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Ionic liquid-promoted one-pot oxidative Michael addition of TMSCN to Baylis–Hillman adducts

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ABSTRACT

The first example of ionic liquid-promoted one-pot oxidative conjugate hydrocyanation of Baylis–Hillman adducts with trimethylsilyl cyanide (TMSCN) is reported. The oxidation of Baylis–Hillman adducts with IBX/[bmim]Br or isomerization-oxidation with $NaNO_3$/[Hmim]HSO_4 systems affords β-ketomethylene compounds or [*E*]-cinnamaldehydes, respectively. These α,β-unsaturated carbonyl compounds undergo Michael addition with TMSCN in the same vessel to afford the corresponding thermodynamically more stable β-cyanated products. Thermodynamically less stable 1,2-addition products were not formed. The present regioselective reactions are promoted by ionic liquids, which can be recycled easily for further use without any loss of efficiency.

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Continuing development in synthetic organic chemistry relies on discovering new, high yielding and selective reactions. The Michael addition of cyanide to α,β-unsaturated carbonyl derivatives is a useful C–C bond forming reaction because the resulting β-cyano adducts can be converted into γ-aminobutyric acids (GABA analogues) under reducing conditions. GABA is the chief inhibitory neurotransmitter in the central nervous system.[1] β-Cyanocarbonyl derivatives are also valuable synthons for a variety of compounds, and thereby enhance the versatility of molecules containing cyano functionalities.[2] Thus, the development of a convenient and efficient methodology for the synthesis of β-cyanocarbonyl compounds is an interesting target for investigation.

One of the best methods for the introduction of a cyanide group involves the reaction of carbonyl compounds with trimethylsilyl cyanide (TMSCN),[3] in contrast to other reagents such as Et_2AlCN,[4] NaCN,[5] KCN[6] and HCN.[7] It is reported that the reaction of α,β-unsaturated carbonyls with TMSCN in the presence of a base as catalyst affords 1,2-adducts.[8] In contrast, on employing Lewis acids such as Et_2AlCN, Et_3Al, $AlCl_3$ and $SnCl_2$, regioselective 1,4-addition takes place.[9] These metallated catalysts have drawbacks such as toxicity, difficult handling and work up, which we have overcome by using ionic liquids as both the reaction media and reaction promoters in the present work.

The Baylis–Hillman reaction is a useful C–C bond forming reaction. The Baylis–Hillman (BH) adducts, which possess dense functionality including allylic hydroxyl and Michael acceptor units, are valuable starting materials for the synthesis of various compounds of chemical and pharmaceutical importance.[10] Regioselective introduction of nucleophiles, viz. C-, S-, N-, O-centred nucleophiles, at either the α- or γ-position of the BH adduct have become powerful tools in synthetic organic chemistry.[10–12] However, there has been no report on the oxidative conjugate hydrocyanation of BH adducts.

Amongst various hypervalent iodine reagents,[13] 2-iodoxybenzoic acid (IBX) has become a reagent of choice due to its easy handling, low cost, tolerance to moisture,[14] mild reaction conditions and zero toxic waste generation. IBX selectively oxidizes alcohols in the presence of olefins, thioethers and amino groups,[15] and is also useful for other elegant oxidative transformations.[16] Similarly, ionic liquids (ILs) have gained considerable interest as environmentally benign reaction media, catalysts and reagents, and are easy to recycle.[17] Recently, Brønsted acidic ionic liquids have been deemed as promising alternatives for acid-catalyzed reactions, and play a dual solvent—catalyst role in a variety of reactions including esterification of carboxylic acids, protection of alcohols and carbonyl groups, oxidation of alcohols, alcohol dehydrodimerization, pinacol/benzopinacol rearrangement in Mannich reactions and for cleavage of ethers.[18]

One-pot sequential multistep reactions are of increasing academic, economical and ecological interest because they address fundamental principles of synthetic efficiency and reaction design. The continued interest of synthetic chemists in the BH reaction, and our ongoing efforts to devise one-pot protocols involving

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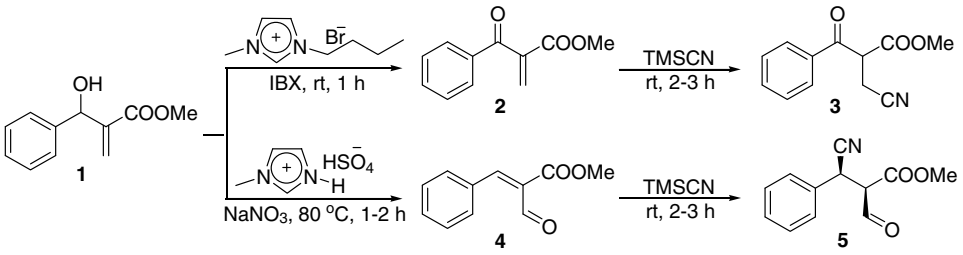


Scheme 1. Ionic liquid-promoted oxidative conjugate addition of TMSCN to BH adducts.

conjugate addition[19] have encouraged us to develop the present ionic liquid-promoted one-pot oxidative hydrocyanation of BH adducts (Scheme 1), which opens up a new aspect of their synthetic utility.

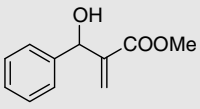
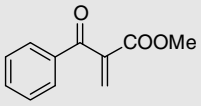
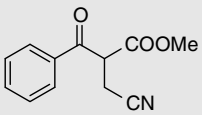
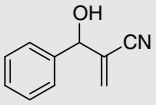
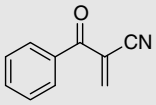
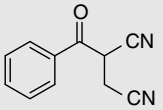
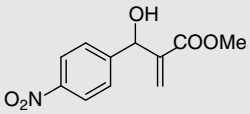
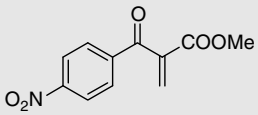
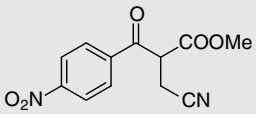
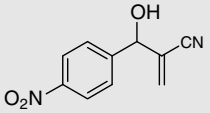
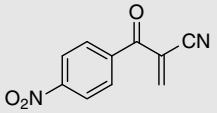
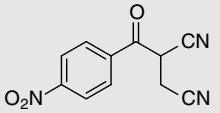
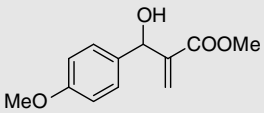
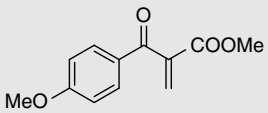
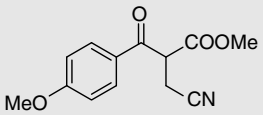
Initially, we examined the reaction in six different ILs, 1-butyl-3-methylimidazolium (bmim) tetrafluoroborate ([bmim]BF4), [bmim]PF6, [bmim]Br, butylpyridinium (bpy) tetrafluoroborate (bpyBF4), bpyPF6 and bpyBr.

Among these ILs, [bmim]Br dissolved IBX at rt and gave the best result in the one-pot oxidative hydrocyanation leading to **3** (Scheme 1). The other five ILs tested did not dissolve IBX even when heated to 80 °C in the presence of a small amount of water and did not give satisfactory yields of **3**. Thus, to achieve the oxidative conjugate addition of TMSCN to BH adducts in one-pot, we oxidized BH adducts **1** to the corresponding carbonyl compounds **2** with IBX in [bmim]Br at rt for 1 h followed by the addition of TMSCN and stirring at rt for a further 2–3 h to afford the corresponding hitherto unknown β-cyanated ketones **3** in 79–89% yields (Scheme 1, Table 1). A plausible mechanism for the hydrocyanation of **2** to afford **3** is depicted in Scheme 2. Other hypervalent iodine reagents such as DMP, $PhI(OAc)_2$ and PhIO gave unsatisfactory results. IBX was found to be the best reagent in terms of conversion.

In order to investigate the substrate scope of the reaction, we converted BH adducts **1** into [*E*]-cinnamaldehyde derivatives **4** via isomerization-oxidation with $NaNO_3$ in the protic ionic liquid [Hmim]HSO_4 employing the known method.[20] Hydrocyanation of **4** with TMSCN in the same vessel afforded new β-cyanated aldehydes **5** in 84–91% yields. The present procedure in its entirety involves stirring of an equimolar mixture of BH adduct **1** and $NaNO_3$ in 1-methylimidazolium hydrogen sulfate [Hmim]HSO_4 for 1–2 h at 80 °C followed by the addition of TMSCN and stirring for a further 2–3 h at rt to afford β-cyanated aldehydes **5** (Scheme 3, Table 1). The formation of **5** was highly diastereoselective in favour of the *syn* isomers. The diastereomeric ratios in the crude ratio isolates of **5** were determined by ^{1}H NMR spectroscopy to note any inadvertent alteration of these ratios during subsequent purification. As determined by ^{1}H NMR spectroscopy, the crude isolates of **5** were found to be diastereomeric mixtures containing 94–97% of the *syn* isomer. The *syn* stereochemistry of molecules **5** was conclusively assigned on the basis of ^{1}H NMR spectra and literature precedent,[21] as the coupling constant ($J_{2,3}$ = 4.0 Hz) for *syn* **5** was lower than that for the minor *anti* isomer ($J_{2,3}$ = 7.9 Hz).

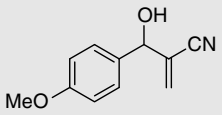
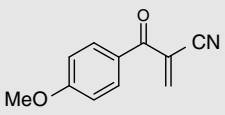
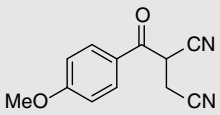
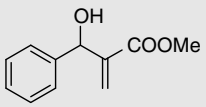
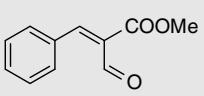
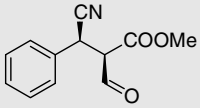
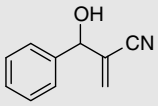
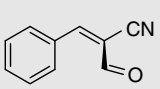
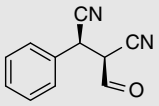
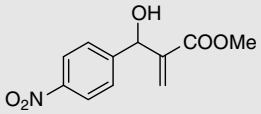
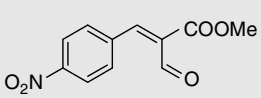
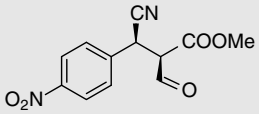
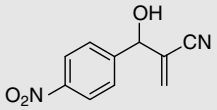
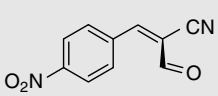
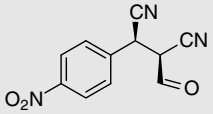
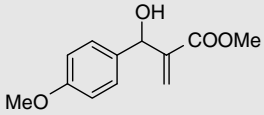
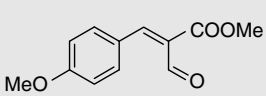
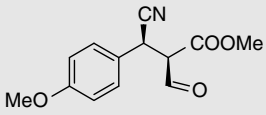
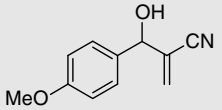
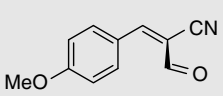
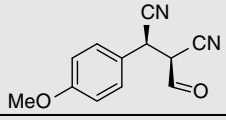
The oxidative conjugate hydrocyanation was also attempted with $NaNO_3$–[Hmim]NO_3 and $NaNO_3$–[Hmim]H_2PO_4 systems under the same reaction conditions. The reaction was unsuccessful in the former case indicating the need for an acidic hydrogen which is absent in [Hmim]NO_3 to catalyze the oxidation of the BH adducts into cinnamaldehydes **4** (Scheme 3). However, the reaction proceeded with the $NaNO_3$–[Hmim]H_2PO_4 system, but relatively low

Table 1
One-pot oxidative conjugate addition of TMSCN to BH adducts **1**

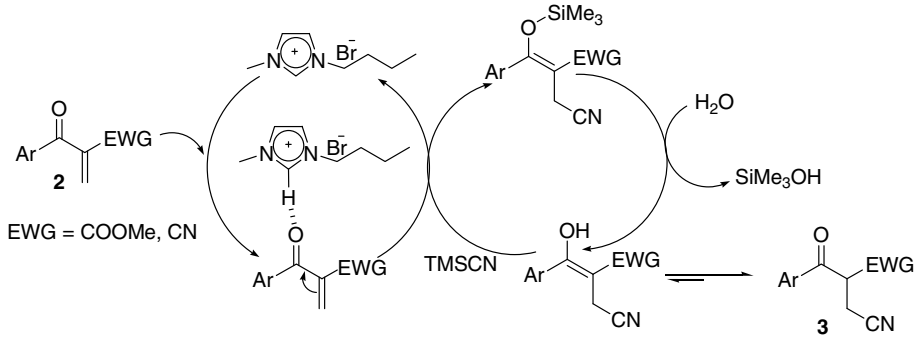
Entry	BH aduct **1**	Oxidized adduct **2** or **4**	Final product **3** or **5**[a]	Reaction time (h)	Yield[b,c] (%)
3a				4	83
3b				3.5	85
3c				3.5	86
3d				3	89
3e				4	79

(*continued on next page*)

Table 1 (*continued*)

Entry	BH aduct **1**	Oxidized adduct **2** or **4**	Final product **3** or **5**[a]	Reaction time (h)	Yield[b,c] (%)
3f				4	82
5a				3.5	86
5b				3.5	87
5c				3	89
5d				3	91
5e				3.5	84
5f				3.5	85

[a] *Syn/anti* representation proposed by Masamune and coworkers has been followed.[27]
[b] Yield of pure products **3** or **5** after column chromatography.
[c] All compounds gave C, H and N analyses within ±0.38% and satisfactory spectral (IR, 1 H NMR, ^{13}C NMR and EIMS) data.

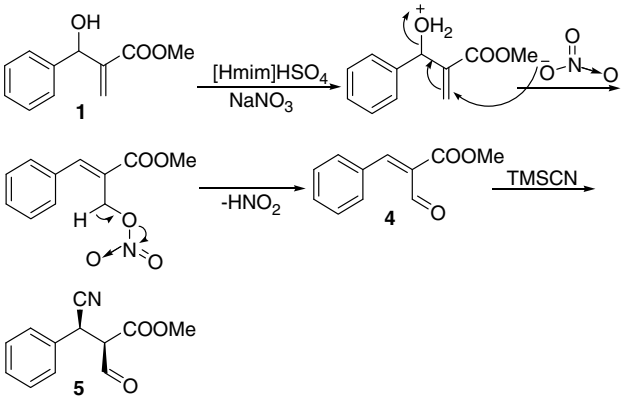


Scheme 2. A plausible mechanism for the conjugate addition of TMSCN to α,β-unsaturated ketone **2** to afford **3**.

yields of **5** (30–37%) were obtained probably due to the lower Brønsted acidity associated with $[H_2PO_4]$. Thus, $[Hmim]HSO_4$ plays a dual role, that is, as an acid catalyst and solvent for both oxidation and hydrocyanation.

The requisite BH adducts and ILs were prepared by employing known methods.[22–24] After isolation of products **3** and **5**, the ionic liquids could be recycled for four times up to 73% recovery and reused without any loss of efficiency.[25,26]

In conclusion, we have presented a novel example of ionic liquid-promoted one-pot oxidative conjugate hydrocyanation of BH adducts. The present method involves an efficient regioselective addition of TMSCN to β-keto-α-methylenes and [*E*]-cinnamaldehydes, obtained from oxidation and isomerization-oxidation of BH adducts, respectively, to afford the corresponding β-cyanated products, which opens up a new aspect for the synthetic utility of BH adducts.



Scheme 3. A plausible mechanism for the formation of **5**.

Acknowledgement

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References and notes

1. (a) Martin, D. L.; Olsen, R. W. *GABA in the Nervous System: The View at Fifty Years*; Lippincott Williams & Wilkins: Philadelphia, 2000; (b) Alger, B. E.; Möhler, H. *Pharmacology of GABA and Glycine Neurotransmission*; Springer: Berlin, New York, 2001; (c) Krogsgaard-Larsen, P.; Froelund, B.; Kristiansen, U.; Frydenvang, K.; Ebert, B. *Eur. J. Pharm. Sci.* **1997**, *5*, 355–384; (d) Krogsgaard-Larsen, P.; Froelund, B.; Joergensen, F. S.; Schousboe, A. *J. Med. Chem.* **1994**, *37*, 2489–2505.
2. Ros, F. *J. Chem. Res.* **2000**, *2000*, 124–125.
3. (a) Hayashi, M.; Kawabata, H.; Inoue, K. *Carbohydr. Res.* **2000**, *325*, 68–71; (b) Hayashi, M.; Kawabata, H.; Shimono, S.; Kakehi, A. *Tetrahedron Lett.* **2000**, *41*, 2591–2594; (c) Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 6072–6073; (d) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928; (e) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514–515.
4. (a) Dahuron, N.; Langlois, N. *Synlett* **1996**, 51–52; (b) Benedetti, F.; Berti, F.; Garau, G.; Martinuzzi, I.; Norbedo, S. *Eur. J. Org. Chem.* **2003**, 1973–1982.
5. Gerrits, P. G.; Marcus, J.; Birikaki, L.; vander Gen, A. *Tetrahedron: Asymmetry* **2001**, *12*, 971–974.
6. Utsugi, M.; Kamada, Y.; Miyamoto, H.; Nakada, M. *Tetrahedron Lett.* **2007**, *48*, 6868–6872.
7. Nagata, W.; Yoshioka, M.; Murakami, M. *J. Am. Chem. Soc.* **1972**, *94*, 4654–4672.
8. (a) Baeza, A.; Najera, C.; Retamosa, M de G.; Sansano, J. M. *Synthesis* **2005**, 2787–2797; (b) He, B.; Li, Y.; Feng, X.; Zhang, G. *Synlett* **2004**, 1776–1778; (c) Higuchi, K.; Onaka, M.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2016–2032.
9. Iida, H.; Moromizata, T.; Hamana, H.; Matsumoto, K. *Tetrahedron Lett.* **2007**, *48*, 2037–2039.
10. (a) Aggarwal, V. K.; Patin, A.; Tisserand, S. *Org. Lett.* **2005**, *7*, 2555–2557; (b) Wasnaire, P.; Wiaux, M.; Touillaux, R.; Markó, I. E. *Tetrahedron Lett.* **2006**, *47*, 985–989; (c) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387–5391; (d) Luo, S.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 555–558; (e) Yeo, J. E.; Yang, X.; Kim, H. J.; Koo, S. *Chem. Commun.* **2004**, 236–237; (f) Racker, R.; Doring, K.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 6932–6939; (g) Lee, K. Y.; Gowrisankar, S.; Kim, N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490; (h) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645.
11. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–892; (b) Basavaiah, D.; Rao, V.; Reddy, R. *J. Chem. Soc. Rev.* **2007**, *36*, 1581–1582.
12. (a) Yadav, J. S.; Reddy, B. V. S.; Singh, A. P.; Basak, A. K. *Synthesis* **2008**, 469–473; (b) Yadav, J. S.; Reddy, B. V. S.; Singh, A. P.; Basak, A. K. *Tetrahedron Lett.* **2007**, *48*, 4169–4172. and 7546–7548.
13. (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997; (b) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271–1287.
14. (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178; (b) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409–458.
15. (a) Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812–2814; (b) Ladziata, U.; Zhdankin, V. V. *Arkivoc* **2006**, *ix*, 26–58.
16. (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993–996; (b) Nicolaou, K. C.; Barn, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233–2244.
17. (a) Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, *63*, 2363–2389; (b) Bao, W.; Wang, Z. *Green Chem.* **2006**, *8*, 1028–1033; (c) Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, *74*, 157–189; (d) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692; (e) Qiao, K.; Yakoyama, C. *Chem. Lett.* **2004**, *33*, 472–473; (f) Sun, W.; Xia, C.-G.; Wang, H.-W. *Tetrahedron Lett.* **2003**, *44*, 2409–2411; (g) Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2005**, *46*, 1489–1491; (h) Earle, M. J.; Katdare, S. P.; Seddon, K. R. *Org. Lett.* **2004**, *6*, 707–710.
18. (a) Cole, A. C.; Jensen, J. L.; Ntai, I.; Tran, K. L. T.; Weaver, K. J.; Forbes, D. C.; Davis, J. H., Jr *J. Am. Chem. Soc.* **2002**, *124*, 5962–5963; (b) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2084; (c) Sheldon, R. *Chem. Commun.* **2001**, *23*, 2399–2407; (d) Zhu, H. P.; Yang, F.; Tang, J.; He, M. Y. *Green Chem.* **2003**, *5*, 38–39; (e) Zhao, G.; Jiang, T.; Gao, H.; Han, B.; Huang, J.; Sun, D. *Green Chem.* **2004**, *6*, 75–77.
19. (a) Yadav, L. D. S.; Awasthi, C.; Rai, V. K.; Rai, A. *Tetrahedron Lett.* **2007**, *48*, 4899–4902. and 8037–8039; (b) Yadav, L. D. S.; Patel, R.; Rai, V. K.; Srivastava, V. P. *Tetrahedron Lett.* **2007**, *48*, 7793–7795; (c) Yadav, L. D. S.; Rai, A.; Rai, V. K.; Awasthi, C. *Synlett* **2007**, 1905–1908; (d) Yadav, L. D. S.; Yadav, S.; Rai, V. K. *Green Chem.* **2006**, *8*, 455–458; (e) Yadav, L. D. S.; Rai, V. K.; Yadav, S. *Tetrahedron* **2006**, *62*, 5464–5468.
20. Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2008**, *49*, 3142–3146.
21. (a) Kamimura, A.; Mitsudera, H.; Asano, S.; Kidera, S.; Kakehi, A. *J. Org. Chem.* **1999**, *64*, 6353–6360; (b) Albertshofer, K.; Thayumanavan, R.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III. *Tetrahedron Lett.* **2007**, *48*, 693–696.
22. Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723–4725.
23. Lancaster, N. L.; Salter, P. A.; Welton, T.; Young, G. B. *J. Org. Chem.* **2002**, *67*, 8855–8861.
24. Mehdi, H.; Bodor, A.; Lantos, D.; Horváth, I. T.; de Vas, D. E.; Binnemans, K. *J. Org. Chem.* **2007**, *72*, 1517–1524.
25. *General procedure for the synthesis of β-cyano ketones* **3**: To a mixture of [bmim]Br (3 mL) and water (0.5 mL) was added IBX (1 mmol). The resulting mixture was stirred at rt for 5–10 min, and BH adduct **1** (1 mmol) was added. The reaction mixture was stirred at rt for 1 h. After complete oxidation (monitored by TLC), TMSCN (1.5 mmol) was added and the reaction mixture was further stirred at rt for 2–3 h (Table 1). Then, it was diluted with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with ether (3 × 10 mL). The combined organic layers were washed with brine solution, dried over $MgSO_4$ and evaporated under reduced pressure. The resulting product was purified by silica gel column chromatography using hexane/ethyl acetate (9:1) as eluent to afford an analytically pure sample of **3**. After isolation of the product, the remaining aqueous layer containing the ionic liquid was washed with ether (2 × 10 mL) to remove any organic impurity and filtered. The filtrate was extracted with CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to afford [bmim]Br, which was used in subsequent runs without further purification. Physical data of representative compounds. *Compound* **3a**: Yellowish solid, yield 83%, mp 95–97 °C. IR (KBr) ν_{max} 3060, 2862, 2238, 1743, 1691, 1602, 1584, 1455, 695, 760 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 2.91 (dd, 1H, *J* = 12.8, 8.4 Hz, β-H), 3.19 (dd, 1H, *J* = 12.8, 3.5 Hz, β-H), 4.10 (dd, 1H, *J* = 8.4, 3.5 Hz, α-H), 3.68 (s, 3H, COOMe), 7.32-7.94 (m, $5H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 14.5, 50.1, 52.2, 116.5, 128.1, 129.1, 130.8, 138.2, 169.8, 198.8. EIMS (*m*/*z*): 217 (M^+). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found C, 65.97; H, 4.80; N, 6.76. *Compound* **3f**: Yellowish solid, yield 82%, mp 142–144 °C. IR (KBr) ν_{max} 2993, 2851, 2248, 2240, 1697, 1605, 1540, 1343, 853 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 2.85 (dd, 1H, *J* = 12.9, 8.5 Hz, β-H), 3.12 (dd, 1H, *J* = 12.9, 3.5 Hz, β-H), 3.61 (s, 3H, OMe), 4.10 (dd, 1H, *J* = 8.5, 3.5 Hz, α-H), 7.10 (d, 2H, *J* = 7.9 Hz, H_{arom}), 7.68 (d, 2H, *J* = 7.9 Hz, H_{arom}). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 11.9, 36.4, 57.6, 115.0, 117.3, 118.2, 129.4, 130.3, 168.0, 198.2. EIMS (*m*/*z*): 214 (M^+). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found C, 67.58; H, 4.38; N, 13.40.
26. *General procedure for the synthesis of β-cyano cinnamaldehydes* **5**: A mixture of BH adduct **1** (1 mmol) and $NaNO_3$ (1 mmol) was stirred in 1 mL of [Hmim]-HSO_4 at 80 °C for 1–2 h. After complete oxidation (monitored by TLC), the reaction mixture was cooled to rt, TMSCN (1.5 mmol) was added and the mixture was further stirred at rt for 2–3 h (Table 1). Then, water (10 mL) was added and the product was extracted with ether (3 × 10 mL). The combined ether extracts were dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate 9.3:0.7) to afford the desired product **5**. After isolation of the product, the remaining aqueous layer containing the ionic liquid was washed with ether (2 × 10 mL) to remove any organic impurity, then H_2SO_4 (2.5 mmol) was added, the mixture was stirred at 80 °C for 1 h, and cooled to about −5 °C in an ice-salt bath. The precipitated solid was filtered off and the filtrate was dried under vacuum to afford the IL [Hmim]HSO_4 which was used in subsequent runs. Physical data of representative compounds. *Compound* **5a**: Yellowish solid, yield 86%, mp 68–69 °C. IR (KBr) ν_{max} 3028, 2856, 2241, 1748, 1720, 1605, 1577, 1455, 1284, 766, 712 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 3.72 (dd, 1H, *J* = 4.0, 2.2 Hz, 2-H), 3.86 (s, 3H, COOMe), 4.48 (d, 1H, *J* = 4.0 Hz, 3-H), 7.13–7.34 (m, $5H_{arom}$), 9.58 (s, 1H, *J* = 2.2 Hz, CHO). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 18.5, 49.9, 57.9, 116.9, 127.7, 127.9, 129.0, 130.5, 171.8, 198.6. EIMS (*m*/*z*): 217 (M^+). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found C, 66.63; H, 5.43; N, 6.13. *Compound* **5f**: Yellowish solid, yield 85%, mp 104–106 °C. IR (KBr) ν_{max} 2998, 2851, 2240, 1730, 1607, 1579, 1386, 847 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 3.70 (dd, 1H, *J* = 4.0, 2.2 Hz, 2-H), 3.71 (s, 3H, OMe), 4.45 (d, 1H, *J* = 4.0 Hz, 3-H), 6.89 (d, 2H, *J* = 7.8 Hz, H_{arom}), 7.3 (d, 2H, *J* = 7.8 Hz, H_{arom}), 9.54 (d, 1H, *J* = 2.2 Hz, CHO). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 22.1, 42.8, 56.2, 112.6, 117.1, 118.1, 124.0, 131.1, 162.5, 198.7. EIMS (*m*/*z*): 214 (M^+). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found C, 66.98; H, 5.09; N, 12.74.
27. Masamune, S.; Ali, S. K. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557–558.