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# Cu–Ni bimetallic reusable catalyst for synthesis of propargylamines *via* multicomponent coupling reaction under solvent-free conditions†

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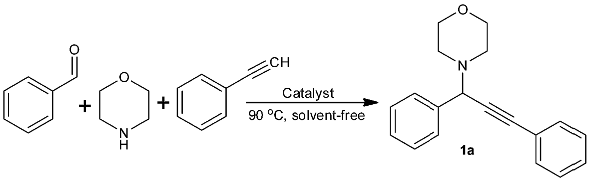
A Cu–Ni bimetallic catalyst has been used as a reusable catalytic system for the multicomponent coupling reaction of aldehydes, phenylacetylene and secondary amines for the synthesis of propargylamines under solvent-free conditions. The reaction did not require any other additives such as an inorganic base. The bimetallic catalyst displayed high activity and gives propargylamines in good to excellent yields. This method provides a wide range of substrate applicability. The catalyst could be magnetically separated and reused without loss in activity.

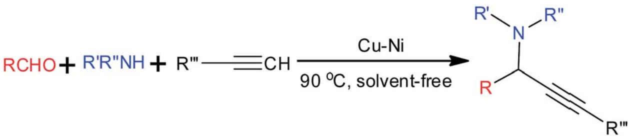
Propargylamines are important synthetic intermediates for synthesis of various nitrogen containing compounds such as β-lactams, oxotremorine analogues, confirmationally restricted peptides, and also they are components of bioactive compounds or natural products.[1] Traditionally, propargylamines are synthesized by nucleophilic attack of lithium acetylides or Grignard reagents, on imines.[2] However, these reagents are stoichiometric, moisture sensitive and require strictly controlled reaction conditions. Propargylamines derivatives can be also synthesised through a three component coupling of an aldehyde, alkyne and amine.[3,4] Recently various transition metal catalysts such as Re,[5] $Hg_2Cl_2$,[6] Zr,[7] Ag,[8] Au,[9] Cu,[10] Ir[11] and Cu/Ru II[12] have been explored for this synthesis. However, most of these methods suffer from various disadvantages such as high reaction temperatures, inert reaction conditions, expensive catalytic systems.

Herein, we wish to report direct multicomponent coupling reaction of aldehydes, phenylacetylene and secondary amine under solvent-free conditions using Cu–Ni bimetallic catalyst (Scheme 1). Cu–Ni bimetallic catalyst was prepared as per reported method.[13] Prepared catalyst was characterized by various techniques such as ICP, XRD and SEM-EDAX.

Inductive coupled plasma (ICP) analysis reveals bulk composition of Cu–Ni was $Cu_{0.49}Ni_{0.51}$ which was also similar to that of precursor solution. Scanning electron microscopy (SEM) images Fig. 1(a and b) gives morphological information that the Cu–Ni present in the form of irregular, dense particles with extremely broad size distribution (<200 nm to >400 nm). Large particles are formed apparently due to agglomeration, as the reaction in between metallic ions and sodium borohydride is strongly exothermic.[14] Energy dispersive X-ray analysis (EDAX), (Fig. 2) shows 48.5% of Cu and 51.5% of Ni as the surface composition, which is nearly the same as that of the bulk. XRD (Fig. 3) pattern shows amorphous nature of catalyst.[15]

To develop an optimal catalytic system, various reaction parameters were studied for the synthesis of **1a** *via* a reaction of benzaldehyde, morpholine and phenylacetylene at 90 °C under solvent-free conditions (Table 1). To assess the standing of Cu–Ni bimetallic catalyst among other Cu based catalysts for formation of corresponding propargylamine, for that some comparative experiments were performed whereas for others data is taken from literature (Table 1, entry 1–5) for this reaction and Cu–Ni system was found to be the most effective (Table 1, entry 9) and (Fig. 4).





Scheme 1 Synthesis of propargylamines by Cu–Ni bimetallic catalyst.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ra06275b

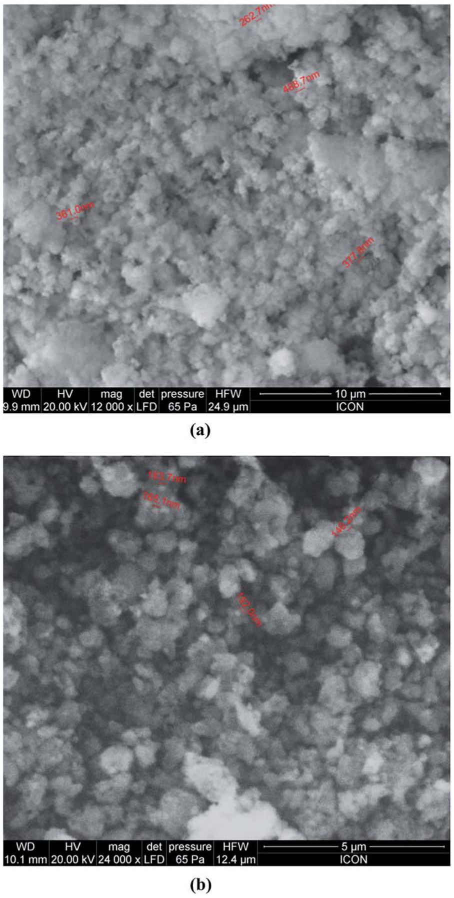


**Fig. 1** (a) & (b) SEM images of Cu–Ni bimetallic catalyst.

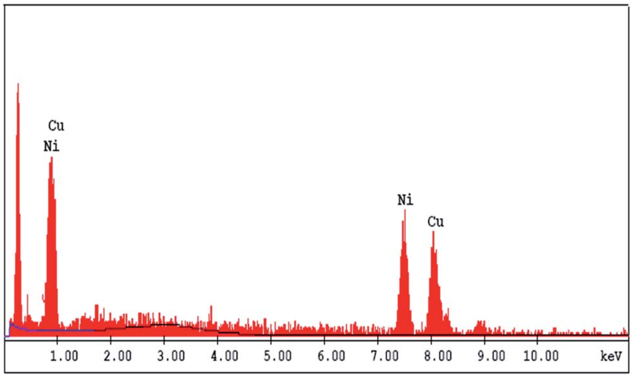


**Fig. 2** EDAX of Cu–Ni bimetallic catalyst.

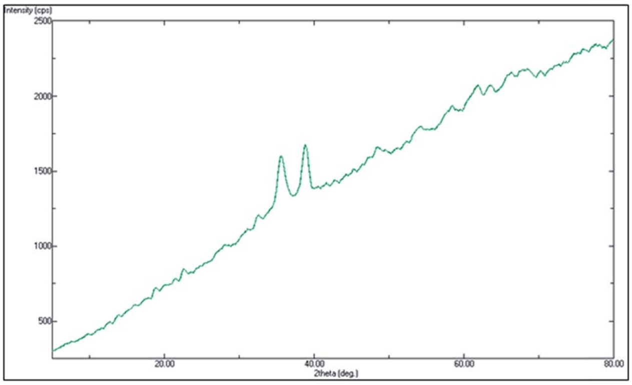


**Fig. 3** XRD of Cu–Ni bimetallic catalyst.

The optimum ratio of aldehyde, amine and alkyne was (1.0 : 1.1 : 1.2 mmol). The multicomponent reaction carried under identical conditions for long time but there was very low self coupled product of phenylacetylene.

Cu–Ni bimetallic catalyst was recovered by simple magnetic separation, after completion of reaction. Ethyl acetate (10 mL) was added, catalyst was collected by magnet (Fig. 5) and the recovered catalyst showing consistent activity even after fifth cycle (Table 2, entry 5). Recovered catalyst after fifth cycle was characterized by SEM, ICP ($Cu_{0.489}Ni_{0.511}$), EDAX (Cu – 48.3% & Ni – 51.7%) which is almost similar to freshly prepared catalyst and XRD shows no significant structural change and leaching of metals in catalyst (Fig. 6, 7 and 8).

To assess substrate scope a number of structurally diverse aldehydes, secondary amines and alkynes have been screened for studying the generality as well as the efficacy of the present

**Table 1** Synthesis of **1a** using Cu-based catalysts[a]

| Entry | Catalyst | wt% | Equivalent ratio of reactants | Time (h) | %Yield[b] | Reference |
|---|---|---|---|---|---|---|
| 1 | CuHAP | 20 | 1 : 1.2 : 1.3 | 6 | 80 | 16a |
| 2[d] | CuI | 32[c] | 1 : 1.2 : 1.5 | 1 | 98 | 16b |
| 3 | AgTPA | 30[c] | 1 : 1.2 : 1.3 | 6 | 80 | 16c |
| 4[d] | CuI in PEG as solvent | 22[c] | 1 : 1.2 : 1.5 | 12 | 85 | 16d |
| 5 | $Si(CH_2)_3SO_3 \cdot CuCl$ | 50[c] | 1 : 1.2 : 1.5 | 16 | 54 | 16e |
| 6 | Cu powder | 20 | 1 : 1.1 : 1.2 | 3 | 37 | TW |
| 7 | Cu nano | 20 | 1 : 1.1 : 1.2 | 3 | 75 | TW |
| 8 | Ni nano | 20 | 1 : 1.1 : 1.2 | 3 | NR | TW |
| 9 | Cu–Ni nano | 20 | 1 : 1.1 : 1.2 | 3 | 93 | TW |

[a] This work (entries 6–9) reaction conditions: benzaldehyde (1.0 mmol), morpholine (1.1 mmol), phenylacetylene (1.2 mmol), catalyst (20 wt%) heated at 90 °C for 3 h. [b] Isolated yields. [c] For ready comparison mole ratio of catalyst was converted into wt%. [d] Catalyst not recovered, NR – no reaction, TW – this work.

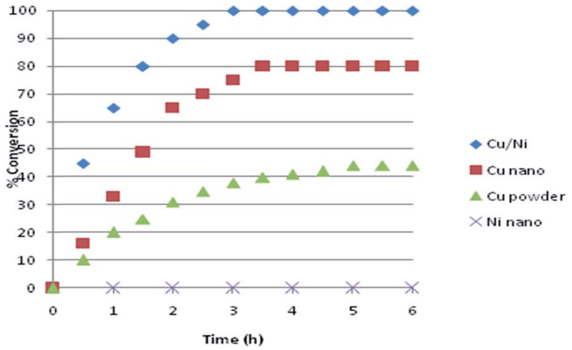


**Fig. 4** Concentration *vs* time plot for the formation of propragylamin.

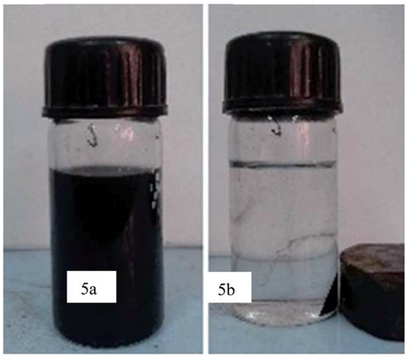


**Fig. 5** (a) Cu–Ni bimetallic catalyst suspended in ethyl acetate after completion of reaction; (b) Cu–Ni bimetallic catalyst was collected using a magnet.

Table 2 Recyclability of the Cu–Ni catalyst for the synthesis of **1a**$^a$

| Run | Time (h) | Yield$^b$ [%] |
|---|---|---|
| 1 | 3 | 93 |
| 2 | 3 | 91 |
| 3 | 3 | 89 |
| 4 | 3 | 86 |
| 5 | 3 | 85 |

$^a$ Reaction conditions: benzaldehyde (1.0 mmol), morpholine (1.1 mmol), phenylacetyline (1.2 mmol), catalyst (20 wt%), heated at 90 °C. $^b$ Isolated yields.

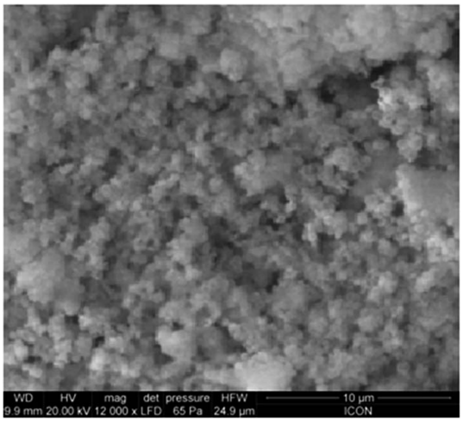


**Fig. 6** SEM image of recovered catalyst after 5th cycle.

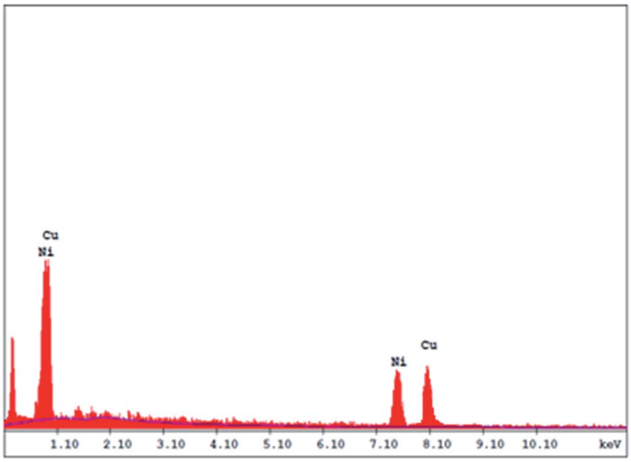


**Fig. 7** EDAX of recovered catalyst after 5th cycle.

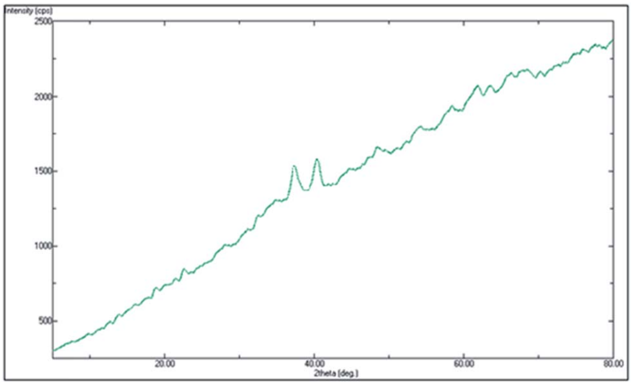


**Fig. 8** XRD of recovered catalyst after 5th cycle.

procedure and results are summarized in Table 3. The different aldehydes aromatic, heteroaromatic and aliphatic were found to undergo these reactions afforded good to excellent yield (Table 3, entries 1–18). Benzaldehyde gave excellent yield in this reaction condition (Table 3, entry 1). In case of benzaldehydes with electron donating group such as methyl, methoxy and hydroxyl gives lower yield as compare to unsubstituted benzaldehyde and benzaldehyde with electron-withdrawing group such as cyano (Table 3, entries 2–5 and 7).

Reaction proceeded equally smooth in case of heteroaromatic aldehydes such as 2-thiophenecarboxaldehyde, 2-furancarboxaldehyde and 4-pyridinecarboxaldehyde to afford respective propargylamines in best yields (Table 3, entries 9–11 and 14). The aliphatic aldehyde such as heptaldehyde and butyraldehyde were reacted smoothly with morpholine and piperidine respectively gives afford the corresponding derivatives in very good yields (Table 3, entries 8 and 15). There was not much difference in yield when we compare secondary amines such as morpholine, piperidine and dibutylamine (Table 3, entries 1, 12 and 16). Sterically hindered aldehyde such as 1-naphthaldehyde with piperidine also gives corresponding

**Table 3** One pot synthesis of propargylamines using Cu–Ni bimetallic catalyst[a]

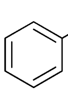
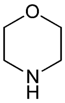
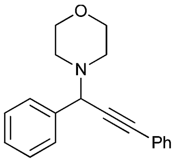
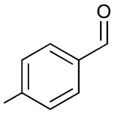
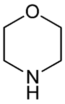
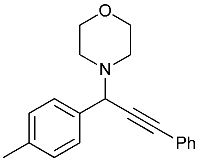
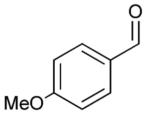
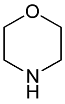
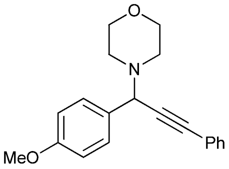
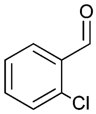
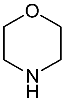
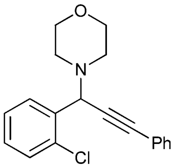
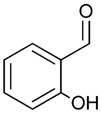
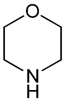
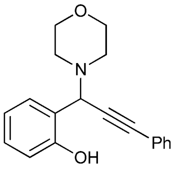
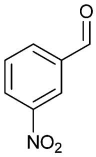
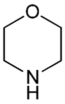
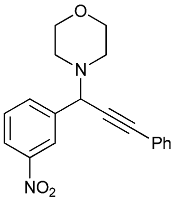
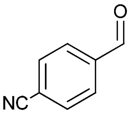
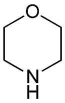
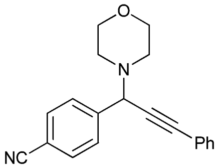
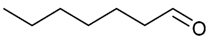
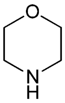
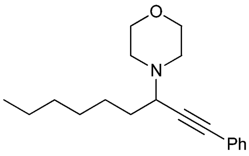
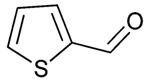
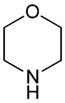
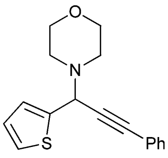
| Entry | Aldehyde | Amine | Acetylene | Product | Time (h) | Isolated yield[b,c] (%) |
|---|---|---|---|---|---|---|
| 1 |  |  | Ph—≡CH |  | 3.0 | 93 |
| 2 |  |  | Ph—≡CH |  | 4.0 | 80 |
| 3 |  |  | Ph—≡CH |  | 3.5 | 83 |
| 4 |  |  | Ph—≡CH |  | 3.0 | 85 |
| 5 |  |  | Ph—≡CH |  | 3.5 | 78 |
| 6 |  |  | Ph—≡CH |  | 3.0 | 85 |
| 7 |  |  | Ph—≡CH |  | 3.0 | 90 |
| 8 |  |  | Ph—≡CH |  | 4.0 | 78 |
| 9 |  |  | Ph—≡CH |  | 3.0 | 95 |

Table 3 (*Contd.*)

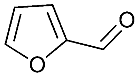
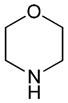
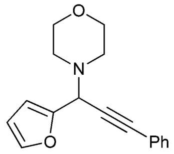
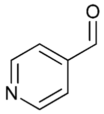
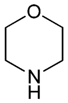
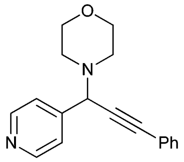
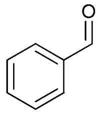
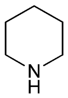
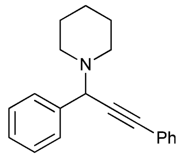
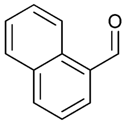
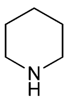
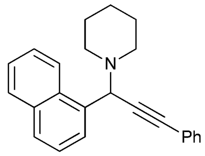
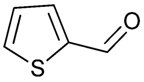
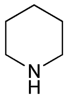
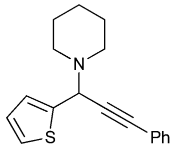
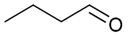
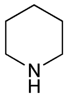
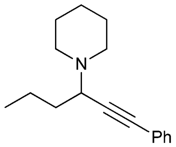
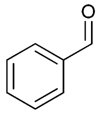
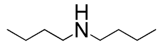
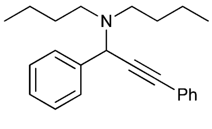
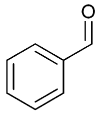
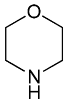
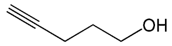
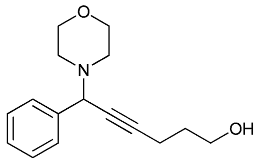
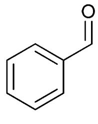
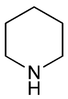
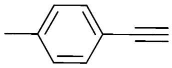
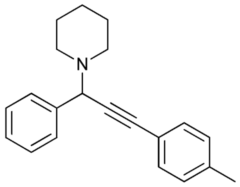
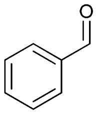
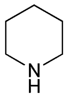
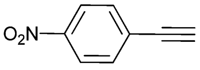
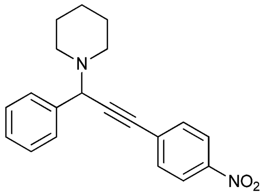
| Entry | Aldehyde | Amine | Acetylene | Product | Time (h) | Isolated yield$^{b,c}$ (%) |
|---|---|---|---|---|---|---|
| 10 |  |  | Ph—≡CH |  | 3.0 | 93 |
| 11 |  |  | Ph—≡CH |  | 2.5 | 90 |
| 12 |  |  | Ph—≡CH |  | 3.0 | 90 |
| 13 |  |  | Ph—≡CH |  | 3.5 | 82 |
| 14 |  |  | Ph—≡CH |  | 3.5 | 88 |
| 15 |  |  | Ph—≡CH |  | 3.5 | 85 |
| 16 |  |  | Ph—≡CH |  | 3.5 | 85 |
| 17 |  |  |  |  | 3.0 | 87 |
| 18 |  |  |  |  | 3.0 | 85 |

Table 3 (*Contd.*)

| Entry | Aldehyde | Amine | Acetylene | Product | Time (h) | Isolated yield$^{b,c}$ (%) |
|---|---|---|---|---|---|---|
| 19 |  |  |  |  | 4.5 | No Reaction |

$^a$ Reaction conditions: aldehyde (1.0 mmol), amine (1.1 mmol), alkyne (1.2 mmol), catalyst (20 wt%), heat at 90 °C. $^b$ Isolated yield. $^c$ The product were identified by GC-MS.

propargylamines in good yield (Table 3, entry 13). As expected, aliphatic alkynes such as 4-pentyne-1-ol gave high yield (Table 3, entry 17). Electron rich substituted aromatic alkyne such as 4-methyl phenylacetylene smoothly reacted with benzaldehyde and pipyridine, gave good yield, there was no reaction in case of electron poor phenylacetylene such as 4-nitro phenyleacetylene (Table 3, entries 18 and 19).

It has been proposed that the multicomponent reaction proceeds through the terminal C–H bond activation of the alkyne by the Cu-based catalyst.[17–20] The copper acetylide intermediate generated, reacts with the iminium ion formed by the reaction of the aldehyde and the amine to yield the corresponding propargylamines, water and Cu–Ni catalyst. Thus regenerated Cu–Ni bimetallic catalyst further in the reaction and completes the catalytic cycle.

## Conclusions

In conclusion a Cu–Ni bimetallic catalyst was explored for the multicomponent coupling of aldehyde, secondary amine and alkyne by C–H bond activation under solvent-free conditions. While most of the reported methods required an inert atmosphere, the present methodology does not require any special operating conditions, thus making procedure simple. Good yields, mild reaction conditions and solvent-free protocol are advantages of this method. Besides, catalyst recovery was achieved using a magnetic separation.

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