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## An efficient synthesis of propargylamines via three-component coupling of aldehydes, amines and alkynes catalyzed by nanocrystalline copper(II) oxide

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## Abstract

An efficient three-component coupling of aldehydes, amines and alkynes to prepare propargylamines, in nearly quantitative yields using nanocrystalline CuO as a catalyst is described. Structurally divergent aldehydes and amines were converted to the corresponding propargylamines. The reaction does not require any co-catalyst. After completion of the reaction, the catalyst was recovered by centrifugation and reused several times with only a slight decrease of activity observed under the same reaction conditions. © 2008 Elsevier Ltd. All rights reserved.

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One-pot multicomponent coupling reactions (MCR), where several organic moieties are coupled in one step is an attractive synthetic strategy.<sup>1,2</sup> The three-component coupling of aldehydes, amines and alkynes ( $A^3$  coupling) is one of the best examples of a MCR, and has received much attention in recent times. The propargylamines obtained by  $A^3$  coupling reactions are versatile synthetic intermediates for biologically active compounds such as  $\beta$ -lactams, conformationally restricted peptides, isosteres, natural products and therapeutic drug molecules.<sup>3–6</sup>

Traditionally, propargylamines are prepared by the amination of propargylic halides, propargylic phosphates or propargylic triflates.<sup>7,8</sup> However, these reagents which are used in stoichiometric amounts, are highly moisture sensitive and require strictly controlled reaction conditions. Recently, mild metal-catalyzed reactions based upon the nucleophilic addition of in situ generated metal acetylides to imines and enamines have been reported for the

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synthesis of propargylamines<sup>9-11</sup> Carreira and Fischer demonstrated the preparation of propargylamines by the reaction of aldimines with trimethylsilyl acetylene using commercially available and air-stable [IrCl(Cod)]<sub>2</sub>.<sup>12</sup> Wei and Li reported the A<sup>3</sup> coupling reaction through C-H bond activation in water using gold, silver and silver in ionic liquids without using any metal co-catalyst.<sup>13-15</sup> Though the yields were good, the scope was limited generally to cyclic amines in the silver catalyzed reaction, and the inert conditions were invariably used for the gold and silver catalyzed reactions in order to obtain good yields. More recently, Tu and co-workers have developed a microwave (MW) promoted CuI catalyzed A<sup>3</sup> coupling reaction.<sup>16</sup> The chiral version of the  $A^3$  coupling reaction for the formation of chiral propargylamines has also been reported using copper and gold complexes as chiral catalysts under homogeneous conditions.<sup>17–21</sup>

Despite the advantages of homogeneous metal catalysts, difficulties in recovering the catalyst from the reaction mixture severely inhibits their wide use in industry. Heterogeneous catalysis supplies the opportunity for easy separation and recycling of the catalyst, easy product purification

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and possibly, continuous or multiple processing of compounds. Thus, the development of improved synthetic methods for the preparation of propargylamines remains an active research area. Previously, we reported the A<sup>3</sup> coupling reaction using heterogeneous catalysts such as copper supported on hydroxyapatite,<sup>22</sup> layered double hydroxide supported gold<sup>23</sup> and zinc dust<sup>24</sup> for the preparation of propargylamines.

Nanocrystalline metal oxides find excellent applications as active adsorbents for gases and destruction of hazardous chemicals.<sup>25</sup> They are also gaining tremendous importance due to their distinct catalytic activities for various organic transformations. Recently, our group has reported various<sup>26-31</sup> organic transformations using different nanocrystalline metal oxides. These high reactivities are due to the high surface areas combined with unusually reactive morphologies. Copper oxide nanoparticles have been of considerable interest due to the role of CuO in catalysis, gas sensors and semiconductors.<sup>32,33</sup> CuO nanoparticles were found to be the effective catalysts for CO and NO oxidation as well as for the oxidation of volatile organic chemicals such as methanol.<sup>34-36</sup> Very recently, we reported the asymmetric hydrosilylation reaction of prochiral ketones catalyzed by nanocrystalline copper oxide (nano CuO) with excellent enantioselectivity.<sup>37</sup>

Herein, we report on the activity of nano CuO for the  $A^3$  coupling reaction to generate propargylamines without using any co-catalyst or additive (Scheme 1).

A series of experiments were carried out in an effort to develop an improved catalytic system for the synthesis of propargylamines by  $A^3$  coupling between benzaldehyde, piperidine and phenylacetylene and the results are summarized in Table 1. Commercially available bulk Cu<sub>2</sub>O gave low yields, while nano CuO afforded excellent yields. When the reaction was conducted with bulk CuO, a poor yield of the product was obtained. When the nano CuO catalyzed  $A^3$  coupling reaction was carried out in solvents other than toluene, such as dry THF, acetonitrile or DCM, a significant decrease in yield was noticed. When water was used as the solvent, only a trace amount of product was observed even after a prolonged reaction time. The optimum ratio of aldehyde, amine and alkyne was found to be 1:1.3:1.5.

Furthermore, a catalyst recycle experiment (Table 2) was carried out. The catalyst was recovered by centrifugation and the  $A^3$  coupling reaction of benzaldehyde, piperidine and phenylacetylene was performed for up to three cycles with only a slight decrease in activity. The catalytic



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Scheme 1.
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Table 1

Three-component coupling of benzaldehyde, piperidine and phenylacetylene with various catalysts and solvents<sup>a</sup>

Entry	Solvent	Catalyst	Yield <sup>b</sup> (%)
1	Acetonitrile	Nano CuO	42°
2	THF	Nano CuO	15 <sup>°</sup>
3	DCM	Nano CuO	22 <sup>c</sup>
4	Toluene	Nano CuO	82 <sup>d</sup>
5	Water	Nano CuO	Trace
6	Toluene	Commercial Cu <sub>2</sub> O	48 <sup>d</sup>
7	Toluene	Commercial CuO	22 <sup>d</sup>

<sup>a</sup> Reaction conditions: benzaldehyde (1 mmol), piperidine (1.3 mmol), phenylacetylene (1.5 mmol), solvent (4 ml), catalyst (10 mol%), 6 h.

<sup>b</sup> Isolated yield.

<sup>c</sup> Reflux temperature.

<sup>d</sup> 90 °C temperature.

Table 2

Recycling of the catalytic system for the three-component coupling of benzaldehyde, piperidine and phenylacetylene

Run	Time (h)	Yield (%)
1	6	82
2	6	80
3	6	79
4	6	76

Reaction conditions: benzaldehyde (1 mmol), piperidine (1.3 mmol), phenylacetylene (1.5 mmol), toluene (4 ml), nano CuO (10 mol %), 90 °C.

activity of nano CuO was evident as no product was obtained in the absence of catalyst.

The general applicability of the nano CuO promoted A<sup>3</sup>coupling reaction was illustrated using a variety of structurally divergent aldehydes and amines possessing a wide range of functional groups. As summarized in Table 3, both aromatic and aliphatic aldehydes afforded the corresponding propargylic amines effectively. The results in Table 3 indicate that the aromatic aldehydes bearing different functional groups such as fluoro, chloro, bromo, methyl or methoxy were able to undergo the A<sup>3</sup> coupling. A low yield was obtained when 4-nitrobenzaldehyde was used as the substrate, increasing the reaction time did not increase the yield. On the other hand, the aliphatic aldehydes (Table 3, entries 1–4 and 14) displayed good reactivity and the corresponding propargylamines were obtained in high yields.

Aliphatic amines such as piperidine, morpholine, pyrrolidine and dibutyl amine gave very good yields of the coupling product in the  $A^3$  coupling reaction of benzaldehyde (Table 3, entries 5–10) or cyclohexylcarboxaldehyde (Table 3, entries 1–4) and phenylacetylene. On the other hand aromatic amines, such as dibenzylamine or phenylbenzylamine gave moderate yields of the product (Table 3, entries 4, 9 and 10). When alkylacetylenes were used in place of phenylacetylene, the corresponding propargylamines were isolated in good yields (Table 3, entries 14 and 15).

The increased catalytic activity of nano CuO over commercially available bulk CuO and Cu<sub>2</sub>O may be attributed

Table 3

Three-component coupling of aldehydes, amines and alkynes catalyzed by nano  $\,{\rm CuO}^{\rm a}$ 

$R^1$ -CHO+ $R^2R^3NH$ + $R^4$ ——	H Nano CuO
$R^1$ = aryl and cyclohexyl	$^{\sim}R^4$

 $R^2$ ,  $R^3$  = dialkyl and dibenzyl

 $R^4$  = alkyl and phenyl

Entry	$R^1$	Amine $(\mathbf{R}^2, \mathbf{R}^3)$	R <sup>4</sup>	Time (h)	Yield <sup>b</sup> (%)
1	Cyclohexyl	Piperidine	Ph	5	84
2	Cyclohexyl	Morpholine	Ph	8	78
3	Cyclohexyl	Dibutyl	Ph	5	75
4	Cyclohexyl	Dibenzyl	Ph	12	68
5	Ph	Piperidine	Ph	6	82
6	Ph	Morpholine	Ph	8	65
7	Ph	Pyrrolidine	Ph	6	81
8	Ph	Dibutyl	Ph	6	78
9	Ph	$R^2 = Ph, R^3 = PhCH_2$	Ph	8	72
10	Ph	Dibenzyl	Ph	10	58
11	$4-ClC_6H_4$	Piperidine	Ph	6	85
12	4-MeOC <sub>6</sub> H <sub>4</sub>	Piperidine	Ph	15	48
13	$4-NO_2C_6H_4$	Piperidine	Ph	18	8
14	Cyclohexyl	Piperidine	$\succ$	5	84
15	Ph	Piperidine	$\succ$	6	75

<sup>a</sup> Reaction conditions as exemplified in the typical experimental procedure.

<sup>b</sup> Isolated yields.

to the higher surface area of nano CuO  $(136 \text{ m}^2/\text{g})$  than bulk CuO  $(1.952 \text{ m}^2/\text{g})$  as well as the higher surface concentration of the reactive sites. As seen with other metal oxides, once they are made into nanoparticles, their reactivity is greatly enhanced. This is thought to be due to the morphological differences, whereas larger crystallites have only a small percentage of the reactive sites on the surface, smaller crystallites will possess a much higher surface concentration of such sites.

It is assumed that the A<sup>3</sup> coupling reaction proceeds by terminal alkyne C–H bond activation by nano CuO catalyst (Scheme 2).<sup>13–16</sup> The copper acetylide intermediate thus generated will react with the iminium ion prepared in situ from the aldehyde and the amine and form the corresponding propargylamine, water and nano CuO. Thus the regen-



Scheme 2. Tentative mechanism for A<sup>3</sup> coupling reaction.

erated nano CuO participates further in the reaction and completes the catalytic cycle.

In summary, an efficient nanocrystalline CuO catalyzed three-component coupling of aldehydes, amines and alkynes has been achieved in toluene. Both aliphatic and aromatic aldehydes as well as amines can be used. The catalyst can be readily recovered and reused for several cycles with only a slight decrease in activity.

Typical procedure for the  $A^3$  coupling reaction: A mixture of benzaldehyde (1 mmol), pyrrolidine (1.3 mmol), phenylacetylene (1.5 mmol) and nano CuO (10 mol %) in toluene (4 ml) was stirred in a round-bottomed flask at 90 °C. The progress of the reaction was monitored by TLC and on completion, the reaction mixture was centrifuged and the centrifugate was concentrated under reduced pressure to afford the crude product, which after chromatography on silica gel gave the corresponding propargylamine, *N*-(1,3diphenyl-2-propynyl)pyrrolidine.

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.60–7.54 (m, 2H), 7.48–7.42 (m, 2H), 7.34–7.18 (m, 6H), 4.87 (s, 1H), 2.70– 2.60 (m, 4H), 1.82–1.70 (m, 4H). ESI MS (*m*/*z*): 262 (M+H)<sup>+</sup>.

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