Efficient One-Pot Synthesis of Propargylamines from Mannich Bases through a Retro-Mannich-Type Fragmentation

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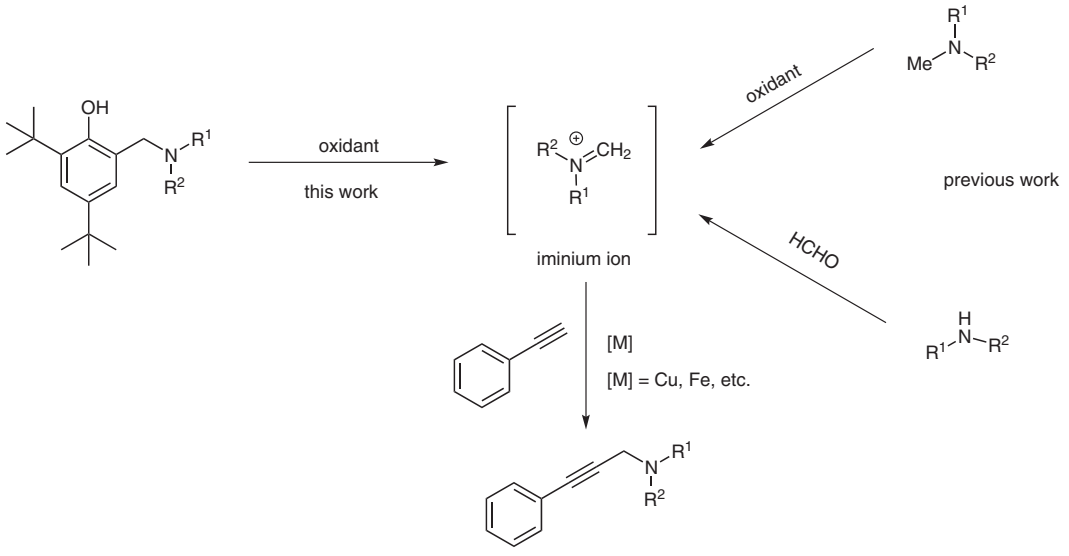
Abstract: An efficient one-pot synthesis of propargylamines is achieved by copper-catalyzed coupling of phenylacetylenes with Mannich bases through a chlorine(1+) or bromine(1+) ion-initiated retro-Mannich-type fragmentation under mild conditions. The Mannich bases are easily prepared from an electron-rich phenol, formaldehyde, and an amine. The protocol provides an appealing alternative for the construction of propargylamines by a simple one-pot procedure.

Key words: copper, catalysis, coupling, Mannich bases, alkynes, amines

The propargylamine group is a common skeletal motif in various nitrogen-containing compounds, and propargylamines are versatile synthetic intermediates for the synthesis of a variety of natural products.[1,2] As a result, the synthesis of propargylamines has attracted considerable interest, and a number of methods have been devised. Propargylamines are usually synthesized by amination of propargylic halides,[3] propargylic phosphates,[4] or propargylic triflates,[5] or through the reaction of lithium acetylides or Grignard reagents with imines or their derivatives.[6] Such reactions require strictly controlled conditions or the use of stoichiometric amounts of organometallic reagents. The development of a new and efficient method for this synthesis is therefore an interesting challenge.

The three-component coupling reaction of aldehydes, alkynes, and amines (the A^3 coupling reaction) has recently attracted a great deal of attention because of its high efficiency and simple operations. Various A^3 coupling reactions have been reported to occur under homogeneous[7] or heterogeneous conditions.[8] In addition, the catalytic enantioselective addition of terminal alkynes to imines or enamines has been developed for the synthesis of chiral propargylamines.[9] The copper- and iron-catalyzed direct oxidative alkynylation of C–H bonds in tertiary amines has recently been shown to provide an attractive approach to the synthesis of propargylamines. Iminium ions are considered to be the key intermediates in these transformations. Generally, iminium ions are generated from aldehydes and amines or through oxidative dehydrogenation of tertiary amines[10] in situ with an oxidant such as *tert*-butyl hydroperoxide,[11] *N*-bromosuccinimide,[12] or di-*tert*-butyl peroxide.[13] In 2010, Nakamura and co-workers reported a copper-catalyzed substitution reaction for the construction of propargylic amines in which the iminium ions are generated through a C(sp)–



Scheme 1 Reactions of terminal alkynes with iminium ion intermediates

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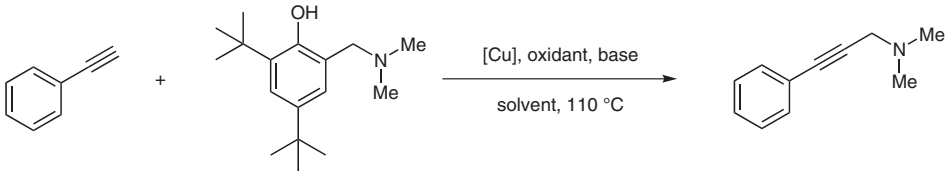
C(sp^3) bond-cleavage reaction.[14] More recently, they successfully synthesized N-tethered 1,6-enynes by a zinc(II)-catalyzed redox dehydrogenative cross-coupling reaction. In this transformation, an internal oxidant in the molecule of the starting materials is used to provide the reactive iminium intermediate.

Table 1 Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

Entry	Metal ion source	Oxidant	Base	Solvent	Yield[b] (%)
1	CuI	NCS	$NaHCO_3$	toluene	61
2	CuBr	NCS	$NaHCO_3$	toluene	68
3	CuCl	NCS	$NaHCO_3$	toluene	71
4	**$CuCl_2·2H_2O$**	**NCS**	**$NaHCO_3$**	**toluene**	**82**
5	$Cu(OAc)_2·H_2O$	NCS	$NaHCO_3$	toluene	63
6	$FeCl_3$	NCS	$NaHCO_3$	toluene	0
7	$Co(acac)_2$	NCS	$NaHCO_3$	toluene	0
8	$NiCl_2·4H_2O$	NCS	$NaHCO_3$	toluene	0
9	$Ni(OAc)_2·2H_2O$	NCS	$NaHCO_3$	toluene	0
10	$Pd(OAc)_2$	NCS	$NaHCO_3$	toluene	0
11	$CuCl_2·2H_2O$	–	$NaHCO_3$	toluene	0
12	$CuCl_2·2H_2O$	NCS	–	toluene	0
13	–	NCS	$NaHCO_3$	toluene	0
14	$CuCl_2·2H_2O$	NBS	$NaHCO_3$	toluene	38
15	$CuCl_2·2H_2O$	*t*-BuOOH[c]	$NaHCO_3$	toluene	56
16	$CuCl_2·2H_2O$	$(t\text{-BuO})_2$	$NaHCO_3$	toluene	0
17	$CuCl_2·2H_2O$	$PhI(OAc)_2$	$NaHCO_3$	toluene	0
18	$CuCl_2·2H_2O$	I_2	$NaHCO_3$	toluene	0
19	$CuCl_2·2H_2O$	NCS	Na_2CO_3	toluene	36
20	$CuCl_2·2H_2O$	NCS	NaOAc	toluene	52
21	$CuCl_2·2H_2O$	NCS	Et_3N	toluene	0
22	$CuCl_2·2H_2O$	NCS	pyridine	toluene	0
23	$CuCl_2·2H_2O$	NCS	$NaHCO_3$	DMF	0
24	$CuCl_2·2H_2O$	NCS	$NaHCO_3$	H_2O	0
25	$CuCl_2·2H_2O$	NCS	$NaHCO_3$	1,4-dioxane	61
26[d]	$CuCl_2·2H_2O$	NCS	$NaHCO_3$	toluene	53
27	$CuCl_2$	NCS	$NaHCO_3$	toluene	82

[a] Reaction conditions: [Cu] (20 mmol%), alkyne **1a** (0.2 mmol), Mannich base **2a** (0.3 mmol), oxidant (0.6 mmol), base (0.6 mmol), solvent (2.0 mL), 110 °C, 6 h, under N_2.
[b] Isolated yield based on **1a**.
[c] 70% in H_2O.
[d] Temperature 90 °C.

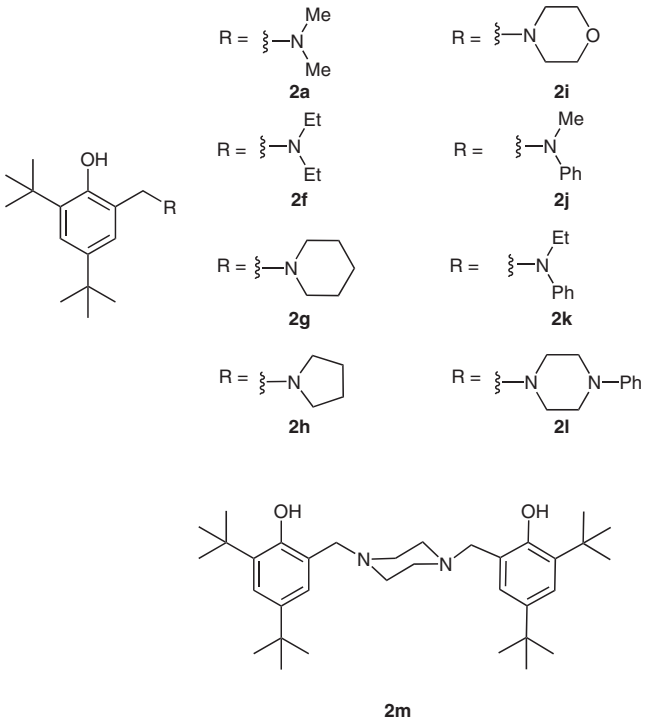
Here, we report an efficient copper-catalyzed coupling reaction of phenylacetylene with a Mannich base under mild conditions, in which iminium ions were generated in situ through a chlorine(1+) or bromine(1+) ion-initiated retro-Mannich-type fragmentation (Scheme 1).[15]

As part of our continued interest in investigating copper-catalyzed coupling reactions,[16] we found that the propargylamine **3aa** was obtained when phenylacetylene (**1a**) was treated with Mannich base **2a** in the presence of copper(II) chloride dihydrate, *N*-chlorosuccinimide, and sodium bicarbonate (Table 1, entry 4). This prompted us to develop a new method for the synthesis of propargylamines from alkynes and Mannich bases.

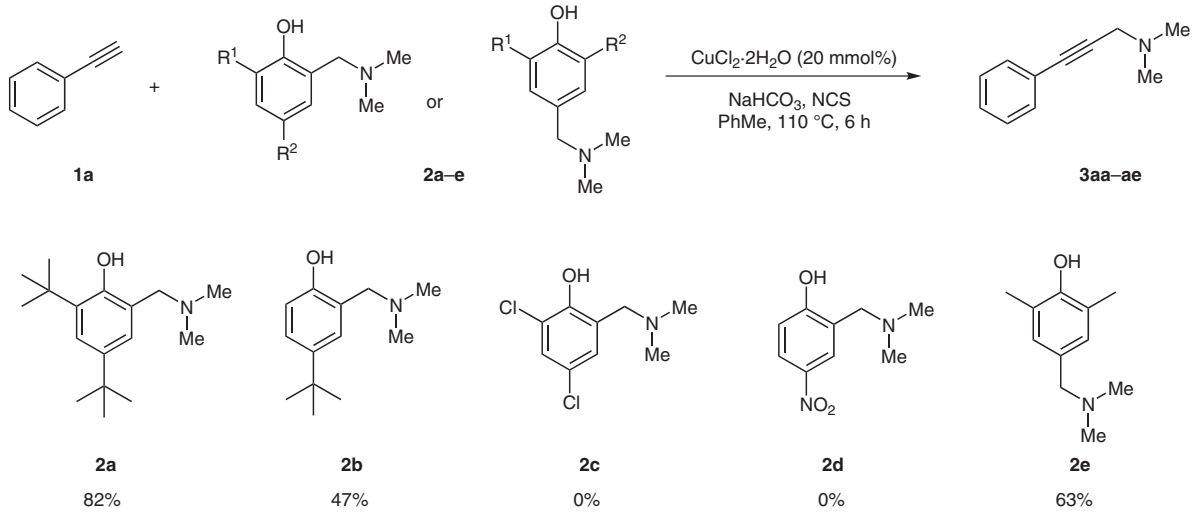
We selected phenylacetylene (**1a**) and Mannich base **2a** as model substrates for optimization of the reaction conditions. In our preliminary studies, we were pleased to find that when we used toluene as the solvent, *N*-chlorosuccinimide as the oxidant, and sodium bicarbonate as the base, phenylacetylene (**1a**) reacted with Mannich base **2a** at 110 °C in the presence of catalytic amount of copper(I) iodide to afford the propargylamine **3aa** in 61% yield (Table 1, entry 1). By screening various metal compounds, we found that copper salts are effective catalysts for the reaction, and that copper(II) chloride dihydrate showed the best catalytic activity, giving an 82% yield (entries 1–5). Other metal salts including salts of iron, cobalt, nickel, or palladium were not effective in this transformation (entries 6–10). No product was detected in the absence of a catalyst (entry 13).

Next, we examined various oxidants, bases, and solvents with copper(II) chloride dihydrate as the catalyst. We found that other oxidants, including *N*-bromosuccinimide, *tert*-butyl hydroperoxide di-*tert*-butyl peroxide, (diacetoxyiodo)benzene, and iodine were either ineffective or less effective than *N*-chlorosuccinimide (entries 14–18). Investigation of a variety of bases revealed that sodium bicarbonate gave the best yield, whereas only trace amounts of the product were detected when organic bases such as triethylamine or pyridine were used (entries 19–22). Therefore, the more inexpensive sodium bicarbonate was chosen for subsequent studies. Control experiments showed that the presence of an oxidant and a base was crucial for the reaction, and no product was detected in the absence of either the oxidant or the base (entries 11 and 12). We also tested the effects of various solvents on the reaction (entries 23–25). Of the tested solvents, toluene gave the best results (entry 4). Temperatures below than 110 °C dramatically decreased the reaction rate and conversion (entry 26).

To evaluate the potential of various Mannich bases in the reaction, other phenol-derived Mannich bases (**2b–e**) were subjected to the reaction conditions optimized for **2a**. As shown in Scheme 2, only the electron-rich



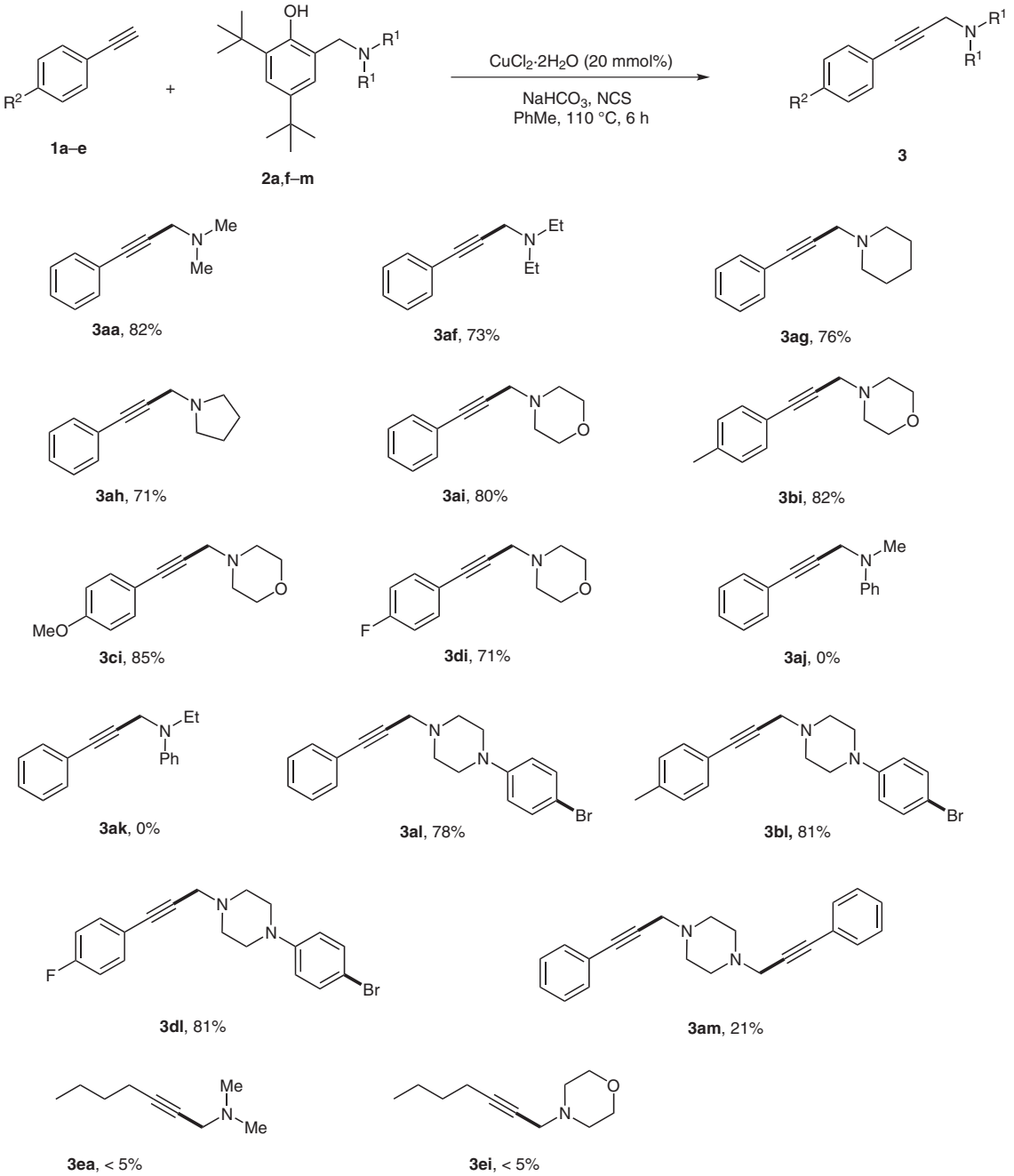
Scheme 3 Various Mannich bases used in the reaction



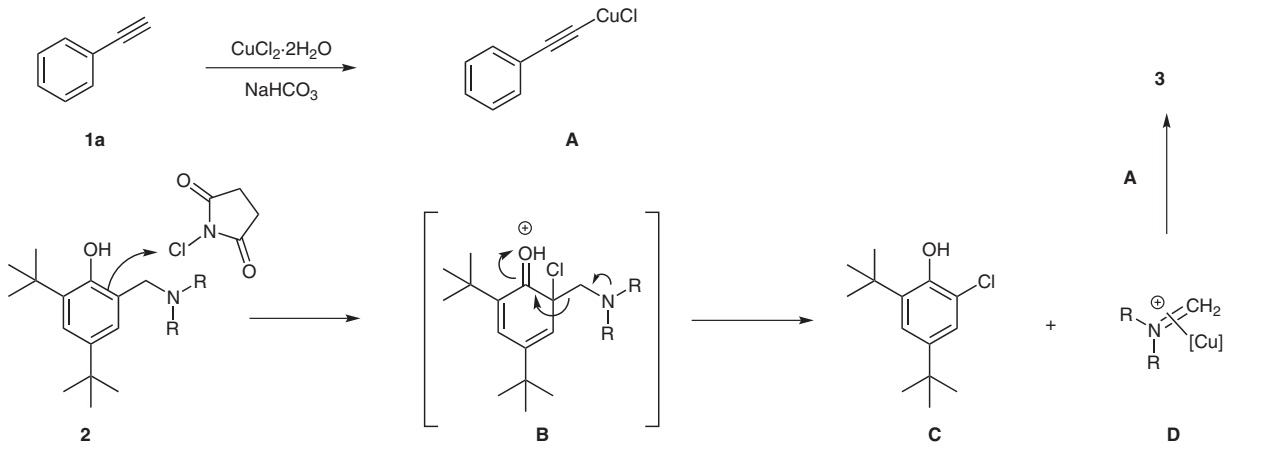
Scheme 2 Results of copper-catalyzed coupling reactions of phenylacetylene and various Mannich bases

Mannich bases **2b** and **2e** gave the corresponding propargylamines; products **3ab** and **3ae** were obtained in yields of 47% and 82%, respectively. Electron-deficient Mannich bases were ineffective, which clearly showed that electronic effects are crucial to the reaction. The position of the substituent groups also affected the reaction rate. When Mannich base **2e** was used, product **3ae** was obtained in lower yield than that obtained from **2a**. We therefore chose 2,4-di-*tert*-butylphenol-type Mannich bases for our further studies on the reaction.

Having determined the optimal reaction conditions, we extended our studies to various combinations of alkynes **1a**–**e** and 2,4-di-*tert*-butylphenol-type Mannich bases **2a** and **2f**–**m** (Scheme 3). As shown in Scheme 4, most Mannich bases with cyclic, heterocyclic, or acyclic secondary aliphatic amine groups gave good yields of the corresponding products under the optimized conditions, the highest yields being obtained from Mannich base **2i**. When Mannich base **2l** was used, only traces of the corresponding product were obtained. It is noteworthy that when *N*-bromosuccinimide was used instead of *N*-chloro-



Scheme 4 Results of copper-catalyzed coupling reactions of alkynes with 2,4-di-*tert*-butylphenol-type Mannich bases. *Reagents and conditions*: $CuCl_2 \cdot 2H_2O$ (20 mmol%), aromatic alkyne (0.2 mmol), Mannich base (0.3 mmol), NCS (0.6 mmol), $NaHCO_3$ (0.6 mmol), toluene (2.0 mL), 110 °C, 6 h, under N_2. NBS was used instead of NCS in the preparations of **3al**, **3bl**, and **3dl**. Yields of **3ea** and **3el** are based on GC/MS studies.



Scheme 5 Possible mechanism for the copper-catalyzed coupling reaction of a Mannich base with a phenylacetylene to give a propargylamine

succinimide the products were obtained in good yields with concomitant bromination of the benzene rings (**3al**, **3bl**, and **3dl**). However, Mannich bases with aromatic secondary amine groups were less reactive in reactions with phenylacetylene (**1a**), and none of the desired products **3aj** and **3ak** were isolated. The symmetrical Mannich base **2m** gave the symmetrical propargylamine **3am** in 21% yield. Both electron-rich and electron-deficient aromatic alkynes were transformed into the corresponding products (**3bi**, **3ci**, and **3di**). Hex-1-yne gave poor results, with only traces of the products being detectable by GC/MS (**3ea** and **3ei**).

A possible mechanism for the copper-catalyzed coupling of an alkyne and a Mannich base is shown in in Scheme 5. In the presence of sodium bicarbonate, the reaction of phenylacetylene (**1a**) with $CuCl_2·2H_2O$ gives the copper(II) acetylide **A**. The reaction of the Mannich base with *N*-chlorosuccinimide gives intermediate **B** which is converted into byproduct **C**[17] and an iminium ion intermediate that reacts with a copper ion to form intermediate **D**. Nucleophilic attack of **A** on **D** leads to the target product **3**.

This mechanism is in accordance with our experimental results. In the reaction of Mannich base **2** with *N*-chlorosuccinimide to form intermediate **B**, the Mannich base acts as a nucleophile and *N*-chlorosuccinimide acts as an electrophile. Electron-withdrawing groups, such as chloro or nitro groups, attached to the Mannich base decrease its nucleophilicity and hinder the reaction. The benzene ring of the copper(II) acetylide intermediate **A** can conjugate with the double bond of the iminium ion intermediate **D** to form a conjugated system, thereby stabilizing intermediate **D**. Aliphatic alkynes cannot stabilize intermediate **D**, and are therefore inert in this reaction.

In summary, we have developed a new and efficient method for synthesizing propargylamines by using 2,4-di-*tert*-butylphenol type-Mannich bases through chlorine(1+) or bromine(1+) ion-initiated retro-Mannich-type fragmentation. Investigations of the detailed mechanism of the reaction and its synthetic applications are currently underway.

Chemicals were purchased from a commercial supplier (Shanghai Chemical Co., Shanghai, China) and used without additional purification. The Mannich bases were synthesized by the methods described in the literature.[18] Melting points were determined on a Yamato melting apparatus Model MP-21. ^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard by using a Bruker DRX 500 (500 MHz) spectrometer. GC analysis was performed on an Agilent GC-6820 chromatograph equipped with a 30 m × 0.32 mm × 0.5 μm HP-Innowax capillary column and a flame-ionization detector. GC/MS spectra were recorded on Thermo TRACE DSQ spectrometer equipped with a TRB-5MS column (30 m × 0.25 mm × 0.25 μm). The progress of the reactions was monitored by TLC (silica gel polygrams SIL G/UV 254 plates). Column chromatography was performed on Silicycle (40–60 mm) silica gel.

Propargylamines 3; General Procedure

NCS or NBS (0.6 mmol) was added to a mixture of $CuCl_2·2H_2O$ (20 mmol%), the Mannich base **2** (0.3 mmol), the phenylacetylene **1** (0.2 mmol), and $NaHCO_3$ (0.6 mmol) in toluene (2.0 mL) under N_2 at r.t., and the soln was then stirred at 110 °C for 6 h. The mixture was then cooled to r.t. and mixed with $CHCl_3$ (10 mL) and H_2O (10 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated by rotary evaporation, and the residue was purified by column chromatography.

1-(4-Bromophenyl)-4-(3-phenylprop-2-yn-1-yl)piperazine (3al)

Preparation by the general procedure from phenylacetylene (**1a**; 20.4 mg, 0.2 mmol), Mannich base **2l** (114 mg, 0.3 mmol), and NBS (0.6 mmol) with purification by flash chromatography [silica gel, PE–EtOAc (3:1)] gave a white solid; yield: 50.2 mg (78%); mp 126–128 °C (MeOH).

IR (KBr): 3064, 2844, 1596, 1421, 1384, 1164, 857, 814, 670, 589, 534 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.44 (m, 2 H, Ar*H*), 7.36–7.30 (m, 5 H, Ar*H*), 6.83–6.80 (m, 2 H, Ar*H*), 3.61 (s, 2 H, C≡CCH_2), 3.25 (t, *J* = 4.9 Hz, 2 × 2 H, ArNCH_2), 2.82 (t, *J* = 4.9 Hz, 2 × 2 H, NCH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.3, 131.9, 131.8, 128.4, 128.3, 123.0, 117.8, 112.0, 85.7, 84.1, 52.0, 49.0, 47.8.

GC/MS (EI, 70 eV): *m/z* = 354.

Anal. Calcd for $C_{19}H_{19}BrN_2$: C, 64.23; N, 7.89; H, 5.39. Found: C, 64.36; N, 7.75; H, 5.59.

1-(4-Bromophenyl)-4-[3-(4-tolyl)prop-2-yn-1-yl]piperazine (3bl)

Preparation by the general procedure from 1-ethynyl-4-methylbenzene (23.2 mg, 0.2 mmol), Mannich base **2l** (114 mg, 0.3 mmol), and NBS (0.6 mmol) with purification by flash chromatography

[silica gel, PE–EtOAc (3:1)] gave a white solid; yield: 59.6 mg (81%); mp 135–137 °C (MeOH).

IR (KBr): 2939, 2845, 2819, 2771, 1605, 1400, 1152, 1012, 917, 817, 530 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.34 (m, 4 H, Ar*H*), 7.14–7.13 (m, 2 H, Ar*H*), 6.83–6.80 (m, 2 H, Ar*H*), 3.79 (s, 2 H, C≡CCH_2), 3.38 (br s, 2 × 2 H, ArNCH_2), 3.03 (br s, 2 × 2 H, NCH_2), 2.36 (s, 3 H, ArCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.3, 138.3, 131.9, 131.7, 129.1, 120.0, 117.8, 111.9, 85.8, 83.4, 52.0, 49.0, 47.9, 21.5.

GC/MS (EI, 70 eV): *m/z* = 368.

Anal. Calcd for $C_{20}H_{21}BrN_2$: C, 65.05; N, 7.59; H, 5.73. Found: C, 64.88; N, 7.42; H, 5.89.

1-(4-Bromophenyl)-4-[3-(4-fluorophenyl)prop-2-yn-1-yl]piperazine (3dl)

Preparation by the general procedure from 1-ethynyl-4-fluorobenzene (24.0 mg, 0.2 mmol), Mannich base **2l** (114 mg, 0.3 mmol), and NBS (0.6 mmol) with purification by flash chromatography [silica gel, PE–EtOAc (3:1)] gave a white solid; yield: 48.4 mg (65%); mp 125–127 °C (MeOH).

IR (KBr): 3038, 2835, 2814, 2771, 1599, 1400, 1230, 1157, 1012, 839, 814, 532 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.34 (m, 4 H, Ar*H*), 7.02–7.00 (m, 2 H, Ar*H*), 6.99–6.80 (m, 2 H, Ar*H*), 3.58 (s, 2 H, C≡CCH_2), 3.24 (t, *J* = 4.9 Hz, 2 × 2 H, ArNCH_2), 2.80 (t, *J* = 4.9 Hz, 2 × 2 H, NCH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.5 (d, J_{CF} = 248.8 Hz), 150.3, 133.7 (d, J_{CF} = 7.5 Hz), 132.0, 119.1, 117.8, 115.6 (d, J_{CF} = 21.3 Hz), 112.0, 84.7, 83.8, 52.0, 49.0, 47.8.

GC/MS (EI, 70 eV): *m/z* = 372.

Anal. Calcd for $C_{19}H_{18}BrFN_2$: C, 61.14; N, 7.51; H, 4.86. Found C, 61.01; N, 7.35; H, 5.09.

4-[3-(4-Methoxyphenyl)prop-2-yn-1-yl]morpholine (3ci)

Preparation by the general procedure from 1-ethynyl-4-methoxybenzene (26.4 mg, 0.2 mmol), Mannich base **2i** (91.5 mg, 0.3 mmol), and NCS (0.6 mmol) with purification by flash chromatography [silica gel, PE–EtOAc (1:1)] gave a yellow oil; yield: 32.8 mg (85%).

IR (KBr): 3007, 2854, 2836, 2814, 2763, 1606, 1509, 1399, 1246, 1115, 1032, 832, 559 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.82 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 3.80 (s, 3 H, ArOCH_3), 3.79 (t, *J* = 4.6 Hz, 2 × 2 H, OCH_2), 3.51 (s, 2 H, C≡CCH_2), 2.67 (s, 2 × 2 H, NCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.6, 133.2, 115.0, 113.9, 85.7, 82.1, 66.8, 55.3, 52.4, 48.1.

GC/MS (EI, 70 eV): *m/z* = 231.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; N, 6.06; H, 7.41. Found: C, 72.58; N, 5.92; H, 7.51.

***N*,*N*-Dimethyl-3-phenylprop-2-yn-1-amine (3aa)**

Preparation by the general procedure from phenylacetylene (**1a**; 20.4 mg, 0.2 mmol), Mannich base **2a** (78.2 mg, 0.3 mmol), and NBS (0.6 mmol) with purification by flash chromatography [silica gel, PE–EtOAc (1:1)] gave a yellow oil; yield: 26.1 mg (82%).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.45 (m, 2 H, Ar*H*), 7.34–7.30 (m, 3 H, Ar*H*), 3.67 (s, 2 H, C≡CCH_2), 2.54 (s, 2 × 3 H, NCH_3).

GC/MS (EI, 70 eV): *m/z* = 159.

The spectral data were in accordance with those reported in the literature.[19]

***N*,*N*-Diethyl-3-phenylprop-2-yn-1-amine (3af)**

Preparation by the general procedure from phenylacetylene (**1a**; 20.4 mg, 0.2 mmol), Mannich base **2f** (87.3 mg, 0.3 mmol), and NCS (0.6 mmol) with purification by flash chromatography [silica gel, PE–EtOAc (1:1)] gave a yellow oil; yield: 27.3 mg (73%).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.41 (m, 2 H, Ar*H*), 7.29–7.28 (m, 3 H, Ar*H*), 3.64 (s, 2 H, C≡CCH_2), 2.63 (t, *J* = 4.8 Hz, 2 × 2 H, NCH_2), 1.12 (t, *J* = 4.8 Hz, 2 × 3 H, NCH$_2$CH_3).

GC-MS (EI, 70 eV): *m/z* = 187.

The spectral data were in accordance with those reported in the literature.[20]

1-(3-Phenylprop-2-yn-1-yl)piperidine (3ag)

Preparation by the general procedure from phenylacetylene (**1a**; 20.4 mg, 0.2 mmol), Mannich base **2g** (90.0 mg, 0.3 mmol), and NBS (0.6 mmol) with purification by flash chromatography [silica gel, PE–EtOAc (1:1)] gave a yellow oil; yield: 30.2 mg (76%).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 2 H, Ar*H*), 7.31–7.28 (m, 3 H, Ar*H*), 3.60 (s, 2 H, C≡CCH_2), 2.71 (br s, 2 × 2 H, NCH_2), 1.78–1.73 (m, 2 × 2 H, NCH$_2$CH_2), 1.50 (s, 2 H, NCH$_2$CH$_2$CH_2).

GC/MS (EI, 70 eV): *m/z* = 199.

The spectral data were in accordance with those reported in the literature.[21]

1-(3-Phenylprop-2-yn-1-yl)pyrrolidine (3ah)

Preparation by the general procedure from phenylacetylene (**1a**; 20.4 mg, 0.2 mmol), Mannich base **2h** (86.7 mg, 0.3 mmol), and NCS (0.6 mmol) with purification by flash chromatography [silica gel, PE–EtOAc (1:1)] gave a yellow oil; yield: 26.3 mg (71%).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.42 (m, 2 H, Ar*H*), 7.30–7.29 (m, 3 H, Ar*H*), 3.64 (s, 2 H, C≡CCH_2), 2.72–2.69 (m, 2 × 2 H, NCH_2), 1.86–1.83 (m, 2 × 2 H, NCH$_2$CH_2).

GC/MS (EI, 70 eV): *m/z* = 185.

The spectral data were in accordance with those reported in the literature.[20]

4-[3-(4-Tolyl)prop-2-yn-1-yl]morpholine (3bi)

Preparation by the general procedure from 1-ethynyl-4-methylbenzene (23.2 mg, 0.2 mmol), Mannich base **2i** (91.5 mg, 0.3 mmol), and NCS (0.6 mmol) with purification by flash chromatography [silica gel, PE–EtOAc (1:1)] gave a yellow oil; yield: 35.3 mg (82%).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.32 (m, 2 H, Ar*H*), 7.12–7.11 (m, 2 H, Ar*H*), 3.83–3.81 (t, *J* = 4.9 Hz, 2 × 2 H, OCH_2), 3.68 (s, 2 H, C≡CCH_2), 2.74 (br s, 2 × 2 H, NCH_3), 2.34 (s, 3 H, ArCH_3).

GC/MS (EI, 70 eV): *m/z* = 215.

The spectral data were in accordance with those reported in the literature.[22]

4-[3-(4-Fluorophenyl)prop-2-yn-1-yl]morpholine (3di)

Preparation by the general procedure from 1-ethynyl-4-fluorobenzene (24.0 mg, 0.2 mmol), Mannich base **2i** (91.5 mg, 0.3 mmol), and NCS (0.6 mmol) with purification by flash chromatography [silica gel, PE–EtOAc (1:1)] gave a yellow oil; yield: 39.3 mg (71%).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.40 (m, 2 H, Ar*H*), 7.02–6.98 (m, 2 H, Ar*H*), 3.78 (t, *J* = 4.6 Hz, 2 × 2 H, OCH_2), 3.50 (s, 2 H, C≡CCH_2), 2.65 (t, *J* = 4.6 Hz, 2 × 2 H, NCH_3).

GC/MS (EI, 70 eV): *m/z* = 219.

The spectral data were in accordance with those reported in the literature.[21]

1,4-Bis(3-phenylprop-2-yn-1-yl)piperazine (3am)
Preparation by the general procedure from phenylacetylene (**1a**; 40.8 mg, 0.4 mmol), Mannich base **2m** (313.2 mg, 0.6 mmol), and NCS (0.6 mmol) with purification by flash chromatography [silica gel, PE–EtOAc (5:1)] gave a yellow solid; yield: 13.2 mg (21% yield); mp 102–104 °C (MeOH) (Lit.[23] mp 103 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.46 (m, 4 H, Ar*H*), 7.35–7.31 (m, 6 H, Ar*H*), 3.71 (s, 4 H, C≡CCH_2), 3.02 (s, 4 × 2 H, NCH_2).

GC/MS (EI, 70 eV): *m/z* = 314.

The spectral data were in accordance with those reported in the literature.[23]

2,4-Di-*tert*-butyl-6-chlorophenol (Byproduct C)
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 2.3 Hz, 1 H, Ar*H*), 7.20 (d, *J* = 2.3 Hz, 1 H, Ar*H*), 5.74 (s, 1 H, O*H*), 1.42 (s, 9 H, CH_3), 1.29 (s, 9 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.3, 143.1, 136.7, 123.3, 122.8, 120.4, 33.4, 34.5, 31.5, 29.4.

GC/MS (EI, 70 eV): *m/z* = 240.

The spectral data were in accordance with those reported in the literature.[24]

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