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Mild and Catalyst-Free Petasis/Decarboxylative Domino Reaction: Chemoselective Synthesis of *N*-Benzyl Propargylamines

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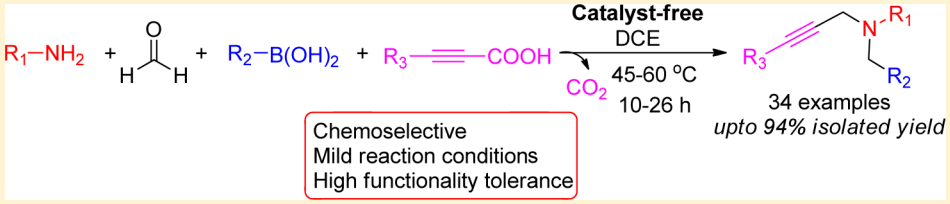
Supporting Information



ABSTRACT: Multicomponent domino reactions are attractive for assembling functionalized compounds. To this end, a one-pot catalyst-free chemoselective synthesis of *N*-benzyl propargylamines is reported with good functional group compatibility. This mild process involves *in situ* formation of an active amine through Petasis reaction of primary amines, formaldehyde solution, and boronic acids, which reacts with propiolic acids to give product in up to 94% yield via decarboxylative coupling reaction.

Propargylamines can be used as important building blocks for the generation of functionalized five-,[1] six-,[2] seven-,[3] and eight-membered[4] nitrogen heterocyclic frameworks. In addition, they have been found within highly potent and irreversible selective monoamine oxidase type-B inhibitors.[5] A common route to the synthesis of propargylamines involves the reaction of an aldehyde with an amine and an alkyne, known as the A^3-coupling reaction.[6] However, examples for the constitution of *N*-benzyl propargylamines have been rarely studied or reported owing to the fact that most of the *N*-substituted benzylamines are not commercially available. As such, the development of more efficient approaches for the preparation of structurally diverse propargylamines is highly desirable for synthetic organic chemistry.

Currently, the transition-metal-catalyzed decarboxylative couplings have been successfully used for C−C bond formation under relatively neutral conditions compared to preformed organometallic reagents.[7,8] In this regard, copper-catalyzed decarboxylative couplings have been used as a valuable synthetic strategy for the formation of propargylamines, employing amino acid,[9] 2-oxoacetic acid,[10] glyoxylic acid,[11] and propiolic acid[12] as starting materials. However, those copper-catalyzed methods usually suffer from some drawbacks in terms of environmental pollution and complication in the purification processes. Recently, the group of Sunwoo Lee reported a metal-free decarboxylative coupling reaction of propiolic acid with secondary amine and paraformaldehyde,[13] similar to the A^3-coupling reaction. Although this method provided a facile approach to propargylamines, no example with a primary amine as starting material was reported due to primary amines being considered as difficult substrates in the A^3-type coupling reaction.[14] Meanwhile, there are a limited number of literature examples in which primary amines were employed in the decarboxylative A^3-coupling reaction.[15] To expand the decarboxylative coupling reaction for the generation of propargylamines to a broad range of starting amines, we envisioned a scenario wherein a primary amine might participate in a Petasis reaction with an aldehyde and a boronic acid,[16] to form an active amine *in situ*, followed by the metal-free decarboxylative A^3-coupling reaction of a propiolic acid (Figure 1).

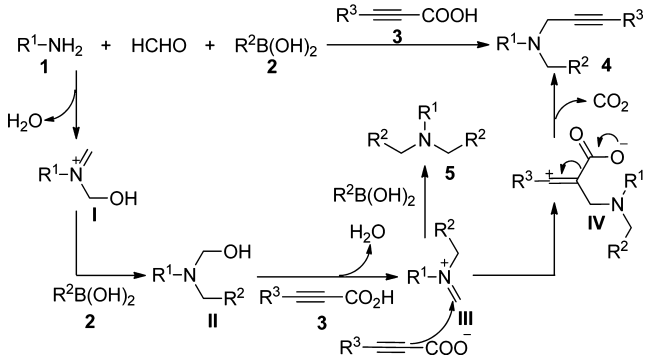


Figure 1. Petasis and decarboxylative domino reaction.

Key to the success of this proposed reaction would be the addition of the aryl boronic acid into imine **I** to produce *N*-benzyl hemiaminal **II**,[17] which in the presence of a propiolic acid results in the formation of iminium salt **III**. It is noteworthy that the related addition of another boronic acid into activated iminium salt **III** has been described to obtain

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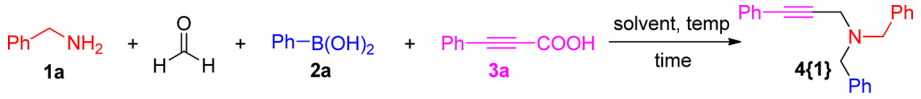
Table 1. Optimization of Reaction Parameters[a]



entry	ratio	solvent	temp [°C]	t [h]	yield [%][b]
1	1.0/2.2/1.1/1.2	toluene	60	10	31
2	1.0/3.2/1.1/1.2	toluene	60	10	69
3	1.0/4.0/1.1/1.2	toluene	60	10	54
4[c]	1.0/3.2/1.1/1.2	toluene	60	10	46
5[c]	1.0/3.2/1.1/1.2	H_2O/toluene (1:15)	60	10	40
6	1.0/3.2/1.1/1.2	DCE	60	10	83
7	1.0/3.2/1.1/1.2	AcOEt	60	10	8
8	1.0/3.2/1.1/1.2	H_2O	60	10	33
9	1.0/3.2/1.1/1.2	CH_3CN	60	10	14
10	1.0/3.2/1.1/1.2	EtOH	60	10	6
11	1.0/3.2/1.1/1.2	DCM	45	10	68
12	1.0/3.2/1.1/1.2	THF	60	10	trace
13	1.0/3.2/1.1/1.2	DCE	60	24	77
14	1.0/3.2/1.1/1.2	DCE	80	5	68
15	1.0/3.2/1.1/1.2	DCE	80	10	65
16	1.0/3.2/1.1/1.2	DCE	45	10	84
17	1.0/3.2/1.1/1.2	DCE	rt	10	73
18	1.0/3.2/1.1/1.2	DCE	rt	26	74
19[d]	1.0/3.2/1.1/1.2	DCE	45	10	65
20[e]	1.0/3.2/1.1/1.2	DCE	45	10	0

[a]Reactions conditions: **1a** (0.5 mmol), formaldehyde solution (1.1−2 mmol), **2a** (0.55 mmol), **3a** (0.6 mmol), and solvent (1.5 mL) in a sealed tube. [b]Isolated yield. [c]Paraformaldehyde was used instead of formaldehyde solution. [d]1.5 equiv of acetic acid was added. [e]Ethyl phenylpropiolate instead of phenylpropiolic acid with 1.5 equiv of acetic acid.

amine **5**.[18] In this note, the alkynyl carbon next to the carboxylate attacks iminium salt **III** to generate intermediate **IV** instead of the above process. Subsequent extrusion of CO_2 through a decarboxylation pathway affords the desired propargylamine in a process similar to the Eschweiler−Clarke methylation.[19] Herein, we report the successful development of such a new catalyst-free one-pot chemoselective synthesis of propargylamines through the Petasis/decarboxylative domino reaction of a primary amine, a formaldehyde solution, an aryl boronic acid, and a propiolic acid.

We initiated our investigation using benzylamine (**1a**), formaldehyde solution, phenylboronic acid (**2a**), and 3-phenylpropiolic acid (**3a**) in toluene at 60 °C for 10 h (Table 1). To our delight, the desired product **4{1}** was obtained in 31% yield (Table 1, entry 1). To improve the yield, various ratios of the four starting materials were examined (Table 1, entries 2 and 3). Among them, 3.2 equiv of formaldehyde solution provided the best yield (Table 1, entry 2). When paraformaldehyde was used instead of formaldehyde solution (Table 1, entries 4 and 5), only 46% and 40% of products were isolated, which is much lower than the case using formaldehyde solution (Table 1, entry 2). Subsequently, solvent screening showed that this reaction was sensitive to the nature of solvents (Table 1, entries 6−12); 1,2-dichloroethane (DCE) provided an improved isolated yield of 83% for **4{1}** (Table 1, entry 6), whereas ethyl acetate, water, acetonitrile, ethanol, dichloromethane, and tetrahydrofuran gave lower yields of the desired product. Eventually, different reaction times and temperatures were also tested, but did not give much improvement of the yield (Table 1, entries 13−18). Remarkably, using 45 °C as the reaction temperature was slightly more efficient than 60 °C to afford the optimal result (Table 1, entry 16). When the reaction was run at room temperature for 10 h, a yield of 73% was obtained (Table 1, entry 17). Prolonging the reaction time to 26 h only produced a minor increase of yield (Table 1, entry 18). In addition, the reaction yield under the optimal conditions can be decreased from 84% to 65% after adding an acid to the reaction (Table 1, entry 19), which could be explained by the adverse effect of an acid to the decarboxylative pathway shown in Figure 1. When ethyl phenylpropiolate was used instead of phenylboronic acid (Table 1, entry 20), no desired product was formed in the presence of 1.5 equiv of acetic acid.

A variety of primary amines were subjected to the optimized conditions to evaluate the scope of the Patisis/decarboxylative domino reaction. For substituted benzylamines, the reaction afforded the corresponding products **4** in moderate to good yield bearing electron-rich and -deficient groups (Table 2, **4{2}**−**4{12}**). In general, halo-substitution led to the cleanest and highest yielding reactions (Table 2, **4{2}**−**4{5}**), and cyano-substitution also gave a good yield (Table 2, **4{6}**). Methoxy-substitution usually afforded lower yields of the products compared to methyl-substitution (Table 2, **4{7}**−**4{12}**). The use of aliphatic amines also gave the desired products in nice yields (Table 2, **4{13}**−**4{15}**). Then, a number of boronic acids were investigated. Both electron-poor and -rich aryl-substituted boronic acids were effective, producing the desired compounds in 59−87% yields (Table 2, **4{16}**−**4{19}**). In addition, the reactions of aromatic naphthalen-1-ylboronic acid, naphthalen-2-ylboronic acid, and thiophen-3-ylboronic acid were also examined. The corresponding coupling products were obtained in high yield (Table 2, **4{20}**−**4{22}**). It is noteworthy that 4-fluorophenyl boronic acid (**2i**), 4-tolylboronic acid (**2g**), 2-methoxyphenyl boronic acid (**2k**), and 4-methoxyphenyl boronic acid (**2l**) also reacted well under standard conditions to give excellent yields in the

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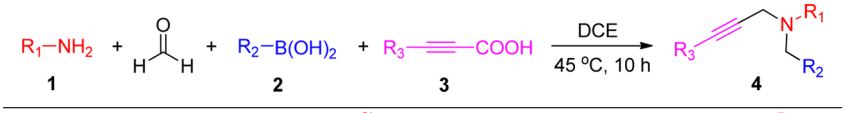
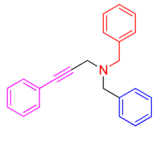
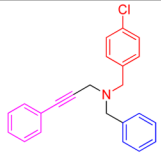
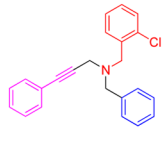
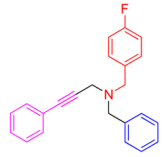
Table 2. Substrate Scope and Limitations[a]

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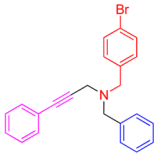	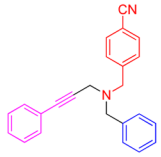	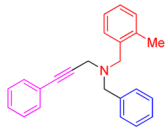	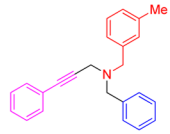
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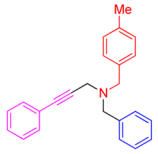	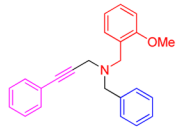	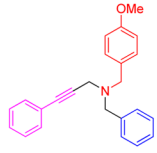	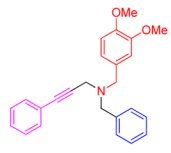
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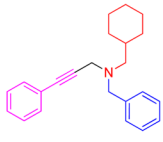	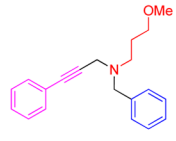	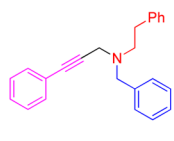	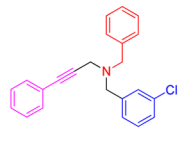
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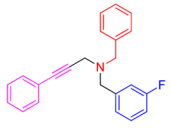	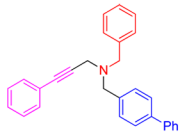	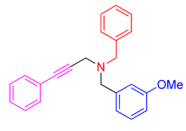	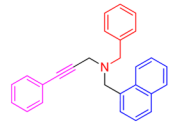
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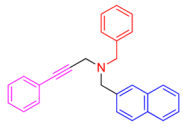	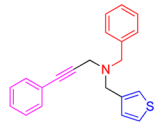	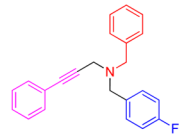	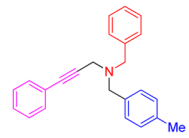
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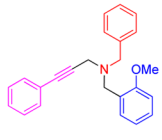	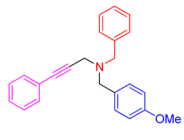	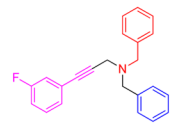	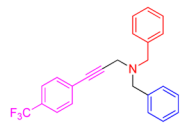
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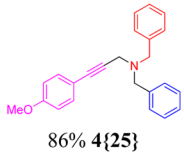
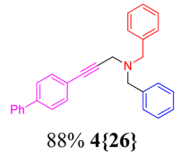
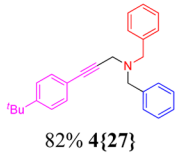
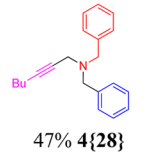
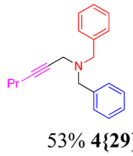
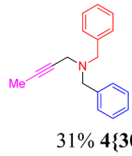
			
86% **4{25}**	88% **4{26}**	82% **4{27}**	47% **4{28}**
			
53% **4{29}**	31% **4{30}**		

[a]Reactions conditions: amine (0.5 mmol), formaldehyde solution (1.6 mmol), boronic acid (0.55 mmol), propiolic acid (0.6 mmol), and DCE (1.5 mL) in a sealed tube; reaction was monitored by TLC plate. [b]This reaction was carried out at 60 °C for 18 h. [c]This reaction was carried out for 26 h.

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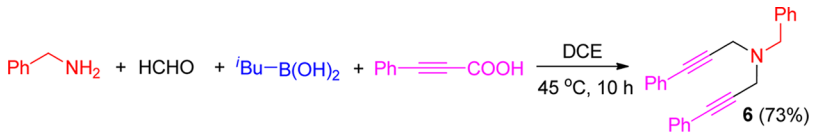
Scheme 1. Selective Coupling Reaction toward Dipropargylamine



formation of **4{4}**$^{\#}$, **4{9}**$^{\#}$, **4{10}**$^{\#}$, and **4{11}**$^{\#}$ when compared to the same structures **4{4}**, **4{9}**, **4{10}**, and **4{11}** from alternative starting materials. Finally, our investigations were focused on the use of various 3-substituted propiolic acids **3** (Table 2, **4{23}**−**4{30}**). Both aromatic and aliphatic propiolic acids were explored as reaction partners, and the results clearly showed that aromatic propiolic acids worked well (Table 2, **4{23}**−**4{27}**) and alkyl propiolic acids afforded the target compounds only in low to moderate yields (Table 2, **4{28}**−**4{30}**). It seemed that substituents on the phenyl ring of the aromatic propiolic acids played important roles in this process, as electron-donating substituents (Table 2, **4{25}**−**4{27}**) led to higher yields than electron-withdrawing groups (Table 2, **4{23}**−**4{24}**).

Not surprisingly, when isobutylboronic acid was used in this protocol, dipropargylamine **6** was obtained in 73% yield (Scheme 1). Only trace amounts of the expected tertiary amine product were observed as indicated by ^{1}H NMR spectroscopy and LC−MS of the crude reaction mixtures, since the Petasis reaction typically did not work with inactive alkylboronic acid.

In summary, we have described a catalyst-free method for the synthesis of *N*-benzyl propargylamines by a multicomponent domino reaction of primary amines with formaldehyde solution, boronic acids, and propiolic acids. The reaction uses commercially available reagents and affords significant advantages over the related transition-metal-catalyzed A^3-coupling or decarboxylative A^3-coupling, in that it proceeds under much milder reaction conditions and displays a broad substrate scope and high chemoselectivity.

EXPERIMENTAL SECTION

General Information. All commercially available reagents were used without purification unless otherwise noted. Column chromatography was performed using silica gel (100−200 mesh). Visualization of the compounds was accomplished with UV light (254 nm) and iodine. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ operating at 400 and 100 MHz, respectively. Proton chemical shifts are reported relative to the residual proton signals of the deuterated solvent $CDCl_3$ (7.26 ppm) or TMS. Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (77.00 ppm) and reported in δ (parts per million) values. Coupling constants J are reported in Hz. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), and multiple (m). High-resolution mass spectra were recorded on a liquid chromatograph mass spectrometer (LCMS-IT-TOF).

General Procedure for the Synthesis of Propagylamines 4. In a vial equipped with a stirring bar, a mixture of amine (0.5 mmol) and formaldehyde solution (1.6 mmol) was dissolved in DCE (1.5 mL). Then boronic acid (0.55 mmol) and propiolic acid (0.6 mmol) were added. The reaction vessel was sealed and heated in an oil bath for 10 h at a temperature of 45 °C. The resulting reaction mixture was loaded on a silica gel column and eluted with 2−5% ethyl acetate in hexane to afford the desired product **4** as a light yellow oil.

*N,N-Dibenzyl-3-phenylprop-2-yn-1-amine (**4{1}**).* Light yellow oil (131.1 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.54 (m, 2H), 7.50−7.48 (m, 4H), 7.40−7.35 (m, 7H), 7.33−7.28 (m, 2H), 3.817 (s, 4H), 3.53 (t, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 139.0, 131.8, 129.1, 128.3, 128.3, 128.0, 127.1, 123.5, 85.90, 84.8, 84.5, 57.8, 42.1; MS (ESI) m/z: 312.2 $[M + H]^+$.

*N-Benzyl-N-(4-chlorobenzyl)-3-phenylprop-2-yn-1-amine (**4{2}**).* Light yellow oil (160.9 mg, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.45 (m, 2H), 7.42−7.40 (m, 2H), 7.38−7.33 (m, 10H), 3.79 (s, 2H), 3.77 (s, 2H), 3.50 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 138.7, 137.5, 132.9, 131.8, 130.4, 129.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.2, 123.3, 86.0, 84.2, 57.8, 57.0, 42.1; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN$ $[M + H]^+$ 346.1357, found 346.1347.

*N-Benzyl-N-(2-chlorobenzyl)-3-phenylprop-2-yn-1-amine (**4{3}**).* Light yellow oil (155.7 mg, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.2 Hz, 1H), 7.57−7.55 (m, 2H), 7.50−7.48 (m, 2H), 7.42−7.36 (m, 6H), 7.32−7.28 (m, 2H), 7.26−7.24 (m, 1H), 3.96 (s, 2H), 3.87 (s, 2H), 3.54 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 138.8, 136.5, 134.7, 131.8, 130.9, 130.0, 129.1, 128.3, 128.0, 127.2, 126.6, 123.4, 86.0, 84.4, 57.9, 54.9, 42.1; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN$ $[M + H]^+$ 346.1357, found 346.1350.

*N-benzyl-N-(4-fluorobenzyl)-3-phenylprop-2-yn-1-amine (**4{4}**).* Light yellow oil (128.8 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.58 (m, 2H), 7.53−7.41 (m, 9H), 7.37−7.33, (m, 1H) 7.13−7.10 (m, 2H), 3.84 (s, 2H), 3.81 (s, 2H), 3.55 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 163.4, 161.0, 138.9, 134.7, 131.9, 130.7, 130.6, 129.1, 128.4, 128.1, 127.3, 123.5, 115.3, 115.1, 86.1, 84.3, 57.8, 57.0, 42.0; HRMS (ESI) m/z calcd for $C_{23}H_{20}FN$ $[M + H]^+$ 330.1653, found 330.1651.

*N-Benzyl-N-(4-bromobenzyl)-3-phenylprop-2-yn-1-amine (**4{5}**).* Light yellow oil (171.7 mg, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.53 (m, 6H), 7.45−7.34 (m, 8H), 3.83 (s, 2H), 3.79 (s, 2H), 3.55 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 138.8, 138.1, 131.9, 131.5, 130.8, 129.1, 128.5, 128.4, 128.2, 127.3, 123.4, 121.0, 86.1, 84.2, 57.8, 57.1, 42.1; HRMS (ESI) m/z calcd for $C_{23}H_{20}BrN$ $[M + H]^+$ 390.0852, found 390.0840.

*4-((Benzyl(3-phenylprop-2-yn-1-yl)amino)methyl)benzonitrile (**4{6}**).* Light yellow oil (127.8 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 2H), 7.62−7.57 (m, 4H), 7.50 (d, J = 6.8 Hz, 2H), 7.44−7.33 (m, 6H), 3.87 (s, 2H), 3.84 (s, 2H), 3.54 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 144.9, 138.4, 132.3, 131.9, 129.6, 129.1, 128.5, 128.3, 127.5, 123.2, 119.1, 111.0, 86.3, 83.8, 58.0, 57.3, 42.4; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_2$ $[M + H]^+$ 337.1699, found 337.1689.

*N-Benzyl-N-(2-methylbenzyl)-3-phenylprop-2-yn-1-amine (**4{7}**).* Light yellow oil (148.4 mg, 91% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.2 Hz, 2H), 7.41 (d, J = 4.8 Hz, 3H), 7.39−7.26 (m, 6H), 7.28−7.21 (m, 3H), 3.8 (s, 4H), 3.5 (s, 2H), 2.5 (s, 3H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 139.0, 137.8, 136.8, 131.8, 130.4, 130.2, 129.2, 128.4, 128.3, 128.0, 127.3, 127.1, 125.6, 123.6, 86.0, 84.6, 58.0, 56.0, 41.7, 19.3; HRMS (ESI) m/z calcd for $C_{24}H_{23}N$ $[M + H]^+$ 326.1903, found 326.1894.

*N-Benzyl-N-(3-methylbenzyl)-3-phenylprop-2-yn-1-amine (**4{8}**).* Light yellow oil (140.3 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.50 (m, 4H), 7.45−7.29 (m, 9H), 7.18−7.16 (m, 1H), 3.86 (s, 2H), 3.83 (s, 2H), 3.58 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 139.0, 138.9, 137.9, 131.9, 129.9, 129.2, 128.4, 128.3, 128.0, 127.9, 127.2, 126.2, 123.6, 86.0, 84.6, 57.9, 57.8, 42.2, 21.5; HRMS (ESI) m/z calcd for $C_{24}H_{23}N$ $[M + H]^+$ 326.1903, found 326.1896.

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N-Benzyl-N-(4-methylbenzyl)-3-phenylprop-2-yn-1-amine ***(4{9})***. Light yellow oil (106.0 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.54 (m, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.40−7.37 (m, 7H), 7.32−7.28 (m, 1H), 7.20 (d, J = 7.6 Hz, 2H), 3.81 (s, 2H), 3.78 (s, 2H), 3.53 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 139.0, 136.7, 135.8, 131.8, 129.1, 129.0, 128.3, 128.0, 127.12, 123.5, 86.0, 84.5, 57.7, 57.5, 42.0, 21.1; HRMS (ESI) m/z calcd for $C_{24}H_{23}N$ $[M + H]^+$ 326.1903, found 326.1893.

N-Benzyl-N-(2-methoxybenzyl)-3-phenylprop-2-yn-1-amine ***(4{10})***. Light yellow oil (102.7 mg, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.50 (m, 5H), 7.40−7.36 (m, 5H), 7.32−7.27 (m, 2H), 7.01 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 4H), 3.59 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 158.1, 139.2, 131.8, 130.5, 129.2, 128.3, 128.2, 128.1, 127.9, 127.2, 127.0, 123.7, 120.5, 110.7, 85.7, 85.2, 58.1, 55.5, 51.5, 42.5; HRMS (ESI) m/z calcd for $C_{24}H_{23}NO$ $[M + H]^+$ 342.1852, found 342.1837.

N-Benzyl-N-(4-methoxybenzyl)-3-phenylprop-2-yn-1-amine ***(4{11})***. Light yellow oil (107.8 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.55 (m, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.42−7.38 (m, 7H), 7.34−7.28 (m, 1H), 6.94 (d, J = 8.4 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 2H), 3.77 (s, 2H), 3.53 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 158.9, 139.1, 131.8, 131.0, 130.3, 129.1, 128.3, 128.0, 127.1, 123.5, 113.8, 85.9, 84.6, 57.7, 57.1, 55.3, 41.9; MS (ESI) m/z: 342.2 $[M + H]^+$.

N-Benzyl-N-(3,4-dimethoxybenzyl)-3-phenylprop-2-yn-1-amine ***(4{12})***. Light yellow oil (126.5 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.55 (m, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.41−7.28 (m, 5H), 7.07 (s, 1H), 7.02 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.80(s, 2H), 3.77 (s, 2H), 3.55 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 149.1, 148.3, 139.0, 131.8, 131.6, 129.1, 128.4, 128.0, 127.2, 123.5, 121.3, 112.4, 111.1, 85.9, 84.6, 57.7, 57.5, 56.0, 55.9, 42.1; HRMS (ESI) m/z calcd for $C_{25}H_{25}NO_2$ $[M + H]^+$ 372.1958, found 372.1942.

N-Benzyl-N-(cyclohexylmethyl)-3-phenylprop-2-yn-1-amine ***(4{13})***. Light yellow oil (88.0 mg, 49% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2H), 7.48−7.43 (m, 2H), 7.38−7.28 (m, 6H), 3.74 (s, 2H), 3.55 (s, 2H), 2.47 (d, J = 7.2 Hz, 2H), 1.93−1.90 (m, 2H), 1.78−1.70 (m, 4H), 1.65−1.48 (m, 4H), 1.40−1.29 (m, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 149.1, 148.3, 139.0, 131.8, 131.6, 129.1, 128.4, 128.0, 127.2, 123.5, 121.3, 112.4, 111.1, 85.9, 84.6, 57.7, 57.5, 56.0, 55.9, 42.1; HRMS (ESI) m/z calcd for $C_{23}H_{27}N$ $[M + H]^+$ 318.2216, found 318.2203.

N-Benzyl-N-(3-methoxypropyl)-3-phenylprop-2-yn-1-amine ***(4{14})***. Light yellow oil (79.4 mg, 54% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.49 (m, 2H), 7.42 (d, J = 7.2 Hz, 2H), 7.38−7.34 (m, 5H), 7.31−7.28 (m, 1H), 3.74 (s, 2H), 3.57 (s, 2H), 3.51 (t, J = 6.4 Hz, 2H), 3.37 (s, 3H), 2.75 (t, J = 7.2 Hz, 2H), 1.91−1.85 (m, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 139.0, 131.8, 129.1, 128.3, 128.0, 127.1, 123.4, 85.6, 84.5, 71.0, 58.6, 58.1, 50.1, 42.3, 27.9; HRMS (ESI) m/z calcd for $C_{20}H_{23}NO$ $[M + H]^+$ 294.1852, found 294.1843.

N-Benzyl-N-phenethyl-3-phenylprop-2-yn-1-amine ***(4{15})***. Light yellow oil (119.1 mg, 73% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.55 (m, 2H), 7.46−7.28 (m, 13H), 3.85 (s, 2H), 3.69 (s, 2H), 2.98 (s, 4H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 140.5, 138.8, 131.8, 129.2, 128.8, 128.5, 128.4, 128.0, 127.2, 126.0, 123.5, 85.7, 84.5, 58.2, 55.4, 42.5, 34.3; MS (ESI) m/z: 326.2 $[M + H]^+$.

N-Benzyl-N-(3-chlorobenzyl)-3-phenylprop-2-yn-1-amine ***(4{16})***. Light yellow oil (102.1 mg, 59% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.53 (m, 2H), 7.47 (d, J = 8.4 Hz, 3H), 7.40−7.28 (m, 9H), 3.80 (s, 2H), 3.77(s, 2H), 3.52(s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 141.2, 138.6, 134.3, 131.8, 129.6, 129.1, 128.4, 128.3, 128.1, 127.4, 127.3, 127.2, 123.3, 86.1, 84.1, 57.8, 57.2, 42.1; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN$ $[M + H]^+$ 346.1357, found 346.1341.

N-Benzyl-N-(3-fluorobenzyl)-3-phenylprop-2-yn-1-amine ***(4{17})***. Light yellow oil (112.3 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.54 (m, 4H), 7.50−7.02 (m, 9H), 7.00−6.98 (m, 1H), 3.81 (s, 2H), 3.80 (s, 2H), 3.53 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 164.3, 161.9, 141.8, 141.7, 138.7, 131.8, 129.8, 129.7, 129.4, 129.1, 128.4, 128.3, 128.1, 127.3, 124.6, 124.5, 123.4, 115.8, 115.6, 114.2, 113.9, 86.1, 84.2, 57.8, 57.2, 42.1; HRMS (ESI) m/z calcd for $C_{23}H_{20}FN$ $[M + H]^+$ 330.1653, found 330.1645.

N-([1,1′-Biphenyl]-4-ylmethyl)-N-benzyl-3-phenylprop-2-yn-1-amine ***(4{18})***. Light yellow oil (147.5 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.50 (m, 13H), 7.46−7.34 (m, 6H), 3.90 (s, 2H), 3.89 (s, 2H), 3.61(s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 164.3, 161.9, 141.8, 141.7, 138.7, 131.8, 129.8, 129.7, 129.4, 129.1, 128.4, 128.3, 128.1, 127.3, 124.6, 124.5, 123.4, 115.8, 115.6, 114.2, 113.9, 86.1, 84.2, 57.8, 57.2, 42.1; HRMS (ESI) m/z calcd for $C_{29}H_{26}N$ $[M + H]^+$ 388.2060, found 388.2054.

N-Benzyl-N-(3-methoxybenzyl)-3-phenylprop-2-yn-1-amine ***(4{19})***. Light yellow oil (147.1 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.57 (m, 2H), 7.53−7.51 (m, 2H), 7.43−7.39 (m, 5H), 7.35−7.28 (m, 2H), 7.11−7.10 (m, 2H), 6.88 (d, J = 7.2 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 2H), 3.83 (s, 2H), 3.57(s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 159.8, 140.7, 139.0, 131.8, 129.3, 129.1, 128.4, 128.1, 127.2, 123.5, 121.5, 114.6, 112.7, 86.0, 84.5, 57.8, 57.7, 55.2, 42.2; HRMS (ESI) m/z calcd for $C_{24}H_{23}NO$ $[M + H]^+$ 342.1852, found 342.1835.

N-Benzyl-N-(naphthalen-1-ylmethyl)-3-phenylprop-2-yn-1-amine ***(4{20})***. Light yellow oil (157.6 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51−8.50 (d, J = 7.2 Hz, 1H), 8.00−7.93 (m, 2H), 7.77−7.40 (m, 14H), 4.37 (s, 2H), 4.02 (s, 2H), 3.63 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 139.0, 134.5, 134.2, 132.9, 132.0, 129.5, 129.4, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.4, 125.9, 125.8, 125.3, 125.2, 123.7, 86.4, 84.7, 58.3, 56.4, 42.0; HRMS (ESI) m/z calcd for $C_{27}H_{23}N$ $[M + H]^+$ 362.1903, found 362.1888.

N-Benzyl-N-(naphthalen-2-ylmethyl)-3-phenylprop-2-yn-1-amine ***(4{21})***. Light yellow oil (161.2 mg, 89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.94 (m, 4H), 7.76−7.55 (m, 7H), 7.50−7.38 (m, 6H), 4.06 (s, 2H), 3.95 (s, 2H), 3.66 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) 139.0, 136.7, 133.6, 133.0, 131.9, 129.3, 128.5, 128.1, 127.9, 127.8, 127.5, 127.3, 126.0, 125.7, 123.6, 86.1, 84.6, 58.1, 57.9, 42.3; HRMS (ESI) m/z calcd for $C_{27}H_{23}N$ $[M + H]^+$ 362.1903, found 362.1886.

N-Benzyl-3-phenyl-N-(thiophen-3-ylmethyl)prop-2-yn-1-amine ***(4{22})***. Light yellow oil (135.2 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.54 (m, 4H), 7.47−7.34 (m, 8H), 7.28−7.27 (m, 1H), 3.91 (s, 2H), 3.86 (s, 2H), 3.61 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) 139.9, 139.0, 131.9, 129.2, 128.6, 128.4, 128.1, 127.3, 125.6, 123.5, 123.0, 86.0, 84.6, 57.7, 52.7, 42.3; HRMS (ESI) m/z calcd for $C_{21}H_{19}NS$ $[M + H]^+$ 318.1311, found 318.1306.

N-Benzyl-N-(4-fluorobenzyl)-3-phenylprop-2-yn-1-amine ***(4{4}$^{\#}$)***. Light yellow oil (148.6 mg, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.55 (m, 2H), 7.50−7.28 (m, 10H), 7.10−7.06 (m, 2H), 3.82 (s, 2H), 3.78 (s, 2H), 3.53 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 163.4, 161.0, 138.9, 134.7, 131.9, 130.7, 130.6, 129.1, 128.4, 128.1, 127.3, 123.5, 115.3, 115.1, 86.1, 84.3, 57.8, 57.0, 42.0; HRMS (ESI) m/z calcd for $C_{23}H_{20}FN$ $[M + H]^+$ 330.1653, found 330.1640.

N-Benzyl-N-(4-methylbenzyl)-3-phenylprop-2-yn-1-amine ***(4{9}$^{\#}$)***. Light yellow oil (153.3 mg, 94% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.51 (m, 4H), 7.42−7.32 (m, 8H), 7.23 (d, J = 7.6 Hz, 2H), 3.84 (s, 2H), 3.82 (s, 2H), 3.56 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 139.0, 136.7, 135.8, 131.8, 129.1, 129.0, 128.3, 128.0, 127.12, 123.5, 86.0, 84.5, 57.7, 57.5, 42.0, 21.1; HRMS (EI) m/z calcd for $C_{24}H_{23}N$ $[M]^+$ 326.1903, found 326.1889.

N-Benzyl-N-(2-methoxybenzyl)-3-phenylprop-2-yn-1-amine ***(4-{10}$^{\#}$)***. Light yellow oil (147.1 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.52 (m, 5H), 7.42−7.29 (m, 7H), 7.05−7.01 (m, 1H), 6.94 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 4H), 3.60 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 158.1, 139.2, 131.8, 130.5, 129.2, 128.3, 128.2, 128.1, 127.9, 127.2, 127.0, 123.7, 120.5, 110.7, 85.7, 85.2, 58.1, 55.5, 51.5, 42.5; HRMS (ESI) m/z calcd for $C_{24}H_{23}NO$ $[M + H]^+$ 342.1852, found 342.1842.

N-Benzyl-N-(4-methoxybenzyl)-3-phenylprop-2-yn-1-amine ***(4-{11}$^{\#}$)***. Light yellow oil (160.9 mg, 94% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.53 (m, 2H), 7.48−7.46 (m, 2H), 7.40−7.30 (m, 8H), 6.92 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 2H), 3.78 (s, 2H), 3.50 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 158.9, 139.0, 131.8, 131.0, 130.3, 129.1, 128.3, 128.0, 127.1, 123.5, 113.8, 85.9, 84.6, 57.6, 57.1, 55.3, 41.9; MS (ESI) m/z 342.2 $[M + H]^+$.

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N,N-Dibenzyl-3-(3-fluorophenyl)prop-2-yn-1-amine (4{23}). Light yellow oil (125.5 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.50 (m, 4H), 7.45−7.27 (m, 9H), 7.14−7.09 (m, 1H), 3.85 (s, 4H), 3.57 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 163.7, 161.3, 138.8, 130.0, 129.9, 129.2, 128.8, 128.4, 128.3, 127.8, 127.7, 127.3, 125.4, 125.3, 118.8, 118.6, 115.6, 115.4, 85.7, 84.8, 57.8, 42.0; HRMS (ESI) m/z calcd for $C_{23}H_{20}FN$ $[M + H]^+$ 330.1653, found 330.1638.

N,N-Dibenzyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-amine (4{24}). Light yellow oil (120.0 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 4H), 7.50−7.47 (m, 4H), 7.42−7.31 (m, 6H), 3.83 (s, 4H), 3.56 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 138.7, 132.1, 129.1, 128.4, 127.3, 125.4, 125.3, 125.2, 87.4, 84.7, 57.9, 42.0; HRMS (ESI) m/z calcd for $C_{24}H_{20}F_3N$ $[M + H]^+$ 380.1621, found 380.1609.

N,N-Dibenzyl-3-(4-methoxyphenyl)prop-2-yn-1-amine (4{25}). Light yellow oil (147.1 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.4 Hz, 4H), 7.42−7.31 (m, 4H), 6.93 (d, J = 8.8 Hz, 6H), 3.88 (s, 3H), 3.83 (s, 4H), 3.53 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 159.5, 139.0, 133.2, 129.2, 128.4, 127.2, 115.6, 114.0, 85.8, 82.8, 57.7, 55.4, 42.2; HRMS (ESI) m/z calcd for $C_{24}H_{23}NO$ $[M + H]^+$ 342.1852, found 342.1845.

3-([1,1′-Biphenyl]-4-yl)-N,N-dibenzylprop-2-yn-1-amine (4{26}). Light yellow oil (170.8 mg, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.69 (m, 6H), 7.61−7.54 (m, 6H), 7.50−7.45 (m, 5H), 7.42−7.39 (m, 2H), 3.93 (s, 4H), 3.65 (s, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 140.9, 140.5, 139.1, 132.4, 129.3, 129.0, 128.5, 128.4, 127.8, 127.3, 127.2, 122.5, 85.9, 85.3, 57.9, 42.3; MS (ESI) m/z 388.2 $[M + H]^+$.

N,N-Dibenzyl-3-(4-(tert-butyl)phenyl)prop-2-yn-1-amine (4{27}). Light yellow oil (151.0 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.50 (m, 6H), 7.47−7.41 (m, 6H), 7.37−7.33 (m, 2H), 3.86 (s, 4H), 3.57 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 151.3, 139.0, 131.6, 129.2, 128.4, 128.3, 127.2, 125.4, 125.3, 120.5, 86.1, 83.7, 57.8, 42.1, 34.8, 31.3; HRMS (ESI) m/z calcd for $C_{27}H_{29}N$ $[M + H]^+$ 368.2373, found 368.2360.

N,N-Dibenzylhept-2-yn-1-amine (4{28}). Light yellow oil (68.7 mg, 47% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 4H), 7.35 (t, J = 7.2 Hz, 4H), 7.30−7.26 (m, 2H), 3.27−3.26 (m, 4H), 2.33−2.30 (m, 2H), 1.64−1.30 (m, 2H), 1.01 (t, J = 7.2 Hz, 2H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 139.1, 129.1, 128.2, 127.0, 86.0, 74.3, 57.5, 41.7, 31.2, 22.0, 18.5, 13.7; MS (ESI) m/z: 292.2 $[M + H]^+$.

N,N-Dibenzylhex-2-yn-1-amine (4{29}). Light yellow oil (73.7 mg, 53% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 4H), 7.37 (t, J = 7.4 Hz, 4H), 7.31−7.28(m, 2H), 3.73 (s, 4H), 3.30 (s, 2H), 2.34−7.30(m, 2H), 1.67−1.64 (m, J = 7.2 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 139.2, 129.1, 128.8, 128.2, 127.0, 85.7, 74.7, 57.6, 41.8, 22.6, 20.9, 13.6; HRMS (ESI) m/z calcd for $C_{20}H_{23}N$ $[M + H]^+$ 278.1903, found 278.1885.

N,N-Dibenzylbut-2-yn-1-amine (4{30}). Light yellow oil (38.8 mg, 31% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.2 Hz, 4H), 7.35 (t, J = 7.4 Hz, 4H), 7.29−7.26 (m, 2H), 3.70 (s, 4H), 3.25 (s, 2H), 1.94 (s, 3H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 139.1, 129.1, 128.4, 128.2, 127.0, 81.0, 73.8, 57.5, 41.8, 29.7; MS (ESI) m/z: 250.2 $[M + H]^+$.

N-Benzyl-3-phenyl-N-(3-phenylprop-2-yn-1-yl)prop-2-yn-1-amine (6). Light yellow oil (122.7 mg, 73% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.48 (m, 6H), 7.41−7.31 (m, 9H), 3.89 (s, 2H), 3.74 (s, 4H); ^{13}C NMR (77 MHz, $CDCl_3$) δ 138.0, 131.8, 129.4, 128.4, 128.3, 128.1, 127.4, 123.2, 85.5, 84.7, 57.4, 43.1; MS (ESI) m/z: 336.2 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

NMR (^{1}H and ^{13}C) spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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