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Propargylic amines constructed via copper-catalyzed three-component coupling of terminal alkynes, benzal halides and amines

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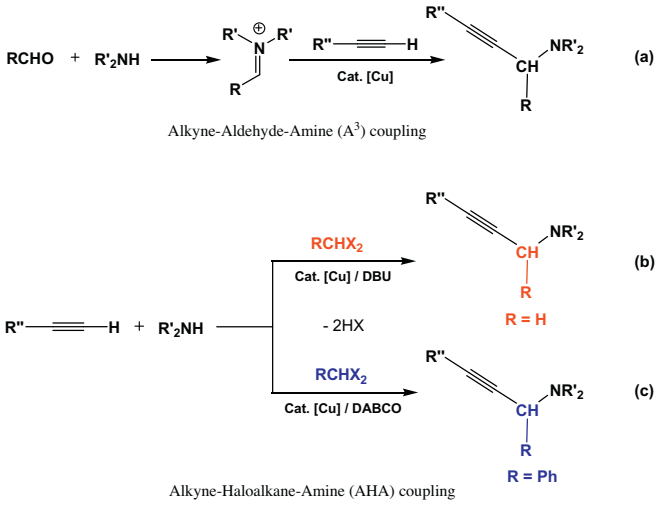
ABSTRACT

A method for the synthesis of propargylic amines has been developed via an efficient copper(I)-catalyzed three-component coupling reaction of alkynes, benzal halides and amines through C–H and C-halogen activation. This reaction is conducted under mild conditions and provides an alternative method for the synthesis of propargylic amines.

Transition metal catalyzed multi-component coupling reactions (MCRs) are an important class of reactions in synthesis. MCRs leading to the formation of new C–C bonds are particularly attractive.[1–6] The well-documented three-component coupling of terminal alkynes, aldehydes and amines (A^3 coupling) is an excellent example of an MCR and provides an elegant synthetic method for the preparation of propargyl amines which are important building blocks for many biologically active compounds (Scheme 1a).[7–11]

Recently, an alternative synthetic method for the preparation of propargylic amines from terminal alkynes, dihalomethanes and amines (AHA coupling) with a copper[12] or gold catalyst[13] was developed (Scheme 1, reaction 1b). This AHA coupling reaction offers a new approach to propargylic amines with C–C and C–N bond formation via C–H and C-halogen activation. However, the reported AHA catalytic system was limited to dihalomethanes as the key component (Scheme 1, reaction b). Herein, we extend this AHA coupling methodology to terminal alkynes, benzal halides and other amine systems (Scheme 1, reaction 1c). This extension greatly widens the substrate scope of the AHA coupling reaction and introduces a chiral center in the product.

The coupling reaction of *tert*-butylacetylene (1 mmol), benzal bromide (1.5 mmol) and diethylamine (2.0 mmol) with 10 mol % of copper(I) chloride and 100 mol % of DBU in acetonitrile at 60 °C afforded the propargylic amine in moderate yield (50%) (Table 1, entry 1). We then chose these substrates for optimization of the reaction conditions (Table 1). The reaction proceeded smoothly at ambient temperature. This lower reaction temperature compared



Scheme 1. A^3- and AHA-coupling reactions.

to previously reported couplings of alkynes, dihalomethanes, and amines (60 °C), is possible probably due to the altered kinetics of the reaction as benzal bromide is more reactive than dihalomethanes. Higher temperatures lead to the formation of *cis*- and *trans*-stilbenes via homocoupling of the *gem*-dihalides.[14,15] Similar to the first generation catalytic system, organic bases were generally better than inorganic bases, possibly because of their improved solubility in the reaction system.[12] It turned out that triethylamine or 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base gave the best yields ranging from 93% to 95%. Among the bases screened,

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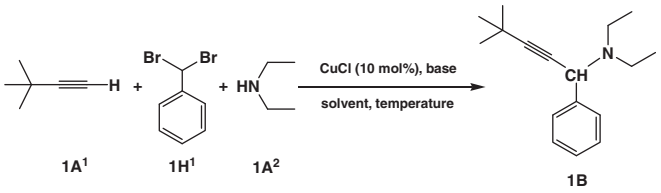
Table 1
Optimization of the reaction conditions[a]



Entry	Solvent	Base	Temp (°C)	Yield (%)
1	CH_3CN	DBU	60	50
2	CH_3CN	DBU	rt	72
3	CH_3CN	Na_2CO_3	rt	79
4	CH_3CN	$NaHCO_3$	rt	48
5	CH_3CN	K_3PO_4	rt	76
6	CH_3CN	Et_3N	rt	95
7	CH_3CN	DABCO	rt	93
8	DMSO	Et_3N	rt	79
9	DMF	Et_3N	rt	89
10	THF	Et_3N	rt	0
11	Hexane	Et_3N	rt	0

[a] Reaction conditions: *tert*-butylacetylene (1.0 mmol), benzal bromide (1.5 mmol), diethylamine (2.0 mmol), base (1 mmol), solvent (2 ml), 36 h.

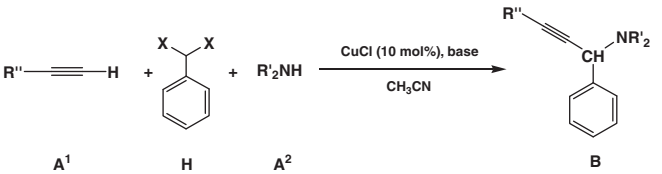
Na_2CO_3, $NaHCO_3$, K_3PO_4 and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in low conversions (Table 1). CH_3CN was the best solvent for the reaction. At room temperature and using Et_3N as the base, the reaction in CH_3CN delivered the corresponding propargylic amine in 95% yield while the reaction in dimethylsulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) gave 79% and 89% yields, respectively. No product was observed when the reaction was carried out in tetrahydrofuran (THF) or hexane under the same conditions (Table 1).

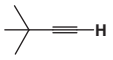
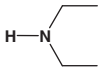
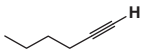
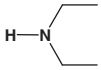
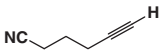
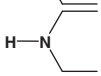
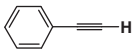
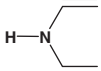
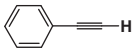
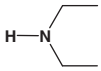
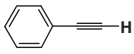
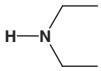
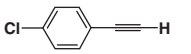
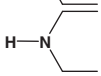
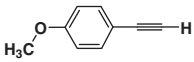
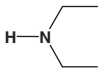
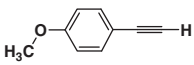
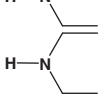
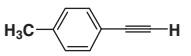
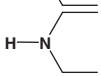
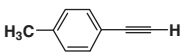
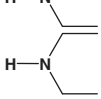
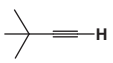
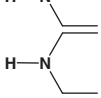
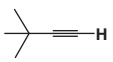
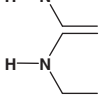
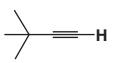
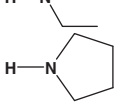
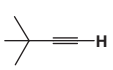
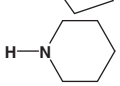
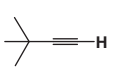
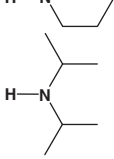
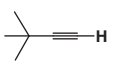
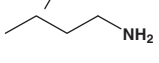
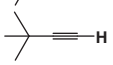
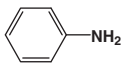
The substrate scope was investigated using the optimized conditions: alkyne (1.0 mmol), benzal halide (1.5 mmol), amine (2.0 mmol) and Et_3N (100 mol %) in CH_3CN at room temperature (Table 2). Firstly, it was found that both benzal bromide and benzal chloride worked well for this three-component coupling reaction (Table 2, entries 1 and 13). However, the reaction temperature for benzal chloride had to be elevated to 80 °C. DABCO was found to be a better base for benzal chloride reactions (Table 2, entries 12 and 13).

The reaction worked well for alkyl-substituted alkynes, giving good to excellent yields of propargylic amines (Table 2, entries 1–3). However, aromatic alkynes were generally less active in this new AHA coupling reaction affording the corresponding propargyl amines in lower yields 22–60% (Table 2, entries 4, 7, 8 and 10). This is because aromatic alkynes are more likely to dimerize than alkyl-substituted alkynes under these conditions.[16,17] As shown in Table 2, electron-donating aromatic alkynes were more reactive in this reaction. Yields of 61% and 70% were achieved for 4-methoxyphenylacetylene and 4-methylphenylacetylene, respectively, under the optimized conditions (Table 2, entries 9 and 11). In contrast, electron-withdrawing aromatic alkynes were relatively inert. Coupling reactions of phenylacetylene with either benzal bromide or benzal chloride resulted in unsatisfactory yields of the corresponding propargylic amines (Table 2, entries 4 and 6). However, a stepwise reaction in which benzal bromide (1.5 mmol), diethylamine (2.0 mmol) and Et_3N (100 mol %) were stirred for 2 h at room temperature followed by the addition of phenylacetylene (1.0 mmol), copper(I) chloride (10 mol %) and acetonitrile (2 ml), improved the yield of the propargylic amine from 22% to 50% (Table 2, entry 5).

The reaction worked well for both cyclic and non-cyclic secondary amines while no product was observed for primary amines (Table 2). There was no reaction for bulky amines, such as diisopropylamine and aniline, probably due to the extra steric hindrance.

Table 2
Substrate scope[a]



Entry	Alkyne (A^1)	X	Amine (A^2)	Yield (%)
1		Br		95
2		Br		76
3		Br		74
4		Br		22
5		Br		50[b]
6		Cl		25[c]
7		Br		60
8		Br		50
9		Cl		61[c]
10		Br		32
11		Cl		70[c]
12		Cl		45
13		Cl		93[c]
14		Br		80
15		Br		81
16		Br		0
17		Br		0
18		Br		0

[a] Unless otherwise noted, the reaction conditions are as follows: alkyne (1.0 mmol), benzal halide (1.5 mmol), amine (2.0 mmol), Et_3N (100 mol %), CH_3CN (2 ml), CuCl (10 mol %), rt 36 h.
[b] Stepwise reaction: benzal bromide (1.5 mmol), diethylamine (2.0 mmol) and Et_3N (100 mol %) were mixed and stirred for 2 h at rt followed by the addition of phenylacetylene (1.0 mmol), copper(I) chloride (10 mol %) and acetonitrile (2 ml).
[c] Reaction at 80 °C with DABCO as the base.

To summarize, the efficient copper(I)-catalyzed three-component coupling reaction of alkynes, benzal dihalides and amines through C–H and C-halogen activation to form propargylic amines under mild conditions has been explored. These reactions offer an alternative procedure for the synthesis of propargylic amines.

Typical procedure for the production of propargyl amines (Table 2, entry 1)

A mixture of *tert*-butylacetylene (1.0 mmol, 82 mg), benzal bromide (1.5 mmol, 250 mg), diethylamine (2.0 mmol, 146 mg), Et_3N (1.0 mmol, 101 mg) and CuCl (10.0 mg, 10.0 mol %) were loaded in a sealed reaction vial (10 mL) with 2 mL of CH_3CN. After stirring at room temperature for 36 h, the reaction mixture was diluted with H_2O (20 mL), extracted with Et_2O (2×10 mL), dried over Na_2SO_4 and concentrated to give the crude product which was further purified by column chromatography on silica gel (CH_2Cl_2) to afford the corresponding propargyl amine. All products gave satisfactory spectroscopic data.

N,N-Diethyl-4,4-dimethyl-1-phenylpent-2-yn-1-amine (1B)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.6 Hz, 2H, Ar-H), 7.32 (t, J = 7.6 Hz, 2H, Ar-H), 7.24 (t, J = 7.6 Hz, 1H, Ar-H), 4.78 (s, 1H, CH), 2.48–2.55 (m, 2H, CH_2), 2.37–2.45 (m, 2H, CH_2), 1.30 (s, 9H, CH_3), 1.03 (t, J = 6.8 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.61, 128.36, 127.81, 126.92, 96.31, 74.05, 56.21, 44.32, 31.44, 27.67, 13.57; GC–MS: *m*/*z*: 243; HRMS (ESI) calcd for $C_{17}H_{26}N_1$ (M+H)$^+$: 244.2060, found 244.2065.

N,N-Diethyl-1-phenylhept-2-yn-1-amine (2B)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.2 Hz, 2H, Ar-H), 7.32 (t, J = 7.2 Hz, 2H, Ar-H), 7.25 (t, J = 7.2 Hz, 1H, Ar-H), 4.80 (s, 1H, CH), 2.49–2.59 (m, 2H, CH_2), 2.39–2.47 (m, 2H, CH_2), 2.32 (dt, J = 7.2 Hz, J = 2.0 Hz, 2H, CH_2), 1.52–1.60 (m, 2H, CH_2), 1.43–1.50 (m, 2H, CH_2), 1.03 (t, J = 7.2 Hz, 6H, CH_3), 0.94 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.51, 128.37, 127.86, 126.99, 87.48, 75.88, 56.42, 44.38, 31.25, 22.02, 18.50, 13.67; GC–MS: *m*/*z*: 243; HRMS (ESI) calcd for $C_{17}H_{26}N_1$ (M+H)$^+$: 244.2060, found 244.2064.

7-(Diethylamino)-7-phenylhept-5-ynenitrile (3B)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 7.2 Hz, 2H, Ar-H), 7.33 (t, J = 7.2 Hz, 2H, Ar-H), 7.26 (t, J = 7.2 Hz, 1H, Ar-H), 4.81 (s, 1H, CH), 2.50–2.58 (m, 6H, CH_2), 2.37–2.45 (m, 2H, CH_2), 1.93(q, J = 6.8 Hz, 2H, CH_2), 1.03 (t, J = 7.2 Hz, 6H, CH_3) ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.91, 128.20, 128.01, 127.23, 119.24, 84.30, 78.34, 56.41, 44.45, 24.96, 18.00, 16.25, 13.53, GC–MS: *m*/*z*: 254; HRMS (EI) calcd for $C_{17}H_{22}N_2$ (M+H)$^+$: 254.1783, found 254.1792.

N,N-Diethyl-1,3-diphenylprop-2-yn-1-amine (4B)[18]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.10 (m, 2H, Ar-H), 7.50–7.53 (m, 2H, Ar-H), 7.28–7.38 (m, 6H, Ar-H), 5.06 (s, 1H, CH), 2.60–2.69 (m, 2H, CH_2), 2.51–2.59 (m, 2H, CH_2), 1.09 (t, J = 7.2 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.85, 131.77, 128.34, 128.27, 128.27, 128.01, 127.22, 123.36, 87.40, 86.07, 56.92, 44.52, 13.56; GC–MS: *m*/*z*: 263.

3-(4-Chlorophenyl)-*N,N*-diethyl-1-phenylprop-2-yn-1-amine (7B)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 7.6 Hz, 2H, Ar-H), 7.43 (d, J = 7.6 Hz, 2H, Ar-H), 7.36 (t, J = 7.6 Hz, 2H, Ar-H), 7.27–7.31 (m, 3H, Ar-H), 5.04 (s, 1H, CH), 2.59–2.68 (m, 2H, CH_2), 2.48–2.57 (m, 2H, CH_2), 1.08 (t, J = 7.2 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.49, 133.93, 132.97, 128.56, 128.26, 128.04, 127.30, 121.76, 87.15, 86.27, 56.88, 44.46, 13.48; GC–MS: *m*/*z*: 297; HRMS (EI) calcd for $C_{19}H_{20}Cl_1N_1$ (M)$^+$: 297.1284, found 297.1289.

N,N-Diethyl-3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-amine (8B)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.0 Hz, 2H, Ar-H), 7.45 (d, J = 8.0 Hz, 2H, Ar-H), 7.36 (t, J = 8.0 Hz, 2H, Ar-H), 7.28 (t, J = 8.0 Hz, 1H, Ar-H), 6.87 (d, J = 8.0 Hz, 2H, Ar-H), 5.05 (s, 1H, CH), 3.83 (s, 3H, CH_3), 2.59–2.68 (m, 2H, CH_2), 2.50–2.59 (m, 2H, CH_2), 1.08 (t, J = 7.2 Hz, 6H, CH_3) ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.38, 140.06, 133.17, 128.40, 128.01, 127.20, 115.54, 113.69, 87.20, 84.47, 56.97, 55.33, 44.53, 13.59; GC–MS: *m*/*z*: 293; HRMS (EI) calcd for $C_{20}H_{23}N_1O_1$ (M)$^+$: 293.1780, found 293.1788.

N,N-Diethyl-1-phenyl-3-*p*-tolylprop-2-yn-1-amine (10B)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 7.6 Hz, 2H, Ar-H), 7.40 (d, J = 7.6 Hz, 2H, Ar-H), 7.35 (t, J = 7.6 Hz, 2H, Ar-H), 7.28 (t, J = 7.6 Hz, 1H, Ar-H), 7.14 (d, J = 7.6 Hz, 2H, Ar-H), 5.05 (s, 1H, CH), 2.60–2.69 (m, 2H, CH_2), 2.50–2.59 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.08 (t, J = 7.2 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.11, 131.67, 129.04, 128.42, 128.03, 127.26, 120.26, 99.99, 87.57, 85.18, 56.97, 44.55, 21.49, 13.52; GC–MS: *m*/*z*: 277; HRMS (EI) calcd for $C_{20}H_{23}N_1$ (M)$^+$: 277.1830, found 277.1839.

1-(4,4-Dimethyl-1-phenylpent-2-ynyl)pyrrolidine (14B)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 7.2 Hz, 2H, Ar-H), 7.32 (t, J = 7.2 Hz, 2H, Ar-H), 7.26 (t, J = 7.2 Hz, 1H, Ar-H), 4.61 (s, 1H, CH), 2.57 (t, 4H, J = 6.8 Hz, CH_2), 1.75 (t, J = 6.8 Hz, 4H, CH_2), 1.27 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.15, 128.31, 128.08, 127.30, 95.77, 75.04, 58.49, 49.99, 31.34, 27.61, 23.44; GC–MS: *m*/*z*: 241; HRMS (EI) calcd for $C_{17}H_{23}N_1$ (M)$^+$: 241.1830, found 241.1832.

1-(4,4-Dimethyl-1-phenylpent-2-ynyl)piperidine (15B)[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, J = 7.6 Hz, 2H, Ar-H), 7.33 (t, J = 7.6 Hz, 2H, Ar-H), 7.26 (t, J = 7.6 Hz, 1H, Ar-H), 4.54 (s, 1H, CH), 2.43 (t, J = 6.0 Hz, 4H, CH_2), 1.56 (quin, J = 6.0 Hz, 4H, CH_2), 1.40 (quin, J = 6.0 Hz, 2H, CH_2), 1.30 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.29, 128.61, 127.89, 127.16, 96.82, 74.28, 61.73, 53.29, 31.55, 27.70, 26.21, 24.59; GC–MS: *m*/*z*: 255.

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Supplementary data

Supplementary data (analytical data and spectra (^{1}H and ^{13}C NMR) for all products and HRMS for new products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.099.

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