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Microwave-Assisted CuCl-Catalyzed Three-Component Reactions of Alkynes, Aldehydes, and Amino Alcohols

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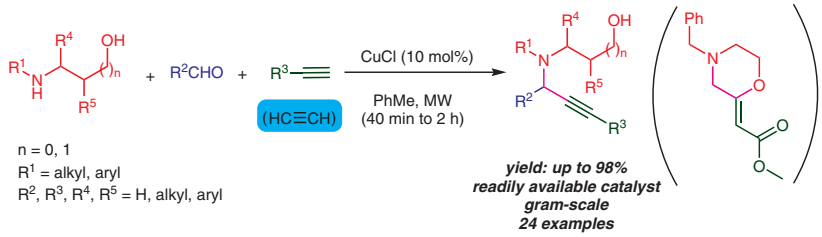


Received: 11.02.2019
Accepted after revision: 12.04.2019
Published online: 08.05.2019
DOI: 10.1055/s-0037-1611536; Art ID: ss-2019-h0080-op

Abstract A microwave (MW)-assisted three-component coupling of amino alcohols, aldehydes, and alkynes is developed under catalysis by CuCl. Compared with thermal conditions, MW irradiation greatly increases the reaction efficiency. The reactions of various primary *N*-alkyl/arylamino alcohols, aliphatic/aromatic aldehydes, and alkynes are systematically investigated, affording the desired products in moderate to good yields. Notably, acetylene is also an effective reactant under the current MW-assisted conditions.

Key words microwave-assisted, three-component reactions, propargylamino alcohols, Cu catalysis, A^3-coupling

Propargylamines are extremely useful in the construction of heterocycles and in pharmacological and pharmaceutical chemistry.[1] As their derivatives, propargylamino alcohols are building blocks for many biologically active compounds, such as the antifungal agent **I**,[2] the phosphodiesterase 7 (PDE7) inhibitor **II**,[3] and the inhibitor of lysine-specific demethylase 1 (LSD1) **III**[4] (Figure 1).

General methods for the synthesis of propargylamino alcohols have been developed: (i) direct alkylation of amino alcohols with propargyl halides,[5] (ii) ring-opening of oxiranes with propargyl amines,[6a,b] and (iii) reductive amination of alkynals and amino alcohols (Scheme 1a).[6c,d] The synthesis of propargylamines has recently gained significant attention in organic synthesis. Examples of traditional methods for the construction of propargylamines include reactions of allenes with amines,[7] imines or enamines with alkynes,[8] and propargyl esters with amines.[9] However, the most extensively employed strategy is the A^3-coupling,[10] a concise reaction developed by Li and co-workers, which involves the three-component condensation of amines, aldehydes, and alkynes (Scheme 1b).[11] A large number of metal catalysts, including Ni(II),[12] Fe(III),[11e,13] Zn(II),[14] Cu(I)/Cu(II),[15] Ru(III),[16] Ag(I),[11b,17] Au(I)/Au(III),[11a,h,18] Ir(I),[19] In(III)[20] and Hg(I)[21] are effective in activating the C–H bond of terminal alkynes to promote the A^3-coupling. Nevertheless, most reactions generally require several hours under thermal conditions. Recently, our group systematically studied the effects of microwaves in microwave-assisted organic synthesis.[22] Our latest results revealed that microwaves (MW) can promote some organic reactions efficiently, especially those with polar reactants in nonpolar solvents because polar reactants are heated and located in 'hot-spot' regions.[22a] We also provided direct evidence for localized superheating of polar reactants in nonpolar solvents.[22b] These effects were further identified and applied in the ring-expansion reactions of oxiranes and thiiranes

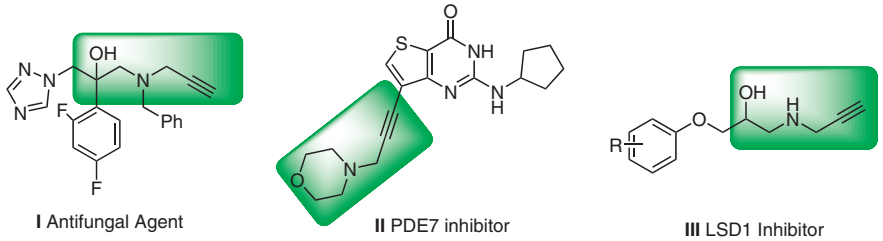
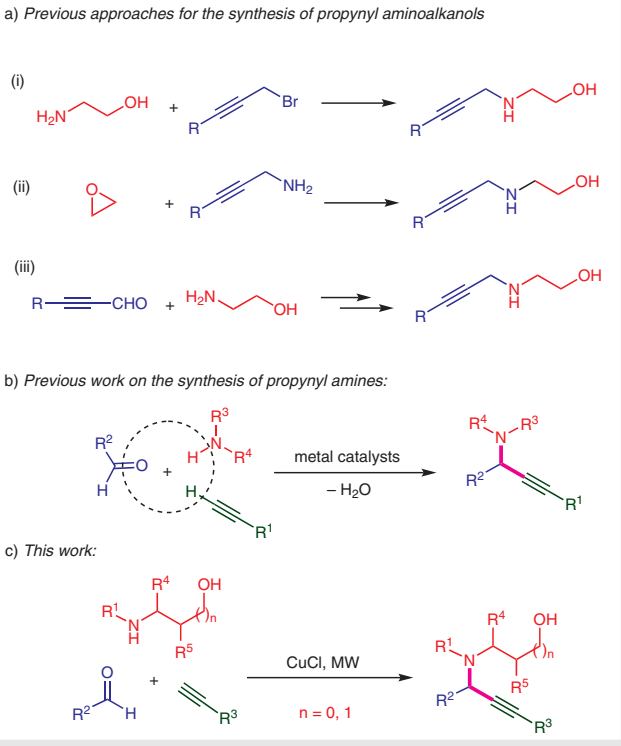


Figure 1 Bioactive molecules with propargyl amino alcohol units

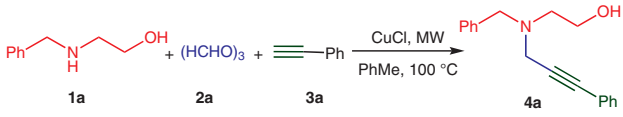
with diazo-β-dicarbonyl compounds.[23] In these transformations, highly polar reactants and weakly polar dichloroethane were used.[23] As is already known, in the A^3-coupling, both amines and aldehydes are highly polar molecules. Thus, we envisioned that microwave irradiation would be very effective for the reaction. Previously, microwave-assisted A^3-coupling was studied by Tu[24a] and Varma's groups,[24b] with freshly prepared CuI and CuBr, respectively, as the catalysts. Later, many reports explored the application of MW in the A^3-coupling of various substrates, such as primary amines,[25] propargylcarboxylic acid[26] and ethyl glyoxalate,[27] in the presence of diverse catalysts, including gold,[28] a graphene oxide supported Cu(II) catalyst,[29] a silver-complex catalyst[30]/silver nanoparticles,[31] and a Cu complex (Scheme 1b).[32] However, to our best knowledge, the three-component condensation of alkynes, aldehydes and amino alcohols has not been explored to date. Herein, we describe an efficient MW-assisted process for the synthesis of propargylic amino alcohols catalyzed by commercially inexpensive CuCl (Scheme 1c).



Scheme 1 Synthesis of propargylic amino alcohols

Our initial work began with 2-(benzylamino)ethanol (**1a**), triformol (**2a**) and phenylacetylene (**3a**) under the catalysis of CuCl (Table 1). CuCl was used directly without any further activation. Following systematic optimizations, the CuCl-catalyzed reaction of **1a**, **2a** and **3a** in toluene at 100 °C for 22 hours (1320 min) gave propargylamino alcohol **4a** in an isolated yield of 84% (Table 1, entry 1). The ratio of aldehyde/amine/acetylene was 1:1.1:1.5 under thermal conditions because amine **1a** acted as both reactant and base in the reaction. The loading of phenylacetylene (**3a**) was increased to 1.5 equivalents with respect to **1a** because formation of a side product from self-coupling of phenylacetylene (the Glaser–Hay coupling)[33] was unavoidable under thermal conditions.[34] The yield dropped to less than 30% when we tested the MW-assisted reaction over 30 minutes (Table 1, entry 2). A significant amount of solid triformol (**2a**) in toluene was recovered, demonstrating that the dissociation of triformol (**2a**) was relatively slow under the current conditions. We hence increased the loading of **2a** to 2 equivalents and the yield of **4a** was dramatically improved to 60% (Table 1, entry 3). Various solvents, including CH_2Cl_2, DCE, EtOH, MeCN and THF, were screened but all gave poor yields (<14%) (Table 1, entry 4). These results demonstrated again that the superheating effect played a crucial role in the reaction involving polar reactants in a nonpolar solvent (toluene).[22] Subsequently, various other Cu(I) and Cu(II) catalysts were evaluated (Table 1, entry 5), but they showed lower catalytic efficiency than CuCl (Table 1, entry 3). In order to prohibit the Glaser–Hay coupling, the

Table 1 Optimization of the Reaction Conditions[a]



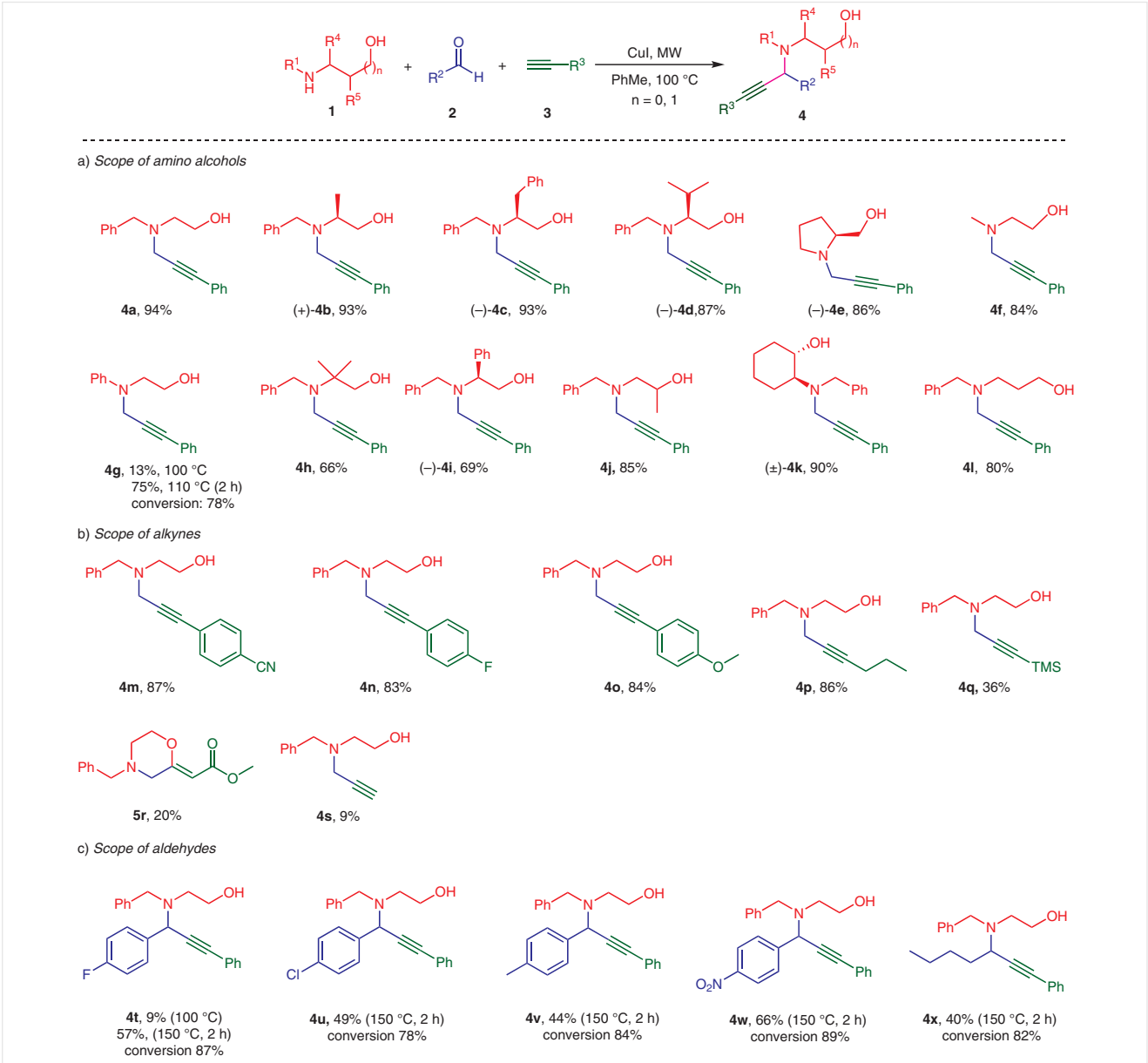
1a 2a 3a 4a

Entry	1a:2a:3a	Conditions	Time (min)	Yield (%)[b]
1	1.1:1:1.5	oil-bath/air	1320 (22 h)	84
2	1.1:1:1.5	MW/air	10–40	<30
3	1:2:1.5	MW/air	10	60
4[c]	1:2:1.5	MW/air	10	<14
5[d]	1:2:1.5	MW/air	10	<58
6	1:2:1.5	MW/N_2	10	76
7	1:2:1.5	MW/N_2	20	79
8	1:2:1.5	MW/N_2	30	91
9	**1:2:1.5**	**MW/N_2**	**40**	**94**
10	1:2:1.5	MW/N_2	60	90
11[e]	1:2:1.5	MW/N_2	40	86
12[f]	1:2:1.5	MW/N_2	40	80

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), **3a** (0.45 mmol) and CuCl (0.03 mmol) in PhMe (2 mL) were stirred under MW irradiation at 100 °C.
[b] Yield of isolated product.
[c] Various solvents, including CH_2Cl_2 (40 °C; 0%), DCE (80 °C; 13%), EtOH (80 °C; 10%), MeCN (80 °C; 14%) and THF (70 °C; trace), were screened under MW irradiation for 10 min (percentages in brackets are reaction yields).
[d] Various copper catalysts, including CuO (4%), $CuCl_2$ (17%), $CuSO_4·5H_2O$ (17%), CuBr (58%), CuI (22%) and CuOTf·0.5PhH (29%), were evaluated under MW irradiation over 10 min (percentages in brackets are reaction yields).
[e] *p*-Xylene was used instead of toluene.
[f] Chlorobenzene was used instead of toluene.

reaction was conducted under a nitrogen atmosphere and the yield was further improved to 76% (Table 1, entry 6). The reaction time was also optimized (Table 1, entries 6–10). The highest yield of the A^3-coupling was obtained after 40 minutes (entry 9). Besides toluene, we also performed the reaction in high-boiling-point *p*-xylene and chlorobenzene, as non- and weakly polar solvents, respectively. Not surprisingly, both solvents gave good yields (entries 11 and 12), albeit slightly lower than that obtained in toluene.

With optimized conditions in hand (Table 1, entry 9), we next studied the scope of various amino alcohols **1**, aldehydes **2** and alkynes **3** (Scheme 2). To extend the generality of the current transformation, a series of *N*-alkylamino alcohols was investigated in couplings with triformol (**2a**) and phenylacetylene (**3a**). First, a variety of amino alcohols **1**, derived from naturally occurring amino acids, including glycine, alanine, phenylalanine, valine, and proline, was investigated. In all these cases the desired products were isolated in good to excellent yields (Scheme 2a, products **4a–g**). Amino alcohols **1a–l** are all secondary amines. When



Scheme 2 Scope of the reaction. Unless otherwise stated, the reaction conditions are as follows: **1a** (0.3 mmol), **2a** (0.6 mmol), **3a** (0.45 mmol), CuCl (0.03 mmol), PhMe (2.0 mL), MW, 100 °C, 40 min. Yields of isolated products are given.

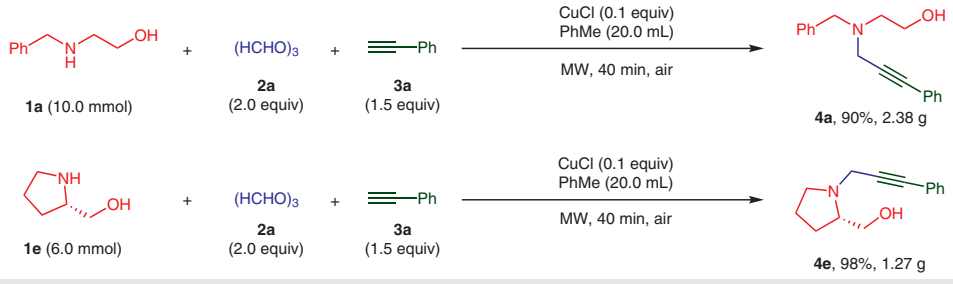
glycinol, a primary amine, was used, the reaction did not proceed under the optimized conditions. The reaction efficiency was slightly affected by the steric hindrance of the substrates. Compared with those of **4a–c**, the yield of **4d** was somewhat lower, while that of **4h**, derived from 2,2-dimethylglycinol, was reduced to 66%. The transformation of *N*-phenylglycinol (**1g**) (13%) was obviously worse than that of **1c** (93%), indicating that the nucleophilicity of the nitrogen atom dramatically controls the reactivity. After a brief optimization, **4g** was obtained in 75% yield by performing the reaction in a sealed tube, raising the temperature to 110 °C and extending the reaction time to 2 hours. Reactions with other unnatural amino alcohols were then attempted to give products **4h–l**. Except for **4h** (66%) and **4i** (69%), in which the nitrogen atoms were sterically hindered by the adjacent substituents, the rest gave the corresponding products **4k–l** in excellent yields. Moreover, it is worth mentioning that, besides **4b**, the other optically active products are levorotatory (**4c–e**,**i**) (Scheme 2a and experimental data).

Next, we examined a range of alkynes (Scheme 2b). Three arylacetylenes bearing various functional groups, including electron-withdrawing cyano (**4m**) and fluoro (**4n**) and electron-donating methxoy at the *para* position of the phenyl group, were reacted with *N*-benzylglycinol (**1a**) and triformol (**2a**) under the optimized conditions, with all of them giving excellent yields. The results also demonstrated that the electronic effects showed limited influence on the alkyne moiety. Moreover, the aliphatic terminal alkyne pent-1-yne also gave the corresponding product **4p** in an excellent yield. Notably, the reaction efficiency was hampered when trimethylsilylacetylene was examined (**4q**). Interestingly, when methyl propiolate was used, a six-membered morpholine product (**5r**) was obtained, albeit with a relatively low yield. These results demonstrated that the lower the nucleophilicity of the alkyne, the less reactive the A^3-coupling. In this protocol, the A^3-coupling occurred first, followed by an intramolecular Michael addition of the alcohol to the propiolate.[35] As a widely used fuel and welding gas, acetylene is also a prevalent chemical feedstock. The reaction of acetylene, produced from calcium carbide (CaC_2) and water, was examined as well. During the manipulation, the reaction vial (10 mL) was charged with acetylene gas (~0.45 mmol = 10 mL/22.4 L) to react with 2-(benzylamino)ethanol (**1a**) (0.3 mmol) and triformol (**2a**) (0.6 mmol), affording 5.0 mg of isolated **4s** (9% yield), probably due to the low solubility of acetylene at high temperature.

To evaluate the scope of the aldehydes, four aromatic (**2t–w**) and one aliphatic aldehyde (**2x**) were explored in reactions with *N*-benzylglycinol (**1a**) and phenylacetylene (**3a**) (Scheme 2c). As is generally known, formaldehyde was the most reactive aldehyde. Just as we anticipated the reactivity of aromatic aldehydes was relatively low. After several modifications, only moderate yields of products **4t–w** were obtained, even after raising the temperature to 150 °C and prolonging the reaction time to 2 hours. In these reactions, both electron-withdrawing groups, such as fluoro (**4t**), chloro (**4u**) and nitro (**4w**), and an electron-donating methyl (**4v**) group, showed similar reactivity. Notably, all the above reactions gave good conversions. Taking **4t** as an example, 35% of *N*-benzylglycinol (**1a**) was recovered, and the conversion of **1a** into **4t** was approximately 87%. Pentanal, a representative aliphatic aldehyde, was also investigated, affording product **4x** with a similar yield and conversion.

Finally, the reactions of two secondary amino alcohols, **1a** and **1e**, were scaled up to assess the reaction utility (Scheme 3). Gratifyingly, the scale-up reactions could be carried out under air without using strict anhydrous solutions, with both giving excellent yields of the corresponding products **4a** and **4e**.

In summary, the A^3-coupling of amino alcohols, aldehydes, and alkynes has been studied in the presence of CuCl under microwave-assisted conditions. Compared with oil-bath thermal conditions which required 22 hours, microwave irradiation promoted the reaction and shortened the reaction time to only 40 minutes. The present results demonstrate that microwave irradiation accelerates the reaction through selectively heating highly polar reactants in a non-polar solvent. Moreover, *N*-alkylamino alcohols gave better reaction efficiencies than *N*-arylated examples. Both aliphatic terminal alkynes and arylacetylenes showed good reactivities, however, methyl propiolate gave rise to a cyclized morpholine derivative. Furthermore, acetylene underwent the A^3-coupling, albeit with low reactivity. Finally, both aliphatic and aromatic aldehydes gave the desired products in moderate yields but required harsh conditions.



Scheme 3 Gram-scale experiments for the synthesis of **4a** and **4e**

Microwave-assisted reactions were carried out using a CEM Discover SP microwave reactor equipped with an infrared temperature detector. Unless otherwise noted, all materials were purchased from commercial suppliers. Reactions were monitored by thin-layer chromatography (TLC) on silica gel GF254 coated 0.2 mm plates (obtained from the Institute of the Yantai Chemical Industry). Column chromatography was performed using Qingdao Haiyang Chemical Ltd. silica gel (200–300). Melting points were recorded on a Yanaco MP-500 melting point apparatus without correction. Specific rotations were recorded using an Andon Paar MCP-200 Modular Circular Polarimeter. IR spectra (KBr pellets, cm^{-1}) were measured on a Nicolet 5700 FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker 400 MHz spectrometer, with TMS as an internal standard; chemical shifts (δ) are reported in parts per million (ppm). All coupling constants (*J*) in the ^1H NMR spectra are absolute values given in hertz (Hz), with peaks labeled as singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), quintet (quin), and multiplet (m). HRMS measurements were recorded on an Agilent LC/MSD TOF mass spectrometer.

Three-Component Coupling; General Procedure

Under a nitrogen atmosphere, amino alcohol **1** (0.3 mmol), aldehyde **2** (0.6 mmol), alkyne **3** (0.45 mmol) and CuCl (3 mg, 0.03 mol) were mixed in toluene (2.0 mL) in a microwave vial. The reaction system was heated at 100 °C for 40 min or 2 h under MW irradiation. The reaction mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with brine (3 × 5 mL) and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel eluting with EtOAc/hexane (1:50 to 1:20).

2-[Benzyl(3-phenylprop-2-yn-1-yl)amino]ethan-1-ol (4a)

Yield: 75 mg (94%); yellow oil; R_f = 0.37 (hexanes/EtOAc = 1:1, v/v).

IR (KBr): 3439, 3060, 2925, 1489, 1362 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.17 (m, 10 H), 3.67 (s, 2 H), 3.58 (t, *J* = 4.8 Hz, 2 H), 3.45 (s, 2 H), 2.75 (t, *J* = 5.2 Hz, 2 H), 2.64 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.1, 131.6, 129.1, 128.4, 128.2, 128.1, 127.3, 123.0, 85.7, 83.8, 58.5, 57.6, 55.0, 42.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO$: 266.1539; found: 266.1544.

(*S*)-2-[Benzyl(3-phenylprop-2-yn-1-yl)amino]propan-1-ol (4b)

Yield: 78 mg (93%); yellow oil; R_f = 0.42 (hexanes/EtOAc = 5:1, v/v); $[\alpha]_D^{20}$ +64.9 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3435, 3061, 2922, 1489, 1408 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.01 (m, 10 H), 3.82 (d, *J* = 13.2 Hz, 1 H), 3.57 (d, *J* = 13.2 Hz, 1 H), 3.49–3.34 (m, 4 H), 3.17–3.06 (m, 1 H), 3.04 (br s, 1 H), 1.08 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.6, 131.5, 129.0, 128.4, 128.2, 128.0, 127.2, 123.0, 86.2, 85.0, 63.2, 58.3, 52.1, 39.8, 11.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO$: 280.1696; found: 280.1700.

(*S*)-2-[Benzyl(3-phenylprop-2-yn-1-yl)amino]-3-phenylpropan-1-ol (4c)

Yield: 98 mg (93%); yellow oil; R_f = 0.51 (hexanes/EtOAc = 5:1, v/v); $[\alpha]_D^{20}$ –19.21 (*c* 1.6, CH_2Cl_2).

IR (KBr): 3446, 3061, 2928, 1600, 1490, 1408 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.07 (m, 15 H), 4.11 (d, *J* = 13.2 Hz, 1 H), 3.85 (d, *J* = 13.2 Hz, 1 H), 3.70 (s, 2 H), 3.62–3.55 (m, 2 H), 3.46 (dd, *J* = 13.2, 4.0 Hz, 1 H), 3.38 (m, 1 H), 3.10 (br s, 1 H), 2.61 (dd, *J* = 12.8, 10.0 Hz, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 139.2, 138.4, 131.5, 129.01, 128.98, 128.5 (2 C), 128.3, 128.2, 127.4, 126.2, 123.0, 86.0, 85.4, 65.2, 60.6, 52.7, 40.0, 33.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{26}NO$: 356.2009; found: 356.2013.

(*S*)-2-[Benzyl(3-phenylprop-2-yn-1-yl)amino]-3-methylbutan-1-ol (4d)

Yield: 80 mg (87%); yellow oil; R_f = 0.57 (hexanes/EtOAc = 5:1, v/v); $[\alpha]_D^{20}$ –27.05 (*c* 2.0, CH_2Cl_2).

IR (KBr): 3465, 3060, 2926, 1489, 1363 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.14 (m, 10 H), 4.00 (d, *J* = 13.2 Hz, 1 H), 3.83 (d, *J* = 13.2 Hz, 1 H), 3.70 (dd, *J* = 11.2, 4.0 Hz, 1 H), 3.53 (s, 2 H), 3.49 (dd, *J* = 10.8, 8.8 Hz, 1 H), 2.90 (br s, 1 H), 2.65 (dt, *J* = 8.4, 4.4 Hz, 1 H), 2.06–1.97 (m, 1 H), 1.06 (d, *J* = 6.4 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 139.2, 131.6, 128.9, 128.4, 128.3, 128.1, 127.2, 123.0, 86.6, 84.8, 69.3, 59.9, 55.3, 38.8, 28.1, 22.3, 19.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{26}NO$: 308.2009; found: 308.2010.

(*S*)-[1-(3-Phenylprop-2-yn-1-yl)pyrrolidin-2-yl]methanol (4e)

Yield: 56 mg (86%); yellow oil; R_f = 0.20 (CH_2Cl_2/MeOH = 25:1, v/v); $[\alpha]_D^{20}$ –23.76 (*c* 1.8, CH_2Cl_2).

IR (KBr): 3403, 3059, 2923, 1489, 1327 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.39 (m, 2 H), 7.33–7.27 (m, 3 H), 3.74 (d, *J* = 17.2 Hz, 1 H), 3.70 (dd, *J* = 11.2, 3.6 Hz, 1 H), 3.65 (d, *J* = 17.2 Hz, 1 H), 3.46 (dd, *J* = 10.8, 3.2 Hz 1 H), 3.12–3.07 (m, 1 H), 2.95–2.91 (m, 1 H), 2.80–2.74 (m, 1 H), 2.43 (br s, 1 H), 1.98–1.67 (m, 4 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 131.7, 128.2, 128.1, 123.0, 84.9, 84.8, 62.1, 61.9, 53.5, 41.8, 27.8, 23.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO$: 216.1383; found: 216.1382.

2-[Methyl(3-phenylprop-2-yn-1-yl)amino]ethan-1-ol (4f)

Yield: 48 mg (84%); yellow oil; R_f = 0.15 (hexanes/EtOAc = 1:1, v/v).

IR (KBr): 3390, 2945, 1489, 1463, 1362 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.26 (m, 2 H), 7.22 (m, 3 H), 3.57 (t, *J* = 5.2 Hz, 2 H), 3.52 (s, 2 H), 2.92 (br s, 1 H), 2.61 (t, *J* = 5.6 Hz, 2 H), 2.33 (s, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 131.6, 128.2, 128.0, 122.9, 85.5, 83.9, 58.6, 57.2, 46.5, 41.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO$: 190.1226; found: 190.1234.

2-[Phenyl(3-phenylprop-2-yn-1-yl)amino]ethan-1-ol (4g)

Yield: 56 mg (75%); yellow oil; R_f = 0.23 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3417, 2954, 1598, 1504, 1378 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.29 (m, 2 H), 7.22–7.16 (m, 5 H), 6.90–6.88 (m, 2 H), 6.77–6.73 (m, 1 H), 4.19 (s, 2 H), 3.78 (q, *J* = 5.6 Hz, 2 H), 3.53 (t, *J* = 5.5 Hz, 2 H), 2.03 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 148.5, 131.7, 129.2, 128.3, 128.2, 122.6, 118.6, 114.6, 85.3, 84.4, 60.1, 53.8, 41.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}NO$: 252.1383; found: 252.1388.

2-[Benzyl(3-phenylprop-2-yn-1-yl)amino]-2-methylpropan-1-ol (4h)

Yield: 58 mg (66%); white solid; mp 74–75 °C; R_f = 0.57 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3452, 3028, 2923, 1598, 1405 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.17 (m, 10 H), 3.77 (s, 2 H), 3.46 (s, 2 H), 3.38 (s, 2 H), 2.98 (br s, 1 H), 1.26 (s, 6 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 139.3, 131.4, 129.1, 128.5, 128.3, 128.0, 127.2, 123.3, 87.0, 85.0, 68.2, 58.7, 50.1, 36.4, 22.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{24}NO$: 294.1852; found: 294.1856.

(*S*)-2-[Benzyl(3-phenylprop-2-yn-1-yl)amino]-2-phenylethan-1-ol (4i)

Yield: 70 mg (69%); yellow solid; mp 94–95 °C; R_f = 0.49 (hexanes/EtOAc = 5:1, v/v); $[\alpha]_D^{20}$ –1.50 (*c* 1.1, CH_2Cl_2).

IR (KBr): 3474, 3060, 2926, 1598, 1490, 1441 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.15 (m, 15 H), 4.10–3.91 (m, 2 H), 3.87–3.75 (m, 1 H), 3.79 (d, *J* = 13.6 Hz, 1 H), 3.54 (d, *J* = 17.2 Hz, 1 H), 3.41 (d, *J* = 13.2 Hz, 1 H), 3.31 (d, *J* = 17.6 Hz, 1 H), 2.39 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.6, 138.0, 131.7, 128.9, 128.8, 128.5, 128.4, 128.2, 128.0, 127.9, 127.2, 123.1, 85.6, 84.8, 66.4, 62.6, 54.3, 39.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{24}NO$: 342.1852; found: 342.1859.

1-[Benzyl(3-phenylprop-2-yn-1-yl)amino]propan-2-ol (4j)

Yield: 71 mg (85%); yellow oil; R_f = 0.41 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3436, 3061, 2929, 1489, 1406 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.15 (m, 10 H), 3.89–3.78 (m, 1 H), 3.78 (d, *J* = 13.2 Hz, 1 H), 3.58 (d, *J* = 12.8 Hz, 1 H), 3.49 (d, *J* = 17.6 Hz, 1 H), 3.39 (d, *J* = 17.6 Hz, 1 H), 3.26 (br s, 1 H), 2.70 (dd, *J* = 12.4, 3.2 Hz, 1 H), 2.33 (dd, *J* = 12.8, 10.4 Hz, 1 H), 1.08 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.0, 131.7, 129.1, 128.4, 128.2, 128.1, 127.4, 123.0, 85.7, 83.8, 63.1, 61.4, 57.8, 42.4, 19.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO$: 280.1696; found: 280.1699.

***trans*-2-[Benzyl(3-phenylprop-2-yn-1-yl)amino]cyclohexan-1-ol (4k)**

Yield: 88 mg (90%); yellow oil; R_f = 0.44 (hexanes/EtOAc = 10:1, v/v).

IR (KBr): 3467, 2930, 2363, 1597, 1489, 1063, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–7.06 (m, 10 H), 4.03 (d, *J* = 13.2 Hz, 1 H), 3.88 (br s, 1 H), 3.71 (d, *J* = 13.2 Hz, 1 H), 3.61 (d, *J* = 17.6 Hz, 1 H), 3.53 (d, *J* = 17.2 Hz, 1 H), 3.63–3.51 (m, 1 H), 2.66 (td, *J* = 12.8, 3.2 Hz, 1 H), 2.32–2.12 (m, 2 H), 1.89–1.62 (m, 2 H), 1.53–1.21 (m, 4 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.7, 131.5, 129.0, 128.4, 128.3, 128.0, 127.3, 123.2, 86.7, 85.0, 69.5, 68.8, 52.7, 40.3, 33.3, 25.7, 24.7, 24.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{26}NO$: 320.2009; found: 320.2013.

3-[Benzyl(3-phenylprop-2-yn-1-yl)amino]propan-1-ol (4l)

Yield: 67 mg (80%); yellow oil; R_f = 0.16 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3363, 2926, 1489, 1453, 1326 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.42 (m, 2 H), 7.41–7.12 (m, 8 H), 4.62 (br s, 1 H), 3.80 (t, *J* = 5.2 Hz, 2 H), 3.73 (s, 2 H), 3.57 (s, 2 H), 2.88 (t, *J* = 6.0 Hz, 2 H), 1.78 (quin, *J* = 5.6 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 137.7, 131.7, 129.2, 128.5, 128.2, 128.1, 127.4, 123.0, 86.1, 83.3, 64.1, 58.1, 53.4, 41.9, 27.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO$: 280.1696; found: 280.1702.

4-{3-[Benzyl(2-hydroxyethyl)amino]prop-1-yn-1-yl}benzonitrile (4m)

Yield: 76 mg (87%); yellow solid; mp 70–71 °C; R_f = 0.35 (hexanes/EtOAc = 1:1, v/v).

IR (KBr): 3480, 2923, 2227, 1604, 1499, 1363 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.4 Hz, 2 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.43–7.30 (m, 5 H), 3.78 (s, 2 H), 3.71 (t, *J* = 5.2 Hz, 2 H), 3.61 (s, 2 H), 2.88 (t, *J* = 5.2 Hz, 2 H), 2.62 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 137.8, 132.2, 132.0, 129.1, 128.5, 127.9, 127.5, 118.4, 111.5, 89.0, 84.3, 58.6, 57.8, 55.1, 42.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_2O$: 291.1492; found: 291.1495.

2-{Benzyl[3-(4-fluorophenyl)prop-2-yn-1-yl]amino}ethan-1-ol (4n)

Yield: 70 mg (83%); yellow oil; R_f = 0.59 (hexanes/EtOAc = 1:1, v/v).

IR (KBr): 3428, 2925, 1601, 1506, 1327, 1220 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.22 (m, 7 H), 7.05 (t, *J* = 8.8 Hz, 2 H), 3.79 (s, 2 H), 3.71 (t, *J* = 5.2 Hz, 2 H), 3.57 (s, 2 H), 2.89 (t, *J* = 5.6 Hz, 2 H), 2.67 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 162.4 (d, *J* = 247.8 Hz), 138.1, 133.6 (d, *J* = 8.3 Hz), 129.1, 128.5, 127.4, 119.1, 115.6 (d, *J* = 21.9 Hz), 84.7, 83.6, 58.5, 57.7, 55.0, 42.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}FNO$: 284.1445; found: 284.1451.

2-{Benzyl[3-(4-methoxyphenyl)prop-2-yn-1-yl]amino}ethan-1-ol (4o)

Yield: 74 mg (84%); yellow oil; R_f= 0.15 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3432, 2932, 2836, 1606, 1508, 1327 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.25 (m, 7 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H), 3.79 (s, 2 H), 3.71 (t, *J* = 5.2 Hz, 2 H), 3.57 (s, 2 H), 2.89 (t, *J* = 5.2 Hz, 2 H), 2.67 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 159.5, 138.2, 133.1, 129.2, 128.4, 127.4, 115.1, 113.9, 85.6, 82.3, 58.5, 57.7, 55.3, 54.9, 42.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_2$: 296.1645; found: 296.1646.

2-[Benzyl(hex-2-yn-1-yl)amino]ethan-1-ol (4p)

Yield: 59 mg (86%); colorless oil; R_f = 0.25 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3415, 2959, 2926, 1451, 738, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 5 H), 3.68 (s, 2 H), 3.62 (t, *J* = 5.4 Hz, 2 H), 3.30 (t, *J* = 2.2 Hz, 2 H), 2.76 (t, *J* = 5.4 Hz, 2 H), 2.67 (br s, 1 H), 2.21 (t, *J* = 7.2, 2.2 Hz, 2 H), 1.56 (sext, *J* = 7.2 Hz, 2 H), 1.02 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.3, 129.1, 128.3, 127.2, 85.7, 74.1, 58.4, 57.5, 54.7, 41.6, 22.4, 20.7, 13.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}NO$: 232.1696; found: 232.1700.

2-{Benzyl[3-(trimethylsilyl)prop-2-yn-1-yl]amino}ethan-1-ol (4q)

Yield: 28 mg (36%); yellow oil; R_f = 0.35 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3402, 2955, 2163, 1457, 1249, 843 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.02 (m, 5 H), 3.48 (s, 2 H), 3.43 (t, *J* = 5.6 Hz, 2 H), 3.12 (s, 2 H), 2.57 (t, *J* = 5.2 Hz, 2 H), 2.44 (br s, 1 H), 0.00 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.0, 129.2, 128.4, 127.4, 100.3, 90.6, 58.4, 57.4, 54.9, 42.3, 0.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{24}NOSi$: 262.1622; found: 262.1627.

Methyl 2-(4-Benzylmorpholin-2-ylidene)acetate (5r)

Yield: 28 mg (20%); yellow oil; R_f = 0.12 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3435, 2923, 1721, 1644, 1208, 1063 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–6.94 (m, 5 H), 4.87 (s, 1 H), 4.21 (t, *J* = 5.2 Hz, 2 H), 3.65 (s, 3 H), 3.53 (s, 2 H), 3.10 (s, 2 H), 2.65 (t, *J* = 5.2 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.6, 163.3, 136.6, 128.9, 128.4, 127.5, 95.7, 68.0, 62.5, 55.1, 50.8, 50.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_3$: 248.1281; found: 248.1288.

2-[Benzyl(prop-2-yn-1-yl)amino]ethan-1-ol (4s)[36]

Yield: 5.0 mg (9%); colorless oil; R_f = 0.19 (hexanes/EtOAc = 3:1, v/v).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H), 3.70 (s, 2 H), 3.65 (t, *J* = 5.3 Hz, 2 H), 3.34 (d, *J* = 2.3 Hz, 2 H), 2.80 (t, *J* = 5.5 Hz, 2 H), 2.55 (br s, 1 H), 2.26 (t, *J* = 2.3 Hz, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.2, 129.1, 128.5, 127.5, 78.1, 73.4, 58.4, 57.4, 54.8, 41.2.

2-{Benzyl[1-(4-fluorophenyl)-3-phenylprop-2-yn-1-yl]amino}ethan-1-ol (4t)

Yield: 61 mg (57%); yellow solid; mp 92–93 °C; R_f = 0.51 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3432, 2925, 1602, 1506, 1222 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.49 (m, 4 H), 7.44–7.26 (m, 8 H), 7.04 (t, *J* = 8.4 Hz, 2 H), 4.93 (s, 1 H), 3.88 (d, *J* = 13.6 Hz, 1 H), 3.70 (ddd, *J* = 10.8, 8.4, 4.4 Hz, 1 H), 3.64 (d, *J* = 13.2 Hz, 1 H), 3.47–3.39 (m, 1 H), 2.84–2.71 (m, 2 H), 2.15 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 162.3 (d, *J* = 244.8 Hz), 138.7, 134.5, 134.4, 131.9, 130.0 (d, *J* = 21.4 Hz), 129.0, 128.6, 128.5, 128.4, 127.5, 122.7, 115.2 (d, *J* = 8.0 Hz), 88.7, 84.1, 58.9, 56.2, 55.6, 51.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}FNO$: 360.1758; found: 360.1762.

2-{Benzyl[1-(4-chlorophenyl)-3-phenylprop-2-yn-1-yl]amino}ethan-1-ol (4u)

Yield: 55 mg (49%); yellow solid; mp 105–106 °C; R_f = 0.47 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3478, 2925, 1488, 1454, 1401 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.52 (m, 4 H), 7.48–7.31 (m, 10 H), 4.98 (s, 1 H), 3.92 (d, *J* = 13.6 Hz, 1 H), 3.75 (ddd, *J* = 10.8, 7.2, 5.6 Hz, 1 H), 3.68 (d, *J* = 13.6 Hz, 1 H), 3.49 (dt, *J* = 11.2, 4.0 Hz, 1 H), 2.83–2.76 (m, 2 H), 2.15 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.6, 137.3, 133.6, 131.9, 129.7, 129.0, 128.6, 128.5 (2 C), 128.4, 127.5, 122.7, 88.8, 83.9, 58.9, 56.3, 55.6, 51.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}ClNO$: 376.1463; found: 376.1452.

2-{Benzyl[3-phenyl-1-(*p*-tolyl)prop-2-yn-1-yl]amino}ethan-1-ol (4v)

Yield: 47 mg (44%); yellow oil; R_f = 0.49 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3439, 2922, 2246, 1598, 1510, 1057 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, *J* = 7.2, 4.0 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.46–7.31 (m, 8 H), 7.21 (d, *J* = 7.6 Hz, 2 H), 4.99 (s, 1 H), 3.93 (d, *J* = 13.6 Hz, 1 H), 3.76–3.70 (m, 1 H), 3.70 (d, *J* = 13.2 Hz, 1 H), 3.49–3.42 (m, 1 H), 2.85–2.76 (m, 2 H), 2.38 (s, 3 H), 2.29 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.9, 137.4, 135.6, 131.8, 129.0 (2 C), 128.5, 128.33, 128.27, 128.21, 127.3, 123.0, 88.3, 84.7, 58.8, 56.5, 55.6, 51.6, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{26}NO$: 356.2009; found: 356.2016

2-{Benzyl[1-(4-nitrophenyl)-3-phenylprop-2-yn-1-yl]amino}ethan-1-ol (4w)

Yield: 76 mg (66%); yellow solid; mp 134–136 °C; R_f = 0.30 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3437, 2949, 1597, 1519, 1057 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.8 Hz, 2 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 7.50 (dd, *J* = 6.0, 2.4 Hz, 2 H), 7.39–7.18 (m, 8 H), 4.95 (s, 1 H), 3.81 (d, *J* = 13.2 Hz, 1 H), 3.66 (td, *J* = 10.4, 4.4 Hz, 1 H), 3.59 (d, *J* = 13.2 Hz, 1 H), 3.44–3.41 (m, 1 H), 2.77–2.60 (m, 2 H), 1.93 (br s, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 147.5, 146.3, 138.2, 131.9, 129.2, 129.0, 128.8, 128.7, 128.5, 127.7, 123.5, 122.2, 89.5, 82.8, 59.2, 56.6, 55.8, 52.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}N_2O_3$: 387.1703; found: 387.1709.

2-[Benzyl(1-phenylhept-1-yn-3-yl)amino]ethan-1-ol (4x)

Yield: 39 mg (40%); yellow oil; R_f = 0.50 (hexanes/EtOAc = 5:1, v/v).

IR (KBr): 3359, 2922, 2852, 1701, 1653, 755, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.10 (m, 10 H), 3.90 (d, *J* = 13.6 Hz, 1 H), 3.75–3.60 (m, 2 H), 3.57 (d, *J* = 13.6 Hz, 1 H), 3.55–3.45 (m, 1 H), 2.92 (ddd, *J* = 13.3, 9.8, 4.9 Hz, 1 H), 2.67 (dt, *J* = 13.3, 3.4 Hz, 1 H), 2.51 (br s, 1 H), 1.78–1.65 (m, 2 H), 1.46–1.35 (m, 2 H), 1.29 (sext, *J* = 7.2 Hz, 2 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 139.1, 131.7, 128.9, 128.4, 128.2, 128.0, 127.2, 123.2, 87.7, 85.1, 58.7, 55.7, 53.3, 52.2, 33.7, 28.7, 22.3, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{28}NO$: 322.2165; found: 322.2170.

Funding Information

This work was supported by the National Natural Science Foundation of China (Grant Nos. 21702014, 21572017 and 21772010), the National Basic Research Program of China (Grant No. 2013CB328905) and the Fundamental Research Funds for the Central Universities (XK1802-6).

Acknowledgment

We are very grateful to Mr. Jun Dong for his generous help with the experiments with acetylene.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611536.

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