green Chemistry* **2000**, 2, 261–262; b) S. Chandrasekhar, Ch. Narasimulu, V. Jagadeeshwar, K. V. Reddy, *Tetrahedron Lett.* **2003**, 44, 3629–3630.
- [8] V. K. Aggarwal, I. Emme, A. Mereu, *Chem. Commun.* **2002**, 1612–1613.
- [9] a) V. Le Boulaire, R. Grée, *Chem. Commun.* **2000**, 2195–2196; b) I. A. Ansari, R. Grée, *Org. Lett.* **2002**, 4, 1507–1509.
- [10] a) H. Stetter, *Angew. Chem. Int. Ed.* **1976**, 15, 639–647; b) D. Enders, K. Breuer, in: *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 1093–1102.
- [11] J. H. Gong, Y. J. Im, K. Y. Lee, J. N. Kim, *Tetrahedron Lett.* **2002**, 43, 1247–1251.
- [12] a) P. E. Harrington, M. A. Tius, *Org. Lett.* **1999**, 4, 649–651; b) C. C. Galopin, *Tetrahedron Lett.* **2001**, 42, 5589–5591.

- [13] a) B. A. Merrill, E. LeGoff, *J. Org. Chem.* **1990**, 55, 2904–2908; b) R. Brettle, D. A. Dunmur, C. M. Marson, M. Pinol, K. Toriyama, *Chem. Lett.* **1992**, 613–616; c) R. A. Jones, M. Karatza, T. N. Voro, P. U. Civcir, A. Franck, O. Ozturk, J. P. Seaman, A. P. Whitmore, D. J. Williamson, *Tetrahedron* **1996**, 52, 8707–8724; d) R. U. Braun, K. Zeitler, T. J. J. Müller, *Org. Lett.* **2001**, 3, 3297–3300.
- [14] S. Raghavan, K. Anuradha, *Tetrahedron Lett.* **2002**, 43, 5181–5183.
- [15] S. Anjaiah, S. Chandrasekhar, R. Grée, *Tetrahedron Lett.* **2004**, 45, 569–571.
- [16] a) D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Helv. Chim. Acta* **1996**, 79, 1899–1902; b) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, 124, 10298–10299; c) M. S. Kerr, T. Rovis, *Synlett* **2003**, 1934–1936.
- [17] M. Lyles-Eggleston, R. Altundas, J. Xia, D. M. N. Sikazwe, P. Fan, Q. Yang, S. Li, W. Zhang, X. Zhu, A. W. Schmidt, M. Vanase-Frawley, A. Shrihkande, A. Villalobos, R. F. Borne, S. Y. Ablordeppey, *J. Med. Chem.* **2004**, 47, 497–508.
- [18] J. H. Teles, J-P. Melder, K. Ebel, R. Schneider, E. Gehr, W. Harder, S. Brode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, 79, 61–83.
-