An Operationally Simple and Scalable Approach to Functionalized Ionic Liquids from Phosphonium and N-Heterocyclic Halide Salts

Christopher J. Meyer, Monika Vogt, James P. Catalino, Brandon L. Ashfeld*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46637, USA
Fax +1(574)6316652; E-mail: bashfeld@nd.edu

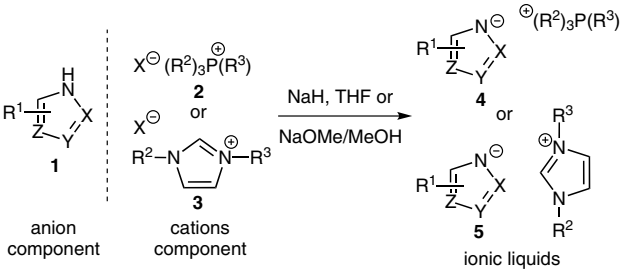
Received: 03.03.2013; Accepted after revision: 23.04.2013

Abstract: An approach toward the synthesis of N-heterocyclic anionic ionic liquids is described. The ionic liquids are readily obtained by the treatment of the sodium salt of the parent N-heterocycle with the halide salt of the desired cation. Good to excellent yields (62–99%) of the corresponding ionic liquids are obtained without the use of excessive materials and time associated with conventional methods for synthesizing heterocyclic based ionic liquids.

Key words: ionic liquids, heterocyclic anions, phosphonium salts, imidazolium salts, triazolium salts

The study of ionic liquids (ILs) constitutes one of the fastest growing areas of research in academia and industry.[1] The interest in ILs is primarily due to their exceptional utility as a broad class of materials for a wide range of applications. Characterized by a low vapor pressure, low flammability, aqueous solubility, and high thermal stability, ILs have become increasingly important as materials for phase-transfer catalysis,[2] biocatalysis,[3] liquid membranes,[4] solar cell design, electrodeposition, lithium batteries,[5] and chemical separations. Additionally, their use as polar solvents in synthetic transformations highlights their potential as a green alternative to conventional organic solvents.[6] In spite of these attractive characteristics, the synthetic approach towards construction of ILs with heterocyclic-based anions employs a method which requires excessive amounts of solvent, reagents, and time.[7] However, the benefits associated with the potential to tune the physiochemical properties of ILs to optimize performance parameters through the design of functionalized heterocyclic frameworks, make the addressing of these issues one of primary importance.[7]

Our interest in the design and synthesis of ILs stems from recent reports highlighting their use as working fluids for the gas-phase separation of pre- and postcombustion CO_2.[8] Although efforts in this area have focused on optimizing the chemical and physical absorption properties of CO_2, there remains a need for an effective method for the large-scale synthesis of ILs efficiently and rapidly, from a variety of heterocyclic scaffolds. Most custom ILs designed for these purposes contain an anionic component with an unsymmetrical phosphonium or imidazolium counterion to enhance the fluidic properties of the material.[9] The most common method for the synthesis of the phosphonium salts involves the acid–base neutralization of a protonated anion precursor and the appropriately ligated phosphonium hydroxide.[10] Although generally effective for common ILs, obtaining the unsymmetrical phosphonium hydroxide requires an anion exchange of the corresponding phosphonium halide that involves prolonged reaction times and excessive amounts of hydroxide and solvents. Thus, a method that provides the desired IL in a single synthetic operation from the protonated anion precursor, without the need for chromatography, in high levels of purity and without extended reaction times that is readily scalable would facilitate the further development of this increasingly important class of materials. We speculated that a simple cation-exchange protocol involving metalation of the protonated heterocycle **1** with either NaH or NaOMe, followed by addition of the desired phosphonium bromide **2** or imidazolium salt **3** directly, would provide ILs **4** and **5**, respectively after a simple aqueous workup (Scheme 1).[11] Herein we report the successful implementation of this method design in the synthesis of a wide assortment of N-heterocyclic anion-based ILs in a highly efficient and cost-effective manner that is readily amenable to large-scale production.



Scheme 1 Cation exchange approach towards IL synthesis

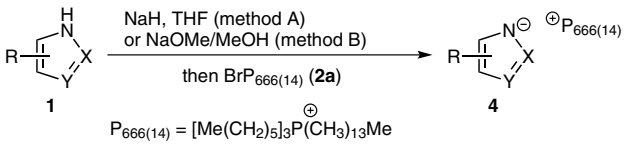
In general, ILs **4** were obtained in good to excellent yields by treatment of N-heterocycle **1** with either NaH (conditions A[12]) or NaOMe (conditions B[12]) followed by the addition of phosphonium bromide **2a** (Table 1). For example, applying conditions A to 2-cyanopyrrole (**1a**) and **2a** yielded pyrrolide IL **4a** in 91% (Table 1, entry 1). The addition of one equivalent of NaOMe to bipyrrole **1b** provided IL **4b** in 88% yield (Table 1, entry 2). Triazolide IL **4c** was readily obtained in 76% yield (Table 1, entry 3). Pyrazoles **1d–f** proved to be effective precursors for the synthesis of IL **4d–f** in excellent yields (Table 1, entries 4–6). The bisthiophene-substituted imidazole-based IL **4g** was obtained in 62% yield (Table 1, entry 7). These re-

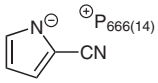
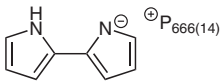
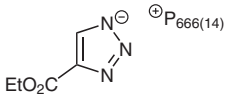
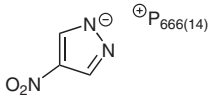
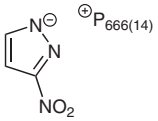
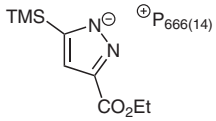
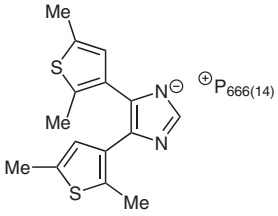
SYNLETT 2013, 24, 1428–1432
Advanced online publication: 17.05.2013
DOI: 10.1055/s-0033-1338806; Art ID: ST-2013-R0194-L
© Georg Thieme Verlag Stuttgart · New York

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

sults demonstrate the applicability of this cation-exchange protocol for the generation of N-heterocyclic anion-based IL without the need for phosphonium hydroxide synthesis.

Table 1 Heterocyclic Anionic Phosphonium Ionic Liquids[a]

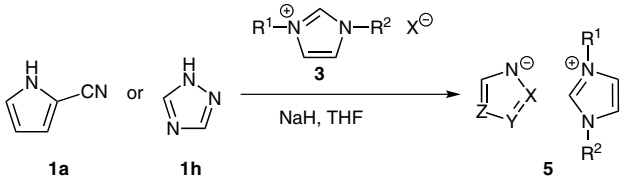


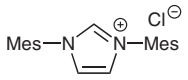
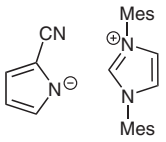
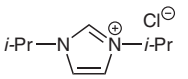
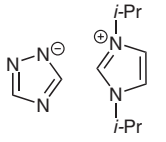
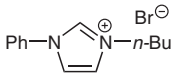
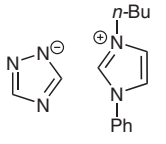
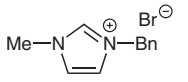
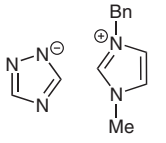
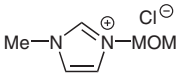
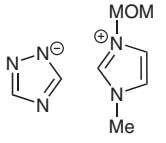
Entry	4	Conditions	Yield (%)[b]
1	 **4a**	A	91
2	 **4b**	B	88
3	 **4c**	A	76
4	 **4d**	A	99
5	 **4e**	A	70
6	 **4f**	A	81
7	 **4g**	B	62

[a] Conditions A: **1** (1.0 equiv), **2a** (1.0 equiv), and NaH (1.0 equiv) in THF (0.1 M), 18 h. Conditions B: **1** (1.0 equiv), **2a** (1.0 equiv), and NaOMe (1.0 equiv) in MeOH (0.1 M), 18 h.
[b] Isolated yields.

Given the general utility of imidazolium-based ILs,[13] we next examined the formation of ILs **5** resulting from the exposure of heterocycles **1a** or **1h** with imidazolium halide salts **3** to NaH (Table 2). Cyanopyrrole **1a** was readily converted into IL **5a** with *N*,*N*-bismesityl imidazolium chloride **3a** in 70% yield (Table 2, entry 1). The alkyl/alkyl, aryl/alkyl, and alkyl/benzyl imidazolium salts **3b**–**d** provided the corresponding triazolide ILs **5b**–**d**, respectively (Table 2, entries 2–4). Interestingly, the methyl/MOM-substituted imidazolium salt **3e** provided IL **5e** in 60% yield (Table 2, entry 5). It is noteworthy that in the formation of ILs **5a**–**e** only trace quantities of the corresponding N-heterocyclic carbenes resulting from C2–H abstraction by the heterocyclic anion were observed by ^{1}H NMR spectroscopy.[14]

Table 2 Heterocyclic Anionic Imidazolium Ionic Liquids[a]



Entry	1	3	5	Yield (%)[b]
1	**1a**	 **3a**	 **5a**	70
2	**1h**	 **3b**	 **5b**	96
3	**1h**	 **3c**	 **5c**	72
4	**1h**	 **3d**	 **5d**	81
5	**1h**	 **3e**	 **5e**	60

[a] Conditions: same as A, Table 1.
[b] Isolated yields

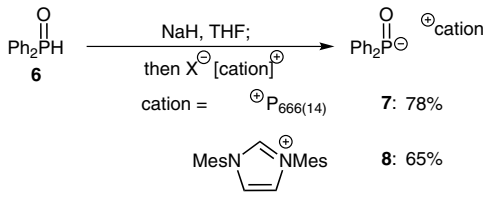
With a general approach established for the synthesis of phosphonium and imidazolium ILs derived from readily

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

© Georg Thieme Verlag Stuttgart · New York

obtained unsymmetrical tetraalkyl phosphonium and imidazolium halides, we turned our attention toward evaluating this method with functionalized cation precursors. In general, good to excellent yields of triazolide ILs **4** and **5** were obtained from the treatment of triazole (**1i**) and a diverse array of phosphonium and heterocyclic halide salts with NaOMe in MeOH (Table 3). Based on a recent report by Tsunashima and co-workers that the presence of phosphorus alkyl ether ligands decreased the viscosity of phosphonium bistriflamide ILs,[15] we initially examined the formation of methyl ether phosphonium triazolide ILs employing this cation-exchange protocol. Treatment of triazole (**1i**) with NaOMe in MeOH followed by the addition of MOM-substituted tributyl phosphonium chloride provided ILs **4h** in a respectable 72% yield (Table 3, entry 1). Truncating the straight alkyl chains on the phosphonium cation to methyl did not hinder the formation of IL **4i** (Table 3, entry 2). Likewise, the length of alkyl substitution on the oxygen-bearing phosphonium ligand proved inconsequential to IL synthesis (Table 3, entry 3). The MEM-substituted phosphonium triazolides **4k** and **4l** were obtained in 77% and 76% yields, respectively (Table 3, entries 4 and 5). Employing the corresponding SEM-substituted phosphonium chloride provided the triazolide IL **4m** in 75% yield (Table 3, entry 6). Given the propensity for imidazolium ILs to generate N-heterocyclic carbenes in situ, we examined C2 alkyl-substituted imidazolium halides to prohibit carbene formation.[16] Thus, imidazolium ILs **5f** and **5g** bearing MOM- and MEM-protected primary alcohols at C2 were obtained in good yields (Table 3, entries 7 and 8). Finally, the triazolium-based IL **5h** was obtained in 91% yield (Table 3, entry 9).

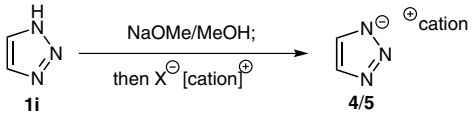
Based on recent reports, most notably by Johnston and coworkers, on the synthetic utility of phosphite anions,[17] we examined the application of this cation-exchange protocol for the synthesis of phosphite anion-based ILs. Gratifyingly, treatment of diphenylphosphite **6** with NaH followed by the unsymmetrical phosphonium bromide **2a** or imidazolium chloride **3a** provided phosphite ILs **7** and **8** in 78% and 65% yield, respectively (Equation 1). Although a relatively unexplored IL motif, phosphite-based ILs offer a number of opportunities for performance optimization through structural modification of the phosphite precursor.

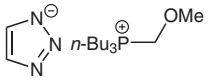
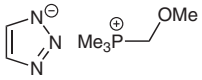
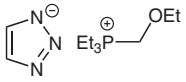
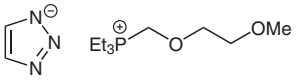
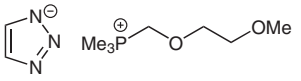
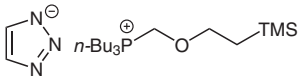
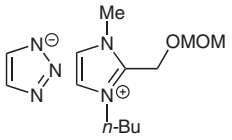
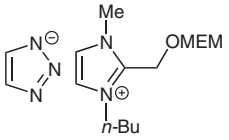
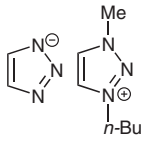


Equation 1

One challenge in applying functionalized ILs as working fluids for industrial purposes is the development of a synthetic method that is readily amenable to large-scale production. Therefore, we examined the scalability of this modified cation-exchange protocol using triazole (**1i**) in the synthesis of the corresponding phosphonium-based ILs (Table 4). Employing a series of unsymmetrical tet-

Table 3 Cation Functional Variability[a]



Entry	X	Ionic liquid	Yield (%)[b]
1	Cl	 **4h**	72
2	Cl	 **4i**	73
3	Cl	 **4j**	81
4	Cl	 **4k**	77
5	Cl	 **4l**	76
6	Cl	 **4m**	75
7	Br	 **5f**	81
8	Br	 **5g**	73
9	Br	 **5h**	91

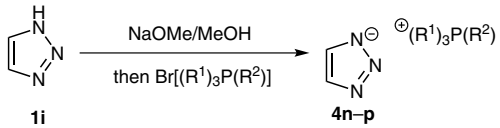
[a] Conditions: same as B, Table 1.
[b] Isolated yields.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

 © Georg Thieme Verlag Stuttgart · New York

raalkyl phosphonium bromides, the corresponding triazolide ILs **4n–p** were obtained in yields ranging from 70–96% on 120 g scale (Table 4, entries 1–3).

Table 4 Large-Scale Production of Ionic Liquids[a]



1i **4n–p**

Entry	R^1	R^2	IL	Yield (%)[b]
1	$CH_3(CH_2)_5$	$CH_3(CH_2)_{13}$	**4n**	93
2	$CH_3(CH_2)_3$	$CH_3(CH_2)_{11}$	**4o**	96
3	CH_3CH_2	$CH_3(CH_2)_5$	**4p**	70

[a] Conditions: **1i** (2.0 equiv), **2** (1.0 equiv), and NaOMe (2.0 equiv) in MeOH (1.0 M), 72 h.
[b] Isolated yields

In conclusion, we have developed a complementary method for the synthesis of functionalized phosphonium and N-heterocyclic cation based ILs that relies on the ease of Na^+ ion cation exchange. The method described herein is applicable to a diverse array of anionic and cationic components containing an assortment of different functional groups. This protocol allows for the direct use of phosphonium halides that obviates the conventional requirement of phosphonium hydroxide synthesis and avoids the complications associated with excessive solvent, reagents, and extended reaction times. The reaction is amenable to large-scale production and requires a simple aqueous wash or filtration to obtain the desired ILs in high levels of purity. Given the ever-increasing interest in functionally diverse ILs, this method should facilitate the discovery of new applications for this important class of materials.

Acknowledgment

The authors thank Professor Joan F. Brennecke (University of Notre Dame) for helpful discussions and the Department of Energy, Advanced Research Projects-Energy, the University of Notre Dame Sustainable Energy Initiative, and the Center for Sustainable Energy at Notre Dame (cSEND) for support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Tang, S.; Baker, G. A.; Zhao, H. *Chem. Soc. Rev.* **2012**, *41*, 4030. (b) Buzzeo, M. C.; Evans, R. G.; Compton, R. G. *ChemPhysChem* **2004**, *5*, 1106. (c) Gordon, C. M. *Appl. Catal., A* **2001**, *222*, 101. (d) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772.

(2) (a) Kumar, V.; Talisman, I. J.; Bukhari, O.; Razzaghy, J.; Malhotra, S. V. *RSC Adv.* **2011**, *1*, 1721. (b) Bender, J.; Jepkens, D.; Hüsken, H. *Org. Process Res. Dev.* **2010**, *14*, 716. (c) Yadav, G. D.; Motirale, B. G. *Ind. Eng. Chem. Res.* **2008**, *47*, 9081. (d) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*, 4281. (e) Wheeler, C.; West, K. N.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* **2001**, 887.

(3) (a) Garcia, S.; Lourenco, N. M. T.; Lousa, D.; Sequeira, A. F.; Mimoso, P.; Cabral, J. M. S.; Afonso, C. A. M.; Barreiros, S. *Green Chem.* **2004**, *6*, 466. (b) Chiappe, C.; Leandri, E.; Lucchesi, S.; Pieraccini, D.; Hammock, B. D.; Morisseau, C. *J. Mol. Catal. B: Enzym.* **2004**, *27*, 243. (c) Persson, M.; Bornscheuer, U. T. *J. Mol. Catal. B: Enzym.* **2003**, *22*, 21. (d) Kim, K.-W.; Song, B.; Choi, M.-Y.; Kim, M.-J. *Org. Lett.* **2001**, *3*, 1507.

(4) (a) Matsumoto, M.; Inomoto, Y.; Kondo, K. *J. Membr. Sci.* **2005**, *246*, 77. (b) Scovazzo, P.; Kieft, J.; Finan, D. A.; Koval, C.; DuBois, D.; Noble, R. *J. Membr. Sci.* **2004**, *238*, 57. (c) Fortunato, R.; Afonso, C. A. M.; Reis, M. A. M.; Crespo, J. G. *J. Membr. Sci.* **2004**, *242*, 197. (d) Branco, L. C.; Crespo, J. G.; Afonso, C. A. M. *Angew. Chem.* **2002**, *114*, 2895.

(5) (a) Arce, A.; Earle, M. J.; Rodriguez, H.; Seddon, K. R. *J. Phys. Chem. B* **2007**, *111*, 4732. (b) Visser, A. E.; Swatloski, R. P.; Rogers, R. D. *Green Chem.* **2000**, *2*, 1. (c) Huddleston, J. G.; Rogers, R. D. *Chem. Commun.* **1998**, 1765.

(6) (a) Rogers, R. D.; Seddon, K. R. *Science* **2003**, *302*, 792. (b) Baleizao, C.; Gigante, B.; Garcia, H.; Corma, A. *Green Chem.* **2002**, *4*, 272. (c) Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000**, *72*, 1391.

(7) (a) Gurkan, B. E.; de la Fuente, J. C.; Mindrup, E. M.; Ficke, L. E.; Goodrich, B. F.; Price, E. A.; Schneider, W. F.; Brennecke, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 2116. (b) Gurkan, B.; Goodrich, B. F.; Mindrup, E. M.; Ficke, L. E.; Massel, M.; Seo, S.; Senftle, T. P.; Wu, H.; Glaser, M. F.; Shah, J. K.; Maginn, E. J.; Brennecke, J. F.; Schneider, W. F. *J. Phys. Chem. Lett.* **2010**, *1*, 3494. (c) Anthony, J. L.; Anderson, J. L.; Maginn, E. J.; Brennecke, J. F. *J. Phys. Chem. B* **2005**, *109*, 6366.

(8) (a) Bara, J. E.; Gabriel, C. J.; Lessmann, S.; Carlisle, T. K.; Finotello, A.; Gin, D. L.; Noble, R. D. *Ind. Eng. Chem. Res.* **2007**, *46*, 5380. (b) Bates, E. D.; Mayton, R. D.; Ntai, I.; Davis, J. H. *J. Am. Chem. Soc.* **2002**, *124*, 926. (c) Brennecke, J. F.; Maginn, E. J. *AlChE J.* **2001**, *47*, 2384.

(9) (a) Cadena, C.; Anthony, J. L.; Shah, J. K.; Morrow, T. I.; Brennecke, J. F.; Maginn, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5300. (b) Anthony, J. L.; Maginn, E. J.; Brennecke, J. F. *J. Phys. Chem. B* **2002**, *106*, 7315.

(10) (a) Ohno, H.; Fukumoto, K. *Acc. Chem. Res.* **2007**, *40*, 1122. (b) Fukumoto, K.; Yoshizawa, M.; Ohno, H. *J. Am. Chem. Soc.* **2005**, *127*, 2398.

(11) (a) Smiglak, M.; Hines, C. C.; Wilson, T. B.; Singh, S.; Vincek, A. S.; Kirichenko, K.; Katritzky, A. R.; Rogers, R. D. *Chem. Eur. J.* **2010**, *16*, 1572. (b) Smiglak, M.; Bridges, N. J.; Dilip, M.; Rogers, R. D. *Chem. Eur. J.* **2008**, *14*, 11314. (c) Katritzky, A. R.; Singh, S.; Kirichenko, K.; Smiglak, M.; Holbrey, J. D.; Reichert, W. M.; Spear, S. K.; Rogers, R. D. *Chem. Eur. J.* **2006**, *12*, 4630.

(12) **General Procedures for IL Synthesis**
Method A: A clean, oven-dried round-bottom flask was charged with NaH (1.0 equiv, 1.0 mmol), flushed with N_2, then suspended in THF (4 mL). A solution of **1** (1 equiv, 1.0 mmol) in THF (1 mL) was added dropwise over 30 min, then stirred until evolution of H_2 ceased. A solution of **2** or **3** (1 equiv, 1.0 mmol) in THF (5 mL) was added and the reaction monitored by ^1H NMR (DMSO-d_6). The resulting mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic fractions were concentrated under reduced pressure to afford the desired IL.
Method B: A clean, oven-dried round-bottom flask was charged with NaOMe/MeOH (0.4 mL of 3.0 M, 1.2 mmol). A solution of **1i** (1.0 equiv, 1.2 mmol) in MeOH (5 mL) was

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

added over 10 min, then stirred at r.t. for 30 min. A solution of **2l** (1.0 equiv, 1.2 mmol) in MeOH (5 mL) was added, whereupon NaCl precipitation was observed. Reaction stirred for 12–18 h, monitored by ^{1}H NMR (DMSO-d_6). Upon completion, MeOH was removed in vacuo, and EtOAc was added (15 mL). Suspended salt was filtered off using Celite and then rinsed with EtOAc (3 × 15 mL). Filtrate was collected and concentrated in vacuo to afford IL **4l** as an orange-yellow oil, 77%. Residual halide content was measured at 5–10% by ion chromatography for each sample. **4l**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.26 (s, 2H), 4.38–4.37 (d, J = 4 Hz, 2 H), 3.70–3.68 (m, 2 H), 3.48–3.46 (m, 2 H), 3.25 (s, 3 H), 1.87–1.83 (d, J = 16 Hz, 9 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 129.2, 73.2, 72.1, 71.2, 63.9, 63.2, 58.2, 5.3, 4.8. HRMS (ESI): *m/z* calcd for the $C_7H_{18}O_2P^+$: 165.1039; found: 165.1059; *m/z* calcd for $C_2H_2N_3^-$: 68.0254; found: 68.0232.

(13) (a) Bao, W.; Wang, Z.; Li, Y. *J. Org. Chem.* **2003**, *68*, 591. (b) Huddleston, J. G.; Visser, A. E.; Reichert, W. M.; Willauer, H. D.; Broker, G. A.; Rogers, R. D. *Green Chem.* **2001**, *3*, 156.

(14) (a) Zhao, G.; Jiang, T.; Gao, H.; Han, B.; Huang, J.; Sun, D. *Green Chem.* **2004**, *6*, 75. (b) Audic, N.; Clavier, H.; Mauduit, M.; Guillemin, J.-C. *J. Am. Chem. Soc.* **2003**, *125*, 9248. (c) Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123.

(15) Tsunashima, K.; Sugiya, M. *Electrochem. Commun.* **2007**, *9*, 2353.

(16) Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957.

(17) Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 2377.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

 © Georg Thieme Verlag Stuttgart · New York

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.