Indium-catalysed multicomponent reaction of acetals with dibenzylamine and alkynes

Xue-Lin Zhang, Qin-Pei Wu* and Qing-Shan Zhang

School of Chemical Engineering and Environment, Beijing Institute of Technology, Beijing 100081, P.R. China

A reaction of acetals with dibenzylamine and alkynes to form propargylamines has been developed via the activation of both C(sp3)-O and C(sp)-H bonds by $InCl_3$. The iminium ion has been found to be the key intermediate.

Keywords: acetals, dibenzylamine, multicomponent reaction, alkynes

Acetals play a key role in natural products,[1] and in synthetic chemistry.[2] They are extensively used as protecting groups in synthetic chemistry[3] and they undergo a large number of reactions such as the Mukaiyama aldol condensation with enol silyl ethers which was reported in 1974.[4] Since then, many examples have reported of the displacement of only one alkoxy groups.[5]

Propargylic carbocations, are readily formed from propargyl alcohol, ethers, and esters in the presence of Lewis acids. They can be stabilised by metals and coupled with various nucleophiles[6,7] such as amines to give propargylic amines.[8,9]

Based on these reports, we reasoned that acetals were probably capable of undergoing multicomponent reactions to give products where both alkoxy groups had been substituted. Specifically, it seemed plausible that the second alkoxy group of an acetal could be displaced by another nucleophile such as an amine once the first alkoxy group had been substituted by an alkynyl group. Overall this would give propargylic amines,[11] which are versatile intermediates for the preparation of natural products,[12] and bioactive molecules.[13] Hence, we conducted a three-component reaction of acetals with alkynes and dibenzylamine (Scheme 1).

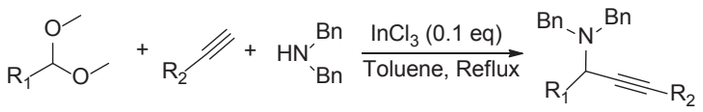
However, the reaction of benzaldehyde dimethyl acetal, phenylacetylene, and dibenzylamine (Bn_2NH) in the presence of $InCl_3$ (10 mol%) failed in 1,2-dichloroethane solution at room temperature but when the mixture was heated to reflux, the desired product was obtained in 64% yield. Acetals are easily hydrolysed in the presence of Lewis acids,[14,15] and there are reports of aldehydes coupling with acetylene and amines to generate propargylic amines in water.[16–20] This led us to attempt the reaction in 1,4-dioxane/H_2O (v/v = 1:1) and aqueous solutions. However, no reaction was observed in either case (Table 1, entries 2 and 3). A more polar aprotic solvent, DMSO, give a much lower yield (Table 1, entry 4, 14%). The examination of a number of solvents showed that toluene gave the highest yield at 98% (Table 1, entries 1–6). Solvents presumably control the formation of intermediates and activate the C–H bond of the alkyne to form the nucleophilic metal acetylide.[21] As shown in Table 1, $InCl_3$ was selected as the catalyst after screening an array of Lewis acids as it is nontoxic and water-tolerant,[21] despite high yields also being obtained in the presence of $SnCl_2$, CuCl, or CuI (Table 1, entries 10, 12 and 14).

Table 1 Results of solvent and catalyst screening[a]

Entry	Catalyst	Solvent	Time/h	Yield/%[b]
1	$InCl_3$	DCE	12	64
2	$InCl_3$	1,4-Dioxane-H_2O (1:1)	12	0
3	$InCl_3$	H_2O	3	0
4	$InCl_3$	DMSO	24	14
5	$InCl_3$	Toluene	12	98
6	$InCl_3$	Acetonitrile	12	81
7	$FeCl_3$	Toluene	5	52
8	$BiCl_3$	Toluene	20	37
9	$AlCl_3$	Toluene	20	17
10	$SnCl_2$	Toluene	20	90
11	$SnCl_4$	Toluene	5	52
12	CuCl	Toluene	12	95
13	CuBr	Toluene	12	74
14	CuI	Toluene	12	91
15	CuOTf	Toluene	4	89
16	$Bi(OTf)_3$	Toluene	12	65

[a]Reaction conditions: phenylacetylene (1.2 equiv.), benzaldehyde dimethyl acetal (1.2 equiv.), dibenzylamine (1.0 equiv.), catalyst (10 mol%), solvent (2.0 mL), reflux.
[b]Isolated yields after flash chromatography.

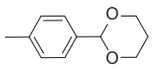
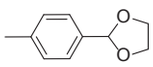
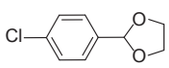
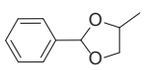
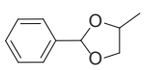
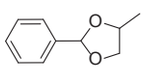
After finding the optimal conditions, we examined the scope of acetals for this double substitution reaction. As shown in Table 2, a variety of acetals reacted smoothly to give the desired propargylamines with good to excellent yields (Table 2, entries 1–8). Electronic variations in the aryl acetals, such as electron-donating or weak electron-withdrawing substituents (*p*-F, *p*-Cl), had only a small effect on the yield (Table 2, entries 2–5). Strongly withdrawing substituents, such as nitro (*p*-NO_2) dramatically decreased the yield (Table 2, entry 6, 20% yield). A study by Singh and colleagues[22] on the use of *p*-nitrobenzaldehyde in coupling reactions with alkynes and amines catalysed by $NiCl_2$ did not give the desired propargylamine. These results may indicate that this disubstitution reaction proceeds *via* an iminium ion intermediate.[23] An electron-donating substituent is required to stabilise the key intermediate. This observation is consistent with the results shown for aldehydes.[24] In contrast to acyclic acetals, the more stable cyclic acetals[14] underwent this reaction to give the corresponding propargylamines with lower yields (Table 2, entries 7–12, 46–68% yields). An acetal with a five membered ring gave a higher yield than one with a six membered ring probably owing to the improved stability of the acetal (Table 2, entry 8 *versus* 7).



Scheme 1 Multicomponent reaction of acetals, dibenzylamine and alkynes.

* Correspondent. E-mail: qpwu@bit.edu.cn

Table 2 Substrate scope of the three-component reaction[a]

Entry	Acetal (R^1)	Alkyne (R^2)	Yield/%[a,b]
1	C_6H_5	C_6H_5	98
2	*p*-ClC_6H_4	C_6H_5	91
3	*p*-FC_6H_4	C_6H_5	92
4	*p*-$CH_3OC_6H_4$	C_6H_5	93
5	*p*-$CH_3C_6H_4$	C_6H_5	92
6	*p*-$NO_2C_6H_4$	C_6H_5	20
7		C_6H_5	52
8		C_6H_5	68
9		C_6H_5	52
10		C_6H_4	46
11		*p*-$CH_3C_6H_4$	50
12		*p*-FC_6H_4	47
13	C_6H_5	*p*-$CH_3C_6H_4$	94
14	C_6H_5	*m*-$CH_3C_6H_4$	95
15	C_6H_5	*p*-$CH_3OC_6H_4$	70
16	C_6H_5	*p*-FC_6H_4	98
17	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	97
18	*p*-ClC_6H_4	*m*-$CH_3C_6H_4$	93
19	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	75
20	*p*-ClC_6H_4	*p*-FC_6H_4	98
21	*p*-FC_6H_4	*p*-$CH_3C_6H_4$	98
22	*p*-FC_6H_4	*p*-FC_6H_4	98
23	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	88
24	*p*-$CH_3OC_6H_4$	*m*-$CH_3C_6H_4$	90
25	*p*-$CH_3OC_6H_4$	*p*-FC_6H_4	93

[a]Reaction conditions: dibenzylamine (1.0 mmol), acetal (1.2 mmol), alkyne (1.2 mmol), $InCl_3$ (0.10 mmol), toluene (2.0 mL), reflux.
[b]Isolated yields after flash chromatography.

In variations of the alkyne substrates, excellent yields were also observed for aryl acetylenes with *p*-methyl or *p*-fluoro groups (> 88%, Table 2, entries 13–18, and 20–25), but substrates with a *p*-methoxy group led to diminished yields (Table 2, 70% for entry 15 *versus* 13, 14, and 16; and 75% for entry 19 *versus* 17, 18, and 20). This could be due to the weak metallation of the *p*-MeO-phenyl acetylene C–H resulting from the electron-donating nature of the MeO group.[25] To determine if the indium acetylide is formed *in situ* during the three-component reaction, a control reaction of amine with alkyne in the absence of an acetal was conducted. A mixture of dibenzylamine (1.2 equiv.) and phenylacetylene was heated under reflux with $InCl_3$ (10 mol%). The corresponding 1,3-diyne product was obtained in a 78% isolated yield. This result indicates that indium acetylide is formed as an intermediate,[11] and is the first example of the dimerisation of acetylene catalysed by $InCl_3$.

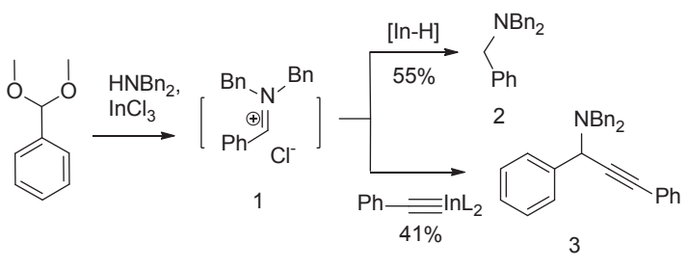
In order to elucidate the reaction pathway, we hoped to intercept the reaction intermediate. Yang and coworkers[26] demonstrated that [In–H] generated by the $InCl_3/Et_3SiH$/MeOH system was an active agent for the reductive amination of aldehydes with various amines. Accordingly, Et_3SiH–$InCl_3$ is able to trap the iminium ion if it occurs in the reaction solution. Under our standard reaction conditions, Et_3SiH (200 mol%) was added to the reaction mixture of benzaldehyde dimethyl acetal, dibenzylamine and phenylacetylene. Both tribenzylamine (the reductive amination product) and the corresponding propargylamine **3** were obtained in roughly equal amounts of 55% and 41% isolated yields, respectively (Scheme 2). Tribenzylamine was formed from the reduction of benzyl iminium ion **1**, formed by substitution of both the methoxy groups of benzaldehyde dimethyl acetal with dibenzylamine. At the same time, a propargylamine product **3** was formed by the attack of indium acetylide on the intermediate **1**. Therefore, these results show that this protocol proceeds *via* an iminium ion intermediate **1**.

Additionally, benzaldehyde dimethyl acetal can be converted into benzyl methyl ether in the presence of $Cu(OTf)_2$ and silane *via* the reduction of the corresponding oxocarbonium ion.[27] This result is consistent with our observations when benzaldehyde dimethyl acetal was treated with Et_3SiH–$InCl_3$. Benzyl methyl ether was not observed in our reduction process as described above (Scheme 2). Thus, the key intermediate, iminium ion **1** is not formed *via* an oxocarbonium ion.[21]

Experimental

All reactions were performed under an argon atmosphere with dry solvents under anhydrous conditions unless otherwise noted. Reactions were monitored by thin-layer chromatography using silica gel F 254 plates. NMR spectra were recorded in $CDCl_3$ on either a Varian 400 MHz or Bruker 500 MHz Fourier-transform spectrometer. Chemical shifts were reported in ppm referenced to tetramethylsilane (TMS) or the $CHCl_3$ solvent residual peak at 7.26 ppm for ^1H and 77.23 ppm for ^{13}C. HRMS data were obtained on a Thermo Scientific LTQ Orbirap Discovery (Bremen, Germany). Melting points were measured on a XT4A (Beijing Keyi) micro-melting point apparatus and are uncorrected.

Acetal (1.2 mmol), alkyne (1.2 mmol), dibenzylamine (0.192 mL, 1.0 mmol), and $InCl_3$ (10 mol%) were added to a flask (25 mL), followed by the addition of toluene (2.0 mL) under argon. The mixture was stirred under reflux and monitored by TLC. The solution was then cooled to r.t., diluted with dichloromethane (5.0 mL), washed with brine. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layer



Scheme 2 Intercepting the reaction intermediate with iminium ion.

was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether) to afford the desired product.

N,N-Dibenzyl-1,3-diphenyl-2-propynylamine:[20] White solid, m.p. 105–106 °C; yield 98% (Table 2, entry 1) and 46% (Table 2, entry 10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2 H), 7.68 (dd, *J* = 7.5, 1.8 Hz, 2 H), 7.48 (d, *J* = 7.5 Hz, 4 H), 7.40 (m, 9 H), 7.29 (dd, *J* = 7.5, 1.8 Hz, 3 H), 4.98 (s, 1 H), 3.84 (d, *J* = 13.5 Hz, 2 H), 3.59 (d, *J* = 13.5 Hz, 2 H).

N,N-Dibenzyl-1-(4-chlorophenyl)-3-phenylprop-2-yn-1-amine:[20] White solid, m.p. 91–92 °C; yield 91% (Table 2, entry 2) and 52% (Table 2, entry 9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.68 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 5H), 7.45 (s, 2H), 7.38 (t, *J* = 7.2 Hz, 6H), 7.30 (d, *J* = 7.2 Hz, 2H), 4.93 (s, 1H), 3.82 (d, *J* = 13.5 Hz, 2H), 3.57 (d, *J* = 13.5 Hz, 2H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.30, 137.87, 133.26, 132.01, 129.69, 128.91, 128.48, 128.46, 128.39, 128.29, 127.17, 123.02, 89.03, 84.08, 55.57, 54.67. HRMS (ESI) calcd for $C_{29}H_{25}ClN$ [M+H$^+$]: 422.16700, found 422.16708.

N,N-Dibenzyl-1-(4-fluorophenyl)-3-phenylprop-2-yn-1-amine: White solid, m.p. 90–91 °C; yield 92% (Table 2, entry 3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.2, 5.6 Hz, 2H), 7.71 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.52–7.45 (m, 7H), 7.41 (t, *J* = 7.5 Hz, 4H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.12 (t, *J* = 8.7 Hz, 2H), 4.97 (s, 1H), 3.86 (d, *J* = 13.5 Hz, 2H), 3.61 (d, *J* = 13.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.25, 161.30, 139.44, 135.01, 132.04, 129.98, 129.91, 128.95, 128.51, 128.41, 127.18, 123.14, 115.07, 88.94, 84.44, 55.50, 54.66. HRMS (ESI) calcd for $C_{29}H_{25}FN$ [M+H$^+$]: 406.19655, found 406.19678.

N,N-Dibenzyl-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-amine: White solid, m.p. 110–111 °C; yield 93% (Table 2, entry 4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.4 Hz, 4H), 7.48 (d, *J* = 7.4 Hz, 4H), 7.44 (d, *J* = 6.1 Hz, 3H), 7.37 (t, *J* = 7.3 Hz, 4H), 7.29 (d, *J* = 7.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 4.94 (s, 1H), 3.85 (t, *J* = 6.5 Hz, 5H), 3.58 (d, *J* = 13.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.96, 139.68, 131.98, 131.26, 129.42, 128.91, 128.42, 128.29, 128.24, 127.00, 123.34, 113.47, 88.45, 85.05, 55.45, 55.30, 54.52. HRMS (ESI) calcd for $C_{30}H_{28}NO$ [M+H$^+$]: 418.21654, found 418.21658.

N,N-Dibenzyl-3-phenyl-1-(p-tolyl)prop-2-yn-1-amine:[20] White solid, m.p. 100–101 °C; yield 92% (Table 2, entry 5), 52% (Table 2, entry 7) and 68% (Table 2, entry 8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.58 (m, 3H), 7.43 (d, *J* = 7.4 Hz, 4H), 7.40–7.27 (m, 8H), 7.21 (t, *J* = 7.3 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 4.91 (s, 1H), 3.79 (d, *J* = 13.5 Hz, 2H), 3.54 (d, *J* = 13.5, 2H), 2.32 (s, 3H).

N,N-Dibenzyl-1-(4-nitrophenyl)-3-phenylprop-2-yn-1-amine: Light yellow solid, m.p. 109–110 °C; yield 20% (Table 2, entry 6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.71–7.62 (m, 2H), 7.46 (d, *J* = 7.4 Hz, 4H), 7.41 (dd, *J* = 5.4, 4.1 Hz, 3H), 7.36 (m, 6H), 7.29–7.25 (m, 2H), 4.97 (s, 1H), 3.83 (d, *J* = 13.5 Hz, 2H), 3.57 (d, *J* = 13.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.49, 138.12, 130.92, 127.85, 127.36, 127.24, 127.06, 126.42, 125.96, 122.21, 108.67, 87.59, 83.63, 54.98, 53.57. HRMS (ESI) calcd for $C_{29}H_{25}N_2O_2$ [M+H$^+$]: 433.19105, found 433.18980.

N,N-Dibenzyl-1-phenyl-3-(p-tolyl)prop-2-yn-1-amine:[28] White solid, m.p. 100–101 °C; yield 50% (Table 2, entry 11) and 94% (Table 2, entry 13); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 4H), 7.40 (m, 6H), 7.35–7.24 (m, 5H), 4.99 (s, 1H), 3.85 (d, *J* = 13.5 Hz, 2H), 3.61 (d, *J* = 13.5 Hz, 2H), 2.46 (s, 3H).

N,N-Dibenzyl-1-phenyl-3-(m-tolyl)prop-2-yn-1-amine: White solid, m.p. 78–80 °C; yield 95% (Table 2, entry 14); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 6H), 7.45–7.35 (m, 6H), 7.30 (m, 5H), 4.99 (s, 1H), 3.85 (d, *J* = 13.5 Hz, 2H), 3.60 (d, *J* = 13.5 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.63, 139.29, 138.17, 132.58, 129.19, 129.11, 128.97, 128.34, 128.16, 127.51, 127.06, 123.12, 88.87, 84.32, 56.10, 54.69, 21.37. HRMS (ESI) calcd for $C_{30}H_{28}N$ [M+H$^+$]: 402.22163, found 402.22165.

N,N-Dibenzyl-3-(4-methoxyphenyl)-1-phenylprop-2-yn-1-amine: White solid, m.p. 109–110 °C; yield 70% (Table 2, entry 15); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 4H), 7.43–7.34 (m, 6H), 7.29 (m, 3H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.97 (s, 1H), 3.90 (s, 3H), 3.84 (d, *J* = 13.5 Hz, 2H), 3.59 (d, *J* = 13.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.61, 139.68, 139.44, 133.41, 128.96, 128.33, 128.13, 127.47, 127.04, 115.46, 114.05, 88.50, 83.15, 56.12, 55.42, 54.67. HRMS (ESI) calcd for $C_{30}H_{28}NO$ [M+H$^+$]: 418.21654, found 418.21655.

N,N-Dibenzyl-3-(4-flurophenyl)-1-phenylprop-2-yn-1-amine: White solid, m.p. 124–125 °C; yield 47% (Table 2, entry 12) and 98% (Table 2, entry 16); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 2H), 7.65 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.48 (d, *J* = 7.4 Hz, 4H), 7.39 (m, 6H), 7.30 (m, 3H), 7.14 (t, *J* = 8.7 Hz, 2H), 4.98 (s, 1H), 3.85 (d, *J* = 13.5 Hz, 2H), 3.58 (d, *J* = 13.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.53, 161.55, 139.53, 139.12, 133.91, 133.85, 128.95, 128.38, 128.31, 128.21, 127.60, 127.12, 119.35, 115.81, 115.63, 87.63, 84.46, 56.07, 54.70. HRMS (ESI) calcd for $C_{29}H_{25}FN$ [M+H$^+$]: 406.19655, found 406.19659.

N,N-Dibenzyl-1-(4-chlorophenyl)-3-(p-tolyl)prop-2-yn-1-amine: White solid, m.p. 126–127 °C; yield 97% (Table 2, entry 17); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 7.9 Hz, 2H), 7.48 (d, *J* = 7.4 Hz, 4H), 7.39 (t, *J* = 7.4 Hz, 6H), 7.33–7.25 (m, 4H), 4.93 (s, 1H), 3.82 (d, *J* = 13.5 Hz, 2H), 3.58 (d, *J* = 13.5 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.39, 138.59, 138.04, 133.23, 131.91, 129.74, 129.24, 128.94, 128.40, 128.28, 127.17, 119.97, 89.14, 83.33, 55.61, 54.69, 21.61. HRMS (ESI) calcd for $C_{30}H_{27}ClN$ [M+H$^+$]: 436.18265, found 436.18303.

N,N-Dibenzyl-1-(4-chlorophenyl)-3-(m-tolyl)prop-2-yn-1-amine: White solid, m.p. 80–81 °C; yield 93% (Table 2, entry 18); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.52–7.47 (m, 6H), 7.39 (t, *J* = 7.3 Hz, 6H), 7.30 (m, 4H), 4.94 (s, 1H), 3.83 (d, *J* = 13.5 Hz, 2H), 3.59 (d, *J* = 13.5 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.36, 138.24, 137.98, 133.26, 132.58, 129.73, 129.37, 129.12, 128.95, 128.42, 128.30, 127.19, 122.85, 89.23, 83.69, 55.60, 54.70, 21.37. HRMS (ESI) calcd for $C_{30}H_{27}ClN$ [M+H$^+$]: 436.18265, found 436.18295.

N,N-Dibenzyl-1-(4-chlorophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-amine: White solid, m.p. 106–107 °C; yield 75% (Table 2, entry 19); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 7.4 Hz, 4H), 7.39 (t, *J* = 7.5 Hz, 6H), 7.30 (m, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 4.93 (s, 1H), 3.91 (s, 3H), 3.82 (d, *J* = 13.4 Hz, 2H), 3.59 (d, *J* = 13.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.73, 139.42, 138.13, 133.43, 133.20, 129.74, 128.94, 128.78, 128.40, 128.27, 127.16, 115.15, 114.10, 88.88, 82.54, 55.62, 55.43, 54.68. HRMS (ESI) calcd for $C_{30}H_{27}ClNO$ [M+H$^+$]: 452.17757, found 452.17801.

N,N-Dibenzyl-1-(4-chlorophenyl)-3-(4-fluorophenyl)prop-2-yn-1-amine: White solid, m.p. 109–110 °C; yield 98% (Table 2, entry 20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.66 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 4H), 7.39 (t, *J* = 7.2 Hz, 6H), 7.30 (m, 2H), 7.16 (t, *J* = 8.7 Hz, 2H), 4.93 (s, 1H), 3.83 (d, *J* = 13.5 Hz, 2H), 3.57 (d, *J* = 13.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.61, 161.62, 139.25, 137.78, 133.93, 133.87, 133.34, 129.67, 128.91, 128.43, 128.34, 127.23, 119.07, 115.86, 115.68, 87.97, 83.82, 55.56, 54.70. HRMS (ESI) calcd for $C_{29}H_{24}ClFN$ [M+H$^+$]: 440.15758, found 440.15784.

N,N-Dibenzyl-1-(4-fluorophenyl)-3-(p-tolyl)prop-2-yn-1-amine: White solid, m.p. 92–93 °C; yield 98% (Table 2, entry 21); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.72 (m, 2H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 4H), 7.39 (t, *J* = 7.1 Hz, 4H), 7.30 (m, 4H), 7.11 (t, *J* = 8.1 Hz, 2H), 4.95 (s, 1H), 3.84 (d, *J* = 13.4 Hz, 2H), 3.59 (d, *J* = 13.4 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.21, 161.25, 139.48, 138.53, 135.10, 131.89, 129.96, 129.90, 129.22, 128.93, 128.37, 128.13, 127.12, 120.03, 115.00, 114.83, 88.98, 83.63, 55.48, 54.62, 21.59. HRMS (ESI) calcd for $C_{30}H_{27}FN$ [M+H$^+$]: 420.21220, found 420.21302.

N,N-Dibenzyl-1,3-bis(4-fluorophenyl)prop-2-yn-1-amine: White solid, m.p. 87–88 °C; yield 98% (Table 2, entry 22); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.71 (m, 2H), 7.69–7.65 (m, 2H), 7.49 (d, *J* = 7.5 Hz, 4H), 7.40 (t, *J* = 7.3 Hz, 4H), 7.31 (m, 2H), 7.14 (m, 4H), 4.95 (s, 1H), 3.85 (d, *J* = 13.3 Hz, 2H), 3.58 (d, *J* = 13.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.57, 163.23, 161.59, 161.28, 139.50, 139.33, 134.85, 133.90, 133.83, 129.90, 129.84, 128.89, 128.40, 128.28, 128.18, 127.56, 127.18, 127.09, 119.15, 119.13, 115.83, 115.65, 115.06, 114.89, 87.80, 84.10, 56.04, 55.42, 54.62. HRMS (ESI) calcd for $C_{29}H_{24}F_2N$ [M+H$^+$]: 424.1877, found 424.1858.

N,N-Dibenzyl-1-(4-methoxyphenyl)-3-(p-tolyl)prop-2-yn-1-amine: White solid, m.p. 148–149 °C; yield 88% (Table 2, entry 23); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J*=8.4 Hz, 2H), 7.55 (d, *J*=7.8 Hz, 2H), 7.46 (d, *J*=7.3 Hz, 4H), 7.35 (t, *J*=7.4 Hz, 4H), 7.26 (m, 4H), 6.92 (d, *J*=8.5 Hz, 2H), 4.90 (s, 1H), 3.81 (d, *J*=16.6 Hz, 5H), 3.55 (d, *J*=13.5 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.91, 139.73, 138.31, 131.84, 131.39, 129.42, 129.14, 128.90, 128.26, 126.95, 120.25, 113.42, 88.50, 84.23, 55.44, 55.29, 54.49, 21.55. HRMS (ESI) calcd for $C_{31}H_{30}NO$ [M+H$^+$]: 432.23219, found 432.23232.

N,N-Dibenzyl-1-(4-methoxyphenyl)-3-(m-tolyl)prop-2-yn-1-amine: White solid, m.p. 95–96 °C; yield 90% (Table 2, entry 24); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J*=8.2 Hz, 2H), 7.49 (d, *J*=7.8 Hz, 6H), 7.41–7.22 (m, 8H), 6.95 (d, *J*=7.8 Hz, 2H), 4.94 (s, 1H), 3.85 (t, *J*=6.6 Hz, 5H), 3.58 (d, *J*=13.5 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.96, 139.72, 138.14, 132.54, 131.34, 129.44, 129.13, 129.07, 128.93, 128.34, 128.30, 127.00, 123.15, 113.46, 88.62, 84.63, 55.46, 55.30, 54.53, 21.34. HRMS (ESI) calcd for $C_{31}H_{30}NO$ [M+H$^+$]: 432.23219, found 432.23194.

N,N-Dibenzyl-3-(4-fluorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-amine: White solid, m.p. 129–130 °C; yield 93% (Table 2, entry 25); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J*=8.2 Hz, 4H), 7.47 (d, *J*=7.4 Hz, 4H), 7.36 (t, *J*=7.3 Hz, 4H), 7.30–7.25 (m, 3H), 7.13 (t, *J*=8.2 Hz, 2H), 6.94 (d, *J*=8.0 Hz, 2H), 4.91 (s, 1H), 3.83 (d, *J*=12.0 Hz, 5H), 3.54 (d, *J*=13.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.47, 161.48, 158.99, 139.60, 133.85, 133.78, 131.13, 129.38, 128.88, 128.31, 127.03, 119.38, 115.75, 115.58, 113.48, 87.35, 84.74, 55.41, 55.30, 54.52. HRMS (ESI) calcd for $C_{30}H_{27}FNO$ [M+H$^+$]: 436.20712, found 436.20645.

Tribenzylamine: White solid, m.p. 89–90 °C (lit.[29] 86.4–88 °C); yield 69% (Scheme 2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J*=7.3 Hz, 6H), 7.33 (t, *J*=7.5 Hz, 6H), 7.28–7.21 (m, 3H), 3.57 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.77, 128.85, 128.33, 126.96, 109.88, 58.04.

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