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$InBr_3$-catalyzed three-component reaction: a facile synthesis of propargyl amines

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ABSTRACT

Indium(III) bromide has been used for the first time for the synthesis of propargyl amines in a one-pot operation from aldehydes, amines and alkynes.

The stereoselective addition of organometallic reagents to aldehydes and imines is one of the most important carbon-carbon bond formation reactions in organic synthesis.[1] Propargyl amines or β-aminoalkynes are versatile intermediates for the construction of nitrogen-containing biologically active molecules and for the synthesis of polyfunctional amino derivatives.[2] The direct method for the synthesis of propargyl amines involves the addition of alkynylmetal 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] Propargyl amines can also be synthesized by one-pot three-component coupling of aldehydes, alkynes, and amines via C–H activation. Several transition metal salts such as gold, copper, silver, and Cu/Ru system have been employed in water as well as in ionic liquids.[6] Recently, solid-supported metal catalysts such as CuI/Al_2O_3, $AuCl_4$/LDH, and Cu/HAP and alternative energy sources like microwave and ultrasound have been utilized in the presence of CuI to accomplish this reaction via C–H activation.[7,8] However, many of these three-component coupling reactions are mainly limited to the aromatic aldehydes and cyclic amines and also involve the use of expensive iridium, gold, and silver salts. Moreover, low conversions are reported with aliphatic aldehydes.[7d]

Recently, indium tribromide has received increasing attention as a water-tolerant, green Lewis acid catalyst for organic synthesis demonstrating highly chemo-, regio-, and stereo-selective results.[9] Compared to conventional Lewis acids, it has advantages of water stability, recyclability, operational simplicity, strong tolerance to oxygen and nitrogen-containing substrates and functional groups, and it can often be used in catalytic amounts.[10] Recently, $InBr_3$ has also been used for the alkynylation of aldehydes and acetals.[11]

In continuation of our interest on the catalytic use of indium tribromide,[12] we herein report a simple and efficient method for the preparation of propargyl amines by means of a three-component coupling of aldehyde, amine, and alkyne. Accordingly, we first attempted the coupling of benzaldehyde (**1**) with morpholine (**2**) and phenyl acetylene (**3**) in the presence of 10 mol % of $InBr_3$ in toluene. The reaction went to completion in 4.5 h and the desired product, 4-(1,3-diphenylprop-2-ynyl)morpholine, **4a** was obtained in 85% yield (Scheme 1).

Encouraged by this result, we turned our attention to various aldehydes, amines, and alkynes. Interestingly, various aldehydes such as *p*-methoxybenzaldehyde, *p*-methylbenzaldehyde, *p*-chlorobenzaldehyde, and *p*-bromobenzaldehyde reacted effectively with morpholine and phenyl acetylene to produce the corresponding propargylic amines in good yields (Table 1, entries **b**–**e**). Similarly, heteroaromatic aldehydes such as thiophene-2-carboxaldehyde and furan-2-carboxaldehyde also participated well in this reaction (Table 1, entries **f** and **g**). In addition to aromatic aldehydes, aliphatic aldehydes such as pentanal, formaldehyde and cyclohexanecarboxaldehyde were also equally effective for this conversion (Table 1, entries **i–k** and **g**). Next, we studied the reactivity of various alkynes in the 3CC reaction. Interestingly, several alkynes such as 1-octyne, 2-ethynylpyridine, 1-*tert*-butyl-4-ethynylbenzene, and but-3-ynyl-benzene underwent smooth coupling to provide a wide range of propargyl amines (Table 1, entries **k**

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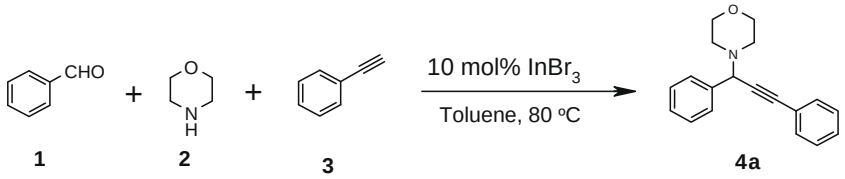


Scheme 1.

and **m**–**o**). Ketones did not give the desired product under these reaction conditions. This method was also successful with various amines such as piperidine, pyrrolidine, and aniline (Table 1, entries **k** and **o**–**r**). In all cases, no propargylic alcohol (an adduct between the aldehyde and alkyne) was obtained under similar reaction conditions. This is because of a rapid formation of the carbon-nitrogen bond from aldehydes and amines. The effects of various indium(III) salts such as $InCl_3$, $In(OTf)_3$, $In(OAc)_3$, and $In(ClO_4)_3$ were screened

Table 1
$Inbr_3$-Catalyzed preparation of propargyl amines

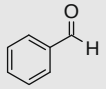
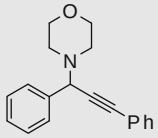
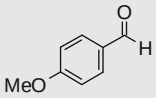
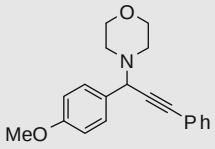
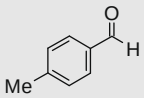
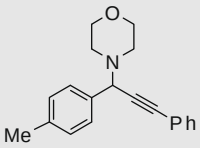
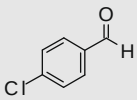
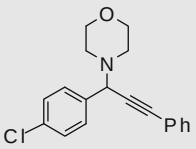
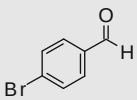
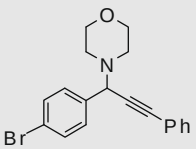
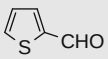
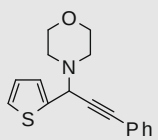
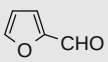
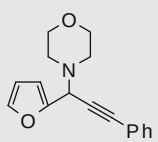
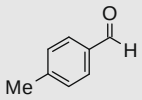
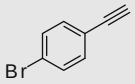
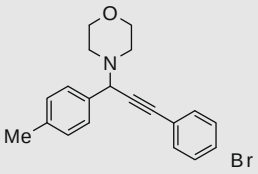
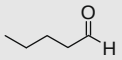
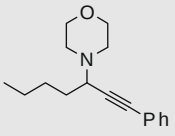
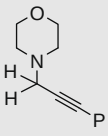
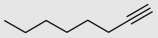
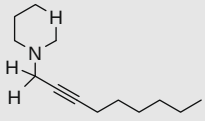
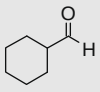
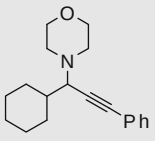
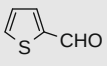
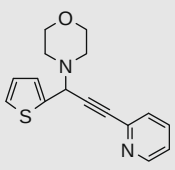
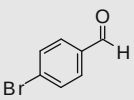
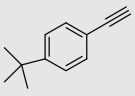
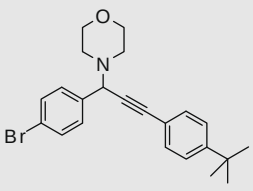
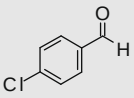
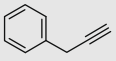
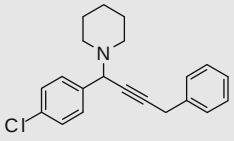
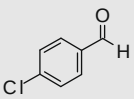
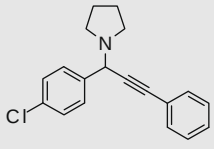
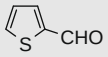
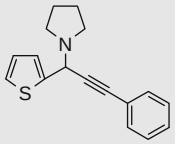
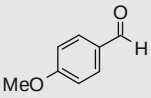
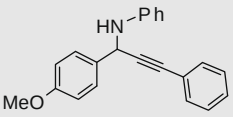
Entry	Aldehyde	Alkyne	Amine	Product[a]	Reaction time (h)	Yield[b] (%)
a					4.5	85
b					4.5	70
c					5.0	85
d					6.0	80
e					5.5	85
f					4.0	95
g					4.5	92

Table 1. (*continued*)

Entry	Aldehyde	Alkyne	Amine	Product[a]	Reaction time (h)	Yield[b] (%)
h					6.0	78
i					6.0	75
j					4.0	90
k					5.5	75
l					5.0	82
m					4.5	70
n					5.0	85
o					7.0	70
p					6.5	78

(*continued on next page*)

Table 1. (*continued*)

Entry	Aldehyde	Alkyne	Amine	Product[a]	Reaction time (h)	Yield[b] (%)
q					4.5	74
r					7.0	70

[a] The products were characterized by NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

for this transformation. Of these catalysts, indium tribromide was found to be the most effective in terms of conversion and selectivity. For example, treatment of benzaldehyde with morpholine and phenyl acetylene in the presence of 10 mol % of $InBr_3$ and 10 mol % of $InCl_3$ for 4.5 h gave the product **4a** in 85% and 70% yields, respectively. Although, indium tribromide is water tolerant, the reaction was unsuccessful either in pure water or in toluene/water (7:3) system. The scope and generality of this process are illustrated with respect to various aldehydes, amines and alkynes and the results are presented in Table 1.[13]

In summary, we have developed a simple, convenient, and efficient protocol for the preparation of propargylic amines by means of coupling of aldehyde, amine, and alkyne in a single-step operation. This method works well for both aliphatic and aromatic substrates. The use of indium bromide makes this method simple, convenient, and practical.

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13. *General procedure*: A mixture of aldehyde (1 mmol), amine (1 mmol), alkyne (1.5 mmol) and $InBr_3$ (10 mol %) in toluene was stirred at 80 °C for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (3 × 10 mL). The combined organic 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 (1:9) to afford pure propargylic amine. *Spectral data for selected products*: Compound **4h**: 4-[3-(4-Bromophenyl)-1-(4-methylphenyl)-2-propynyl] morpholine: solid, mp 139–142 °C. IR (KBr): 3426, 3026, 2966, 2921, 2849, 2240, 1657, 1484, 1446, 1388, 1268, 1112, 1069, 1000, 968, 929, 856, 814 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *v* 7.48–7.40 (m, 4H), 7.37–7.32 (m, 2H), 7.15–7.09 (m, 2H), 4.67 (s, 1H), 3.74–3.61 (m, 4H), 2.63–2.48 (m, 4H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *v* 137.4, 134.4, 133.1, 131.4, 128.8, 128.3, 122.2, 121.8, 87.0, 86.5, 67.0, 61.7, 49.7, 21.0. LCMS: *m*/*z* 370 (M^+). HRMS calcd for $C_{20}H_{21}NOBr$ ($M+H^+$): 370.0799. Found: 370.1086. Compound **4j**: 4-(3-Phenyl-2-propynyl)morpholine: IR (KBr): *v* 3057, 2958, 2925, 2854, 2813, 2760, 2261, 1719, 1599, 1489, 1390, 1326, 1070, 1006, 911, 861, 756, 692, 666, 560, 525 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *v* 7.36–7.10 (m, 5H), 3.63–3.50 (m, 4H), 3.37 (s, 2H), 2.53–2.40 9 m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): *v* 131.6, 128.1, 128.0, 122.9, 85.5, 83.9, 66.8, 52.3, 48.0. LCMS: *m*/*z* 202 (M+1). HRMS calcd for $C_{13}H_{16}NO$ ($M+H^+$): 202.1225. Found: 202.1231. Compound **4n**: 4-{1-(4-bromophenyl)-3-[4-(*tert*-butyl) phenyl]-2-propynyl} morpholine: IR (KBr): *v* 2957, 2857, 2364, 1591, 1476, 1394, 1315, 1274, 1113, 1070, 1008, 836, 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *v* 7.53–7.29 (m, 8H), 4.69 (s, 1H), 3.73–3.62 (m, 4H), 2.62–2.53 (m, 4H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): *v* 151.5, 137.0, 131.4, 131.1, 130.0, 125.1, 121.5, 119.5, 88.9, 83.4, 66.9, 61.2, 49.6, 34.5, 31.0. LCMS: *m*/*z* 412 (M^+). HRMS calcd for $C_{23}H_{27}NOBr$ ($M+H^+$): 412.1268. Found: 412.1276.