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An efficient synthesis of propargylamines using a silica gel anchored copper chloride catalyst in an aqueous medium

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Abstract—The design and development of a silica gel anchored copper chloride heterogeneous catalyst for the synthesis of propargylamines using an amine, an aldehyde, and an alkyne through C–H activation in water is described. Both aliphatic and aromatic aldehydes and amines are used for the reaction. The catalyst was recovered quantitatively by simple filtration and reused several times.

Transition metal catalyzed multi-component reactions are a powerful synthetic tools to access complex structures from simple precursors by one-pot procedures. The three-component coupling of aldehydes, alkynes, and amines (A^3 coupling) is one of the best examples of such a process and has received much attention.[1] The resultant propargylamines obtained by A^3 coupling reactions are important synthetic intermediates for potential therapeutic agents and polyfunctional amino derivatives.[2] Traditionally, these compounds are synthesized by nucleophilic attack of lithium acetylides or Grignard reagents on imines or their derivatives.[3] However, these reagents are stoichiometric, highly moisture sensitive, and require strictly controlled reaction conditions. Besides, sensitive functionalities such as esters are not tolerated. Thus there is a need for a general and efficient synthetic protocol that is applicable to a wide range of propargylamines. Several transition metal catalysts such as silver salts,[4] gold salts,[5] copper salts,[6] Ir complexes[7] and Cu/Ru[8] bimetallic systems under homogeneous conditions have all been used for this reaction and later their chiral equivalents were also reported.[9] In our earlier reports we described the ultrasound assisted synthesis of propargylamines using CuI as catalyst.[10] Recently, an A^3 coupling reaction was reported using immobilization of silver and copper salts in an ionic liquid.[11] Our group has reported the same using Cu–HAP and LDH–$AuCl_3$ under heterogeneous conditions.[12]

Even though some of the above reported procedures are general, environmentally friendly and applicable to both aliphatic and aromatic aldehydes and amines, there are no reports on the recyclability of the catalyst in water.

The immobilization and chemical modification of homogeneous catalysts to form heterogeneous analogues of well-defined structures anchored to an insoluble matrix is an area of current interest. The development of heterogeneous catalysts for the synthesis of fine chemicals in industrial processes is advantageous over homogeneous catalysts, since heterogeneous catalysts are easy to separate, and can potentially be reused.[13] The synthesis of mesoporous silica has greatly expanded the possibilities for the design of open pore structures.[14] As a result of their large surface area, well-defined pore size and pore shape, these materials have great potential in industrial processes. The pore walls of mesoporous materials are easily modified with either purely inorganic or with hybrid, semi-organic, functional groups.[15]

In the present work, silica gel anchored copper chloride[16] was synthesized using 3-mercaptopropyltrimethoxysilane as a spacer in order to explore its activity in A^3 coupling reactions.

The three-component coupling of benzaldehyde, piperidine, and phenylacetylene using the $Si(CH_2)_3SO_3CuCl$

Keywords: Propargylamines; Silica gel anchored copper chloride; Mesoporous silica; Terminal alkynes and imines.
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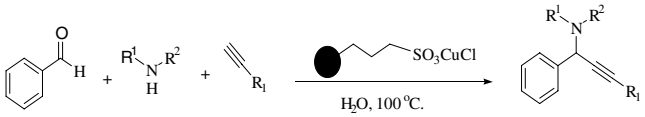


Scheme 1.

catalyst in water at 100 °C afforded the desired propargylamine in 86% yield (Scheme 1). The reaction proceeded very well in water as well as in other organic solvents such as toluene, THF, DMF, and acetonitrile.[17] At room temperature, only a trace amount of the product was formed and the reaction devoid of the catalyst gave no product despite prolonged reaction times. The optimum ratio of aldehyde, amine and alkyne was found to be 1:1.2:1.5.

With optimal reaction conditions in hand, we further examined the reusability of the catalyst for the A^3 coupling reaction. It is worth noting that the catalyst was recovered quantitatively and reused four times with only a slight decrease in activity (Table 1). Having established the reusability of the catalyst, we carried out the coupling reactions of a variety of aldehydes, amines, and alkynes to understand the scope and generality of the catalyst, and the results are shown in Tables 2–4.

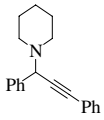
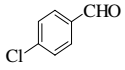
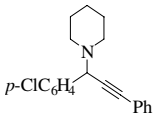
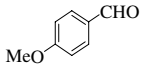
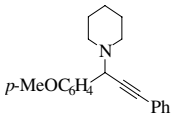
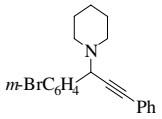
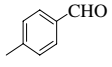
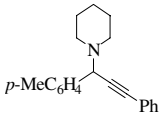
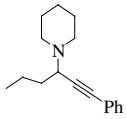
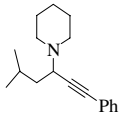
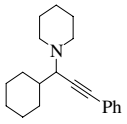
Initially various aldehyde substrates were added with piperidine and phenylacetylene. The aldehydes used for this study included aromatic, aliphatic and hetero-

Table 1. Recovery and reuse of $Si(CH_2)_3SO_3CuCl$ for the three-component coupling reaction of an aldehyde, an amine and an alkyne[a]

Entry	Run	Isolated yield (%)
1	1	86
2	2	80
3	3	75
4	4	75

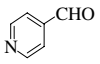
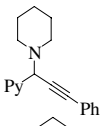
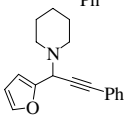
[a] Reaction conditions: aldehyde (1 mmol); amine (1.2 mmol); alkyne (1.5 mmol); 50 mg of catalyst (5 mol %) and H_2O (3 mL) at 100 °C for 10 h.

Table 2. Three-component coupling reaction of various aldehydes, with piperidine, and phenylacetylene[a]

Entry	Aldehyde	Product	Time (h)	Yield[b] (%)
1			10	86
2			12	79
3			14	75
4			12	75
5			16	72
6			8	98
7			8	92
8			8	95

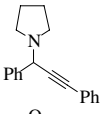
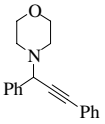
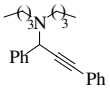
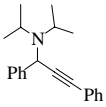
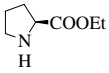
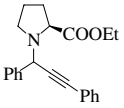
(*continued on next page*)

Table 2 (*continued*)

Entry	Aldehyde	Product	Time (h)	Yield[b] (%)
9			10	80
10			10	85

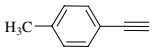
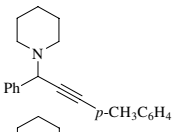
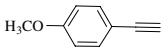
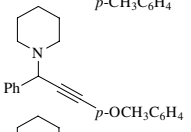
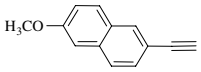
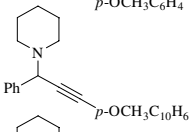
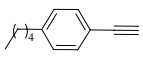
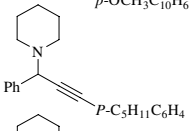
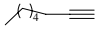
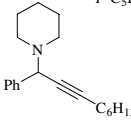
[a] Reaction conditions as exemplified in the typical experimental procedure.[18]
[b] Isolated yields after column chromatography.

Table 3. Three-component coupling reaction of benzaldehyde, various amines and phenylacetylene[a]

Entry	Amine	Product	Time (h)	Yield[b] (%)
1			10	92
2			16	54
3			12	85
4			12	68
5			10	52[c]

[a] Reaction conditions as exemplified in the typical experimental procedure.[18]
[b] Isolated yields after column chromatography.
[c] Products obtained in a diastereomeric ratio of 78:22.

Table 4. Three-component coupling reaction of benzaldehyde, piperidine, and various alkynes[a]

Entry	Alkyne	Product	Time	Yield[b]
1			8	92
2			8	86
3			10	71
4			10	80
5			24	60

[a] Reaction conditions as exemplified in typical experimental procedure.
[b] Isolated yields after column chromatography.

cyclic examples, and the results are shown in Table 2. Irrespective of the electronic nature of the substituent, aromatic aldehydes reacted smoothly to give the corresponding products in good yields (Table 2, entries 1–5). On the other hand, aliphatic aldehydes (entries 6–8) reacted rapidly and gave excellent yields without any trimerization. In addition, heteroaromatic aldehydes displayed high reactivity and gave good yields of products (entries 9–10).

To expand the scope of amine substrates, we used benzaldehyde and phenylacetylene as model substrates and examined various secondary amines in the A^3 coupling reaction. The order of reactivity for these amines in terms of yields and the reaction time was pyrrolidine > piperidine > dialkylamines > morpholine. Cyclic amines gave the desired product in excellent yields except morpholine (Table 2, entry 2). On the other hand, (*S*)-ethyl prolinoate gave the desired product in 52% yield with a diastereomeric ratio of 78:22.

Several terminal alkynes were examined for the coupling using benzaldehyde and piperidine as the model substrates (Table 3). *p*-Methyl and *p*-methoxy-substituted phenylacetylenes were more reactive compared to *p*-pentyl-substituted phenylacetylene and *p*-methoxynapthyl acetylene (Table 4, entries 1–4). It is noteworthy that with an aliphatic alkyne, the reaction was slow affording a lower yield (Table 4, entry 5).

To conclude, we have developed a simple and efficient method for the synthesis of propargylamines via C–H activation using silica gel anchored CuCl in water without using any organic solvent or co-catalyst. This protocol is an environmentally friendly process and can be used to generate a diverse range of acetylenic amines in good to excellent yields. The simple procedure for catalyst preparation, easy recovery and reusability of the catalyst is expected to contribute to its utilization for the development of benign chemical process and products.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.116.

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16. Catalyst preparation and XPS, TGA–MS, AAS, and FTIR characterization data is given in the Supplementary data.
17. Organic solvents such as DMF, toluene, THF, and acetonitrile gave the 1-(1,3-diphenyl-prop-2-ynyl)-piperidine in 90%, 95%, 92%, and 85% yields at their reflux temperatures in 10 h.
18. *Typical procedure for the A_3 coupling reaction*: A mixture of benzaldehyde (106 mg, 1 mmol), piperidine (102 mg, 1.2 mmol), phenylacetylene (153 mg, 1.5 mmol) and 50 mg of catalyst (0.05 mol %) was taken in a round-bottomed flask and stirred at reflux temperature. After completion of the reaction (monitored by TLC) the catalyst was removed by filtration. After removing the solvent, the crude material was chromatographed on silica gel to afford the pure product. All products gave satisfactory spectroscopic data. Spectroscopic data for all new compounds are reported.
1-(3-Phenyl-1-propyl-prop-2-ynyl)-piperidine (Table 2, entry 6): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.97 (t, 3H, $J = 6.7$), 1.40–1.68 (m, 10H), 2.44–2.55 (m, 4H), 3.45 (t, 1H, $J = 7.36$), 7.23–7.25 (m, 3H), 7.36–7.39 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.92, 20.16, 24.44, 26.06, 35.52, 58.21, 85.50, 87.90, 123.34, 127.71, 128.13, 131.62. ESI-MS (*m*/*z*): 241 $(M)^+$. Anal. Calcd for

$C_{17}H_{23}N$: C, 84.59; H, 9.60; N 5.80. Found: C, 84.54; H, 9.63; N, 5.81.

1-(1-Isobutyl-3-phenyl-prop-2-ynyl)-piperidine (Table 2, entry 7): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.10 (d, 6H, $J = 6.6$), 1.41–1.49 (m, 2H), 1.55–1.63 (m, 4H), 1.83–1.97 (m, 1H), 2.33–2.45 (m, 2H), 2.56–2.65 (m, 4H), 2.94 (t, 1H, $J = 7.6$), 7.23–7.27 (m, 3H), 7.37–7.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 14.22, 20.42, 24.48, 26.27, 30.29, 50.44, 57.30, 86.15, 87.53, 123.44, 127.93, 128.29, 131.84. ESI-MS (*m/z*): 255 $(M)^+$. Anal. Calcd for $C_{18}H_{25}N$: C, 84.65; H, 9.87; N, 5.48. Found: C, 84.63; H, 9.91; N, 5.47.

4-(3-Phenyl-1-piperidin-1-yl-prop-2-ynyl)-pyridine (Table 2, entry 9): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.85–0.88 (m, 2H), 1.39–1.48 (m, 4H), 2.45–2.50 (m, 4H), 4.79 (s, 1H), 7.28–7.32 (m, 5H), 7.48 (d, 2H, $J = 4.6$), 7.63 (d, 2H, $J = 7.55$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.56, 26.27, 50.73, 62.39, 86.02, 88.22, 123.42, 127.47, 128.03, 128.45, 128.52, 131.85, 138.67. ESI-MS (*m/z*): 276 $(M)^+$. Anal. Calcd for $C_{19}H_{20}N_2$: C, 84.57; H, 7.29; N, 10.14. Found: C, 84.54; H, 7.32; N, 10.13.

(1,3-Diphenyl-prop-2-ynyl)-diisopropyl-amine (Table 3, entry 4): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.04 (d, 6H, $J = 6.6$), 2.95–3.02 (m, 1H), 4.92 (s, 1H), 7.40–7.26 (m, 6H),7.55–7.50 (m, 2H), 7.67–7.62 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.66, 23.83, 46.59, 50.41, 85.82, 91.62, 123.90, 126.75, 127.78, 127.84, 128.29, 129.00, 131.30, 142.14. ESI-MS (*m/z*): 291 $(M)^+$. Anal. Calcd for $C_{21}H_{25}N$: C, 86.55; H, 8.65; N, 4.81. Found: C, 86.53; H, 8.69; N, 5.78.

1-(1-Phenyl-3-p-tolyl-prop-2-ynyl)-piperidine (Table 4, entry 1): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.41–1.63 (m, 2H), 1.54–1.63 (m, 4H), 2.51–2.56 (m, 4H), 2.38 (s, 3H), 4.76 (s, 1H), 7.1 (d, 2H, $J = 8.0$), 7.23–7.40 (m, 5H), 7.61 (d, 2H, $J = 8.8$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.22, 24.17, 25.90, 53.27, 62.07, 84.93, 87.63, 121.41, 128.38, 128.65, 128.77, 128.94, 137.78, 138.31. ESI-MS (*m/z*): 289 $(M)^+$. Anal. Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4. 84. Found: C, 87.14; H, 8.07; N, 4.80.

1-[3-(4-Methoxy-phenyl)-1-phenyl-prop-2-ynyl]-piperidine (Table 4, entry 2): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.42–1.63 (m, 6H), 2.51–2.56 (m, 4H), 3.81 (s, 3H), 4.75 (s, 1H), 6.81 (d, 2H, $J = 8.8$), 7.23–7.43 (m, 5H), 7.59 (d, 2H, $J = 8.$ 8). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.33, 25.79, 50.55, 55.23, 62.40, 83.96, 88.02, 13.85, 127.62, 128.10, 128.72, 133.20, 159.47. ESI-MS (*m/z*): 305 $(M)^+$. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.54; H, 7.63; N, 4.56.

1-[3-(6-Methoxy-naphthalen-2-yl)-1-phenyl-prop-2-ynyl]-piperidine (Table 4, entry 3): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.42–1.49 (m, 2H), 1.57–1.68 (m, 4H), 2.57–2.64 (m, 4H), 3.91 (s, 3H), 5.28 (s,1H), 7.04–7.91 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.28, 26.18, 50.82, 55.29, 62.23, 87.10, 90.81, 105.82, 118.18, 124.16, 127.54, 128.27, 128.34, 129.03, 129.60, 131.52, 132.95, 156.79. ESI-MS (*m/z*): 355 $(M)^+$. Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.43; H, 7.13; N, 3.92.

1-[3-(4-Pentyl-phenyl)-1-phenyl-prop-2-ynyl]-piperidine (Table 4, entry 4): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.87 (t, 3H, $J = 6.5$), 1.22–1.27 (m, 4H), 1.40–1.59 (m, 8H), 2.45–2.49 (m, 2H), 2.53–2.61 (m, 4H), 4.71 (s, 1H), 7.02 (d, 2H, $J = 7.9$), 7.22–7.34 (m, 5H) 7.53 (d, 2H, $J = 7.7$). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.97, 18.77,22.55, 24.41, 26.13, 28.47, 28.97, 31.32, 43.23, 50.59, 61.96, 84.52, 87.82, 127.15, 127.23, 127.83, 128.23, 128.52, 128.91, 130.33, 139.21, 142.23. ESI-MS (*m/z*): 345 $(M)^+$. Anal. Calcd for $C_{25}H_{31}N$: C, 86.90; H, 9.04; N, 4.05. Found: C, 86.87; H, 9.08; N, 4.02.

1-(1-Phenyl-non-2-ynyl)-piperidine (Table 4, entry 5): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.89–0.93 (m, 3H), 1.30–1.68 (m, 14H), 2.28–2.33 (m, 2H), 2.40–2.44 (m, 4H), 4.49 (s, 1H), 7.27–7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.97, 22.40, 24.26, 25.88, 30.98, 31.27, 35.68, 50.44, 62.40, 78.52, 80.48, 127.54, 128.08, 128.67, 131.71. ESI-MS (*m/z*): 283 $(M)^+$. Anal. Calcd for $C_{20}H_{29}N$: C, 84.75; H, 10.31; N, 4.94. Found: C, 84.71; H, 10.37; N, 4.91.