Copper(I)-Catalysed Deacetylenative Cross-Coupling Reaction of Terminal Alkynes with Propargylic Amines via C(sp)–C(sp^3) Bond Cleavage

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Abstract: The catalytic deacetylenative coupling reaction of terminal alkynes with various N-substituted propargylic amines proceeded in the presence of CuCl (10 mol%) and Na_2HPO_4 (4 equiv) in THF at 130 °C to give the corresponding substituted propargylic amines in good to high yields.

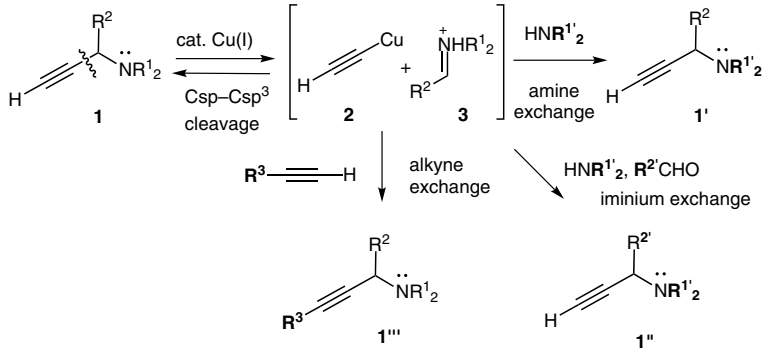
Key words: alkynes, amines, copper, cleavage, catalysis

Recently, much attention has been focused on transition-metal-catalyzed C–H bond activation and subsequent C–C bond-forming reactions in modern organic chemistry.[1] In particular, the formation of C–C bonds via an iminium intermediate generated by the activation of the α-sp^3 C–H bonds of nitrogen in amines is one of the attractive strategies for selective cross-dehydrogenative coupling (CDC).[2] Murahashi et al. were the first to report an amine substitution reaction through direct C–H activation to generate iminium intermediates,[3] and related transformations were subsequently developed based on this amine exchange reaction.[4] Li and co-workers developed the copper-catalyzed CDC[2] of tertiary amines with terminal alkynes,[5] active methylenes, and nitromethane.[6] Although this coupling reaction required additive oxidants, such as O_2, H_2O_2, and some peroxides, this protocol has been utilized not only for the activation of the α-sp^3 C–H bonds of nitrogen in amines but also for the activation of the α-sp^3 C–H bonds of oxygen in ethers,[7] benzylic sp^3 C–H bonds,[8] and even alkane C–H bonds.[9]

We have recently reported that propargylic amines undergo a substitution reaction in the presence of a copper(I) catalyst to afford substituted propargylic amines.[10] In this transformation, the C(sp)–C(sp^3) bond cleavage of propargylic amines **1** is the key step for the generation of copper acetylides **2** and iminium intermediates **3**. Iminium intermediates **3** undergo fragment exchange with additional aldehydes, amines, and/or alkynes to yield substituted propargylic amines **1′**–**1‴** (Scheme 1). Furthermore, we found that the redox CDC reaction of propargylic amines and terminal alkynes also proceeded in the presence of zinc(II) catalysts, giving the N-tethered 1,6-enynes.[11]

Although the transformation was able to be utilized for the deacetylenative homocoupling reaction, which is one of the convenient reactions for the synthesis of symmetric 1,4-diamino-2-butynes,[12] the reaction conditions still need improvement prior to application in the deacetylenative coupling reaction of terminal alkynes with propargylic amines.[10] In the current study, we succeeded in the deacetylenative cross-coupling reaction of alkynes with various N-substituted propargylic amines under modified reaction conditions.

The deacetylenative coupling reaction of phenylacetylene with *N*,*N*-dihexylnon-1-yn-3-amine (**1a**) was initially examined under various conditions, and the results are shown in Table 1. Previously, we reported that the reaction proceeded in the presence of CuCl catalyst (20 mol%) and *n*-Oct$_3$N (0.5 equiv) at 100 °C in THF for 24 hours, giving *N*,*N*-dihexyl-1-phenylnon-1-yn-3-amine (**2a**) in 33% yield (Table 1, entry 1).[10] We found that elevating the temperature to 130 °C affected the reaction yield:



Scheme 1 Copper-catalyzed alkyne substitution reactions of propargylic amines

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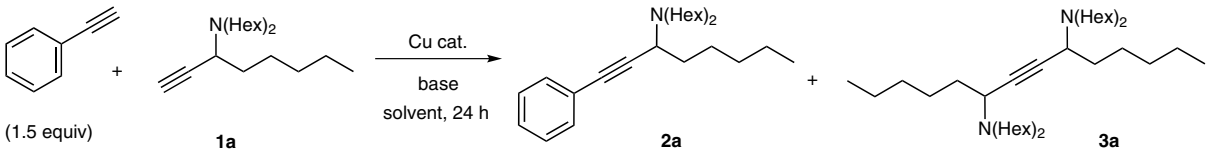
Compound **2a** was obtained in 66% yield (Table 1, entry 2) when the reaction was carried out at 130 °C. Decreasing the amount of CuCl catalyst to 10 mol% and 5 mol% resulted in a slight increase of the yields (Table 1, entries 3 and 4). However, deacetylenative homocoupling product **3a**[12] was generated in 4% yield under the 5 mol% catalyst condition (Table 1, entry 4). Then, the effect of bases on the deacetylenative coupling reaction was examined. Na_2HPO_4 was found to be an effective base for the reaction: the yield of **2a** was increased to 81% (10 mol% CuCl in Table 1, entry 5) and 83% (5 mol% CuCl in Table 1, entry 6), and this was accompanied by an increase in the amount of generated **3a**. *N*,*N*-Dimethylaminopyridine (DMAP) or Cs_2CO_3 was not an efficient base for the current transformation (Table 1, entries 7 and 8). The effect of solvents was also examined. Although the reaction proceeded in various solvents, such as EtOAc, ethylene dichloride (EDC), and cyclopentyl methyl ether (CPME), at 130 °C, the yields of **2a** were reduced to 44–65% after 24 hours (Table 1, entries 9–11). It should be noted that both *n*-Oct_3N and Na_2HPO_4 were effective for the deacetylenative coupling reaction. Since Na_2HPO_4 is an inorganic base and readily removed from the reaction mixture, the purification process of the products using Na_2HPO_4 was much simpler than that using *n*-Oct_3N. Therefore, Na_2HPO_4 was employed for further experiments.

After a suitable set of conditions for the deacetylenative coupling reaction were established, we investigated the reaction of phenylacetylene with various propargylic amines **1**. The results are shown in Table 2. The reaction was performed in the presence of CuCl catalyst (10 mol%) and Na_2HPO_4 (4 equiv) at 130 °C in THF. Under these reaction conditions, isobutyl (**1b**), dihexyl (**1c**),[13] diallyl (**1d**), morpholyl (**1e**), dicyclohexyl (**1f**), and *N*-ethylbenzyl (**1g**) propargylic amines underwent the deacetylenative coupling reaction to give corresponding 5-methyl-1-phenylhex-1-yn-3-amines **2b**–**g** in 72–98% yields (Table 2, entries 1–6).[14] It should be noted that a propargylic moiety selectively undergoes the deacetylenative coupling in the presence of allylic moieties (Table 2, entry 3).

The reaction did not proceed with *N*,*N*-bis(pyridine-2-ylmethyl)prop-2-yn-1-amine. In addition, *N*,*N*-dibenzylprop-2-yn-1-amine (**1h**), which has no substituent at the propargylic position, gave corresponding product **2h** in 30% yield (Table 2, entry 7). These results indicate that the substituents at the propargylic position markedly affect the current transformation. A variety of substituted propargylic *N*,*N*-dibenzylamines, such as *n*-pentyl (**1i**), isopropyl (**1j**), cyclohexyl (**1k**), benzyl (**1l**), and phenethyl (**1m**), were employed for the deacetylenative coupling reaction to afford corresponding substituted *N*,*N*-dibenzyl-3-phenylprop-2-yn-1-amines **2i**–**m** in 58–81% yields (Table 2, entries 8–12). The reaction was also applied to heteroaromatic substituted propargylic *N*,*N*-dibenzylamines, such as 2-furanyl (**1n**) and 3-furanyl (**1o**) substituted propargylic amines, and corresponding 3-phenylprop-2-yn-1-amines **2n** and **2o** were obtained in 61% and 51%

Table 1 Optimization of Reaction Conditions[a]



Entry	Catalyst (mol%)	Solvent	Base	Temp (°C)	Yield of **2a** (%)[b]	Yield of **3a** (%)[c]
1	CuCl (20)	THF	*n*-Oct_3N (0.5)	100	33	–
2	CuCl (20)	THF	*n*-Oct_3N (0.5)	130	66	–
3	CuCl (10)	THF	*n*-Oct_3N (0.5)	130	77	–
4	CuCl (5)	THF	*n*-Oct_3N (0.5)	130	81	4
5	CuCl (10)	THF	Na_2HPO_4 (4.0)	130	81	3
6	CuCl (5)	THF	Na_2HPO_4 (4.0)	130	83	7
7	CuCl (10)	THF	DMAP (2.0)	130	9 (68)	–
8	CuCl (10)	THF	Cs_2CO_3 (2.0)	130	4 (95)	–
9	CuCl (10)	EtOAc	Na_2HPO_4 (4.0)	130	65 (16)	10
10	CuCl (10)	EDC	Na_2HPO_4 (4.0)	130	44 (9)	–
11	CuCl (10)	CPME	Na_2HPO_4 (4.0)	130	44 (38)	–

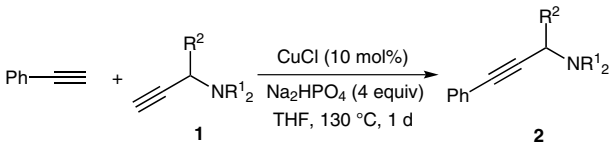
[a] Unless otherwise specified, the reactions were carried out with propargylic amines **1** (0.3 mmol) and phenylacetylene (0.45 mmol) in the presence of CuCl (5–20 mol%) and a base in THF (1.2 mL) under N_2 atmosphere using a sealed vial tube.
[b] Yield of product isolated after silica gel chromatography. Percentage of recovered **1a** is indicated in parenthesis.
[c] '–' indicates 'not observed'.

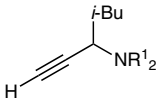
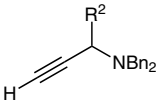
yields, respectively (Table 2, entries 13 and 14). However, phenyl and 3-pyridinyl group (R^2) substituted propargylic *N*,*N*-dibenzylamines did not undergo the deacetylenative coupling reaction.

We next examined the alkyne substitution reaction with various terminal alkynes. The results are shown in Table 3. The reaction of **1b** with 4-ethynylanisole, 1-hexyne gave corresponding 3-substituted 1-isobutyl-propargylic amines **2p** and **2q** in 73% and 64% yields, respectively. Ethyl propiolate, propargyl alcohol, and 3-butyn-1-ol were also employed for the deacetylenative coupling reaction and ethyl 4-(dibenzylamino)-6-methylhept-2-ynoate (**2r**), 4-(dibenzylamino)-6-methylhept-2-yn-1-ol (**2s**), and 5-(dibenzylamino)-7-methyloct-3-yn-1-ol (**2t**) were obtained in moderate yields with the recovery of **1b**. These products shown in Table 3 were not able to be obtained under the previously reported conditions.[10]

In conclusion, we have developed an efficient method for the synthesis of 3-substituted propargylic amines **2** from corresponding propargylic amines **1**, which employs the copper-catalyzed deacetylenative coupling reaction. A propargylic moiety selectively underwent the deacetylenative coupling in the presence of allylic moieties. Elevating the temperature to 130 °C is essential not only for improvement of the reaction yields but also for application to alkynes with various functionalities. Under the cur-

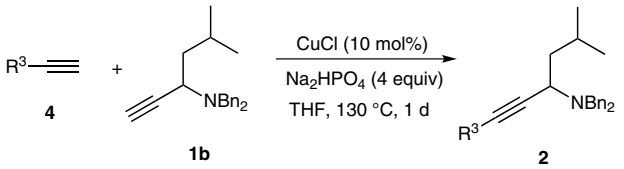
Table 2 Copper-Catalyzed Alkyne Substitution Reaction of **1** with Various Propargylic Amines **2**[a]

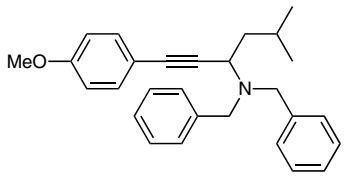
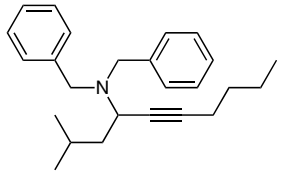
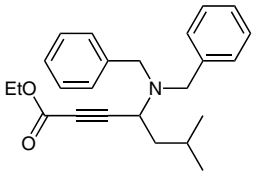
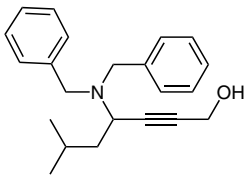
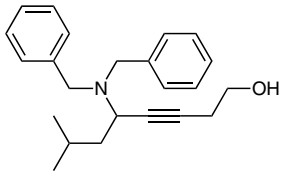


Entry	**1**		**2**	Yield (%)[b]
				
1	R^1 = Bn	**1b**	**2b**	98
2	R^1 = *n*-Hex	**1c**	**2c**	94
3	R^1 = allyl	**1d**	**2d**	80
4	NR^1_2 = morpholyl	**1e**	**2e**	89
5	R^1 = Cy	**1f**	**2f**	72
6	R^1 = (Et)(Bn)	**1g**	**2g**	84
				
7	R^2 = H	**1h**	**2h**	30[d]
8	R^2 = *n*-Pent	**1i**	**2i**	79
9	R^2 = *i*-Pr	**1j**	**2j**	81
10	R^2 = Cy	**1k**	**2k**	58[e]
11	R^2 = Bn	**1l**	**2l**	59
12	R^2 = $BnCH_2$	**1m**	**2m**	80
13	R^2 = 	**1n**	**2n**	61
14	R^2 = 	**1o**	**2o**[c]	51

[a] Unless otherwise specified, the reactions were carried out with propargylic amines **1** (0.3 mmol) and phenylacetylene (0.45 mmol) in the presence of CuCl (0.03 mmol) and Na_2HPO_4 (1.20 mmol) in THF (1.2 mL) at 130 °C under N_2 atmosphere using a sealed vial tube.
[b] Yield of product isolated after silica gel chromatography.
[c] CuCl (0.06 mmol) and phenylacetylene (3.0 equiv) were used.
[d] Compound **1h** was recovered in 36% yield.
[e] Compound **1k** was recovered in 15% yield.

Table 3 Copper-Catalyzed Alkyne Substitution Reaction of Propargylamine **1b** with Various Alkynes **4**[a,b,e]



Entry	Product	Yield (%)
1	 **2p**	73
2	 **2q**[c]	64 (35)
3	 **2r**	56 (31)
4	 **2s**[d]	48 (37)
5	 **2t**	60 (34)

[a] Unless otherwise specified, the reactions were carried out with propargylic amine **1b** (0.3 mmol) and terminal alkynes **4** (0.45 mmol) in the presence of CuCl (0.03 mmol) and Na_2HPO_4 (1.20 mmol) in THF (1.2 mL) at 130 °C under N_2 atmosphere using a sealed vial tube.
[b] Yield of product isolated by silica gel chromatography.
[c] 1-Hexyne (3.0 equiv) was used.
[d] Propargyl alcohol (3.0 equiv) was used.
[e] Percentage of recovered **1b** is indicated in parenthesis.

rent reaction conditions, the amounts of acetylenes and copper catalysts were able to be reduced. Furthermore, the copper-catalyzed deacetylenative cross-coupling reaction was shown to be applicable to various terminal alkynes having labile functional groups, such as ester and alcohol, and propargylic amines without generating the deacetylenative homocoupling products. The current study offers an important protocol for C(sp)–C(sp^3) bond cleavage in organic synthesis.

Typical Procedure for the Synthesis of *N*,*N*-Dihexyl-1-phenyloct-1-yn-3-amine (2a)
To a mixture of **1a** (88 mg, 0.3 mmol), CuCl(I) (3 mg, 0.03 mmol), and Na_2HPO_4 (170 mg, 1.2 mmol) in THF (1.2 mL) was added ethynylbenzene (50 μL, 0.45 mmol) in a sealed vial tube under N_2, and the mixture was stirred at 130 °C for 1 d. After insoluble materials were removed by Celite filtration, the filtrate was concentrated under vacuo. The residue was purified by column chromatography on silica gel with hexane–EtOAc as eluent to give **2a**[10] (90 mg, 81% yield) as colorless oil. In a similar manner, **2b**–**t** were obtained from the corresponding **1b**–**o** in 30–98% yields.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **Typical Procedure for the Preparation of *N*,*N*-Dihexyl-5-methylhex-1-yn-3-amine (1c, Table 2, Entry 2)**
To a solution of CuBr(I) (0.036 g, 0.25 mmol) in toluene (100 mL) were added ethynyltrimethylsilane (0.69 mL, 5

mmol), isobutylaldehyde (0.54 mL, 5 mmol), and *N*,*N*-dihexylamine (1.17 mL, 5 mmol) under nitrogen atmosphere, and the mixture was stirred for 2 d at r.t. The mixture was filtered on a Celite bed and concentrated. The residue was dissolved in THF (10 mL) and TBAF (1 M in THF, 1.6 mL) was added at 0 °C. The mixture was stirred at 0 °C for 30min, diluted with H_2O, and extracted with Et_2O. The organic layer was washed with brine, dried over anhyd $MgSO_4$, and concentrated. Purification by column chromatography on silica gel with hexane as eluent gave the amine **1c** (1.15 g, 82% yield) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (td, *J* = 7.6, 2.4 Hz, 1 H), 2.51–2.44 (m, 2 H), 2.33–2.26 (m, 2 H), 2.15 (d, *J* = 2.4 Hz, 1 H), 1.88 (nonet, *J* = 6.8 Hz, 1 H), 1.48–1.23 (m, 18 H), 0.92–0.86 (m, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.5, 71.7, 51.7, 51.5, 43.3, 32.0, 28.8, 27.4, 25.0, 22.9, 22.8, 22.6, 14.3. IR (neat): 3309, 2929, 2858, 1467, 1379, 1166, 1093 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{19}H_{38}N$ $[M + H]^+$: 280.3004; found: 280.3002.

(14) ***N*,*N*-Dihexyl-5-methyl-1-phenylhex-1-yn-3-amine (2c, Table 2, Entry 2)**

Yield 101 mg (94%); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.37 (m, 2 H), 7.30–7.23 (m, 3 H), 3.74 (t, *J* = 7.6 Hz, 1 H), 2.59–2.52 (m, 2 H), 2.44–2.37 (m, 2 H), 1.95 (sept, *J* = 6.8 Hz, 1 H), 1.57 (t, *J* = 7.2 Hz, 2 H), 1.52–1.22 (m, 16 H), 0.96 (t, *J* = 6.4 Hz, 6 H), 0.90–0.87 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.8, 128.3, 127.7, 123.9, 89.5, 84.4, 52.2, 51.8, 43.3, 32.0, 28.7, 27.4, 25.1, 22.8, 22.7, 14.2. IR (neat): 2955, 2928, 2857, 1597, 1488, 1466, 1378, 1366, 1312, 1166, 1092, 1026, 911, 754, 690, 584, 527 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{25}H_{42}N$ $[M + H]^+$: 356.3317; found: 356.3312.

