A simple method for the preparation of propargylamines using molecular sieve modified with copper(II)

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A new, heterogeneous, 4 Å molecular sieve-supported copper(II) catalyst was developed and was used successfully in the A^3 coupling of alkynes, aldehydes and amines under simple reaction conditions.

Introduction

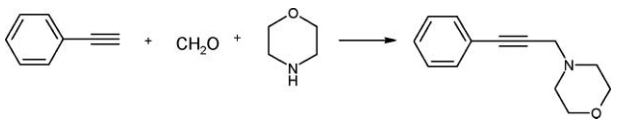
The metal-catalyzed carbon–carbon bond formation has become one of the most important reactions in preparative organic chemistry, even on an industrial scale. From this point of view, some metals have a large literature background *e.g.* Pd in the Heck, Sonogashira, Stille, or Suzuki–Miyaura couplings, or Ru in metathesis, but other metals such as nickel, iron, copper, *etc.* also have an increasing synthetic importance.

Propargylamines are versatile synthons in the preparation of organic compounds, especially different N-heterocycles. The conventional methods for their synthesis involve the amination of propargylic halides, phosphates or triflates.[1] Another possible way is the reaction of lithium acetylides or Grignard reagents with imines or their derivatives.[2,3] However, these methods require the use of stoichiometric amounts of organometallic reagents and strictly controlled reaction conditions. Furthermore, protection of sensitive functional groups, such as aldehyde, is also necessary. Thus, the development of a new efficient method has been an interesting synthetic challenge. In the course of this research transition metal complex catalysts were developed for the activation of the C–H bond of the terminal alkyne containing iridium,[4] indium,[5] zinc,[6] silver,[7] or copper.[8] Wei and Li have reported the highly efficient three-component coupling reaction (alkyne–amine–aldehyde or A^3 reaction) through C–H activation in water using gold,[9] but the use of these homogeneous catalysts have some disadvantages, as they are expensive, not recyclable, and their separation from the reaction mixture is tedious. This led to the elaboration of different heterogeneous, recyclable catalysts. Lo and co-workers[10] developed a gold-based complex, which was successfully used in aqueous media for the preparation of propargylamines with good yield. Other metal-based heterogeneous catalysts were also used successfully in the A^3-reaction, *e.g.* Ag^I-tungstophosphoric acid,[11] Cu^I anchored on a silica gel support[12] or on USY-zeolite,[13] Cu^{II} salt on a hydroxyapatite support,[14] or N-heterocyclic carbene–Cu^I on a silica support.[15] The main disadvantages of these methods are the high price of the catalyst,[11,15] the tedious preparation of it,[12,15] the sensitivity of copper^I compounds,[12,13,15] or problems with the reusability/recyclability.[13]

Results and discussion

Recently our research group developed a new, heterogeneous Pd catalyst, Pd^0 on Mg–La mixed oxide, which was used successfully in the Heck,[16] Sonogashira,[17] and Suzuki reactions.[18] Then, good results were obtained with Ni^{II} on the same support in the Kumada coupling.[19] Continuing this work, we examined the possibility of the applicability of a heterogeneous copper catalyst in the A^3 coupling.

First, we tested different basic materials as supports. These were Mg:La 3 : 1 mixed oxide (MgLaO), Mg:Al 2 : 1 hydrotalcite (HT), and 4 Å molecular sieves (4A). These solid bases were treated with $CuCl_2$ in deionized water at room temperature for 12 h. The copper content of the catalysts thus obtained was 0.77, 0.67, and 1.00 mmol g^{-1}, respectively (determined by ICP-OES). These catalysts were examined in the reaction of formaldehyde, phenylacetylene and morpholine (Scheme 1) under solvent-free conditions. The results are summarized in Table 1. After the reaction time indicated in the table, the reaction mixture was diluted with methyl-*tert*-butyl ether, the solid was filtered out, the solvent was evaporated, and then the residues were examined with both ^1H NMR spectroscopy and GC-MS.



Scheme 1

As is shown, the best result was obtained with Cu^{II} on 4A as basic support (Table 1, entry 4). In the case of Cu^{II}–MgLa and Cu^{II}–HT, the main product was N-hydroxymethyl-morpholine, the known intermediate of the A^3 coupling. Based on these results

Table 1 Selection of the catalyst for the A^3 coupling[a]

	Catalyst	Reaction time/h	Yield (%)[b]
1	Cu^{II}–HT	14	12 (26)[c]
2	Cu^{II}–MgLa (3 : 1)	24	14 (42)[c]
3	Cu^{II}–4A	14	56
4	*Cu^{II}–4A*	*24*	*92*
5	Cu^{II}–4A[d]	24	90
6	Cu^{II}–4A[e]	24	33

[a] 5 mmol morpholine, 5 mmol paraformaldehyde, 6 mmol phenylacetylene, 0.5 g catalyst. [b] Isolated yield, corrected with the results of GC-MS. [c] The main product is hydroxymethyl-morpholine (its yield is shown in parentheses). [d] 0.2 g catalyst was used. [e] 0.2 mmol Cu/g support.

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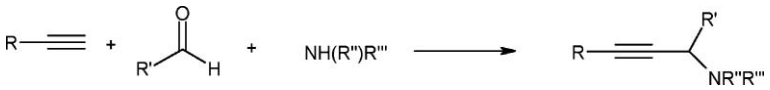
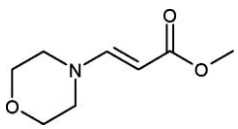


Scheme 2

we investigated the reaction of different alkynes, amines and aldehydes in the presence of Cu^{II}–4A (Scheme 2). The results are summarized in Table 2.

Generally, after 24 h stirring at room temperature phenylacetylene, formaldehyde and secondary amines gave the desired products in high isolated yield (see entries 1–6). The primary *n*-butylamine gave significantly lower yield (entry 7). Aromatic amines failed to react (entries 8–9). In the case of diphenylamine, because of its melting point (54 °C) the reaction was conducted at 60 °C. In the reaction of aniline, the main product was N-methylene aniline, formed from *N*-hydroxymethyl-aniline by dehydration. Butyraldehyde gave the desired product with quantitative yield (entry 10). The aliphatic 1-heptyne failed to react under solvent-free conditions at room temperature, probably due to the high viscosity of the mixture. While using acetonitrile as solvent[15] the appropriate propargylamine was obtained in moderate yield (entry 11). Methyl acetylenecarboxylate showed violent reaction with both morpholine and dibutylamine, but instead of the formation of propargylamines, an addition of the amine to the C≡C bond occurred together with the formation of some polymeric products. This could be concluded from the ^{1}H NMR spectra (olefinic protons of the morpholine adduct—see Scheme 3—were found at 4.70 and 7.35 ppm) and from GC-MS examination of the product mixture. The addition of an amine to the C≡C bond is known in the literature,[20] the *E* adduct is formed even without the addition of any catalyst.



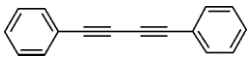
Scheme 3

Meparfynol (3-methylpent-1-yn-3-ol) showed no reactivity at room temperature, but in refluxing toluene the desired propargylamine was obtained with excellent yield (entry 15). *trans*-Cinnamaldehyde under the same conditions gave the desired product in quantitative preparative yield (entry 16).

Reaction of aromatic aldehydes such as veratraldehyde, 3,4,5-trimethoxybenzaldehyde or 4-chlorobenzaldehyde (in acetonitrile) at room temperature (entries 17–19) gave no, or poor results; the aldehydes could be recovered from the reaction mixture. Thus, experiments were performed to determine the optimal reaction conditions for aromatic aldehydes (see Table 3). The reaction of *p*-chlorobenzaldehyde, phenylacetylene and morpholine was used for this purpose.

In acetonitrile at 60 °C 60%, while at 80 °C 78% of product was obtained, but with increasing temperature, the amount of the phenylacetylene dimer 1,3-diphenyl-but-1,3-diyn (Scheme 4) also increased significantly. This dimer is produced in a Glaser-type self coupling.[21]

By changing acetonitrile to toluene at 110 °C the yield increased to 89%, and the propargylamine/Glaser-dimer ratio was



Scheme 4

significantly better. The Glaser coupling strongly consumes the phenylacetylene—this was shown by the presence of a significant amount of unreacted aldehyde in the reaction mixture. Thus, instead of 20 mol%, 50 mol% excess of phenylacetylene was added, and the desired propargylamine was obtained in nearly quantitative yield and with formation of less than 10% dimeric product. Based on these results the reaction was repeated with several aldehydes. The results are summarized in Table 4

The big disadvantage of the transition metal-catalyzed reactions is that the metal often contaminates the product, or its separation is very tedious. Copper is known to form complexes with amines. This could mean that during such a long reaction, either at room temperature or by heating, a remarkable amount of copper would be detectable in the liquid phase. We investigated the products isolated in the reactions and the X-ray fluorescence analysis showed that in most of the cases the copper content of the products was less than 1 ppm. Thus, we could consider that our catalyst system is stable enough to avoid the copper contamination of the product.

The catalyst can be easily recovered from the reaction mixture and it is reusable without any purification. In the reaction of phenylacetylene, paraformaldehyde and morpholine, the same catalyst gave 92, 89 and 81% yields in the 1st, 2nd and 3rd cycle, respectively.

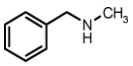
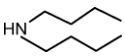
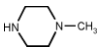
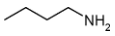
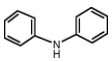
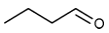
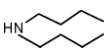
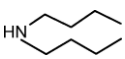
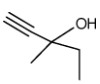
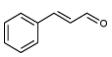
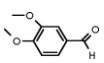
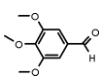
Although A^3 coupling is described with aldehydes, we examined ketones, too, namely acetone and acetophenone. In these cases, instead of an A^3-type reaction, the Glaser-type self coupling of phenylacetylene occurred and 1,3-diphenyl-but-1,3-diyn was obtained in good yield (95 and 50%, respectively) (Scheme 5).

The original Glaser method described the use of ammonium chloride and cuprous salt in the presence of atmospheric oxygen for the coupling. When we reacted phenylacetylene in the presence of ammonium chloride, acetone, and Cu^{II}–4A, the yield of 1,3-diphenyl-but-1,3-diyn decreased to 34%. We examined the possibility of a cross-coupling Glaser reaction. Phenylacetylene and meparfynol were reacted with acetone and morpholine in the presence of Cu^{II}–4A. After 24 h stirring at room temperature the reaction mixture was examined by GC-MS. The results showed that phenylacetylene is more reactive than meparfynol, since the amount of the phenylacetylene dimer was predominant in the mixture, the amount of meparfynol dimer was almost negligible (Scheme 6). This is in good correlation with the results obtained in the A^3 coupling, *i.e.* both meparfynol and heptyne gave weaker yield than phenylacetylene.

Conclusion

Thus, copper^{II} supported on 4 Å molecular sieves is a good, easily recoverable and reusable catalyst for the A^3 coupling of aliphatic

Table 2 A^3 coupling in the presence of Cu^{II}–4A[a]

	Alkyne	Aldehyde	Amine	Yield (%)[b]
1		CH_2O		92
2		CH_2O		93
3		CH_2O		76
4		CH_2O		96
5		CH_2O		70
6		CH_2O		72
7		CH_2O		40
8		CH_2O		1[c,d]
9		CH_2O		7[d]
10				98
11		CH_2O		2[d] (27)[e]
12		CH_2O		4[d]
13		CH_2O		—[f]
14		CH_2O		—[f]
15		CH_2O		— (94[g])
16				99[g]
17				1[e,h]
18				3[e,h]
19				10[e,h]

[a] 5 mmol amine, 5 mmol aldehyde, 6 mmol phenylacetylene, 0.5 g catalyst. [b] Isolated yield, corrected with the results of GC-MS. [c] At 60 °C [d] Based on GC-MS. [e] In acetonitrile. [f] Instead of A^3 coupling an addition of the amine to the C≡C bond occurred (see text). [g] In refluxing toluene. [h] Based on the ^1H NMR spectra.

Table 3 Effect of the reaction conditions to the A^3 coupling of *p*-chlorobenzaldehyde

	Solvent	T/°C	Molar ratio[a]	Yield (%)
1	acetonitrile	rt	1.2 : 1	10[b]
2	acetonitrile	60	1.2 : 1	60[b,c]
3	acetonitrile	80	1.2 : 1	78 [b,c]
4	toluene	110	1.2 : 1	89[c]
5	toluene	110	1.5 : 1	96[c]

[a] Phenylacetylene : aldehyde ratio. [b] Based on the ^1H NMR spectra. [c] Based on GC-MS

Table 4 A^3 coupling of aromatic aldehydes with phenylacetylene[a]

	Aldehyde	Yield (%)
1		96
2		70
3		99
4		90
5		89
6		70
7		54

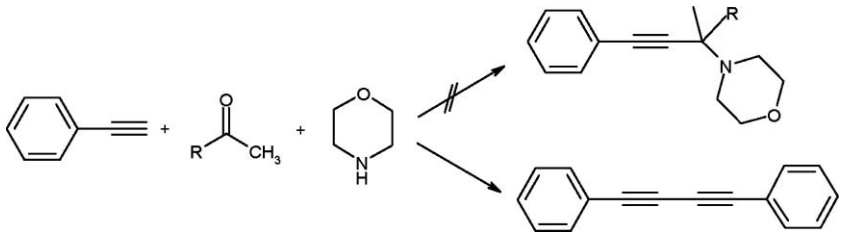
[a] 5 mmol amine, 5 mmol aldehyde, 7.5 mmol phenylacetylene, 0.5 g catalyst, toluene, reflux, 15 h. Isolated yields, corrected with the results of GC-MS and ^1H NMR spectra

aldehydes, alkynes and secondary amines at room temperature under solvent-free conditions. Aromatic aldehydes in boiling toluene yielded the desired propargylamines almost quantitatively.

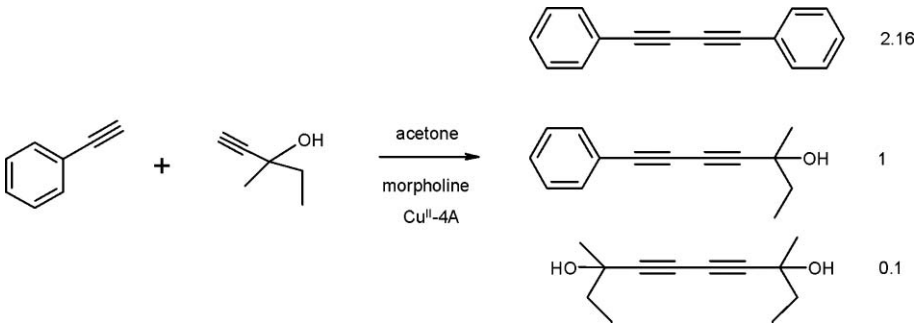
Experimental

^1H NMR spectra were made on BRUKER Avance-300 or 500 instruments using TMS as internal standard in $CDCl_3$.

GC-MS spectra were made on Shimadzu GC-2010, GC-MS QP2010S instrument, column: HP-5MS, 30 m × 0.25 mm ×



Scheme 5



Scheme 6

0.25 µm, Temperature program: 40 °C (10 min) → 10 °C min^{-1} → 300 °C (26 min).

IR spectra were made on BRUKER Tensor 37 instrument.

XRF examinations

Canberra isotope excitation instrument with SCD, exciting source: ^{125}I.

TLC

Merck Kieselgel 60 F_{254} plates, hexane–acetone 4 : 1 eluent, detection either by UV light at 254 nm or by heating after spraying with phosphoromolybdic acid solution.

Preparation of the catalysts

2 g of support and 0.34 g (2 mmol) of $CuCl_2 \cdot 2H_2O$ in 200 ml deionized water were stirred at room temperature for 12 h. Then the solid was filtered out, washed with deionized water and then with acetone, and dried in an oven at 120 °C for 1 h.

Typical procedure for the reaction of aliphatic aldehydes

6 mmol (660 µl) of phenylacetylene, 5 mmol of aldehyde, 5 mmol of amine and 0.5 g Cu^{II}–4A were stirred at room temperature for 24 h. Then the mixture was diluted with methyl-*tert*-butyl ether, the solid was filtered out, washed with the same solvent, the filtrate was evaporated and the product was characterized.

***N*-(3-Phenylprop-2-ynyl)morpholine.** Yellowish oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.62 (m, 4H, 2×N–CH_2); 3.48 (s, 2H, C≡C–CH_2); 3.75 (m, 4H, 2×O–CH_2); 7.29 (m, 3H, ArH); 7.42 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): spectral data are in agreement with the reported ones[22] GC: R_t: 26.65 min. MS *m*/*z*(%): 201(M$^+$,25), 170(25), 143(40), 115(100). IR(film): ν 3056, 2959, 2855, 2813, 2762, 1682, 1598, 1489, 1453, 1331, 1116, 1006, 862, 758, 692, 666 cm^{-1}. Anal. Calcd. for $C_{13}H_{15}NO$: C 77.61, H 7.46, N 6.97%, found: C 77.53, H 7.49, N 7.02%.

***N*-(3-Phenylprop-2-ynyl)-*N*-methyl-benzylamine.** Yellowish oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.39 (s, 3H, CH_3); 3.50 (s, 2H, $PhCH_2$); 3.63 (s, 2H, C≡C–CH_2); 7.28–7.29 (m, 7H, ArH); 7.36–7.47 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$): spectral data are in agreement with the reported ones.[23] GC: R_t: 29.17 min. MS *m*/*z*(%): 235(M$^+$, 25), 158(45), 144(30), 115(100), 91(70). Anal. Calcd. for $C_{17}H_{17}N$: C 86.81, H 7.23, N 5.96%, found: C 86.79, H 7,31, N 6.02%.

***N*-(3-Phenylprop-2-ynyl)pyrrolidine.** Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.83 (m, 4H, 2×CH_2); 2.70 (m, 4H, 2×N–CH_2); 3.63 (s, 2H, C≡C–CH_2); 7.27–7.29 (m, 4H, ArH); 7.43 (m, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 131.5, 128.4, 128.0, 123.0, 84.7, 77.3, 53.2, 48.2, 25.3. GC: R_t: 25.25 min. MS *m*/*z*(%): 185(M$^+$, 30), 156(50), 115(100), 89(15), 70(20). Anal. Calcd. for $C_{13}H_{15}N$: C 84.32, H 8.11, N 7.57%, found: C 84.39, H 8.04, N 7.64%.

***N*,*N*-Dibutyl-*N*-(3-phenylprop-2-ynyl)-amine.** Yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.93 (t, 6H, 2×CH_3); 1.34–1.36 (sex, 4H, 2×CH_2–CH_3); 1.48 (qui, 4H, 2×CH_2); 2.53 (t, 4H, 2×NCH_2); 3.61 (s, 2H, C≡C–CH_2); 7.28 (m, 3H, ArH); 7.42 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 131.5, 128.7, 128.1, 122.7, 84.4, 77.2, 49.3, 33.5, 20.2, 17.5. GC: R_t: 27.46 min. MS *m*/*z*(%): 243(M$^+$, 5), 200(55), 115(100). IR(film): ν 2957, 2931, 2871, 2817, 1598, 1489, 1458, 1376, 1320, 1094, 755, 690 cm^{-1}. Anal. Calcd. for $C_{17}H_{25}N$: C 83.95, H 10.29, N 5.76%, found: C 84.03, H 10.32, N 5.69%.

***N*-(3-Phenylprop-2-ynyl)piperidine.** Yellowish oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.44–1.66 (m, 6H, CH_2–CH_2–CH_2); 2.41–2.66 (m, 4H, 2×N–CH_2); 3.47 (s, 2H, C≡C–CH_2); 7.28 (m, 3H, ArH); 7.42 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): spectral data are in agreement with the reported ones.[22] GC: R_t: 26.33 min. MS

m/*z*(%): 199 (M^+, 30), 170(10), 156(40), 115(100). Anal. Calcd. for $C_{14}H_{17}N$: C 84.42, H 8.54, N 7.04%, found: C 84.42, H 8.61, N 7.11%.

***N′*-Methyl-*N*-(3-phenylprop-2-ynyl)piperazine.** Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.26 (s, 3H, N-CH_3); 2.40-2.69 (m, 8H, 2×N-CH_2–CH_2–N); 3.50 (s, 2H, C≡C–CH_2); 7.26–7.30 (m, 3H, ArH); 7.46-7.47 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 131.8, 128.6, 128.2, 123.1, 84.3, 77.3, 55.2, 53.7, 48.3, 47.5. GC: R_t: 27.43 min. MS *m*/*z*(%): 214(M^+, 10), 158(25), 143(25), 115(55), 97(100), 56(55). Anal. Calcd. for $C_{14}H_{18}N_2$: C 78.50, H 8.41, N 13.08%, found: C 78.57, H 8.39, N 13.03%.

***N*-(3-Phenylprop-2-ynyl)-butylamine.** Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.93 (t, 3H, CH_3); 1.32–1.34 (m, 2H, CH_2–CH_3); 1.42–1.44 (m, 2H, CH_2); 2.40 (m, 2H, N–CH_2); 3.07 (s, 1H, NH); 3.22 (s, 2H, C≡C–CH_2); 7.30–7.34 (m, 3H, ArH); 7.47–7.50 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): spectral data are in agreement with the reported ones.[24] MS *m*/*z*(%): 187(M^+, 7), 144(60), 115(100). IR(film): *ν* 2957, 2929, 2871, 1490, 1442, 1327, 1142, 755, 691 cm^{-1}. Anal. Calcd. for $C_{13}H_{17}N$: C 83.42, H 9.09, N 7.49%, found: C 83.38, H 9.12, N 7.41%.

***N*,*N*-Diphenyl-*N*-(3-phenylprop-2-ynyl)-amine.** GC: R_t: 33.38 min. MS *m*/*z*(%): 283(M^+, 90), 206(20), 168(65), 115(100), 77(30).

***N*-Phenyl-*N*-(3-phenylprop-2-ynyl)-amine.** GC: R_t: 29.33 min. MS *m*/*z*(%): 207(M^+, 50), 178(10), 130(15), 115(100).

***N*-Methylene-aniline.** GC: R_t: 13.60 min. MS *m*/*z*(%): 105(M^+, 100), 77(90), 51(45).

***N*-(3-Phenyl-1-propyl-prop-2-ynyl)morpholine.** Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.97 (t, 3H, CH_3); 1.55 (sex, 2H, CH_2–CH_3); 1.66 (q, 2H, CH_2); 2.56 (m, 2H, N–CH_2); 2.72 (m, 2H, N–CH_2); 3.50 (t, 1H, C≡C–CH_2); 3.74 (m, 4H, 2×O–CH_2); 7.28–7.30 (m, 3H, ArH); 7.42–7.51 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 131.5, 128.3, 128.1, 123.1, 84.7, 77.6, 66.2, 52.7, 48.1, 33.8, 21.3, 16.1. GC: R_t: 28.44 min. MS *m*/*z*(%): 243(M^+, 5), 200(100), 128(15), 115(45). Anal. Calcd. for $C_{16}H_{21}NO$: C 79.01, H 8.64, N 5.76%, found: C 78.98, H 8.66, N 5.71%.

***N*-(Oct-2-ynyl)morpholine.** Yellowish oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.86 (t, 3H, CH_3); 1.31 (m, 4H, CH_2–CH_2); 1.48 (m, 2H, CH_2); 2.16 (t, 2H, CH_2–C≡C); 2.51 (m, 4H, 2×N–CH_2); 3.66 (m, 6H, 2×O–CH_2, C≡C–CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 84.5, 77.2, 65.4, 52.6, 48.2, 31.1, 28.7, 22.1, 18.5, 14.1. GC: R_t: 23.94 min. MS *m*/*z*(%): 195(M^+, 25), 138(20), 122(20), 108(100), 86(75), 67(45), 42(70). Anal. Calcd. for $C_{12}H_{21}NO$: C 73.85, H 10.77, N 7.18%, found: C 73.88, H 10.71, N 7.12%.

***N*,*N*-Dibutyl-(oct-2-ynyl)amine.** GC: R_t: 24.96 min. MS *m*/*z*(%): 237(M^+, 5), 194(100), 152(40), 41(30).

Methyl (*E*)-3-(4-morpholinyl)-2-propenoate. Yellowish oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.41 (m, 2H, N–CH_2); 2.50 (m, 2H, N–CH_2); 3.66 (s, 3H, O–CH_3); 3.71 (m, 4H, 2×O–CH_2); 4.70 (d, 1H, = CH–N); 7.35 (dd, 1H, = CH–CO). ^{13}C NMR ($CDCl_3$): spectral data are in agreement with the reported ones.[25] GC: R_t: 24.30 min. MS *m*/*z*(%): 171(M^+, 65), 156(30), 140(80), 112(100), 82(90), 55(60), 42(70).

Methyl (*E*)-3-(*N*,*N*-dibutylamino)-2-propenoate. Yellowish oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.93 (t, 6H, 2×CH_3); 1.33 (m, 4H, 2×CH_2); 1.51 (m, 4H, 2×CH_2); 2.62 (t, 4H, 2×CH_2); 3.66 (s, 3H, O–CH_3); 4.53 (d, 1H, = CH–N); 7.43 (dd, 1H, = CH–CO). ^{13}C NMR ($CDCl_3$): spectral data are in agreement with the reported ones.[25] GC: R_t: 26.13 min. MS *m*/*z*(%): 213(M^+, 20), 182(45), 170(65), 140(75), 128(90), 98(65), 84(100).

***N*-(4-Hydroxy-4-methyl-hex-2-ynyl)morpholine.** Yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.04 (t, 3H, CH_3); 1.47 (s, 3H, CH_3); 1.70 (q, 2H, CH_2); 2.57 (m, 5H, 2×N–CH_2, OH); 3.32 (s, 2H, CH_2–C≡C); 3.75 (t, 4H, 2×O–CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 89.6, 77.4, 68.6, 66.7, 52.2, 47.4, 36.6, 29.5, 9.1. GC: R_t: 23.59 min. MS *m*/*z*(%): 197(M^+, 10), 179(10), 168(15), 96(25), 86(55), 56(35), 43(100). IR(film): *ν* 3410, 2971, 2933, 2860, 1658, 1455, 1290, 1206, 1163, 1116, 1002, 915, 863, 775 cm^{-1}. Anal. Calcd. for $C_{11}H_{19}NO_2$: C 67.01, H 9.64, N 7.11%, found: C 67.09, H 9.69, N 7.12%.

***N*-[3-Phenyl-1-((*E*)-2-phenylethenyl)-prop-2-ynyl]-morpholine.** yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.70 (m, 2H, N–CH_2); 2.82 (m, 2H, N–CH_2); 3.82 (m, 4H, 2×O–CH_2); 4.42 (d, 1H, CH–C≡C); 6.33 (dd, 1H, = CH–CH); 6.94 (d, 1H, CH=CH), 7.20 (d, 1H, ArH); 7.27–7.38 (m, 5H, ArH); 7.46–7.49 (m, 2H, ArH); 7.52–7.57 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.5, 133.6, 132.0, 128.7, 128.4, 128.0, 126.7, 123.0, 88.6, 84.4, 77.3, 67.2, 60.0, 50.1. GC: R_t: 34.69 min. MS *m*/*z*(%): 303(M^+, 25), 217(95), 202(65), 115(100), 86(40), 56(50). IR(film): *ν* 3288, 3058, 3029, 2957, 2854, 2690, 2222, 1953, 1679, 1598, 1490, 1451, 1321, 1118, 1071, 1003, 970, 865, 757, 725, 692 cm^{-1}. Anal. Calcd. for $C_{21}H_{21}NO$: C 83.17, H 6.93, N 4.62%, found: C 83.10, H 6.90, N 4.68%.

***N*-(3-Phenyl-1-(3,4,5-trimethoxyphenyl)-prop-2-ynyl)-morpholine.** ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.66 (s, 1H, CH–C≡C).

Typical procedure for the reaction of aromatic aldehydes

7.5 mmol (660 μl) of phenylacetylene, 5 mmol of aldehyde, 5 mmol of amine and 0.5 g Cu^{II}–4A in 2 ml toluene were stirred under reflux for 15 h. Then the mixture was cooled, diluted with methyl-*tert*-butyl ether, the solid was filtered out, washed with the same solvent, the filtrate was evaporated and the product was characterized.

***N*-(3-Phenyl-1-(4-chlorophenyl)-prop-2-ynyl)morpholine.** Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.40 (m, 2H, N–CH_2); 2.61 (m, 2H, N–CH_2); 3.72 (d, 4H, 2×O–CH_2); 4.76 (s, 1H, CH–C≡C); 7.13 (d, 2H, ArH); 7.33–7.35 (m, 3H, ArH); 7.50–7.52 (m, 2H, ArH); 7.58 (d, 2H, ArH). ^{13}C NMR ($CDCl_3$): spectral data are in agreement with the reported ones.[26] GC: R_t: 33.85 min. MS *m*/*z*(%): 311(M^+, 15), 225(100), 189(35), 86(40), 56(65). Anal. Calcd. for $C_{19}H_{18}ClNO$: C 73.19, H 5.78, N 4.49%, found: C 73.11, H 5.74, N 4.41%.

***N*-(3-Phenyl-1-(3,4-dimethoxyphenyl)-prop-2-ynyl)-morpholine.** Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.65 (m, 4H, 2×N–CH_2); 3.75 (m, 4H, 2×O–CH_2); 3.90 (s, 3H, O–CH_3); 3.93 (s, 3H, O–CH_3); 4.74 (s, 1H, CH–C≡C); 6.87 (d, 1H, ArH); 7.00 (d, 1H, ArH), 7.19–7.21 (m, 2H, ArH); 7.34–7.41 (m, 2H, ArH); 7.50–7.56 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):

149.1, 148.8, 132.0, 130.6, 128.5, 128.4, 127.0, 123.2, 122.0, 121.0, 88.5, 85.5, 67.4, 62.0, 56.4, 56.2, 50.1. GC: R_t: 35.44 min. MS m/z(%): 337(M^+, 5), 251(100), 207(20), 165(15), 115(100), 55(15). Anal. Calcd. for $C_{21}H_{23}NO_3$: C 74.78, H 6.82, N 4.15%, found: C 74.71, H 6.91, N 4.21%.

***N*-(3-Phenyl-1-(3-nitrophenyl)-prop-2-ynyl)morpholine.** Orange oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):): 2.64 (m, 4H, 2×N–CH_2); 3.75 (m, 4H, 2×O–CH_2); 4.88 (s, 1H, CH–C≡C); 7.16 (d, 1H, ArH); 7.23 (d, 1H, ArH); 7.33–7.37 (m, 2H, ArH); 7.52–7.57 (m, 2H, ArH); 8.00 (d, 1H, ArH); 8.17 (d, 1H, ArH); 8.54 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 148.5, 140.6, 134.6, 132.0, 129.3, 128.8, 128.4, 128.3, 123.6, 123.0, 122.5, 90.0, 83.8, 83.3, 67.1, 61.4. GC: R_t: 35.64 min. MS m/z(%): 322(M^+, 10), 236(45), 200(45), 190(40), 86(45), 56(100). IR(film): ν 3288, 3079, 2959, 2856, 2825, 2219, 1682, 1531, 1490, 1453, 1349, 1116, 1004, 907, 862, 758, 730, 692 cm^{-1}. Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C 70.81, H 5.59, N 8.70%, found: C 70.84, H 5.51, N 8.76%.

***N*-(1,3-Diphenyl-prop-2-ynyl)morpholine.** Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.68 (m, 4H, 2×N–CH_2); 3.77 (m, 4H, 2×O–CH_2); 4.83 (s, 1H, CH–C≡C); 7.34–7.41 (m, 5H, ArH); 7.52–7.57 (m, 3H, ArH); 7.68 (d, 2H, ArH). ^{13}C NMR ($CDCl_3$): spectral data are in agreement with the reported ones.[26] GC: R_t: 32.15 min. MS m/z(%): 277(M^+, 15), 200(25), 191(100), 86(30), 56(45). Anal. Calcd. for $C_{19}H_{19}NO$: C 82.31, H 6.86, N 5.05%, found: C 82.27, H 6.81, N 5.09%.

***N*-(3-Phenyl-1-(4-methoxyphenyl)-prop-2-ynyl)-morpholine.** Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm):): 2.61 (m, 4H, 2×N–CH_2); 3.72 (m, 4H, 2×O–CH_2); 3.80 (s, 3H, O–CH_3); 4.73 (s, 1H, CH–C≡C); 6.89 (d, 2H, ArH); 7.31–7.33 (m, 3H, ArH); 7.49–7.55 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$): spectral data are in agreement with the reported ones.[26] GC: R_t: 34.33 min. MS m/z(%): 307(M^+, 10), 221(100), 178(20). Anal. Calcd. for $C_{20}H_{21}NO_2$: C 78.18, H 6.84, N 4.56%, found: C 78.12, H 6.91, N 4.59%.

***N*-(3-Phenyl-1-(2-pyridyl)-prop-2-ynyl)morpholine.** Brownish oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.07 (m, 4H, 2×N–CH_2); 3.93 (m, 4H, 2×O–CH_2); 6.43 (t, 1H, ArH); 6.58 (t, 1H, ArH); 6.72 (s, 1H, CH–C≡C); 7.18–7.35 (m, 3H, ArH); 7.44–7.58 (m, 3H, ArH); 8.21 (d, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 132.3, 128.9, 127.1, 121.9, 117.8, 115.1, 111.1, 105.9, 77.4, 67.6, 54.3. GC: R_t: 34.05 min. MS m/z(%): 278(M^+, 100), 220(65), 193(15), 95(50), 78(45). Anal. Calcd. for $C_{18}H_{18}N_2O$: C 77.70, H 6.47, N 10.07%, found: C 77.76, H 6.49, N 10.10%.

***N*-(3-Phenyl-1-(3-hydroxyphenyl)-prop-2-ynyl)morpholine.** Yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.63 (m, 4H, 2×N–CH_2); 3.73 (m, 4H, 2×O–CH_2); 4.67 (s, 1H, OH); 4.72 (s, 1H, CH–C≡C); 7.16–7.18 (m, 3H, ArH); 7.23–7.25 (m, 2H, ArH); 7.31–7.33 (m, 3H, ArH); 7.48–7.50 (m, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.5, 131.7, 130.6, 128.3, 128.2, 122.8, 123.3, 121.3, 115,4, 84.3, 81.6, 66.2, 52.7, 48.2. GC: R_t: 34.65 min. MS m/z(%): 293(M^+, 20), 207(100), 178(20), 115(15), 86(55), 56(65). Anal. Calcd. for $C_{19}H_{19}NO_2$: C 77.82, H 6.48, N 4.78%, found: C 77.89, H 6.48, N 4.72%.

Glaser coupling. a mixture of 660 µl (6 mmol) of phenylacetylene, 2 ml of acetone, 5 mmol of morpholine and 0.5 g Cu^{II}–4A were stirred at room temperature for 24 h. Then the solid was filtered off, washed with acetone, and the filtrate was evaporated.

1,3-Diphenyl-but-1,3-diyne. White solid, m.p. 84–85 °C (lit.: 86–88 °C[27]), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32–7.37 (m, 6H, ArH); 7.51–7.55 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 74.11, 81.72, 122.03, 128.52, 129.43, 132.35. GC: R_t: 29.58 min. MS m/z(%): 202(M^+, 100), 174(5), 150(10), 101(10), 88(10). Anal. Calcd. for $C_{16}H_{10}$: C 95.05, H 4.95%, found: C 95.08, H 4.92%.

5-Hydroxy-5-methyl-1-phenyl-hept-1,3-diyne. GC: R_t: 26.55 min. MS m/z(%): 198(M^+, 10), 169(45), 126(15), 115(10), 43(100).

3,8-Dihydroxy-3,8-dimethyl-dec-4,6-diyne. GC: R_t: 23.48 min. MS m/z(%): 165(M^+, 20), 93(20), 43(100).

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