

Ionic Liquid-Supported Aldehyde: A Highly Efficient Scavenger for Primary Amines

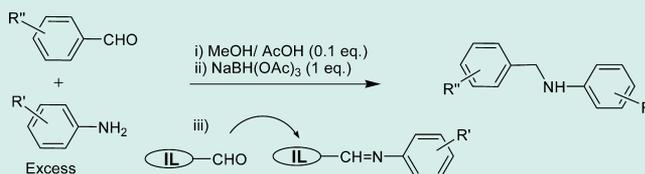
Manoj Kumar Muthayala and Anil Kumar*

Department of Chemistry, Birla Institute of Science and Technology, Pilani, 333031 Rajasthan, India

S Supporting Information

ABSTRACT: Novel aldehyde-functionalized ionic liquids have been synthesized and used as scavengers for primary amines in the synthesis of secondary amines. The yields of secondary amines are high (82–90%) with high purity. The advantages of the protocol over that with a polymer-supported aldehyde scavenger are the shorter reaction time, the homogeneous reaction medium, the high level of loading of the aldehyde group, easy monitoring of reaction, and characterization of intermediates.

KEYWORDS: ionic liquid, functionalized ionic liquid, scavenger, reductive amination, secondary amines



Combinatorial synthesis is a very useful technique for the rapid synthesis of a library of compounds in the quest for pharmaceutically active compounds.^{1,2} In parallel synthesis, when two or more reagents are being coupled, one reagent is used in excess to drive the reaction to completion. Purification in combinatorial chemistry is an interesting and often challenging process. To remove the excess reagent or byproduct in parallel synthesis, most commonly an immobilized scavenger is added to the reaction mixture. Scavengers are the materials that scavenge or quench a particular excessive reagent or byproduct in the reaction mixture. Polymer-supported scavengers are most commonly used in combinatorial synthesis. Simple filtration removes polymer-supported scavengers to give pure product, thus avoiding column chromatography.^{3–5} However, there are some downsides with these scavengers. First, one has to use an excess of resin-bound scavengers because of the ratio of less functional groups to polymer. In addition, because of the biphasic system of the reaction medium, rates of reaction are considerably slower than those of the solution-phase system. To fulfill the swelling requirement of polymer-supported reagents, one has to use large amounts of a suitable solvent. Several alternative, e.g., PEG-supported,⁶ silica-supported,⁷ fluorous-phase,^{8–10} and aqueous-phase,^{11,12} scavengers have been developed to overcome some of these limitations of traditional polymer-supported scavengers.

Because of specific chemical and physical properties, ionic liquids (ILs) have received considerable attention for applications in organic transformations. For example, ILs can be used in catalysis, electrochemistry, liquid/liquid extractions, purification processes, and organic synthesis. Physical properties of ionic liquids such as viscosity, hydrophobicity, melting point, and solubility can be fine-tuned by changing the anions and altering the length of the alkyl groups on the cations.¹³ Functionalized ionic liquids (FILs)^{14–20} have been used as scavengers in parallel synthesis. Song et al.²¹ used [2-aemim][PF₆] ionic liquid as a scavenger for trapping

electrophiles in solution-phase parallel synthesis. Cai et al.²² has used a new diol-functionalized 2,2-bis[1-(1-methylimidazolium)]methylpropane-1,3-diol hexafluorophosphate as a scavenger for aldehydes. They have also used carboxyl-functional ionic liquid [cmmim][PF₆] as a scavenger for benzyl chloride, amines, and methanesulfonyl chlorides.²³ A commercial process of biphasic acid scavenging has been developed by Maase and Massonne.²⁴ Lei et al. used a water-soluble 1-(2-aminoethyl)pyridinium bromide as a scavenger for the solution-phase synthesis of amides and sulfonamides.²⁵ The main objective here is to reduce waste generation, minimize solvent requirement, and optimize scale-up potential. Easy monitoring and time saving have made the FILs more favorable than polymer-supported scavengers.

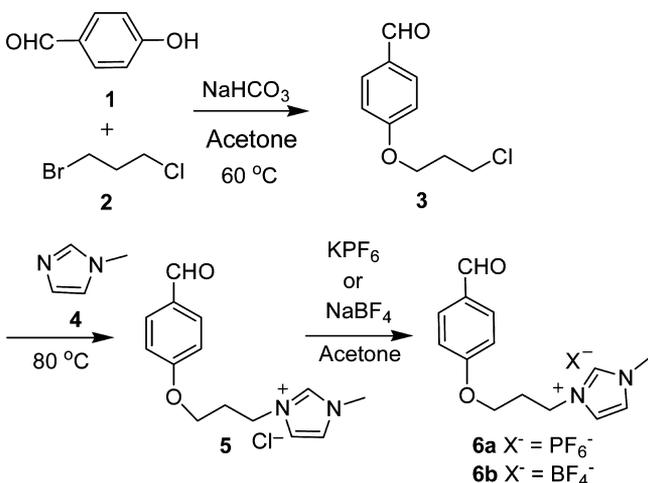
On the other hand, reductive amination is a powerful tool for the synthesis of structurally diverse secondary amines that are used in high-throughput syntheses toward compound libraries of potential drug candidates. In continuation of our efforts to explore the synthetic utility of the ionic liquid and to develop new and ecofriendly reaction methodologies,^{26–29} herein, we report synthesis of a novel ionic liquid-supported aldehyde and its use as a scavenger to remove primary amines in the synthesis of secondary amines in the solution phase.

Synthesis of two different aldehyde-functionalized ionic liquids is achieved as shown in Scheme 1. Reaction of 4-hydroxybenzaldehyde (1) with 1-chloro-3-bromopropane (2) in the presence of sodium bicarbonate gave monoalkylated aldehyde 3. Reaction of 3 with *N*-methylimidazole (4) at 80 °C gave the corresponding chloride salt (5). Anion exchange of 5 with KPF₆ and NaBF₄ resulted in corresponding ionic liquids 6a and 6b, respectively.

Received: August 20, 2011

Revised: November 4, 2011

Published: November 7, 2011

Scheme 1. Synthesis of Ionic Liquid-Supported Aldehydes **6a** and **6b**

The structure of **6a** and **6b** is confirmed by ^1H NMR and high-resolution mass spectrometry. The ^1H NMR spectrum showed a singlet at δ 9.84 for the aldehydic proton, a singlet at δ 3.82 for the methyl protons of *N*-methyl, two triplets and a multiplet at 4.39, 4.14 and 2.35 ppm for OCH_2 , NCH_2 and CH_2 , respectively, and other aromatic protons of imidazolium and the aryl ring. In the ESI-MS spectrum, a peak appeared at 245.13 $[\text{M} - \text{PF}_6]^+$ or $[\text{M} - \text{BF}_4]^+$ for both **6a** and **6b**.

After synthesizing ionic liquid-supported aldehydes **6a** and **6b**, we studied their scavenging properties by reacting them with *p*-chloroaniline (**7b**) under different conditions. Only 60% of **8b** was obtained when **7b** was reacted with **6a** in methanol under reflux conditions after 6 h. Adding a catalytic amount of acetic acid dramatically increased the yield of **8b** to 87% in 4 h at room temperature. The imine of **6a** (**8b**) precipitates out in methanol (Figure 1B), whereas the imine of **6b** was completely

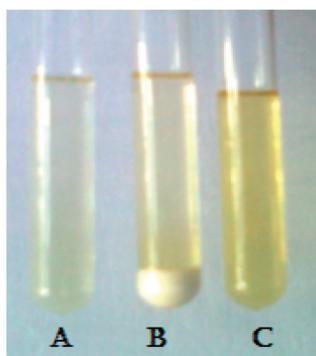


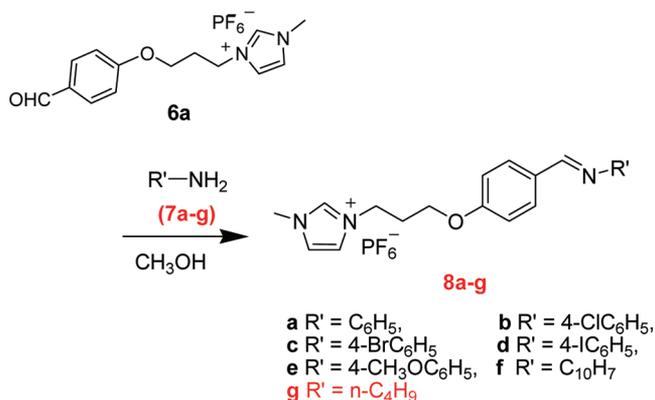
Figure 1. Capture of **7b** in **6a** and **6b**: (A) only methanol and **7b**, (B) methanol with **7b** and **6a**, and (C) methanol with **7b** and **6b**.

soluble in methanol (Figure 1C). Thus, simple filtration and washing with appropriate solvents separated **8b** from the reaction mixture when **6a** was used. The isolated yield of **8b** was 52% when **6b** was used (Table 1, entry 2). Reaction of seven different amines (**7a–g**) with **6a** was studied to give corresponding ionic liquid-supported imines (**8a–g**) (Scheme 2). The structure of ionic liquid-supported imines was confirmed by ^1H NMR and ^{13}C NMR analysis (Supporting Information). In all aromatic amines (**7a–f**), the corresponding ionic liquid-supported imines (**8a–f**, respectively) precipitated

Table 1. Yields of Ionic Liquid-Supported Imines

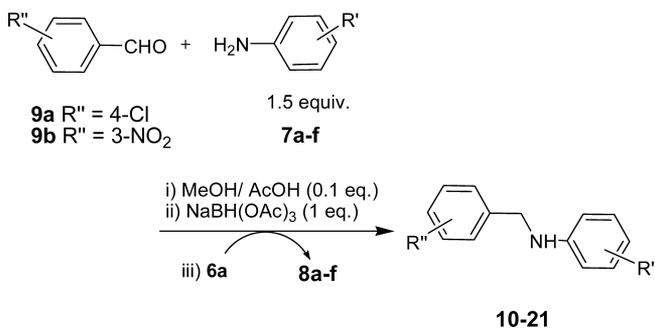
entry	R'	imines	yield (%) ^a
1	C_6H_5	8a	87 (60) ^b
2	$4\text{-ClC}_6\text{H}_4$	8b	87 (52) ^c
3	$4\text{-BrC}_6\text{H}_4$	8c	86
4	$4\text{-IC}_6\text{H}_4$	8d	86
5	$4\text{-CH}_3\text{OC}_6\text{H}_4$	8e	89
6	C_{10}H_7	8f	85
7	C_4H_9	8g	70

^aIsolated yield. ^bIn the absence of 0.1 mol % acetic acid. ^cIsolated yield when **6b** was used.

Scheme 2. Capture of Amines Using **6a**

in methanol and were removed by filtration; however, for *n*-butylamine (**7g**), the ionic liquid-supported imine (**8g**) was liquid and did not precipitate in methanol. In this case, methanol was evaporated and excess amine was removed by extraction with ethyl acetate, leaving behind **8g**.

Next, the application of **6a** as a scavenger for primary amines was demonstrated in the parallel synthesis of secondary amines. 4-Chlorobenzaldehyde (**9a**) was reacted with excess 4-chloroaniline (**7b**) in methanol to give the imine, which was then reduced to *N*-(4-chlorobenzyl)-4-chlorobenzeneamine (**11**) via addition of $\text{NaBH}(\text{OAc})_3$. After completion of the reduction of imine, an excess of **7b** was removed by precipitation of **8b** upon reaction with **6a** (Scheme 3). Using

Scheme 3. Synthesis of Secondary Amines Using **6a** as a Scavenger

this methodology, a small library of secondary amines was synthesized. The yield and purity of different secondary amines (**10–21**) are listed in Table 2. All the synthesized secondary amines were characterized by ^1H NMR and ^{13}C NMR spectroscopic data (Supporting Information). The method is

Table 2. Synthesis of Secondary Amines Using 6a as a Scavenger

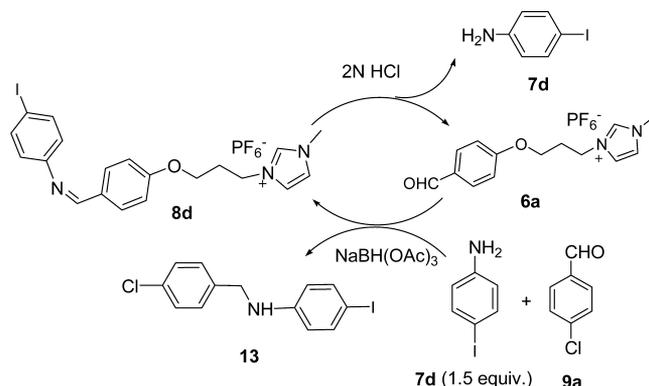
Entry	Aldehyde	Amine	Secondary amines	% Yield ^a (Purity) ^b
1	9a	7a		84 (96)
2	9a	7b		85 (98)
3	9a	7c		82 (95)
4	9a	7d		83 ^c (>94)
5	9a	7e		86 (98)
6	9a	7f		82 (96)
7	9b	7a		92 (99)
8	9b	7b		90 (96)
9	9b	7c		88 (98)
10	9b	7d		87 (99)
11	9b	7e		90 (98)
12	9b	7f		88 (97)

^aIsolated yield. ^bPurity determined by HPLC. ^cYields of **13** in the second and third cycle were 80 and 78%, respectively.

simple and gives high yield of secondary amines with high purities in a shorter reaction time. Guinó et al. used polymer-supported aldehyde as a scavenger for the synthesis of a small library of secondary amines, and it took ~3 days to complete the process;³⁰ with our method, the synthesis and purification process was complete in 9–10 h.

To reuse ionic liquid-supported aldehyde **6a**, we regenerated it via treatment with a 2 N HCl solution after filtration from the reaction mass (Scheme 4). The regenerated **6a** was reused for scavenging of aniline **7d** three times without much loss of activity (Table 2, entry 4).

In conclusion, we have synthesized a novel aldehyde-functionalized ionic liquid and used it as a scavenger for primary amines in the synthesis of secondary amines. The yields of secondary amines are high (82–90%) with high purity. The ionic liquid-supported aldehyde is a highly efficient scavenger for the primary amines, and the time required for the complete process using this scavenger is shorter than that for the polymer-supported aldehyde scavenger.

Scheme 4. Reuse of 6a as a Scavenger

EXPERIMENTAL PROCEDURES

Synthesis of Ionic Liquid-Supported Aldehydes (6a and 6b). A mixture of **3** (0.025) and 1-methylimidazole (0.027 mol) was heated at 80 °C for 6 h to give a thick viscous liquid. The viscous liquid was washed with ethyl acetate (2 × 10 mL) to remove unreacted starting materials to give pure chloride salt. Ion exchange of chloride was performed in dry acetone (50 mL) using potassium hexafluorophosphate (0.041 equiv) for **6a** or sodium tetrafluoroborate (0.041 equiv) for **6b** at room temperature for 48 h. After complete exchange of chloride anion as indicated by silver nitrate, acetone was evaporated. In the case of **6a**, the resulting solution was washed with water to remove salts and the ionic liquid was extracted with dichloromethane (DCM) (3 × 50 mL), dried with anhydrous sodium sulfate, and evaporated under reduced pressure to yield pure **6a** (4.30 g, 90%). In the case of **6b**, the reaction mixture was dissolved in DCM, and salts were removed by repeated filtrations through 60–120 mesh silica gel columns. Finally, DCM was evaporated to yield pure **6b** (3.86 g, 93%).

6a: white solid; mp 92–95 °C; ¹H NMR (300 MHz, DMSO) δ 9.85 (s, 1H), 9.03 (s, 1H), 7.86 (d, *J* = 8.78 Hz, 2H), 7.75 (s, 1H), 7.65 (s, 1H), 7.05 (d, *J* = 8.78 Hz, 2H), 4.39 (t, *J* = 7.0 Hz, 2H), 4.14 (t, *J* = 6.2 Hz, 2H), 3.85 (s, 3H), 2.35–2.26 (m, 2H); ¹³C NMR (101 MHz, DMSO) δ 191.9, 163.6, 137.22, 132.36, 130.18, 124.10, 122.92, 115.31, 65.51, 46.92, 36.07, 29.28; ESI-MS *m/z* calcd for C₁₄H₁₇F₆N₂O₂P 390.0932, found 245.1302 [M – PF₆]⁺.

6b: white solid; mp 51–52 °C; ¹H NMR (300 MHz, DMSO) δ 9.84 (s, 1H), 9.06 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.74 (s, 1H), 7.64 (s, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 4.37 (t, *J* = 6.9 Hz, 2H), 4.16 (t, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 2.34–2.26 (m, 2H); ¹³C NMR (101 MHz, DMSO) δ 191.94, 163.59, 137.17, 132.31, 130.23, 124.05, 122.86, 115.32, 65.54, 46.81, 36.15, 29.31; ESI-MS *m/z* calcd for C₁₄H₁₇BF₄N₂O₂ 332.1319, found 245.1298 [M – BF₄]⁺.

General Procedure for the Synthesis of Ionic Liquid-Supported Imines. A mixture of ionic liquid-supported aldehyde (**6a** or **6b**) (0.0025 equiv) and amine (**7a–g**) (0.003 equiv) in methanol in the presence of 0.1% acetic acid was stirred for 4 h at 30 °C. In the case of **6a**, a solid precipitated and was filtered and washed with methanol to yield the pure compound. For **6b**, it was soluble in methanol, and thus, the solvent was evaporated and the residue obtained washed with ethyl acetate (3 × 15 mL) to yield the pure compound.

8a: mp 151–154 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.13 (s, 1H), 8.54–8.49 (m, 1H), 7.90–7.86 (m, 2H), 7.79 (t, *J* = 2.0 Hz, 1H), 7.69 (t, *J* = 2.0 Hz, 1H), 7.42–7.35 (m, 2H), 7.24–7.18 (m, 3H), 7.04–7.00 (m, 2H), 4.36 (t, *J* = 6.9 Hz, 2H), 4.11 (t, *J* = 6.0 Hz, 2H), 3.84 (s, 3H), 2.34–2.26 (m, 2H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 161.23, 160.22, 152.16, 137.19, 130.90, 129.63, 129.60, 126.04, 124.05, 122.89, 121.35, 115.13, 65.27, 46.86, 36.18, 29.40; ESI-MS *m/z* calcd for C₂₀H₂₂F₆N₃OP 465.1405, found 320.1789 [M – PF₆]⁺.

General Procedure for Solution-Phase Synthesis of Secondary Amines. Substituted benzaldehyde (1 mmol) and amine (1.5 mmol) were added to a round-bottom flask containing methanol (3.0 mL) and stirred for 2 h at room temperature. Sodium triacetoxyborohydride (0.75 equiv) was added to the reaction mixture and the mixture stirred for an additional 30 min. After completion of reductive amination, **6a** (2 equiv) and 0.1 mol % acetic acid were added to the reaction mixture, and the mixture was stirred for an additional 4 h. After completion of the reaction as indicated by TLC, the solid was filtered and the resulting solution was evaporated to yield the pure secondary amine.

General Procedure for Regeneration of Ionic Liquid-Supported Aldehyde (6a). To the ionic liquid-supported imines (**8d**) (50 mg) was added 2 N HCl (1.0 mL), and the mixture was stirred vigorously for 4 h. While the reaction progressed, the color of the ionic liquid amine changed from colorless to yellowish. After completion of the reaction, the reaction mixture was neutralized with NaHCO₃ and the compound was extracted with DCM (3.0 mL). The organic layer was dried with sodium sulfate and evaporated and extracted with a hexane/ethyl acetate mixture (1:1, v/v) to remove 4-iodoaniline (**7d**). After removal of **7d**, the residue was dried under reduced pressure to yield the ionic liquid aldehyde (**6a**). The yield was 28 mg (85%).

■ ASSOCIATED CONTENT

● Supporting Information

General experimental details, ¹H and ¹³C NMR data of compounds **10–21**, copies of NMR spectra for compounds **3**, **6a**, **8a–g**, and **10–21**, experimental procedures for synthesis of 4-(3-chloropropoxy)benzaldehyde (**3**), and characterization data for compounds **8b–8g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*Department of Chemistry, Birla Institute of Technology and Science, Pilani, Rajasthan, India, PIN-333 031. Phone: +91-1596-245073. Fax: +91-1596-244183. E-mail: anilkumar@bits-pilani.ac.in.

Funding

We thank the Council of Scientific and Industrial Research (CSIR), New Delhi [01(2214)/08/EMR-II], for financial support.

■ REFERENCES

- (1) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. Solid-phase organic reactions ii: A review of the literature nov 95–nov 96. *Tetrahedron* **1997**, *53*, 5643.
- (2) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. Solid-phase organic reactions: A review of the recent literature. *Tetrahedron* **1996**, *52*, 4527.

- (3) Hodge, P. Synthesis of organic compounds using polymer-supported reagents, catalysts, and/or scavengers in benchtop flow systems. *Ind. Eng. Chem. Res.* **2005**, *44*, 8542–8553.

- (4) Baxendale, I. R.; Ley, S. V. Synthesis of the alkaloid natural products (+)-plicane and (–)-obliquine, using polymer-supported reagents and scavengers. *Ind. Eng. Chem. Res.* **2005**, *44*, 8588–8592.

- (5) Azuaje, J.; Coelho, A.; Maatougui, A. E.; Blanco, J. M.; Sotelo, E. Supported *p*-toluenesulfonic acid as a highly robust and eco-friendly isocyanide scavenger. *ACS Comb. Sci.* **2011**, *13*, 89–95.

- (6) Falchi, A.; Taddei, M. Peg-dichlorotriazine (peg-dct): A new soluble polymer-supported scavenger for alcohols, thiols, phosphines, and phosphine oxides. *Org. Lett.* **2000**, *2*, 3429–3431.

- (7) Kang, L.-Q.; Cai, Y.-Q.; Peng, Y.-Q.; Ying, X.-L.; Song, G.-H. Silica-supported sulfonic acid-functionalized ionic liquid coated with [bmim][pf₆] as a scavenger for the synthesis of amides. *Mol. Diversity* **2011**, *15*, 109–113.

- (8) Linclau, B.; Sing, A. K.; Curran, D. P. Organic-fluorous phase switches: A fluorous amine scavenger for purification in solution phase parallel synthesis. *J. Org. Chem.* **1999**, *64*, 2835–2842.

- (9) Lindsley, C. W.; Zhao, Z.; Leister, W. H. Fluorous-tethered quenching reagents for solution phase parallel synthesis. *Tetrahedron Lett.* **2002**, *43*, 4225–4228.

- (10) Zhang, W.; Chen, C. H.-T.; Nagashima, T. Fluorous electrophilic scavengers for solution-phase parallel synthesis. *Tetrahedron Lett.* **2003**, *44*, 2065–2068.

- (11) Ghanem, N.; Martinez, J.; Stien, D. A new high-loading water-soluble scavenger for anhydrides, acid chlorides and isocyanates. *Tetrahedron Lett.* **2002**, *43*, 1693–1695.

- (12) Lin, C.-E.; Richardson, S. K.; Garvey, D. S. L-Cysteine as a water-soluble cation scavenger in the removal of the 2,4,6-trimethoxybenzyl group from thiols. *Tetrahedron Lett.* **2002**, *43*, 4531–4533.

- (13) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. Chemical and biochemical transformations in ionic liquids. *Tetrahedron* **2005**, *61*, 1015–1060.

- (14) Miao, W.; Chan, T. H. Ionic-liquid-supported synthesis: A novel liquid-phase strategy for organic synthesis. *Acc. Chem. Res.* **2006**, *39*, 897–908.

- (15) Kamal, A.; Chouhan, G. A task-specific ionic liquid [bmim]scn for the conversion of alkyl halides to alkyl thiocyanates at room temperature. *Tetrahedron Lett.* **2005**, *46*, 1489–1491.

- (16) Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Mayton, R.; Sheff, S.; Wierzbicki, A.; Davis, J. J. H.; Rogers, R. D. Task-specific ionic liquids for the extraction of metal ions from aqueous solutions. *Chem. Commun.* **2001**, 135–136.

- (17) Lee, S. Functionalized imidazolium salts for task-specific ionic liquids and their applications. *Chem. Commun.* **2006**, 1049–1063.

- (18) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. Functionalized ionic liquids catalyzed direct aldol reactions. *Tetrahedron* **2007**, *63*, 1923–1930.

- (19) Bates, E. D.; Mayton, R. D.; Ntai, I.; Davis, J. H. CO₂ capture by a task-specific ionic liquid. *J. Am. Chem. Soc.* **2002**, *124*, 926–927.

- (20) D'Anna, F.; Marullo, S.; Noto, R. Ionic liquids/[bmim][n₃] mixtures: Promising media for the synthesis of aryl azides by snar. *J. Org. Chem.* **2008**, *73*, 6224–6228.

- (21) Song, G.; Cai, Y.; Peng, Y. Amino-functionalized ionic liquid as a nucleophilic scavenger in solution phase combinatorial synthesis. *J. Comb. Chem.* **2005**, *7*, 561–566.

- (22) Cai, Y.; Liu, Y. A diol-functionalized ionic liquid: An efficient, simple, and recoverable “capture and release” reagent for aldehydes. *Monatsh. Chem.* **2009**, *140*, 39–44.

- (23) Cai, Y.; Zhang, Y.; Peng, Y.; Lu, F.; Huang, X.; Song, G. Carboxyl-functional ionic liquids as scavengers: Case studies on benzyl chloride, amines, and methanesulfonyl chloride. *J. Comb. Chem.* **2006**, *8*, 636–638.

- (24) Maase, M.; Massonne, K. Biphasic acid scavenging utilizing ionic liquids: The first commercial process with ionic liquids. In *Ionic Liquids IIIb: Fundamentals, Progress, Challenges, and Opportunities*; American Chemical Society: Washington, DC, 2005; Vol. 902, pp 126–132.

(25) Lei, M.; Tao, X.-L.; Wang, Y.-G. A practical, water-soluble, ionic scavenger for the solution-phase syntheses of amides. *Helv. Chim. Acta* **2006**, *89*, 532–536.

(26) Kumar, A.; Rao, M. S.; Ahmad, I.; Khungar, B. A simple and facile synthesis of amidoalkyl naphthols catalyzed by $\text{Yb}(\text{otf})_3$ in ionic liquids. *Can. J. Chem.* **2009**, *87*, 714–719.

(27) Kumar, A.; Jain, N.; Chauhan, S. M. S. Biomimetic oxidation of veratryl alcohol with H_2O_2 catalyzed by iron(III) porphyrins and horseradish peroxidase in ionic liquid. *Synlett*, **2007**, 411–414.

(28) Kumar, A.; Ahmad, I.; Rao, M. S. Ytterbium(III) triflate catalyzed synthesis of calix[4]pyrroles in ionic liquids. *Can. J. Chem.* **2008**, *86*, 899–902.

(29) Kumar, A.; Rao, M. S.; Ahmad, I.; Khungar, B. An efficient and simple one-pot synthesis of β -acetamido ketones catalyzed by ytterbium triflate in ionic liquid. *Aust. J. Chem.* **2009**, *62*, 322–327.

(30) Guinó, M.; Brulé, E.; de Miguel, Y. R. Recycling and reuse of a polymer-supported scavenger for amine sequestration. *J. Comb. Chem.* **2003**, *5*, 161–165.