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Propargylamine Synthesis by Copper-Catalyzed Oxidative Coupling of Alkynes and Tertiary Amine *N*-Oxides

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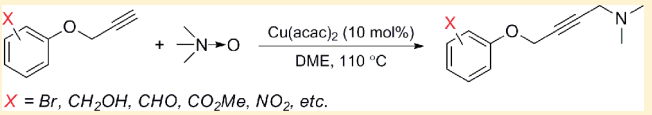
Supporting Information

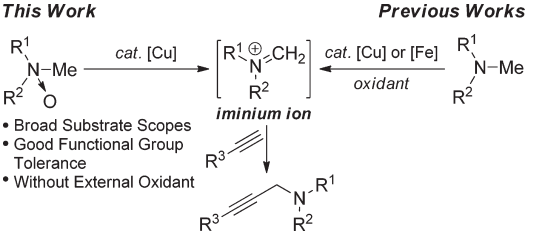
ABSTRACT: An efficient method for synthesizing *N*,*N*-dimethylpropargylamines is described. The synthesis exploited the Cu(II)-catalyzed oxidative alkynylation reaction of trimethylamine *N*-oxides with alkynes in the absence of external oxidant. Both aromatic and aliphatic alkynes were utilized to achieve the corresponding products in moderate to excellent yields. The reaction conditions tolerated ester, hydroxy, and aldehyde groups.



The development of convenient and efficient methods for the synthesis of propargylamines has attracted considerable attention. Propargylamines can be utilized as versatile and key synthetic intermediates for the preparation of several natural products[1] and bioactive compounds.[2] Over the past two decades, three main methods have been developed for the preparation of propargylamines. One method involves the substitution reactions of functionalized tertiary amines with alkynyllithium, -magnesium,[3] or -aluminum[4] reagents. These reactions need leaving groups and stoichiometric nucleophiles. Another method involves the transition-metal-catalyzed three-component one-pot coupling reactions (A^3-coupling reactions) of aldehydes, alkynes, and secondary amines. These reactions require prefunctionalized aldehydes to form iminium ion intermediates in situ.[5−7] The last method involves the copper- and iron-catalyzed direct oxidative alkynylations of C−H bonds in tertiary amines. These reactions also proceed via iminium ion intermediates generated from the oxidative dehydrogenation reactions[8] of tertiary amines with an oxidant such as ^{t}BuOOH,[9] *N*-bromosuccinimide,[10] or $(^t\text{BuO})_2$[11] in situ (Scheme 1). Among these methods, the third one is the most economical and practical. However, the requirement of external oxidants is disadvantageous because some alkynes bearing sensitive substituents such as the aldehyde group could not be used. In addition, aliphatic alkynes usually have low reactivities in such reactions.

Iminium ion intermediates[12] could also be generated by the decomposition of corresponding tertiary amine *N*-oxides. The decomposition requires appropriate promoters such as trifluoroacetic anhydride,[13] sulfur dioxide,[14] iron salts,[15] and copper salts.[16] Moreover, we supposed that tertiary amine *N*-oxides may also undergo direct oxidative alkynylations in the presence of a copper salt without using an external oxidant. Indeed, when the reactions of trimethylamine *N*-oxide with various terminal alkynes were treated at the optimized conditions, *N*,*N*-dimethylpropargylamines were obtained in satisfactory yields (Scheme 1). This protocol showed a broad substrate scope and good functional group tolerance, and we report our results herein.

Scheme 1. Reaction of Terminal Alkynes with Iminium Ion Intermediates



In our initial studies, the reaction of phenylacetylene (**1a**) with trimethylamine *N*-oxide dihydrate (**2**) was chosen as a model reaction for optimizing the reaction conditions. The optimization included selecting the most suitable copper catalysts and solvents at 110 °C under a nitrogen atmosphere (Table 1). Several copper salts were tested in tetrahydrofuran (THF). These include CuBr, CuI, Cu(II) trifluoromethanesulfonate [$Cu(OTf)_2$], Cu(II) acetate monohydrate [$Cu(OAc)_2\cdot H_2O$], $CuF_2\cdot 2H_2O$, and Cu(II) acetylacetonate [$Cu(acac)_2$] (entries 2−7). The Cu(II) salts exhibited higher catalytic activities than Cu(I) salts, and $Cu(acac)_2$ had the highest activity. On the contrary, the Cu(I) salt CuBr demonstrated the most effective catalytic activity in the oxidative alkynylations of tertiary amines in the presence of an oxidant.[9] No reaction was observed in the absence of a copper catalyst (entry 1). The solvents were then screened using $Cu(acac)_2$ as the catalyst (entries 8−12). Both polar [THF, dioxane, and acetonitrile (CH_3CN)] and nonpolar solvents [1,2-dimethoxyethane (DME), 1,2-dichloroethane, (DCE), and methyl *tert*-butyl ether (MTBE)] were examined, and DME proved to be the best solvent (entry 10). Therefore, the subsequent reactions of the terminal alkynes **1a**−**p** with trimethylamine *N*-oxide

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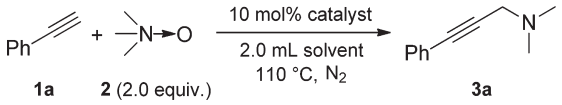
Table 1. Catalyst and Solvent Screening[a]



entry	catalyst	solvent	time (h)	yield[b] (%)
1	none	THF	12	N.R.[c]
2	CuBr	THF	6	48
3	CuI	THF	4	trace
4	$Cu(OTf)_2$	THF	12	74
5	$Cu(OAc)_2 \cdot H_2O$	THF	10	62
6	$CuF_2 \cdot 2H_2O$	THF	12	62
7	$Cu(acac)_2$	THF	10	77
8	$Cu(acac)_2$	dioxane	12	77
9	$Cu(acac)_2$	CH_3CN	4	trace
10	$Cu(acac)_2$	DME	4	84
11	$Cu(acac)_2$	DCE	6	24
12	$Cu(acac)_2$	MTBE	10	trace

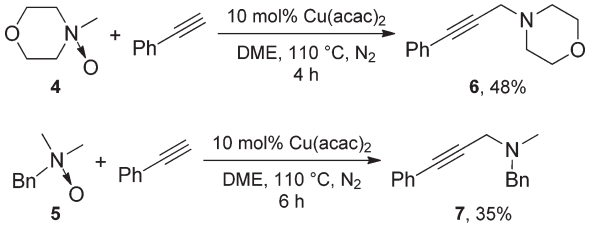
[a] Reaction conditions: phenylacetylene (51.1 mg, 0.5 mmol), trimethylamine *N*-oxide dihydrate (111.1 mg, 1.0 mmol), catalyst (0.05 mmol), solvent (2.0 mL), 110 °C, under a nitrogen atmosphere. [b] Isolated yield. [c] No reaction.

dihydrate **2** were performed in the presence of $Cu(acac)_2$ as a catalyst in DME at 110 °C under a nitrogen atmosphere.

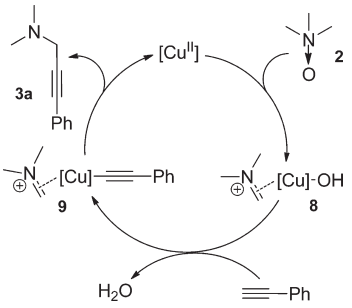
The reactions of the terminal alkynes **1a**−**p** with trimethylamine *N*-oxide dihydrate **2** were performed under the optimized conditions, and the results are summarized in Table 2. The reactions of the aromatic alkynes phenylacetylene (**1a**) and 4-methylphenylacetylene (**1b**) with trimethylamine *N*-oxide dihydrate **2** smoothly proceeded to furnish the corresponding popargylamines **3a** and **3b** in high yields (84% and 93%, respectively; entries 1 and 2). There was a slight decrease in the reaction yield when 4-bromophenylacetylene (**1c**), which bore the electron-withdrawing group Br on its benzene ring, was examined (80% yield of **3c**; entry 3). However, only a moderate yield was obtained from the reaction of **2** with 4-fluorophenylacetylene (**1d**), which bore the strong electron-withdrawing group F on its benzene ring (68% yield of **3d**; entry 4). These results indicated that the reaction yield was remarkably influenced by the electronic property of the substituent linked on the benzene ring of the aromatic alkyne. Regarding the aliphatic alkynes **1e**−**p** (entries 5−17), all except **1f** underwent the desired reactions efficiently to give the corresponding products **3e** and **3g**−**p** in moderate to good yields (entries 5, 7−16; 67%−89% yields). Previous studies have shown that aliphatic alkynes showed poor reactivities in the copper-catalyzed direct oxidative alkynylation of tertiary amines in the presence of an oxidant.[9] In the present study, product 1-(*N*,*N*-dimethylamino)-4-phthalimido-2-butyne (**3h**) appeared to be an interesting intermediate that can be used for the synthesis of propargylic diamines.[17] The reaction conditions employed were found to tolerate ester, hydroxy, and aldehyde groups. Aldehyde group is well-known to be easily oxidized to carboxyl group in the presence of a conventional oxidant.

The above results prompted us to investigate the direct oxidative alkynylation of other tertiary amine *N*-oxides to determine the scope of tertiary amine *N*-oxide substrates. When *N*-methylmorpholine *N*-oxide monohydrate (**4**)[18] and benzyldimethylamine *N*-oxide (**5**) were treated with phenylacetylene

Scheme 2. Reactions of *N*-Methylmorpholine *N*-Oxide Monohydrate (4) and Benzyldimethylamine *N*-Oxide (5)



Scheme 3. Possible Mechanism for the Direct Oxidative Alkynylation of Tertiary Amine *N*-Oxides to Propargylamines



under standard conditions, the corresponding products **6** and **7** were obtained in low yields (48% and 35%, respectively; Scheme 2).

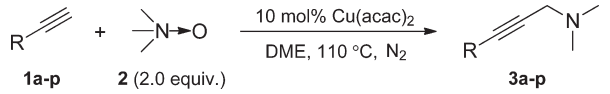
A possible mechanism[19] for the direct oxidative alkynylation of tertiary amine *N*-oxides to propargylamines is shown in Scheme 3. The reaction of **2** with a Cu(II) catalyst[16] could produce the iminium ion intermediate **8** (coordinated to copper hydroxide). This intermediate could then react with phenylacetylene to generate iminium ion intermediate **9** (coordinated to copper acetylide). The nucleophilic attack[9b] of copper acetylide on the iminium ion intermediate **9** yields the desired product **3a**. The Cu(II) catalyst is regenerated after the reaction. The reactions of the less acidic aliphatic alkynes also proceeded efficiently to give the corresponding products in satisfactory yields. The efficiency is possibly attributed to the strong basicity of the [Cu]-OH generated in situ.

In conclusion, we have established a new, simple, and effective method for synthesizing propargylamines using tertiary amine *N*-oxides in the absence of external oxidant. Aside from aromatic alkynes, the less acidic aliphatic alkynes could also be utilized in the Cu(II)-catalyzed direct oxidative alkynylation of trimethylamine *N*-oxide. Although the reactions of some tertiary amine *N*-oxides showed inferior efficiencies, the present method can be valuably complemented with previous methods for synthesizing propargylamines.

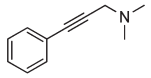
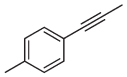
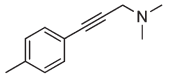
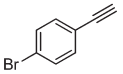
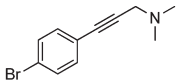
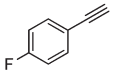
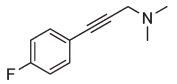
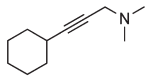
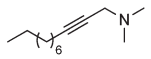
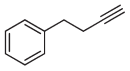
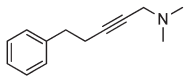
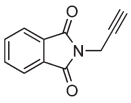
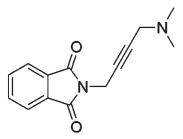
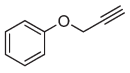
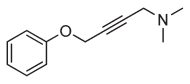
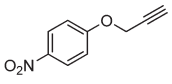
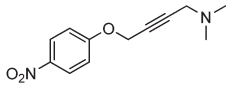
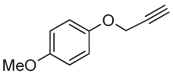
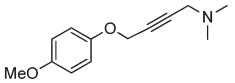
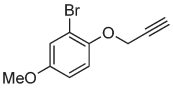
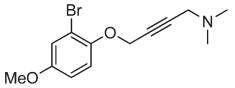
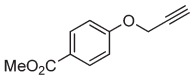
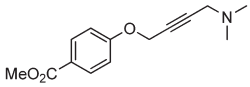
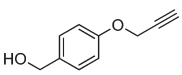
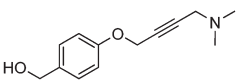
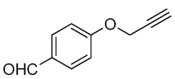
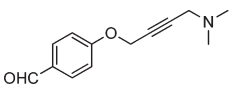
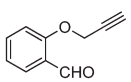
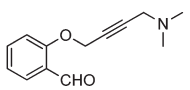
EXPERIMENTAL SECTION

All reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques. THF, DME, dioxane, and MTBE were distilled from sodium/benzophenone. DCE and MeCN were distilled from CaH_2. NMR spectra were run in $CDCl_3$ on a 400 MHz instrument and recorded at the following frequencies: proton (^1H, 400 MHz), carbon (^{13}C, 100 MHz).

Table 2. Copper-Catalyzed Oxidative Alkynylation of the C−H Bond in Trimethylamine *N*-Oxide To Yield Propargylamines[a]



1a-p **2** (2.0 equiv.) **3a-p**

entry	alkyne **1**		time (h)	product **3**		yield (%)[b]
1		**1a**	4		**3a**	84
2		**1b**	5		**3b**	93
3		**1c**	5		**3c**	80
4		**1d**	5		**3d**	68
5		**1e**	4		**3e**	85
6		**1f**	5		**3f**	53
7		**1g**	4		**3g**	84
8[c]		**1h**	2		**3h**	71
9		**1i**	4		**3i**	89
10		**1j**	7		**3j**	79
11		**1k**	4		**3k**	83
12		**1l**	4		**3l**	72
13		**1m**	4		**3m**	76
14[d]		**1n**	4		**3n**	72
15		**1o**	4		**3o**	74
16		**1p**	1		**3p**	67

[a] Conditions: terminal alkyne **1** (0.5 mmol), trimethylamine *N*-oxide dihydrate (111.1 mg, 1.0 mmol), $Cu(acac)_2$ (13.1 mg, 0.05 mmol), DME (2.0 mL), 110 °C, nitrogen atmosphere. [b] Isolated yield. [c] DME (4.0 mL) was used. [d] Reaction was carried out at 120 °C.

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General Procedure for the Synthesis of Propargylamines (3a−p). A mixture of alkyne (0.5 mmol), $Cu(acac)_2$ (13.1 mg, 0.05 mmol), trimethylamine *N*-oxide dihydrate (111.1 mg, 1.0 mmol), and DME (2.0 mL) was placed in a 25 mL sealed tube under a nitrogen atmosphere. The mixture was then stirred at 110 °C until the reaction was completed (as determined by thin-layer chromatography). The solvent was then removed under reduced pressure. Finally, the residue was purified by chromatography on silica gel (petroleum ether:ethyl acetate, 3:1) to afford propargylamines.

N,N-Dimethyl-3-phenylprop-2-yn-1-amine (**3a**):[20] yield 84%, 66.9 mg, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 6H), 3.47 (s, 2H), 7.29−7.30 (m, 3H), 7.43−7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.3, 48.6, 84.6, 85.2, 123.2, 128.0, 128.3, 131.7.

N,N-Dimethyl-3-(p-tolyl)prop-2-yn-1-amine (**3b**):[21] yield 93%, 81.0 mg, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.37 (s, 6H), 3.46 (s, 2H), 7.11 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 44.4, 48.8, 84.0, 85.4, 120.3, 129.2, 131.7, 138.2.

3-(4-Bromophenyl)-N,N-dimethylprop-2-yn-1-amine (**3c**): yield 80%, 95.3 mg, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 6H), 3.45 (s, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.5, 48.7, 84.3, 86.1, 122.3, 122.4, 131.7, 133.3; HRMS (EI) m/z calcd for $C_{11}H_{12}NBr$ $[M]^+$ 237.0153, found 237.0158.

3-(4-fluorophenyl)-N,N-dimethylprop-2-yn-1-amine (**3d**):[21] yield 68%, 60.4 mg, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 6H), 3.45 (s, 2H), 6.97−7.02 (m, 2H), 7.40−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.4, 48.7, 84.3, 84.5, 115.6 (d, J = 11.9 Hz), 119.4, 133.7 (d, J = 8.2 Hz), 162.5 (d, J = 247.4 Hz); HRMS (EI) m/z calcd for $C_{11}H_{12}NF$ $[M]^+$ 177.0954, found 177.0954.

3-Cyclohexyl-N,N-dimethylprop-2-yn-1-amine (**3e**):[22] yield 85%, 70.3 mg, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26−1.77 (m, 10H), 2.28 (s, 6H), 2.40 (m, 1H), 3.21 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0, 26.1, 29.2, 33.1, 44.3, 48.4, 74.8, 89.8.

N,N-Dimethylundec-2-yn-1-amine (**3f**):[23] yield 53%, 51.9 mg, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86−0.90 (m, 3H), 1.27−1.49 (m, 12H), 2.18−2.22 (m, 2H), 2.28 (s, 6H), 3.20 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 18.9, 22.8, 29.06, 29.09, 29.3, 29.4, 32.0, 44.3, 48.4, 75.0, 85.6.

N,N-Dimethyl-5-phenylpent-2-yn-1-amine (**3g**):[22] yield 84%, 79.0 mg, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 6H), 2.52 (tt, J = 7.6 Hz, 2.0 Hz, 2H), 2.84 (t, J = 7.6 Hz, 2H), 3.22 (t, J = 2.0 Hz), 7.19−7.23 (m, 3H), 7.27−7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 35.4, 44.2, 48.2, 75.8, 84.5, 126.3, 128.4, 128.5, 140.8.

2-(4-(Dimethylamino)but-2-yn-1-yl)isoindoline-1,3-dione (**3h**):[17] yield 71%, 86.3 mg, white solid, mp 94−96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 6H), 3.21 (t, J = 1.8 Hz, 2H), 4.50 (t, J = 1.9 Hz, 2H), 7.73−7.75 (m, 2H), 7.87−7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3, 44.2, 47.9, 78.42, 78.43, 123.5, 132.1, 134.1, 167.1.

N,N-Dimethyl-4-phenoxybut-2-yn-1-amine (**3i**):[24] yield 89%, 84.3 mg, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 6H), 3.29 (s, 2H), 4.74 (s, 2H), 6.70−7.00 (m, 3H), 7.28−7.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.1, 48.0, 56.1, 80.0, 82.7, 115.0, 121.3, 129.4, 157.7.

N,N-Dimethyl-4-(4-nitrophenoxy)but-2-yn-1-amine (**3j**): yield 79%, 92.7 mg, yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 6H), 3.28 (t, J = 1.8 Hz, 2H), 4.84 (t, J = 1.8 Hz, 2H), 7.06 (d, J = 9.3 Hz, 2H), 8.22 (d, J = 9.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.4, 48.1, 56.9, 78.6, 84.4, 115.2, 126.0, 142.1, 162.7; IR (neat) 752, 845, 997, 1111, 1230, 1261, 1342, 1455, 1514, 1591, 1608, 2778, 2823, 2862, 2940, 3084 cm^{-1}; HRMS (EI) m/z calcd for $C_{12}H_{14}N_2O_3$ $[M]^+$ 234.1004, found 234.1001.

4-(4-Methoxyphenoxy)-N,N-dimethylbut-2-yn-1-amine (**3k**): yield 83%, 91.0 mg, colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 6H), 3.28 (t, J = 1.8 Hz, 2H), 3.77 (s, 3H), 4.68 (t, J = 1.9 Hz, 2H), 6.84 (d, J = 9.2 Hz, 2H), 6.93 (d, J = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.1, 48.0, 55.7, 56.9, 80.2, 82.6, 114.5, 116.1, 151.8, 154.3; IR (neat) 825, 1013, 1038, 1106, 1209, 1359, 1456, 1508, 2776, 2831, 2860, 2941, 3045 cm^{-1}; HRMS (EI) m/z calcd. for $C_{13}H_{17}NO_2$ $[M]^+$ 219.1259, found 219.1254.

4-(2-Bromo-4-methoxyphenoxy)-N,N-dimethylbut-2-yn-1-amine (**3l**): yield 72%, 107.4 mg, yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 6H), 3.28 (s, 2H), 3.77(s, 3H), 4.75 (s, 2H), 6.81 (dd, J = 10.0 Hz, 3.0 Hz, 1H), 7.04 (d, J = 10.0 Hz, 1H), 7.12 (d, J = 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.1, 48.0, 55.8, 58.3, 79.7, 83.2, 113.3, 113.6, 116.3, 118.8, 148.5, 154.8; IR (neat) 800, 842, 863, 1002, 1041, 1105, 1213, 1277, 1456, 1493, 1575, 1604, 2776, 2824, 2860, 2940 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{16}NO_2Br$ $[M]^+$ 297.0364, found 297.0367.

Methyl 4-((4-(dimethylamino)but-2-yn-1-yl)oxy)benzoate (**3m**): yield 76%, 94.0 mg, light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 6H), 3.29 (s, 2H), 3.89 (s, 3H), 4.79 (s, 2H), 7.01 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.3, 48.1, 52.1, 56.4, 79.4, 83.5, 114.7, 123.4, 131.7, 161.5, 166.9; IR (neat) 846, 1003, 1105, 1171, 1281, 1435, 1509, 1581, 1606, 1717, 2776, 2823, 2861, 2948 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{17}NO_3$ $[M]^+$ 247.1208, found 247.1203.

(4-((4-(Dimethylamino)but-2-yn-1-yl)oxy)phenyl)methanol (**3n**): yield 72%, 79.0 mg, colorless solid; mp 61−63 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88 (s, 1H), 2.25 (s, 6H), 3.27 (s, 2H), 4.62 (s, 2H), 4.73 (s, 2H), 6.97 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.2, 48.0, 56.3, 64.9, 80.1, 82.7, 115.0, 128.6, 134.3, 157.3; IR (neat) 812, 1010, 1175, 1216, 1458, 1511, 1586, 1610, 2782, 2826, 2866, 2945, 3358 cm^{-1}; HRMS (EI) m/z calcd. for $C_{13}H_{17}NO_2$ $[M]^+$ 219.1259, found 219.1254.

4-((4-(Dimethylamino)but-2-yn-1-yl)oxy)benzaldehyde (**3o**): yield 74%, 80.6 mg, yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 6H), 3.29 (s, 2H), 4.82 (s,2H), 7.10 (d, J = 8.7 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 9.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.2, 48.0, 56.4, 79.1, 83.8, 115.3, 130.5, 131.9, 162.6, 190.9; IR (neat) 832, 1000, 1162, 1225, 1455, 1508, 1579, 1600, 1696, 2777, 2823, 2941 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{15}NO_2$ $[M]^+$ 217.1103, found 217.1111.

2-((4-(Dimethylamino)but-2-yn-1-yl)oxy)benzaldehyde (**3p**): yield 68%, 73.9 mg, yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 6H), 3.28 (s, 2H), 4.87 (s, 2H), 7.07 (dd, J = 7.6 Hz, 7.4 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.56 (dd, J = 8.4 Hz, 7.4 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 10.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.2, 48.0, 56.9, 79.1, 83.9, 113.5, 121.5, 128.5, 135.7, 160.6, 189.6; IR (neat) 758, 999, 1102, 1219, 1459, 1482, 1599, 1689, 2776, 2823, 2861, 2940 cm^{-1}; HRMS (ES) m/z calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1181, found 218.1182.

Procedure for the Synthesis of Propargylamine 4-(3-Phenylprop-2-yn-1-yl)morpholine (6).[25] A mixture of phenylacetylene (51.1 mg, 0.5 mmol), $Cu(acac)_2$ (13.1 mg, 0.05 mmol), *N*-methylmorpholine *N*-oxide monohydrate (202.8 mg, 1.5 mmol), and DME (2.0 mL) was placed in 25 mL sealed tube under a nitrogen atmosphere. The mixture was then stirred at 110 °C until the reaction was complete (as determined by thin-layer chromatography). The solvent was then removed under reduced pressure. Finally, the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to afford **6** (colorless oil) in 48% yield (48.5 mg): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.65 (t, J = 4.6 Hz, 4H), 3.51 (s, 2H), 3.77 (t, J = 4.6 Hz, 4H), 7.29−7.32 (m, 3H), 7.42−7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.2, 52.6, 67.0, 84.2, 85.7, 123.1, 128.3, 128.4, 131.8.

Procedure for the Synthesis of *N*-Benzyl-*N*-methyl-3-phenylprop-2-yn-1-amine (7).[9b] A mixture of phenylacetylene (51.1 mg, 0.5 mmol), $Cu(acac)_2$ (0.05 mmol), *N,N*-dimethyl-1-phenylmethanamine oxide (151.2 mg, 1.0 mmol), and DME (2.0 mL) was placed in 25 mL sealed tube under a nitrogen atmosphere. The mixture was then stirred at 110 °C until the reaction was completed (as determined by thin-layer chromatography). The solvent was then removed under

reduced pressure. Finally, the residue was purified by chromatography on silica gel (petroleum ether:ethyl acetate, 10:1) to afford **7** (colorless oil) in 35% yield (41.5 mg): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 3.51 (s, 2H), 3.64 (s, 2H), 7.24−7.38 (m, 8H), 7.46−7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.2, 45.9, 60.4, 84.6, 85.9, 123.5, 127.4, 128.2, 128.4, 128.5, 129.4, 131.9, 138.6.

■ ASSOCIATED CONTENT

Supporting Information. Characterization for compounds, including copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) For selected recent references, see: (a) Farwick, A.; Helmchen, G. *Org. Lett.* **2010**, *12*, 1108. (b) Jiang, B.; Xu, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2543. (c) Yoon, T.; Shair, M. D.; Danishefsky, S. J.; Shulteo, G. K. *J. Org. Chem.* **1994**, *59*, 3752.

(2) For selected recent references, see: (a) Giles, R. L.; Nkansah, R. A.; Looper, R. E. *J. Org. Chem.* **2010**, *75*, 261. (b) Samai, S.; Nandi, G. C.; Singh, M. S. *Tetrahedron Lett.* **2010**, *51*, 5555. (c) Nakamura, H.; Ishikura, M.; Sugiishi, T.; Kamakura, T.; Biellmann, J.-F. *Org. Biomol. Chem.* **2008**, *6*, 1471. (d) Trybulski, E. J.; Zhang, J.; Kramss, R. H.; Mangano, R. M. *J. Med. Chem.* **1993**, *36*, 3533.

(3) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968.

(4) Ahn, J. H.; Joung, M. J.; Yoon, N. M.; Oniciu, D. C.; Katritzky, A. R. *J. Org. Chem.* **1999**, *64*, 488.

(5) Selected examples of copper-catalyzed A^3-coupling reactions: (a) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581. (b) Fodor, A.; Kiss, Á.; Debreczeni, N.; Hell, Z.; Gresitsb, I. *Org. Biomol. Chem.* **2010**, *8*, 4575. (c) Nakamura, S.; Ohara, M.; Nakamura, Y.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2010**, *16*, 2360. (d) Patil, M. K.; Keller, M.; Reddy, B. M.; Pale, P.; Sommer, J. *Eur. J. Org. Chem.* **2008**, 4440. (e) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405. (f) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (g) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem. Int., Ed.* **2003**, *42*, 5763. (h) Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268.

(6) Selected examples of gold-catalyzed A^3-coupling reactions: (a) Zhang, X.; Corma, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4358. (b) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529. (c) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.

(7) Selected examples of other metal-catalyzed A^3-coupling reactions: (a) Namitharan, K.; Pitchumani, K. *Eur. J. Org. Chem.* **2010**, 411. (b) Zhang, Y.; Li, P.; Wang, M.; Wang, L. *J. Org. Chem.* **2009**, *74*, 4364. (c) Chen, W.-W.; Nguyen, R. V.; Li, C.-J. *Tetrahedron Lett.* **2009**, *50*, 2895. (d) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473. (e) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319. (f) Satoshi, S.; Takashi, K.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2534.

(8) For selected recent reviews, see: (a) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Res.* **2011**, *111*, 1293. (b) Yeung, C. S.; Dong, V. M. *Chem. Res.* **2011**, *111*, 1215. (c) Yoo, W.-J.; Li, C.-J. *Top. Curr. Chem.* **2010**, *292*, 281. (d) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

(9) (a) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810.

(10) Niu, M.; Yin, Z.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 3961.

(11) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701.

(12) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.

(13) Ahond, A.; Cavé, A.; Kan-Fan, C.; Husson, H.-P.; de Rostolan, J.; Potier, P. *J. Am. Chem. Soc.* **1968**, *90*, 5622.

(14) Edward, J. T.; Whiting, J. *Can. J. Chem.* **1971**, *49*, 3502.

(15) (a) Hancock, M. T.; Pinhas, A. R. *Organometallics.* **2002**, *21*, 5155. (b) Ferris, J. P.; Gerwe, R. D.; Gapski, G. R. *J. Am. Chem. Soc.* **1967**, *89*, 5270.

(16) Rousselett, G.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1995**, *36*, 4999.

(17) Jeon, H.-B.; Lee, Y.; Qiao, C.; Huang, H.; Sayre, L. M. *Bioorg. Med. Chem.* **2003**, *11*, 4631.

(18) VanRheenen, V.; Cha, D. Y.; Hartley, W. M. *Org. Synth.* **1978**, *58*, 43.

(19) Hwang, D.-R.; Uang, B.-J. *Org. Lett.* **2002**, *4*, 463.

(20) Bieber, L. W.; da Silva, M. F. *Tetrahedron Lett.* **2004**, *45*, 8281.

(21) Mhamed, L.; Henri, D.; Maurice, S. *Synthesis* **2005**, *8*, 1359.

(22) Schlogl, K.; Pelousek, H. *Monatsh. Chem.* **1961**, *92*, 51.

(23) Shaibakova, M. G.; Makhmudiyarov, G. A.; Khalilov, L. M.; Paramonov, E. A.; Ibragimov, A. G.; Dzhemilev, U. M. *Russ. J. Org. Chem.* **2010**, *46*, 422.

(24) Manukyan, M. O.; Babakhanyan, A. V.; Panosyan, G. A.; Gyul'nazaryan, A. Kh.; Kocharyan, S. T. *Russ. J. Gen. Chem.* **2007**, *77*, 1370.

(25) Shaibakova, M. G.; Titova, I. G.; Makhmudiyarov, G. A.; Ibragimov, A. G.; Dzhemilev, U. M. *Russ. J. Org. Chem.* **2010**, *46*, 43.