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Nano indium oxide catalyzed efficient synthesis of propargylamines via C–H and C–Cl bond activations

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ABSTRACT

A simple, and efficient nano In_2O_3 catalyzed one-pot three-component coupling of terminal alkyne, dichloromethane, and secondary amine has been developed for the synthesis of propargylamines under mild reaction conditions. The catalyst was recovered and reused for three times without significant loss of catalytic activity.

The development of synthetic strategies for C–H bond activation is one of the most important areas in organic chemistry.[1] Three-component coupling of an aldehyde, an alkyne, and an amine (A^3 coupling) via C–H bond activation has received considerable interest for the synthesis of propargylamines in recent times.[2] Propargylamines are synthetically versatile intermediates for the preparation of biologically active molecules.[3] In an alternative way very recently, Contel and Urriolabeitia reported an efficient three-component coupling of alkynes, dihaloalkanes, and amines (AHA coupling) to afford propargylamines.[4] This coupling involves the methylene fragment from dichloromethane by a gold-catalyzed C–Cl bond activation. At the same time Zhang et al. reported the AHA coupling catalyzed by copper(I) chloride.[5] Despite the advantages of homogeneous metal catalyst, difficulties in recovering and recycling severely obstruct its wide use in industry. Therefore, development of improved synthetic method for the preparation of propargylamines is highly desirable. Metal nanoparticles have been used widely as an efficient catalyst in organic reactions due to their high catalytic activity, ease of handling, reusability, and benign character.[6] Indium(III) compounds are mild and water-tolerant Lewis acids and show high regio-, stereo-, and chemoselectivity.[7] We have also found that indium(III) compounds are very efficient catalysts for coupling reactions.[8] However, until now the use of nano In_2O_3 as a catalyst is limited in organic synthesis.[9] This inspired us to focus on the use of nano In_2O_3 as a catalyst. Herein, we wish to report a remarkable catalytic activity of readily available nano In_2O_3 for a three-component coupling of alkynes, dichloromethane, and amines to afford propargylamines (Scheme 1).

Initially we carried out the coupling reaction of phenylacetylene, dichloromethane, and *n*-dibutylamine in dichloromethane solvent using nano In_2O_3 as a catalyst at 40 °C for 16 h. Although the reaction did not proceed well, we were able to isolate the coupling product in 28% yield. Encouraged by this result, we turned our attention to optimize the reaction conditions. Optimization was achieved by varying solvent, base, and catalyst. When the reaction was carried out in DMSO solvent at 65 °C, the yield of the product was increased. Better yield was obtained by adding a base. The results reported in Table 1 revealed that nano In_2O_3 (5 mol %) was better suited to afford propargylamines in DMSO solvent in presence of DABCO (1 equiv) at 65 °C.[10] Among the bases, DABCO was superior to some other bases such as K_2CO_3 and DBU. DMSO appeared to be the best choice among the common solvents such as CH_3CN, DMF. With respect to the quantity of the catalyst, there was no significant enhancement in yields when the amount of catalyst was increased from 5 to 10 mol % while decreasing the amount of catalyst decreased the yield. Lower conversions were obtained when indium oxide powder and other metal catalysts such as NiO (nano), La_2O_3, CuO (nano), ZnO (nano), and $FeCl_3$ were used.

Encouraged by these results, we next briefly investigated the substrate-scope and the results are summarized in Table 2. Aromatic alkynes such as phenylacetylene, and 4-ethynyl toluene underwent coupling to afford propargylamines in excellent yields. Heteroaryl and aliphatic alkynes also afforded desired products in good yields. Both cyclic and acyclic secondary amines such as

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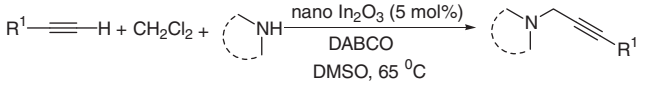
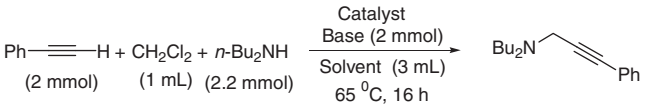


Scheme 1. Nano In_2O_3 catalyzed three-component coupling.

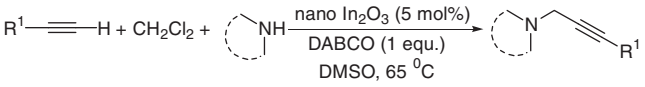
Table 1
Optimization of the reaction conditions



Entry	Catalyst	Base	Solvent	Yields[a] (%)
1	In_2O_3 (nano, 5 mol %)	DABCO	CH_3CN	62
2	In_2O_3 (nano, 5 mol %)	DABCO	DCE	60
3	In_2O_3 (nano, 5 mol %)	DABCO	1,4-Dioxane	65
4	In_2O_3 (nano, 5 mol %)	DABCO	DMF	78
5	In_2O_3 (nano, 5 mol %)	DABCO	DMSO	84
6	In_2O_3 (nano, 5 mol %)	DBU	DMSO	64
7	In_2O_3 (nano, 5 mol %)	K_2CO_3	DMSO	68
8	In_2O_3 (nano, 2 mol %)	DABCO	DMSO	65
9	In_2O_3 (nano, 10 mol %)	DABCO	DMSO	86
10	In_2O_3 (powder, 5 mol %)	DABCO	DMSO	56
11	La_2O_3 (5 mol %)	DABCO	DMSO	20
12	ZnO (nano, 5 mol %)	DABCO	DMSO	72
13	CuO (nano, 5 mol %)	DABCO	DMSO	70
14	NiO (nano, 5 mol %)	DABCO	DMSO	38
15	$FeCl_3$ (5 mol %)	DABCO	DMSO	70

[a] Isolated yields.

Table 2
One-pot synthesis of propargylamines



Entry	Alkyne R^1	Amine	Time (h)	Yields[a] (%)
1	Ph	n-Bu_2NH	15	84
2	Ph	n-Oc_2NH	15	82
3	Ph	Pyrrolidine	20	72
4	Ph	Piperidine	16	80
5	Ph	Morpholine	20	68
6	4-MeC_6H_4	n-Bu_2NH	18	84
7	4-MeC_6H_4	n-Oc_2NH	18	82
8	4-MeC_6H_4	Piperidine	16	85
9		n-Oc_2NH	18	82
10	n-C_4H_9	n-Bu_2NH	20	65

[a] Isolated yields.

piperidine, pyrrolidine, morpholine, dibutyl amine, and dioctyl amine reacted well under these conditions. However, the reaction with *N*-methylaniline was not successful. In general reactions are clean, and products were obtained in high yields. The structures of all the products were determined from their spectral and analytical data and by direct comparison with the authentic samples. Regarding the mechanistic path of the present reactions, we assume that it follows the similar route as described for the gold[4] and copper[5] catalyzed reactions. Accordingly, the plausible reaction path will be the initial formation of alkynylindium species which reacts with dichloromethane followed by coupling of amine to afford propargylamines. In_2O_3 nanoparticles are recyclable without loss of significant catalytic activity. In a typical experiment the catalyst was reused for three times (recovery amount, 88% and yield, 76% after 3rd run for entry 1, Table 2).

In summary, an efficient nano In_2O_3 catalyzed three-component coupling of alkyne, dichloromethane, and amines has been achieved. To the best of our knowledge, this is the first time report of a non-transition metal catalyzed synthesis of propargylamines based on C–H and C–Cl bond activations. This finding should stimulate new applications of nano In_2O_3 in organic synthesis as an efficient catalyst.

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10. *General procedure*: A mixture of alkyne (2 mmol), amine (2.2 mmol), dichloromethane (1 mL), DABCO (2 mmol), and nano In_2O_3 (5 mol %) in

DMSO (3 mL) was stirred at 65 °C for appropriate time. After completion, the reaction mixture was diluted with a 1:1 mixture of water/ethyl acetate (10 mL) and In_2O_3 was recovered by centrifugation. The reaction mixture was extracted with diethyl ether (2 × 10 mL) and dried over Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography to obtain the analytically pure product. New compounds were properly characterized by their spectral and analytical data. *n-Dibutyl-(3-p-tolyl-prop-2-ynyl)-amine* (Table 2, entry 6): light yellow liquid; IR (KBr) 3452, 2921, 2291, 2146, 1631 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, J = 8.0 Hz, 2H), 7.11–7.09 (d, J = 8.0 Hz, 2H), 3.63 (s, 2H), 2.57–2.54 (t, J = 7.5 Hz 4H), 2.35 (s, 3H), 1.53–1.47 (m, 4H), 1.38–1.25 (m, 4H), 0.93 (t, J = 7.5 Hz 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.9, 131.5, 128.9, 120.2, 85.3, 83.5, 53.6, 42.7, 29.6, 29.5, 21.4, 20.7, 14.0; Anal. Calcd for $C_{18}H_{27}N$: C, 83.99; H, 10.57; N, 5.44. Found: C, 83.86; H, 10.44; N, 5.31. *n-Dioctyl-(3-p-tolyl-prop-2-ynyl)-amine* (Table 2, entry 7): light yellow liquid; IR (KBr) 3463, 2952, 2216, 1643 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 3.65 (s, 2H) 2.56 (t, J = 7.4 Hz, 4H), 2.34 (s, 3H), 1.53 (m, 2H), 1.31–1.27 (m, 22H), 0.87 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 131.6, 128.9, 120.0, 85.4, 82.9, 53.9, 42.6, 31.8, 29.5, 29.3, 27.5, 27.2, 22.6, 21.4, 14.1; Anal. Calcd for $C_{26}H_{43}N$: C, 84.48; H, 11.73; N, 3.79. Found: C, 84.36; H, 11.62; N, 3.63. *1-(3-p-Tolyl-prop-2-ynyl)-piperidine* (Table 2, entry 8): light yellow liquid; IR (KBr) 3498, 2937, 2214, 1652 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, J = 8.0 Hz, 2H), 7.08–7.06 (d, J = 8.0 Hz, 2H), 3.48 (s, 2H), 2.58 (m, 4H), 2.31 (s, 3H), 1.67–1.62 (m, 4H), 1.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.9, 131.5, 128.9, 120.0, 85.3, 83.7, 53.2, 48.3, 25.7, 23.7, 21.3; Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98; N, 6.57. Found: C, 84.38; H, 8.82; N, 6.42. *n-Dioctyl-(3-thiophen-3-yl-pro-2-ynyl)-amine* (Table 2, entry 9): yellow liquid; IR (KBr) 3406, 2904, 2150, 1677 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 2.0 Hz, 1H), 7.24–2.23 (m, 1H), 7.09 (d, J = 5.5 Hz, 1H), 3.61 (s, 2H), 2.53 (t, J = 7.5 Hz, 4H), 1.52–1.49 (m, 2H), 1.30–1.26 (m, 22H), 0.87 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 130.2, 128.4, 125.2, 122.4, 84.1, 80.3, 54.1, 42.9, 31.9, 29.7, 29.4, 29.3, 27.7, 27.5, 22.8, 14.2; Anal. Calcd for $C_{23}H_{39}NS$: C, 76.39; H, 10.87; N, 3.87. Found: C, 76.26; H, 10.73; N, 3.75. *n-Dibutyl-hept-2-ynyl-amine* (Table 2, entry 10): Light yellow liquid; IR (KBr) 3452, 2918, 2287, 2144, 1685 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.36 (s, 2H), 2.45–2.37 (m, 4H), 2.19–2.16 (m, 2H), 1.49–1.23 (m, 12H), 0.9–0.88 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 85.4, 74.4, 53.6, 42.3, 31.1, 29.7, 29.6, 29.3, 22.0, 20.8, 20.8, 18.5, 14.1, 13.7; Anal. Calcd for $C_{15}H_{29}N$: C, 80.65; H, 13.08; N, 6.27. Found: C, 80.49; H, 12.95; N, 6.12.