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Microwave-Assisted Cu(I)-Catalyzed Synthesis of Unsymmetrical 1,4-Diamino-2-butynes via Cross-A^3-Coupling/Decarboxylative A^3-Coupling

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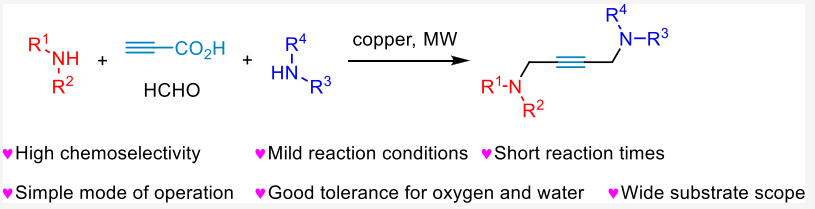

ABSTRACT: 1,4-Diamino-2-butynes display both chemical and physiological properties. Here a highly efficient synthesis avenue to generate unsymmetric 1,4-diamino-2-butynes has been developed by microwave-assisted Cu(I)-catalyzed cross-A^3-coupling/decarboxylative coupling of two different amines, formaldehyde, and propiolic acid through a domino process. This multicomponent reaction provides a series of target products in moderate to good yields with high chemoselectivity.

INTRODUCTION

Propargylamines have attracted much attention from chemists since their discovery as important units of various biologically active compounds and drug molecules.[1] They serve as versatile building blocks for the formation of nitrogen-containing heterocyclic compounds such as oxazolidinones,[2] aminoindolizines,[3] pyrroles,[4] 2-aminoimidazoles,[5] and pyrrolidines.[6] In the past two decades, several synthesis methods have been developed such as amination of propargylic halides,[7] stoichiometric addition of lithium acetylides or Grignard reagents to imines,[8] CDC reactions,[9] and multicomponent domino reactions.[10] Among these, the (decarboxylative) A^3-coupling reaction[11] is the most popular approach for the rapid synthesis of diverse propargylamines.[12] Also 1,4-diamino-2-butynes have gained a lot of attention in recent years, due to their potential value in the drug discovery.[13] Presently, several novel and practical methods for the construction of 1,4-diamino-2-butynes have been reported. In 2011, Nakumura's group developed a Cu(I)-catalyzed deacetylenative coupling of propargylic amines for the synthesis of 1,4-diamino-2-butynes (Scheme 1a).[14] Afterward, Van der Eycken and co-workers described a Cu(I)-catalyzed A^3-coupling/decarboxylative coupling of a propiolic acid, an aldehyde, and an amine for the generation of symmetric 1,4-diamino-2-butynes (Scheme 1b).[15] Then, Bolm and Hernández reported an efficient strategy for the preparation of 1,4-diamino-2-butynes via a copper-catalyzed cross-coupling employing calcium carbide as alkynyl sources (Scheme 1c).[16] Despite significant advances, these methods only provided symmetrical 1,4-diamino-2-butynes. Therefore, it seems challenging to develop synthetic approaches for the construction of unsymmetrical 1,4-diamino-2-butynes.

In 2017, Feng and co-workers successfully reported the first example for the direct synthesis of trisubstituted unsymmetrical 1,4-diamino-2-butynes via a microwave-assisted copper-catalyzed cross-A^3-coupling/decarboxylative A^3 domino reaction of an amine, two kinds of aldehydes, and a propiolic acid (Scheme 1d).[17] Undoubtedly, the key for the chemoselectivity of this method is the difference in reactivity of formaldehyde compared to the other aldehyde. Inspired by this work, we wonder whether a new kind of unsymmetrical 1,4-diamino-2-butynes can be produced using two different amines, an aldehyde, and propiolic acid (Scheme 1e). Obviously, the biggest challenge for this strategy is the chemoselective control to avoid the generation of the symmetrical 1,4-diamino-2-butynes. Our previous work on two-step A^3-coupling and decarboxylative A^3-coupling revealed that the structure of the intermediate terminal propargylamine, *in situ* formed from the decarboxylative A^3-coupling, is playing an important role in the control of the reaction selectivity.[18] For example, we observed that some terminal propargylamines seem to react much easier to afford the A^3-coupling product, but in some cases, the result

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Scheme 1. Various Routes towards 1,4-Diamino-2-butynes[14−17]

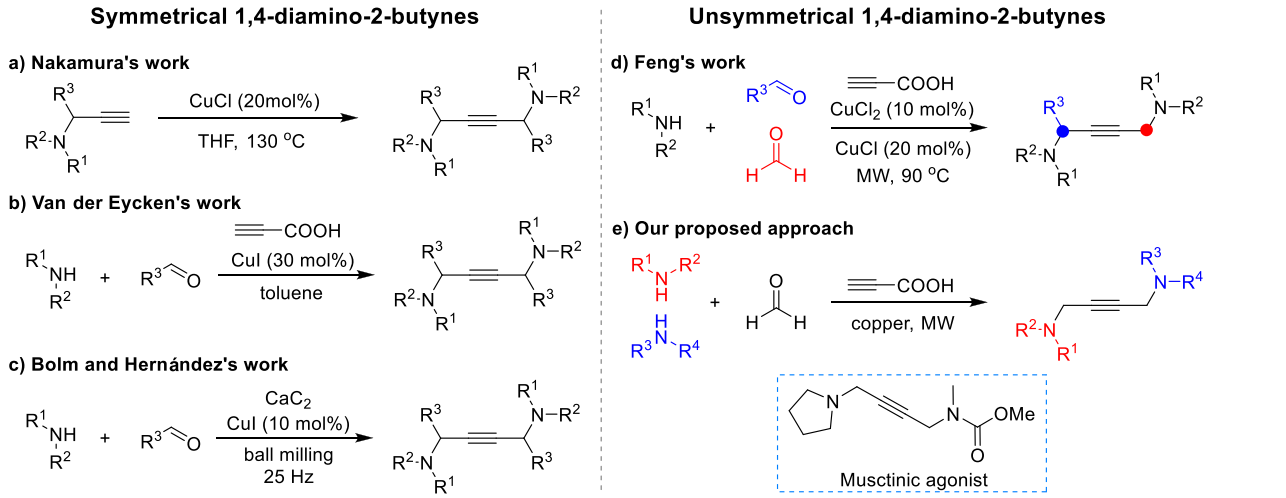
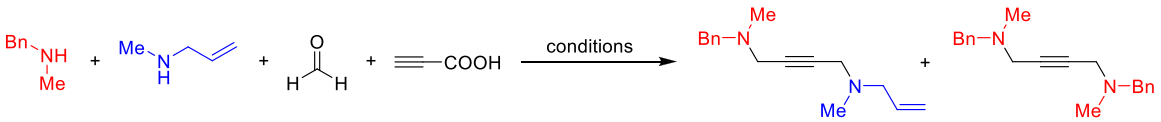


Table 1. Exploration of the Optimal Conditions[a]



1a 2a 3 4 5a 6a

entry	catal. (mol %)	solvent	time (h)	temp. (°C)	yield (%)[b] 5a	6a
1	CuI (30)	DCE	12	80	34	33
2	CuI (30)	toluene	12	80	45	28
3	CuI (30)	paraxylene	12	80	52	45
4	CuI (30)	THF	12	80	44	41
5	CuI (30)	CH_3CN	12	80	63	23
6	CuI (30)	dioxane	12	80	57	36
7	CuBr (30)	CH_3CN	12	80	47	35
8	CuCl (30)	CH_3CN	12	80	46	42
9	$CuBr_2$ (30)	CH_3CN	12	80	43	32
10	$CuCl_2$ (30)	CH_3CN	12	80	36	30
11	$Cu(OAc)_2$ (30)	CH_3CN	12	80	27	31
12	$Cu(OTf)_2$ (30)	CH_3CN	12	80	51	27
13	CuI (40)	CH_3CN	12	80	56	34
14	CuI (20)	CH_3CN	12	80	48	32
15	CuI (20) + $CuBr_2$ (10)	CH_3CN	12	80	41	32
16	CuI (20) + CuCl (10)	CH_3CN	12	80	47	25
17	$CuBr_2$ (20) + CuBr (10)	CH_3CN	12	80	45	31
18	CuI (30)	CH_3CN	MW, 30 min[c]	80	78	14
19[d]	CuI (30)	CH_3CN	MW, 30 min[c]	80	54	22
20[e]	CuI (30)	CH_3CN	MW, 30 min[c]	80	67	25
21[f]	CuI (30)	CH_3CN	MW, 30 min[c]	80	74	18
22	CuI (30)	CH_3CN	MW, 30 min[c]	90	72	24
23	CuI (30)	CH_3CN	MW, 30 min[c]	70	67	29

[a]Unless otherwise stated, the reactions were performed with **1a** (0.5 mmol), **2a** (0.7 mmol), a 37 wt % solution of formaldehyde **3** (1.5 mmol), **4** (0.7 mmol), copper catalyst, and solvent (0.5 mL) in a sealed tube. [b]Yields after column chromatography. [c]MW = Microwave irradiation. [d]**2a** (0.5 mmol) was used. [e]**1a** (0.7 mmol) and **2a** (0.5 mmol) were used. [f]**4** (0.4 mmol) was used.

is similar to Nakumura's work[14] on deacetylenative couplings of terminal propargylamines.

RESULTS AND DISCUSSION

In this context, we initiated the studies by investigating the reaction of *N*-methylbenzylamine **1a**, *N*-methylprop-2-en-1-amine **2a**, formaldehyde **3**, and propiolic acid **4** in the presence of 30 mol % CuI (Table 1, entry 1). Gratifyingly, 34% yield of desired product **5a** was obtained in 1,2-dichloroethane (DCE) at 80 °C under conventional heating for 12 h, compared to 33% yield of symmetrical 1,4-diamino-2-butyne **6a** as a main byproduct. Encouraged by this result, we started to evaluate the different reaction parameters. First, a variety of solvents was investigated, revealing acetonitrile as the best one. The reaction worked equally well in paraxylene and dioxane (Table 1, entries

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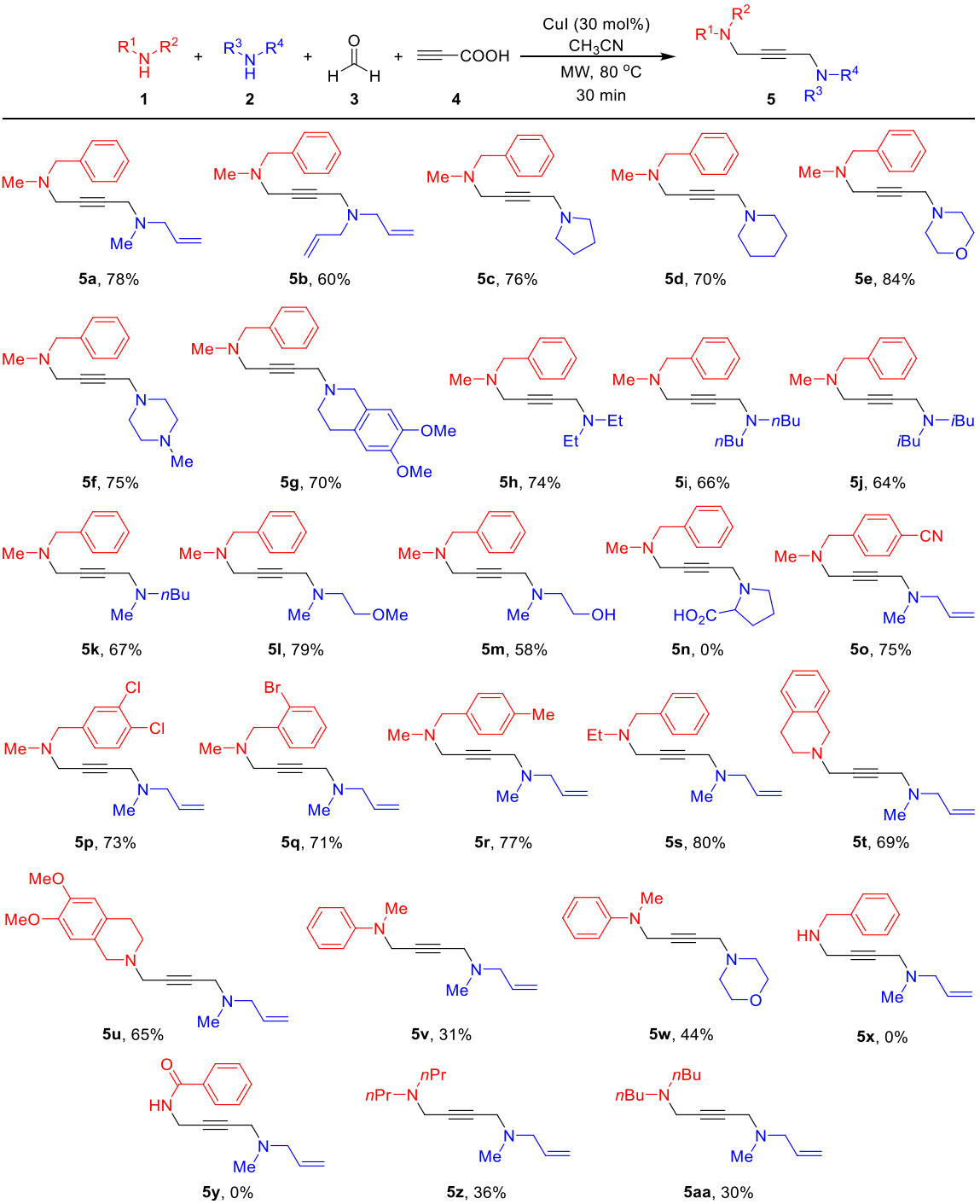
Table 2. Scope and Limitations of the Method[a]



[a]The reactions were carried out with amine **1** (0.5 mmol), amine **2** (0.7 mmol), formaldehyde **3** (1.5 mmol), propiolic acid **4** (0.7 mmol), and CuI (30 mol %) in CH_3CN (0.5 mL) at 80 °C with a maximum power 100 W for 30 min; yields after column chromatography.

2−6). Then, we examined a series of copper sources for improving the yield of the desired product. However, no better result was obtained when CuI was replaced by other copper sources (entries 7−12). Further studies showed that increasing or lowering the catalytic amount of CuI delivered a decreased yield of the targeted product (entries 13 and 14). Considering the fact that the combination of Cu(I) and Cu(II) catalysts is known to promote the A^3-type reaction,[19] the use of a mixed Cu catalyst was tested. However, this did not result in an increased yield of the desired product **5a** (entries 15−17). Remarkably, 78% yield of the targeted product was formed when the reaction was performed under microwave irradiation for 30 min (entry 18). Subsequently, we varied the concentration of the starting materials under microwave irradiation, but this did not provide a further improvement of the yield (entries 19−21). Increasing or reducing the reaction temperature was found to be less efficient for the reaction (entries 22 and 23).

With the optimal conditions in hand, we next examined the substrate scope of this reaction by exploring a series of two different amines, **1** and **2**. A first set of reactions was performed

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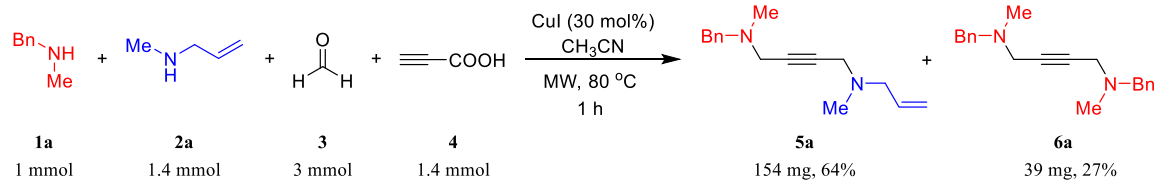
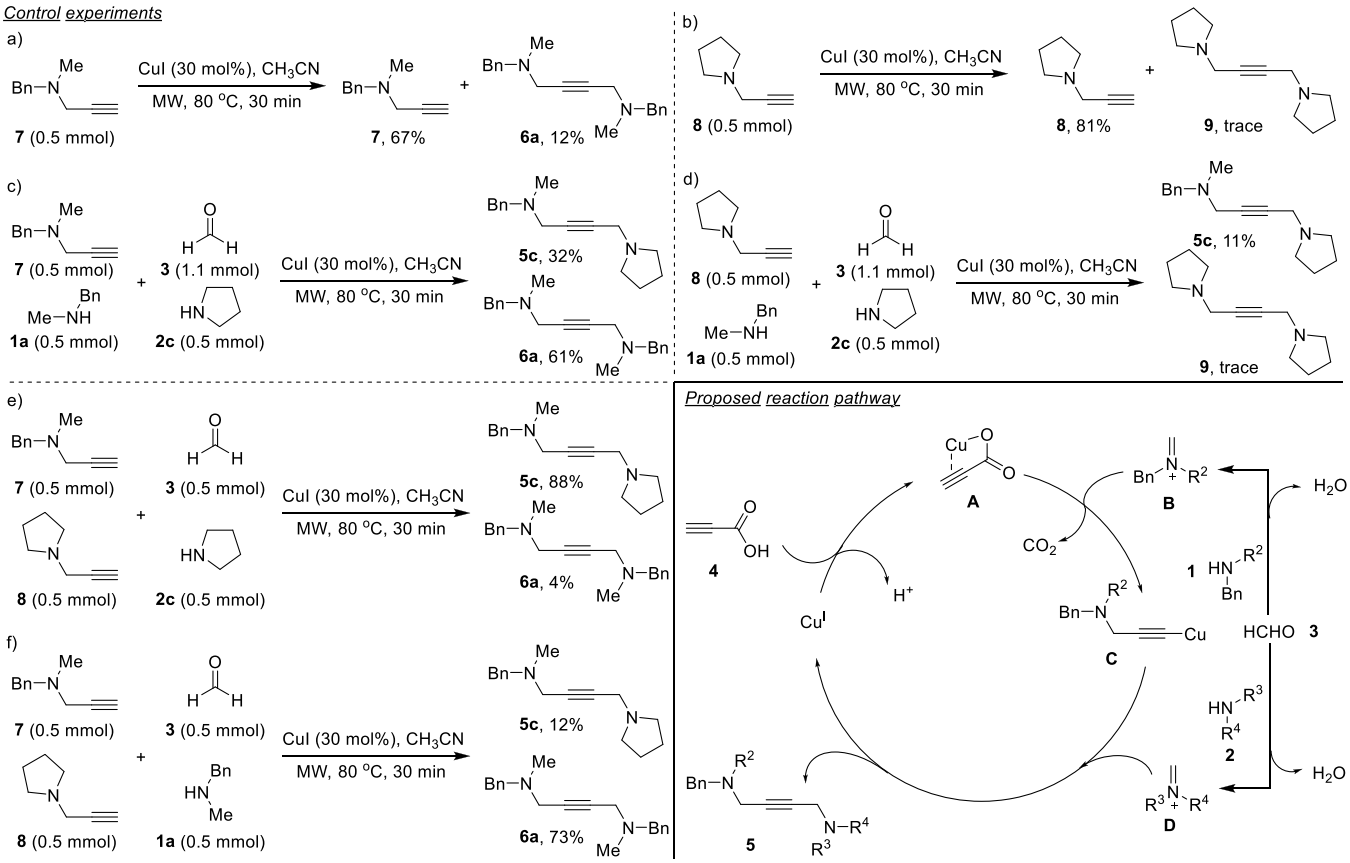
Scheme 2. Millimole Scale of 5a



Scheme 3. Mechanism Studies



with *N*-methylbenzylamine. The results depicted in Table 2 showed that allylic, cyclic, and heterocyclic secondary amines afforded the corresponding products in moderate to good yields (**5a**−**5g**). Various aliphatic secondary amines were also suitable for this reaction (**5h**−**5l**). Although the chain length and steric hindrance could obviously affect the effectiveness of the reaction. To our satisfaction, desired product **5m** could be obtained in 58% yield when 2-(methylamino)ethan-1-ol was employed as reaction substrate. However, with DL-proline, the reaction met with failure. Next, we turned our attention to *N*-substituted benzylamines bearing electron-withdrawing or electron-donating groups and tetrahydroisoquinolines using the standard conditions. Corresponding compounds **5o**−**5u** were obtained in 65−80% yield. Remarkably, *N*-methylaniline yielded compounds **5v**−**5w** in low yields. It is worth noting that a low yield of symmetrical 1,4-diamino-2-butynes, formed from *N*-substituted benzylamine, was detected in the most cases. Desired products **5x** and **5y** could not be detected when benzylamine and benzamide were employed as starting materials respectively. Additionally, when nonbenzylic aliphatic amines were employed, the cross-coupling reaction afforded products **5z** and **5aa** in relatively low yields (36 and 30%, respectively) with the byproduct of symmetrical 1,4-diamino-2-butyne. Finally, the practical applicability of the process for the formation of **5a** has been demonstrated by performing the reaction on a 1.0 mmol scale, affording unsymmetrical product **5a** in 64% yield compared to symmetrical product **6a** in 27% yield (Scheme 2).

In order to understand the process of the reaction, some control experiments were performed. Previous work by Nakumura[14] described the copper-catalyzed deacetylenative coupling of terminal propargylamines. In our case, a low yield (12%) of deacetylenative coupling product **6a** was obtained when terminal propargylamine **7** was used (Scheme 3a). However, using terminal propargylamine **8** as starting material, the deacetylenative coupling process was not observed at all (Scheme 3b). The reaction of **7** in the presence of *N*-methylbenzylamine **1a**, pyrrolidine **2c**, and formaldehyde **3** under our optimized reaction conditions resulted in 32% yield of unsymmetrical product **5c** and 61% yield of symmetrical product **6a**, respectively (Scheme 3c). Interestingly, the use of **8** instead of **7** led to a tremendously lower reactivity, as only **5c** was obtained in a mere 11% yield (Scheme 3d). Additionally, when a mixture of both **7** and **8** was used to react with **2c** and **3**,

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desired product **5c** was obtained in 88% yield with only 4% yield of **6a** which was yielded via deacetylenative coupling of **7** (Scheme 3e). Subsequently, changing **2c** for **1a**, only a 12% yield of unsymmetrical product **5c** was obtained, compared to 73% yield of symmetrical product **6a** (Scheme 3f). These observations suggest that terminal propargylamine **7**, *in situ* generated from *N*-methylbenzylamine **1a**, is much more reactive than terminal propargylamine **8**, generated from nonbenzylic aliphatic amine in both the deacetylenative coupling and the A^3-coupling, and that the *in situ* formed imine from *N*-methylbenzylamine **1a** and **3** is also much easier trapped by the intermediate terminal propargylamine than the one formed from nonbenzylic aliphatic amin **2c** and **3**. On the basis of our experimental results and the previous literature,[17,18] a plausible mechanism is proposed (Scheme 3). Initially, cation exchange between the copper salt and propiolic acid **4** gives copper acetylide complex **A**, which undergoes a decarboxylative coupling with imine **B**, which is *in situ* generated from *N*-substituted benzylamine **1** and formaldehyde, resulting in the formation of intermediate **C**. This undergoes coupling with another imine, **D**, generated from nonbenzylic aliphatic amine **2** and formaldehyde to afford the desired product with concomitant regeneration of the Cu(I) catalyst.

CONCLUSIONS

In summary, we have developed a microwave-assisted Cu(I)-catalyzed cross-A^3-coupling/decarboxylative coupling of two different amines, formaldehyde, and a propiolic acid for the construction of unsymmetric 1,4-diamino-2-butynes with moderate to good yields and high chemoselectivity. Mild reaction conditions, short reaction times, simple mode of operation, wide substrate scope, and good tolerance for oxygen and water make this strategy an efficient tool for the synthesis of various functional molecules.

EXPERIMENTAL SECTION

General Information. All catalysts, reagents, and reactants were purchased from commercial suppliers and 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 on a Bruker AM (300 or 400 MHz) spectrometer at ambient temperature using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts are reported in values δ (ppm) and coupling constants given in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). HRMS (ESI) spectrometry data were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer [Synapt G2 high definition mass spectrometer (HDMS), Waters, Milford, MA]. Samples were infused at 3 μL min^{-1}, and spectra were obtained in the positive ionization mode with a resolution of 15 000 [full width at half-maximum (fwhm)] with leucine encephalin as lock mass.

Microwave Irradiation Experiments. All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. The reactions were carried out in 10 mL glass tubes, sealed with a Teflon septum, and placed in the microwave cavity. The reactions were irradiated at the required set temperature and power for the stipulated time and then cooled to ambient temperature with air jet cooling.

General Procedure for the Synthesis of Unsymmetric 1,4-Diamino-2-butynes 5. A mixture of nonbenzylic aliphatic amine **2** (0.7 mmol, 1.4 equiv), and 37 wt % formaldehyde **3** (121.6 mg, 1.5 mmol) was dissolved in CH_3CN (0.5 mL) applying a microwave vial along with a magnetic stir bar. This mixture was stirred at room temperature for 1−2 min, and then CuI (28.6 mg, 0.15 mmol), amine **1** (0.5 mmol, 1 equiv), and propiolic acid **4** (49 mg, 0.7 mmol) were added (the sequential addition of the two amines is beneficial to the formation of unsymmetrical product **5**). The reaction vessel was sealed and irradiated in the dedicated CEM-Discover monomode microwave apparatus at a ceiling temperature of 80 °C and a maximum power of 100 W for 30 min. The resulting reaction mixture was loaded on a silica gel column and flashed with a mixture of EtOAc and hexane to afford desired product **5** as light yellow oil.

Millimole-Scale Synthetic Procedure for the Synthesis of 5a. A mixture of amine **2a** (99.4 mg, 1.4 mmol), and 37 wt % formaldehyde **3** (243.2 mg, 3 mmol) was dissolved in CH_3CN (1 mL) applying a microwave vial along with a magnetic stir bar. This mixture was stirred at room temperature for 5 min, and then CuI (57.1 mg, 30 mol %), amine **1a** (121 mg, 1 mmol), and propiolic acid **4** (98 mg, 1.4 mmol) were added (the sequential addition of the **2a** and **1a** is beneficial to the formation of the **5a**). The reaction vessel was sealed and irradiated in the dedicated CEM-Discover monomode microwave apparatus at a ceiling temperature of 80 °C and a maximum power of 100 W for 1 h. The resulting reaction mixture was loaded on a silica gel column and flashed with a mixture of EtOAc and hexane to afford desired product **5a** as light yellow oil in 64% yield and byproduct **6a** as light yellow oil in 27% yield.

*N^1-Allyl-N^4-benzyl-N^1,N^4-dimethylbut-2-yne-1,4-diamine (**5a**).* Product **5a** (94.3 mg, 78% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.32 (m, 4H), 7.26 (t, J = 5.2 Hz, 1H), 5.91−5.86 (m, 1H), 5.26−5.15 (m, 2H), 3.58 (s, 2H), 3.40 (s, 2H), 3.34 (s, 2H), 3.10 (d, J = 6.6 Hz, 2H), 2.34 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.4, 135.4, 129.1, 128.2, 127.1, 118.0, 80.0, 79.8, 60.1, 59.0, 45.3, 41.9, 41.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{22}N_2$ 243.1856. Found 243.1857.

*N^1,N^1-diallyl-N^4-benzyl-N^4-methylbut-2-yne-1,4-diamine (**5b**).* Product **5b** (80.6 mg, 60% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 4H), 7.29−7.22 (m, 1H), 5.97−5.75 (m, 2H), 5.33−5.05 (m, 4H), 3.59 (s, 2H), 3.46 (s, 2H), 3.34 (s, 2H), 3.18 (d, J = 6.6 Hz, 4H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.5, 135.4, 129.1, 128.2, 127.1, 118.0, 79.7, 60.0, 56.4, 45.2, 41.9, 41.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{18}H_{24}N_2$ 269.2012. Found 269.2015.

*N-Benzyl-N-methyl-4-(pyrrolidin-1-yl)but-2-yn-1-amine (**5c**).* Product **5c** (91.8 mg, 76% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.17 (m, 5H), 3.57 (s, 4H), 3.33 (s, 2H), 2.85−2.65 (m, 4H), 2.33 (s, 3H), 1.95−1.77 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.3, 129.1, 128.3, 127.2, 80.0, 79.7, 60.2, 52.4, 45.2, 43.3, 41.9, 23.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{22}N_2$ 243.1856. Found 243.1849.

*N-Benzyl-N-methyl-4-(piperidin-1-yl)but-2-yn-1-amine (**5d**).* Product **5d** (89.7 mg, 70% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 4H), 7.27−7.24 (m, 1H), 3.57 (s, 2H), 3.34−3.33 (m, 4H), 2.54 (s, 4H), 2.33 (s, 3H), 1.77−1.55 (m, 4H), 1.45 (d, J = 4.8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.5, 129.1, 128.2, 127.1, 80.5, 79.6, 60.2, 53.3, 48.0, 45.3, 41.9, 25.9, 23.98. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{24}N_2$ 257.2012. Found 257.2005.

*N-Benzyl-N-methyl-4-morpholinobut-2-yn-1-amine (**5e**).* Product **5e** (108.3 mg, 84% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.18 (m, 5H), 3.87−3.65 (m, 4H), 3.58 (s, 2H), 3.44−3.24 (m, 4H), 2.68−2.49 (m, 4H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.2, 129.1, 128.3, 127.2, 80.1, 79.8, 66.8, 60.1, 52.2, 47.5, 45.2, 41.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{22}N_2O$ 259.1805. Found 259.1810.

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*N-Benzyl-N-methyl-4-(4-methylpiperazin-1-yl)but-2-yn-1-amine (**5f**).* Product **5f** (101.6 mg, 75% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with DCM/MeOH = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.11 (m, 5H), 3.56 (s, 2H), 3.38 (s, 2H), 3.32 (s, 2H), 2.82−2.51 (m, 8H), 2.40 (s, 3H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.3, 129.1, 128.2, 127.1, 80.2, 79.8, 60.3, 54.8, 51.3, 47.1, 45.6, 45.3, 41.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{25}N_3$ 272.2121. Found 272.2117.

*N-Benzyl-4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-N-methylbut-2-yn-1-amine (**5g**).* Product **5g** (127.4 mg, 70% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.14 (m, 5H), 6.57 (d, J = 23.3 Hz, 2H), 3.83 (d, J = 3.0 Hz, 6H), 3.72 (s, 2H), 3.57 (d, J = 3.7 Hz, 4H), 3.34 (s, 2H), 2.87−2.85 (m, 4H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.5, 147.2, 138.4, 129.1, 128.2, 127.1, 126.4, 125.7, 111.3, 109.4, 80.1, 60.2, 55.9, 54.1, 49.9, 47.0, 45.3, 41.9, 28.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{28}N_2O_2$ 365.2223. Found 365.2224.

*N^1-Benzyl-N^4,N^4-diethyl-N^1-methylbut-2-yne-1,4-diamine (**5h**).* Product **5h** (90.3 mg, 74% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.20 (m, 5H), 3.57 (s, 2H), 3.50 (s, 2H), 3.32 (s, 2H),2.62−2.57 (m, 4H), 2.33 (s, 3H), 1.10 (t, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.5, 129.1, 128.2, 127.1, 79.7, 79.2, 60.1, 47.3, 45.2, 41.9, 40.8, 12.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{24}N_2$ 245.2012. Found 245.2012.

*N^1-Benzyl-N^4,N^4-dibutyl-N^1-methylbut-2-yne-1,4-diamine (**5i**).* Product **5i** (99.3 mg, 66% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.19 (m, 5H), 3.57 (s, 2H), 3.47 (s, 2H), 3.32 (s, 2H), 2.59−2.41 (m, 4H), 2.33 (s, 3H), 1.57−1.39 (m, 4H), 1.35−0.95 (m, 4H), 0.93 (t, J = 7.2 Hz, 6H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 138.5, 129.1, 128.2, 127.1, 80.1, 79.1, 60.0, 53.6, 45.2, 41.9, 29.7, 20.7, 14.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{20}H_{32}N_2$ 301.2638. Found 301.2641.

*N^1-Benzyl-N^4,N^4-diisobutyl-N^1-methylbut-2-yne-1,4-diamine (**5j**).* Product **5j** (96.1 mg, 64% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 4H), 7.27−7.24 (m, 1H), 3.58 (s, 2H), 3.40 (s, 2H), 3.32 (s, 2H), 2.33 (s, 3H), 2.23 (d, J = 7.3 Hz, 4H), 1.81−1.61 (m, 2H), 0.90 (d, J = 6.6 Hz, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.5, 129.2, 128.2, 127.1, 80.7, 78.7, 62.6, 60.0, 45.2, 42.8, 41.8, 26.1, 20.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{20}H_{32}N_2$ 301.2638. Found 301.2647.

*N^1-Benzyl-N^4-butyl-N^1,N^4-dimethylbut-2-yne-1,4-diamine (**5k**).* Product **5k** (86.4 mg, 67% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 4H), 7.29−7.22 (m, 1H), 3.57 (s, 2H), 3.40 (s, 2H), 3.33 (s, 2H), 2.55−2.40 (m, 2H), 2.33 (s, 6H), 1.55−1.42 (m, 2H), 1.42−1.27 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.5, 129.1, 128.2, 127.1, 80.0, 79.6, 60.1, 55.6, 45.8, 45.2, 41.9, 29.7, 20.6, 14.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{26}N_2$ 259.2169. Found 259.2169.

*N^1-Benzyl-N^4-(2-methoxyethyl)-N^1,N^4-dimethylbut-2-yne-1,4-diamine (**5l**).* Product **5l** (103.2 mg, 79% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.15 (m, 5H), 3.58 (s, 2H), 3.55−3.41 (m, 4H), 3.35 (d, J = 9.0 Hz, 5H), 2.71 (t, J = 5.5 Hz, 2H), 2.40 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ138.2, 129.1, 128.3, 127.2, 79.9, 79.7, 70.3, 60.1, 58.9, 54.9, 46.2, 45.2, 42.1, 41.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{24}N_2O$ 261.1961. Found 261.1966.

*2-((4-(Benzyl(methyl)amino)but-2-yn-1-yl)(methyl)amino)-ethan-1-ol (**5m**).* Product **5m** (71.2 mg, 58%) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.21 (m, 5H), 3.64 (t, J = 5.3 Hz, 2H), 3.57 (s, 2H), 3.46 (s, 2H), 3.33 (s, 2H), 2.83 (s, 1H), 2.67 (d, J = 4.9 Hz, 2H), 2.39 (s, 3H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.0, 129.2, 128.3, 127.3, 80.2, 79.5, 60.1, 58.4, 57.0, 46.0, 45.2, 41.8, 41.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{22}N_2O$ 247.1805. Found 247.1806.

*4-(((4-(Allyl(methyl)amino)but-2-yn-1-yl)(methyl)amino)-methyl)benzonitrile (**5o**).* Product **5o** (100.4 mg, 75% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 5.93−5.79 (m, 1H), 5.31−5.03 (m, 2H), 3.63 (s, 2H), 3.44−3.23 (m, 4H), 3.09 (d, J = 6.5 Hz, 2H), 2.33 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.4, 135.3, 132.1, 129.5, 118.9, 118.0, 111.0, 80.4, 79.2, 59.6, 59.1, 45.5, 41.9, 41.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{21}N_3$ 268.1808. Found 268.1810.

*N^1-Allyl-N^4-(3,4-dichlorobenzyl)-N^1,N^4-dimethylbut-2-yne-1,4-diamine (**5p**).* Product **5p** (133.1 mg, 73% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.29 (m, 2H), 7.17 (t, J = 7.8 Hz, 1H), 6.02−5.70 (m, 1H), 5.26−5.15 (m, 2H), 3.72 (s, 2H), 3.42−3.40 (m, 4H), 3.10 (d, J = 6.6 Hz, 2H), 2.36 (d, J = 13.8 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.7, 135.4, 133.1, 132.5, 129.0, 128.7, 126.9, 118.0, 80.2, 79.6, 59.0, 57.5, 45.8, 45.4, 41.9, 41.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{20}Cl_2N_2$ 311.1076. Found 311.1067.

*N^1-Allyl-N^4-(2-bromobenzyl)-N^1,N^4-dimethylbut-2-yne-1,4-diamine (**5q**).* Product **5q** (113.6 mg, 71% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.27 (dd, J = 9.6, 5.3 Hz, 1H), 7.20−7.01 (m, 1H), 5.91−5.82 (m, 1H), 5.37−5.05 (m, 2H), 3.69 (s, 2H), 3.42 (s, 4H), 3.11 (d, J = 6.5 Hz, 2H), 2.36 (d, J = 9.2 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 139.5, 137.8, 135.4, 132.8, 130.9, 128.5, 127.2, 124.8, 118.0, 80.1, 79.8, 63.9, 59.4, 59.0, 45.7, 45.4, 41.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{21}BrN_2$ 321.0961. Found 321.0959.

*N^1-Allyl-N^1,N^4-dimethyl-N^4-(4-methylbenzyl)but-2-yne-1,4-diamine (**5r**).* Product **5r** (98.6 mg, 77% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 5.89−5.83 (m, 1H), 5.25−5.15 (m, 2H), 3.54 (s, 2H), 3.39 (s, 2H), 3.33 (s, 2H), 3.10 (d, J = 6.6 Hz, 2H), 3.10 (d, J = 6.6 Hz, 2H), 2.34 (d, J = 4.4 Hz, 9H), 2.34 (d, J = 4.4 Hz, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.7, 135.4, 129.0, 117.9, 79.9, 59.84 (s), 59.0, 45.4, 45.1, 41.7, 21.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{24}N_2$ 257.2012. Found 257.2016.

*N^1-Allyl-N^4-benzyl-N^4-ethyl-N^1-methylbut-2-yne-1,4-diamine (**5s**).* Product **5s** (102.8 mg, 80% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.29 (m, 4H), 7.26−7.23 (m, 1H), 6.00−5.63 (m, 1H), 5.37−5.08 (m, 2H), 3.64 (s, 2H), 3.39−3.37 (m, 4H), 3.10 (d, J = 6.6 Hz, 2H), 2.64−2.58 (m, 2H), 2.34 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.8, 135.4, 129.1, 128.2, 127.0, 118.0, 79.6, 59.0, 57.7, 47.4, 45.4, 41.6, 41.1, 12.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{24}N_2$ 257.2012. Found 257.2014.

*N-Allyl-4-(3,4-dihydroisoquinolin-2(1H)-yl)-N-methylbut-2-yn-1-amine (**5t**).* Product **5t** (87.6 mg, 69% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.05 (m, 3H), 7.04−7.02 (m, 1H), 5.85−5.80 (m, 1H), 5.30−5.01 (m, 2H), 3.77 (s, 2H), 3.55 (s, 2H), 3.36 (s, 2H), 3.06 (d, J = 6.6 Hz, 2H), 2.95 (t, J = 5.8 Hz, 2H), 2.84 (t, J = 5.9 Hz, 2H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.3, 134.6, 133.8, 128.6, 126.5, 126.1, 125.6, 118.0, 79.9, 59.1, 54.4, 49.8, 47.1, 45.4, 41.7, 29.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{22}N_2$ 255.1856. Found 255.1856.

*N-Allyl-4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-N-methylbut-2-yn-1-amine (**5u**).* Product **5u** (102.1 mg, 65% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^{1}H NMR

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(400 MHz, $CDCl_3$) δ 6.60 (s, 1H), 6.54 (s, 1H), 5.88−5.79 (m, 1H), 5.36−5.04 (m, 2H), 3.83 (t, J = 3.5 Hz, 6H), 3.69 (s, 2H), 3.54 (s, 2H), 3.36 (s, 2H), 3.07 (d, J = 6.6 Hz, 2H), 2.85−2.81 (m, 4H), 2.32 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.5, 147.2, 135.2, 126.4, 125.7, 118.0, 111.3, 109.4, 79.9, 59.1, 55.9, 54.0, 49.8, 47.0, 45.4, 41.7, 28.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{26}N_2O_2$ 315.2067. Found 315.2068.

*N^1-Allyl-N^1,N^4-dimethyl-N^4-phenylbut-2-yne-1,4-diamine (**5v**).* Product **5v** (35.3 mg, 31% yield) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, J = 7.9 Hz, 2H), 6.86 (d, J = 8.2 Hz, 2H), 6.79 (t, J = 7.2 Hz, 1H), 5.82−5.76 (m, 1H), 5.21−4.96 (m, 2H), 4.07 (s, 2H), 3.27 (s, 2H), 3.08−2.83 (m, 5H), 2.21 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.2, 135.3, 129.0, 117.9, 114.4, 80.5, 78.6, 58.8, 45.3, 42.8, 41.5, 38.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{20}N_2$229.1699. Found 229.1694.

*N-Methyl-N-(4-morpholinobut-2-yn-1-yl)aniline (**5w**).* Product **5w** (53.4 mg, 44%) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 2:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, J = 7.9 Hz, 2H), 6.93−6.69 (m, 3H), 4.06 (s, 2H), 3.82−3.54 (m, 4H), 3.23 (s, 2H), 2.96 (s, 3H), 2.55−2.34 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.2, 129.0, 118.1, 114.4, 80.9, 78.5, 66.8, 52.2, 47.5, 42.8, 38.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{20}N_2O$ 245.1648. Found 245.1643.

*N^1-Allyl-N^1-methyl-N^4,N^4-dipropylbut-2-yne-1,4-diamine (**5z**).* Product **5z** (40.5 mg, 36%) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 5.96−5.76 (m, 1H), 5.24−5.13 (m, 2H), 3.45 (s, 2H), 3.35 (s, 2H), 3.06 (d, J = 6.6 Hz, 2H), 2.53−2.37 (m, 4H), 2.31 (s, 3H), 1.54−1.44 (m, J = 14.8, 7.4 Hz, 4H), 0.90 (t, J = 7.4 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.4, 117.9, 79.7, 79.2, 58.9, 55.8, 45.3, 42.0, 41.6, 20.6, 11.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{26}N_2$ 223.2169. Found 223.2171.

*N^1-Allyl-N^4,N^4-dibutyl-N^1-methylbut-2-yne-1,4-diamine (**5aa**).* Product **5aa** (37.6 mg, 30%) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 10:1). ^1H NMR (400 MHz, $CDCl_3$) δ 5.89−5.79 (m, 1H), 5.24−5.14 (m, 2H), 3.44 (s, 2H), 3.35 (s, 2H), 3.06 (d, J = 6.6 Hz, 2H), 2.57−2.36 (m, 4H), 2.30 (s, 3H), 1.49−1.41 (m, 4H), 1.37−1.28 (m, 4H), 0.92 (t, J = 7.3 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.4, 117.9, 79.7, 79.2, 58.9, 53.6, 45.4, 41.9, 41.6, 29.6, 20.7, 14.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{30}N_2$ 251.2482. Found 251.2480.

Procedure for the Synthesis of the Intermediates 7 and 8. Intermediates **7** and **8** were prepared according to a reported literature.[20] To a mixture of a *N*-methylbenzylamine (3 mmol, 1 equiv) and K_2CO_3 (3.6 mmol, 1.2 equiv) in acetone (15 mL) was added propargyl bromide (3.6 mmol, 1.2 equiv), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered, and the filtrate was removed under reduced pressure to yield the crude product, which was purified by column chromatography over silica gel (hexane/ethyl acetate = 10:1).

*N-Benzyl-N-methylprop-2-yn-1-amine (**7**).* The title compound was obtained according to the above procedure. Product **7** (310 mg, 65%) was obtained as a yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 10:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.15 (m, 5H), 3.57 (s, 2H), 3.30 (s, 2H), 2.34 (s, 3H), 2.27 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.3, 129.1, 128.3, 127.2, 78.5, 73.3, 59.9, 44.8, 41.7.

*1-(Prop-2-yn-1-yl)pyrrolidine (**8**).* The title compound was obtained according to the above procedure. Product **8** (193 mg, 59%) was obtained as a yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 10:1). ^1H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 2H), 2.62 (s, 4H), 2.21 (s, 1H), 1.81 (s, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 79.61 (s), 72.20 (s), 52.39 (s), 42.87 (s), 23.79 (s).

***N^1*,*N^4*-Dibenzyl-*N^1*,*N^4*-dimethylbut-2-yne-1,4-diamine (6a).** The title compound was obtained according to the millimole-scale synthetic procedure for the synthesis of **5a**. Product **6a** (39 mg, 27%) was obtained as a light yellow oil (purified by silica gel column chromatography eluting with hexane/ethyl acetate = 4:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.19 (m, 5H), 3.61 (s, 2H), 3.37 (s, 2H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 138.4, 129.2, 128.3, 127.2, 80.0, 60.1, 45.3, 41.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}N_2$ 293.2012. Found 293.2014.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00537.

Copies of ^1H, $^{13}C\{^1H\}$ NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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