LETTER

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# [bmim]$PF_6$/CuBr: a novel and recyclable catalytic system for the synthesis of propargyl amines

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**A novel and efficient method has been developed for the synthesis of propargyl amines in a one-pot operation from aldehydes, amines and alkynes by using copper(I) bromide immobilized in ionic liquids. The ionic liquid containing catalyst can be recovered and recycled in three to four subsequent runs with gradual decrease in activity**

The stereoselective addition of organometallic reagents to aldehydes and imines is one of the most important carbon-carbon bond-forming reactions in organic synthesis.[1] Propargyl amines are important synthetic intermediates for the synthesis of various polyfunctional amino derivatives and also for the synthesis of many biologically active compounds.[2] The simplest and most straightforward method for the synthesis of propargyl amines involves the addition of alkynyl metal reagents to imines.[3] Addition of alkynes to imines, enamines, nitrones and acyliminium ions using copper salts has been reported to produce propargyl amines.[4] Asymmetric versions of enamine-alkyne and imine-alkyne additions have also been reported to produce enantiomerically pure propargyl amines.[5]

Recently, ionic liquids have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability, and immiscibility with a number of organic solvents, negligible vapor pressure and recyclability.[6] Their non-volatile character and thermal stability makes them potentially attractive alternatives to environmentally unfavorable organic solvents, notably chlorinated hydrocarbons. They are particularly promising as solvents for the immobilization of transition metal catalysts, Lewis acids and enzymes (Fig 1).[7] As a result of their green credentials and potential to enhance reaction rates and selectivities, ionic liquids are finding increasing applications in organic synthesis.[8]

In view of the emerging importance of imidazolium based ionic liquids as novel reaction media, we wish to explore the use of ionic liquids as a recyclable solvent system for the three-component coupling reaction of aldehydes, amines and alkynes to produce propargylic amines in excellent yields (Scheme 1). Accordingly, treatment of benzaldehyde and aniline with phenyl acetylene in the presence of 30 mol % of CuBr in [bmim]$PF_6$ at 60 °C afforded the corresponding *N*-(1,3-diphenyl-2-propynyl)aniline in 89% yield. In a similar fashion, various imines (formed *in situ* from aldehydes and amines in the ionic liquid) reacted smoothly with alkynes to produce the corresponding propargylic amines. The reactions proceeded efficiently in ionic liquids and were complete within 3.5–6.0 h. Both electron-rich and electron-deficient aldehydes and amines afforded the corresponding propargylic amines in excellent yields (75–89%) with high selectivity, whereas ketones did not give the desired product under these reaction conditions. From the results are presented in Table 1, the scope and generality of this process is illustrated with respect to various aldehydes, amines and alkynes.

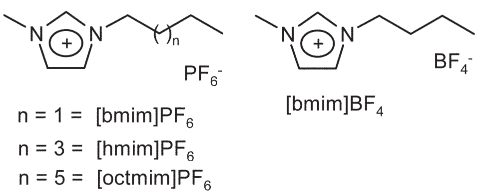
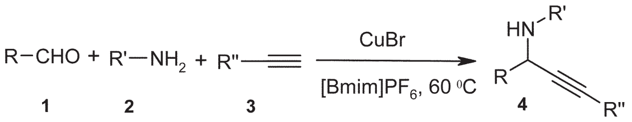


**Fig. 1** Chemical structures of ionic liquids.



**Scheme 1**

Acid-sensitive aldehydes such as cinnamaldehyde worked well without any decomposition or polymerization under these reaction conditions (**4h**, Table 1). Even sterically hindered amines and alkynes also gave the corresponding propargylic amines in high yields (**4h**, **4i**, **4l** and **4m**, Table 1). In all cases, no propargylic alcohol (an adduct between the aldehyde and alkyne) was obtained under similar reaction conditions. This is because of the rapid formation of imines from aldehydes and amines in ionic liquids. The reactivity of alkynes and aldimines was studied in both hydrophilic (*i.e.*, [bmim]$BF_4$) and hydrophobic (*i.e.*, [bmim]$PF_6$) ionic liquids. [bmim]$BF_4$ was also equally effective for this conversion. Among the various copper salts, such as CuCl, CuBr, $Cu(OAc)_2$ and $Cu(OTf)_2$, tested, CuBr was found to be the most effective catalyst in terms of conversion reaction rates. Compared to conventional solvents, enhanced reaction rates, improved yields and high selectivity are the features obtained in ionic liquids. For example, treatment of benzaldehyde and *p*-anisidine with phenyl acetylene in the presence of 30 mol % copper bromide in [bmim]$PF_6$ at 60 °C for 3.5 h afforded the corresponding *N*-(1,3-diphenyl-2-propynyl)-4-methoxyaniline (**4c**) in 85% yield whereas the same reaction in refluxing THF after 8.0 h gave the product in 60% yield as a mixture of propargyl amine and 2,4-disubstituted quinoline in an 8:2 ratio.

Similar results were also obtained using ionic liquids having longer alkyl chains such as 1-hexyl-3-methylimidazolium hexafluorophosphate ([hmim]$PF_6$) or 1-octyl-3-methylimidazolium

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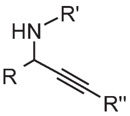
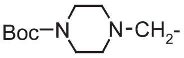
**Table 1** Synthesis of propargylic amines using copper(I) bromide in ionic liquid [bmim]$PF_6$

| Aldehyde R–CHO<br>R | Amine R'–$NH_2$<br>R' | Alkyne R''–≡<br>R'' | Product[a]<br><br> | Time/h | % Yield[b] |
|---|---|---|---|---|---|
| $C_6H_5$ | $C_6H_5$ | *n*-$CH_3(CH_2)_2$ | **4a** | 4.0 | 89 |
| 4-$MeOC_6H_4$ | $C_6H_5$ | *n*-$CH_3(CH_2)_5$ | **4b** | 5.0 | 83 |
| 4-$MeOC_6H_4$ | *n*-$CH_3(CH_2)_3$ | *n*-$CH_3(CH_2)_5$ | **4c** | 3.5 | 85 |
| 4-$ClC_6H_4$ | 3,5-(F,F)$C_6H_3$ | $HO(CH_2)_2$ | **4d** | 5.5 | 81 |
| 4-$BrC_6H_4$ | 3,4-$(MeO)_2C_6H_3$ | Allyl-$O(CH_2)_6$ | **4e** | 6.0 | 88 |
| 4-$FC_6H_4$ | 3,5-(F,F)$C_6H_3$ | $BnOCH_2$ | **4f** | 4.5 | 85 |
| 4-$BnOC_6H_4$ | 3,4-$(MeO)_2C_6H_3$ | <br> | **4g** | 5.0 | 87 |
| Ph–CH=CH | 3-$NO_2C_6H_4$ | 2,6-$(CH_3)_2C_6H_3OCH_2$ | **4h** | 6.5 | 89 |
| $C_6H_5$ | 4-$MeOC_6H_4$ | $C_6H_5$ | **4i** | 4.5 | 87 |
| 4-$BrC_6H_4$ | 3,4-$(OCH_2O)C_6H_3$ | $C_6H_5$ | **4j** | 5.5 | 84 |
| 3,4-$(MeO)_2C_6H_3$ | 4-$FC_6H_4$ | $C_6H_5$ | **4k** | 5.0 | 82 |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | **4l** | 4.5 | 89 |
| *n*-$CH_3(CH_2)_6$ | $C_6H_5CH_2$ | $C_6H_5$ | **4m** | 5.5 | 85 |

[a] All products were characterized by $^1$HNMR, IR and mass spectroscopy [b] Isolated and unoptimized yields

hexafluorophosphate ([octmim]$PF_6$). However, the products were obtained in low yields (30–55%) when 1-*n*-butyl-3-methylimidazolium chloride ([bmim]Cl) was used as a solvent. These results clearly indicate that the efficiency of the ionic liquid is strongly influenced by the nature of the anion only.

Another advantage in the use of ionic liquids as a novel reaction medium for this transformation is that these ionic solvents can be easily recovered after completion of the reaction and can be reused in successive runs. The products were easily separated by simple extraction with diethyl ether and the remaining ionic liquid was thoroughly washed with ether and recycled in further reactions with gradual decrease in activity. For instance, benzaldehyde, aniline and phenyl acetylene in [bmim]$PF_6$ ionic liquid afforded 89%, 85%, and 80% yields over three cycles. However, on the addition of more catalyst to the fourth run, no decrease in yield was obtained in runs carried out using a recycled ionic liquid and the results are presented in Table 2.

The simple experimental and product isolation procedures, combined with ease of recovery and reuse of this novel reaction media, are expected to contribute to the development of a clean process for the synthesis of propargylic amines. Furthermore, the recovery and reuse of the catalyst is especially easy in ionic liquids compared to organic solvents.

In summary, this paper demonstrates the successful use of ionic liquids as a novel and convenient reaction media for the three-component coupling reaction of aldehydes, amines and alkynes to produce propargylic amines in excellent yields in a single-step operation. This method is very useful for the synthesis of propargylic amines, especially from acid-sensitive substrates. The notable features of this procedure are the mild reaction conditions, simplicity in operation, improved yields and reaction rates, cleaner reaction profiles and recyclability of the ionic liquids, making this method useful and attractive for the synthesis of propargylic amines.

**Table 2** Recyclability of the CuBr/[bmim]$PF_6$ system for the coupling of aniline, benzaldehyde and phenylacetylene[a]

| Run | CuBr/mol % | Time/h | % Yield |
|---|---|---|---|
| 1 | 30 | 4.5 | 89 |
| 2 | 0 | 5.0 | 85 |
| 3 | 0 | 6.0 | 80 |
| 4 | 30 | 3.5 | 92 |
| 5 | 0 | 5.5 | 87 |

[a] Aldehyde:amine:alkyne = 1:1:1; 1 mmol of each compound used

## Experimental

Melting points were determined on a Fisher–John melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 IR spectrometer. Silica gel (60–120 mesh) was used for column chromatography. $^1$H NMR spectra were recorded in $CDCl_3$ on Varian FT-200 (200 MHz) and Bruker Avance (300 MHz) machines using TMS as internal standard. Mass spectra were taken on a Finnigan Mat-1210 double focusing spectrometer.

### General procedure

A mixture of aldehyde (1 mmol), amine (1 mmol) and alkyne (1 mmol) and CuBr (30 mol %) in [bmim]$PF_6$ (2.0 mL) was stirred at 60 °C for the appropriate time (see Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated *in vacuo* and the resulting product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate–*n*-hexane (2:8) to afford pure propargylic amine. The rest of the ionic liquid was further washed with ether and recycled in subsequent runs. Spectral data for all products (Table 1) follow.

**4a.** Yellow oil; IR (neat): $\nu_{max}$: 3400 , 3056, 2976, 2944, 1584, 1488, 1328, 752 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.95 (t, $J = 6.7$ Hz, 3H), 1.45–1.60 (m, 2H), 2.20 (t, $J = 6.5$ Hz, 2H), 3.90–4.00 (br s, NH, 1H), 5.20 (s, 1H), 6.65–6.75 (m, 3H), 7.10–7.20 (m, 2H), 7.45 (m, 1H), 7.50–7.60 (m, 2H), 7.85–7.95 (m, 2H); EI-MS: $m/z$ (%) 249 $[M]^+$ (12), 157 (100), 129 (37), 115 (25), 91 (27), 51 (6).

**4b.** Yellow oil, IR (neat): $\nu_{max}$: 3408 (br s), 2928, 2864, 1600, 1488, 1424, 1232, 1152, 1008, 832 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.98 (t, $J = 6.7$ Hz, 3H), 1.30–1.50 (m, 4H), 1.55–1.78 (m, 4H), 2.40 (t, $J = 6.5$ Hz, 2H), 3.78 (s, 3H), 4.56 (s, 1H), 6.80 (d, $J = 8.0$ Hz, 2H), 7.10–7.30 (m, 5H), 7.40 (d, $J = 8.0$ Hz, 2H); EI-MS: $m/z$ (%) 321 $[M]^+$ (15), 230 (100), 197 (7), 159 (31), 147 (20), 121 (100), 91 (87), 43 (20).

**4c.** Pale yellow oil, IR (neat): $\nu_{\max}$: 3440 (br s), 2928, 2848, 1616, 1520, 1456, 1232, 1152, 1024, 736 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 0.80–1.00 (m, 6H), 1.20–1.40 (m, 12H), 1.50–1.60 (m, 2H), 2.30–2.40 (t, $J = 6.5$ Hz, 2H), 3.78 (s, 3H), 4.70 (s, 1H), 6.80 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H); EI-MS: $m/z$ (%) 301 [M]$^+$ (20), 252 (6), 244 (10), 230 (19), 215 (63), 187 (6), 167 (6), 161 (100), 135 (53), 134 (16), 121 (81), 105 (10), 91 (11), 77 (25), 57 (26), 43 (42), 36 (7).

**4d.** Yellow oil, IR (neat): $\nu_{\max}$: 3376 (br s), 2972, 2832, 1616, 1504, 1264, 1136, 1056, 848 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.80–2.00 (br s, OH, 1H), 2.42 (t, $J = 6.9$ Hz, 2H), 3.62 (t, $J = 6.9$ Hz, 2H), 5.18 (s, 1H), 6.60–6.80 (m, 3H), 7.30 (d, $J = 7.8$ Hz, 2H), 7.50 (d, , $J = 7.8$ Hz, 2H); EI-MS: $m/z$ (%) 319 [M]$^+$ (10), 287 (19), 218 (29), 155 (12), 142 (45), 129 (60), 105 (90), 77 (100), 43 (37).

**4e.** Pale yellow oil, IR (neat): $\nu_{\max}$: 3456 (br s), 2944, 2864, 1616, 1520, 1456, 1200, 1040, 848 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.30–1.60 (m, 8H), 2.20 (m, 2H), 3.40 (t, 2H, $J =$ 6.7 Hz), 3.58 (s, 3H), 3.60 (s, 3H), 3.98 (d, 2H, $J =$ 6.7 Hz), 4.40–4.60 (br s, NH, 1H), 5.10–5.20 (m, 2H), 5.30 (s, 1H), 5.80–5.60 (m, 1H), 6.30 (m, 2H), 6.90 (d, $J = 8.0$ Hz, 1H), 7.30 (dd, $J = 8.0$ and 2.3 Hz, 1H), 7.45–7.55 (m, 3H); FAB-MS: $m/z$ (%) 486 [M]$^+$ (5), 320 (3), 207 (3), 185 (5), 109 (15), 95 (31), 83 (36), 161 (35), 69 (53), 55 (100).

**4f.** Yellow oil; IR (neat): $\nu_{\max}$: 3410 (br s), 3034, 2858, 1603, 1514, 1453, 1227, 1093, 846 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 4.00–4.10 (br s, NH, 1H), 4.15 (s, 2H), 4.44 (s, 2H), 5.22 (s, 1H), 6.60–6.80 (m, 3H), 7.05 (m, 1H), 7.20–7.40 (m, 5H), 7.50 (m, 2H); EI-MS: $m/z$ (%) 380 [M]$^+$ (15), 377 (3), 230 (22), 223 (31), 141 (8), 91 (100), 51 (10).

**4g.** Yellow oil; IR (neat): $\nu_{\max}$: 3420 (br s), 2935, 2865, 1680, 1632, 1504, 1456, 1236, 1216, 1168, 1120, 1040, 992 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 1.42 (s, 9H), 2.40 (t, 4H, $J = 6.5$ Hz), 3.36 (s, 2H), 3.40 (t, 4H, $J = 6.5$ Hz), 3.72 (s, 3H), 3.80 (s, 3H), 4.40–4.50 (br s, 1H, NH), 5.05 (s, 2H), 5.20 (m, 1H), 6.18 (dd, $J = 8.0$ and 2.3 Hz, 1H), 6.38 (d, $J = 2.3$ Hz, 1H), 6.62 (d, $J = 8.0$ Hz, 1H), 6.98 (d, $J = 8.0$, 2H), 7.38–7.55 (m, 5H), 7.58 (d, $J = 8.0$ Hz, 2H). FAB-MS: $m/z$ (%) 571 [M]$^+$ (12), 551 (5), 524 (3), 417 (3), 207 (3), 123 (10), 109 (18), 95 (37), 83 (35), 55 (100).

**4h.** Yellow oil; IR (neat): $\nu_{\max}$: 3376 (br s), 2928, 2864, 1600, 1520, 1360, 1168, 1040, 832 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 2.30 (s, 6H), 4.15–4.25 (br s, NH, 1H), 4.70 (s, 2H), 5.00 (s, 1H), 6.20–6.25 (dd, $J = 15.0$ and 2.3 Hz, 1H), 6.50 (s, 1H), 6.60 (s, 1H), 6.80–6.85 (d, $J = 15.0$ Hz, 1H), 6.90–6.95 (dd, $J = 7.8$ and 2.3 Hz, 1H), 7.20–7.35 (m, 7H), 7.50 (s, 1H), 7.60 (d, $J = 7.8$ Hz, 1H). EI-MS: $m/z$ (%) 412 [M]$^+$ (16), 136 (77), 118 (100), 91 (100), 77 (12), 65 (35), 51 (16), 39 (30).

**4i.** Yellow oil, IR (neat): $\nu_{\max}$: 3344 (brs), 3056, 2928, 2832, 1600, 1504, 1232, 1040, 832 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz): δ 3.70 (s, 3H), 3.65–3.75 (brs, NH,1H), 5.38 (s, 1H), 6.60–6.80 (m, 4H), 7.20–7.30 (m, 4H), 7.35–7.40 (m, 4H), 7.60 (d, $J = 8.0$ Hz, 2H). EIMS: $m/z$: 313 (M$^+$ 8), 236 (10), 191 (96), 165 (3), 121 (31), 119 (96), 117 (100), 84 (32), 55 (47), 37 (6).

**4j.** Yellow oil, IR (neat): $\nu_{\max}$: 3392 (br s), 3040, 2896, 2832, 1632, 1472, 1200, 1056, 832 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.80–3.90 (br s, NH, 1H), 5.30 (s, 1H), 5.85 (s, 2H), 6.30 (s, 1H), 6.60 (d, $J = 7.8$ Hz, 1H), 7.25 (m, 3H), 7.35 (m, 2H), 7.45–7.50 (m, 5H). EI-MS: $m/z$ (%) 396 [M]$^+$ (15), 304 (7), 270 (6), 217 (2), 190 (2), 166 (2), 137 (2), 121 (31), 119 (95), 117 (100), 82 (25), 47 (36), 35 (28).

**4k.** Yellow oil; IR (neat): $\nu_{\max}$: 3344 (br s), 2912, 2848, 1616, 1504, 1264, 1136, 960, 832 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 3.50 (s, 6H), 4.45–4.55 (br s, NH, 1H), 5.40 (s, 1H), 6.20 (m, 1H), 6.80–6.85 (m, 1H), 6.90–7.00 (m, 3H), 7.20 (m, 3H), 7.35 (m, 2H), 7.65–7.70 (m, 2H). EI-MS: $m/z$ (%) 361 [M]$^+$ (10), 156 (7), 142 (26), 124 (67), 122 (61), 105 (100), 95 (25), 84 (36), 77 (80), 49 (70).

**4l.** Pale yellow solid, m.p. 85 °C; IR (neat): $\nu_{\max}$: 3424 (br s), 3088, 3040, 1600, 1488, 1308, 1280, 1055 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 3.98–4.05 (br s, NH, 1H), 5.42 (s, 1H), 6.65–6.78 (m, 3H), 7.10–7.40 (m, 10H), 7.55–7.60 (m, 2H). FAB-MS: $m/z$ (%) 283 [M]$^+$ (11), 206 (7), 191 (100), 165 (3), 109 (7), 69 (23), 55 (31).

**4m.** Pale yellow solid, m.p. 83 °C; IR (neat): $\nu_{\max}$: 3456 (br s), 3088, 2944, 2848, 1600, 1488, 1424, 1055, 880 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 0.98 (t, $J = 6.7$ Hz, 3H), 1.20–1.40 (m, 8H), 1.45–1.55 (m, 2H), 1.65–1.80 (m, 2H), 3.50 (t, $J = 6.5$ Hz, 1H), 3.80–4.10 (m, 2H), 7.20–7.50 (m, 10H). EI-MS: $m/z$ (%) 319 [M]$^+$ (5), 203 (100), 151 (5), 102 (3), 39 (10).

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