# Copper(I)-Catalyzed Substitution Reactions of Propargylic Amines: Importance of C(sp)−C(sp³) Bond Cleavage in Generation of Iminium Intermediates

Tsuyuka Sugiishi, Akifumi Kimura, and Hiroyuki Nakamura*

Department of Chemistry, Faculty of Science, Gakushuin University, Mejiro, Toshima-ku, Tokyo 171-8588, Japan

Received December 27, 2009; E-mail: hiroyuki.nakamura@gakushuin.ac.jp

Amines are not suitable leaving groups for organic synthesis. In general, C−N bond activation is carried out by converting amines into ammonium and iminium ions.[1] A few examples using amines as leaving groups include nucleophilic substitution reactions of highly electron-deficient aromatic compounds,[2] palladium-catalyzed carbonylation,[3,4] deprotection of N-allylamines,[5] and palladium- and ruthenium-catalyzed amine exchange reactions.[6,7] In particular, direct C−H activation to generate iminium intermediates in amine exchange reactions was first reported by Murahashi and co-workers[6] and has become one of the most important strategies for related transformations.[8] Li and co-workers developed the copper-catalyzed cross-dehydrogenative coupling (CDC)[9] of tertiary amines with terminal alkynes,[10] active methylenes, and nitromethane (eq 1).[11] We have developed a palladium-catalyzed hydride transfer reaction for the synthesis of allenes **3** via iminium complex **2** (eq 2, path a).[12,13] In this paper, we report the copper-catalyzed substitution reaction of propargylic amines. In this transformation, the C(sp)−C(sp³) bond cleavage step is essential for generating copper acetylides and iminium intermediates **4**, which undergo fragment exchange with additional aldehydes, amines, and alkynes to give **5** (eq 2, path b).
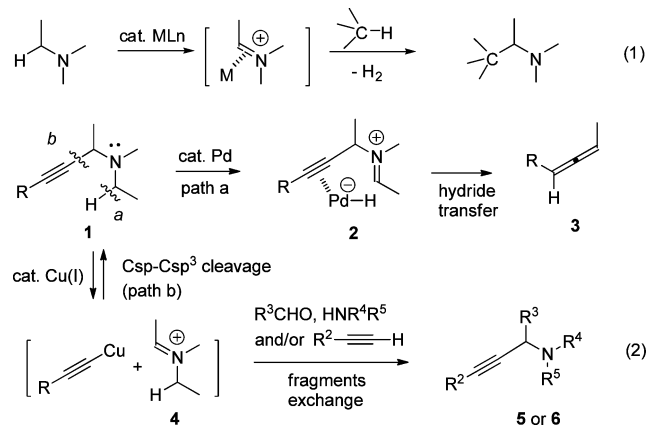
The results are shown in Table 1. When N,N-dicyclohexylpropargylamine (**1a**) was treated with 3 equiv of dibenzylamine in the presence of CuBr catalyst (20 mol %) in THF at 100 °C in a sealed vial tube, the substitution reaction proceeded, generating the corresponding amine-exchanged product **5a** in 73% yield (entry 1). Propargylic amines **1b** and **1c**, which have a substituent at R², also underwent the substitution reaction with dibenzylamine to give propargylic dibenzylamines **5b** and **5c** in 55 and 64% yields, respectively (entries 2 and 3). The reaction was also applied to 1-substituted propargylic amines **1d** (R³ = 4-FC₆H₄), **1e** (R³ = 4-CH₃C₆H₄), and **1f** (R³ = Ph), and the corresponding propargylic dibenzylamines (**5d**−**f**) were obtained in 52−74% yield (entries 4−6). The substitution reactions proceeded not only with diben-

zylamine but also with various secondary amines (entries 7−15) to give the corresponding amine-exchanged products (**5g**−**o**) in good to high yields. The use of toluene (entries 8−11 and 15) or dioxane (entry 12) instead of THF as the solvent was more effective in certain cases. The substitution reaction using N-methylaniline resulted in a relatively low yield (30%) (entry 15). The reactions of **1g** and **1h** with dibenzylamine gave **5f** in 61 and 68% yield, respectively (entries 16 and 17).

Table 1. CuBr-Catalyzed Substitution Reactions of Propargylic Amines **1** with Secondary Amines (HNR⁴R⁵)ᵃ

entry	propargylic amine 1	HNR⁴R⁵	time (h)	yield of 5 (%)ᵇ	
1	**1a**: R²=H	HNBn₂	48	**5a**	73
2	**1b**: R²=Ph	HNBn₂	24	**5b**	55
3	**1c**: R²=4-BrC₆H₄	HNBn₂	35	**5c**	64
4	**1d**: R³=4-FC₆H₄	HNBn₂	27	**5d**	60
5	**1e**: R³=4-CH₃C₆H₄	HNBn₂	48	**5e**	52
6	**1f**: R³=Ph	HNBn₂	16	**5f**	74
7	**1f**	HN(ⁱPr)Bn	12	**5g**	87
8	**1f**	HN(Bn)CH₂CH(CH₃)Ph	12	**5h**	85ᶜ
9	**1f**	HN(Et)Bn	12	**5i**	72ᶜ
10	**1f**	HNEt₂	8	**5j**	>99ᶜ
11	**1f**	HN(ⁿHex)₂	3.5	**5k**	48ᶜ
12	**1f**	HN(CH₂CH₂OH)₂	2	**5l**	>99ᵈ
13	**1f**	HN(allyl)₂	12	**5m**	67
14	**1f**	morpholine	12	**5n**	66
15	**1f**	HN(Ph)Me	24	**5o**	30ᶜ
16	**1g**: R¹=Et	HNBn₂	11	**5f**	61ᶜ
17	**1h**: R¹=ⁱPr	HNBn₂	6	**5f**	68ᶜ

ᵃ The reactions of propargylic amines **1** (0.5 mmol) with disubstituted amines (HNR⁴R⁵) were carried out in the presence of CuBr (0.1 mmol) in THF (1.5 mL) at 100 °C under an Ar atmosphere using a vial tube. ᵇ Isolated yields based on **1**. ᶜ Toluene was used as the solvent. ᵈ Dioxane was used as the solvent.

To clarify the mechanism, we examined the substitution reactions of dibenzylamine with **1f** in the presence of 4-tolaldehyde and **1e** in the presence of benzaldehyde [Scheme S1 in the Supporting Information (SI)]. Interestingly, N,N-dibenzyl-1-phenylpropargylamine (**5f**) was obtained as the major product in both cases. These results suggest that the substitution reaction involves C(sp)−C(sp³)

Table 2. CuCl-Catalyzed Alkyne Substitution Reactions of Propargylic Amines with Various Alkynes[a]

entry	R⁶	base[b]	1	1 or 6	yield (%)[c]
1[d]	Ph	$^nBu_3N$	1a	1b	74
2[d]	Ph	Na_2HPO_4	1i	6a	83
3	Ph	$^nBu_3N$	1j	6b	47
4	4-biphenyl	$^nOct_3N$	1a	6c	44
5	$4-CH_3C_6H_4$	Na_2HPO_4	1a	6d	48
6	$4-CH_3C_6H_4$	Na_2HPO_4	1i	6e	61
7	$4-CH_3OC_6H_4$	$^nBu_3N$	1a	6f	58
8	$4-CH_3OC_6H_4$	Na_2HPO_4	1i	6g	53
9	2-(6-CH₃O)Naph	$^nOct_3N$	1a	6h	58
10	$4-(CH_3)_2NC_6H_4$	$^nOct_3N$	1a	6i	44
11	$4-CF_3C_6H_4$	Na_2HPO_4	1a	6j	63
12	Ph(CH₃)C(OH)	$^nBu_3N$	1a	6k	40
13	EtO_2C	Na_2HPO_4	1a	6l	42
14	Ph	Na_2HPO_4	1k	6m	73
15	Ph	$^nOct_3N$	1l	6n	33
16	$4-CH_3OC_6H_4$	Na_2HPO_4	1k	6o	39

[a] The reaction of propargylic amines **1** (0.3 mmol) with alkynes **7** (0.9 mmol) was carried out in the presence of CuCl (0.06 mmol) in THF (1.2 mL) at 100 °C under an Ar atmosphere using a vial tube. [b] The amount of each base used in the reaction was as follows: Na_2HPO_4 (1.2 mmol); $^nBu_3N$ (0.3 mmol); $^nOct_3N$ (0.15 mmol). [c] Isolated yields based on **1**. [d] Using 5 equiv of phenylacetylene.

bond cleavage at the propargylic position (**1** → **4** in eq 2). Thus, we next investigated the alkyne substitution reaction of propargylic amines with additional alkynes **7**.

The results of the alkyne substitution reaction are summarized in Table 2. The reaction of **1a** with phenylacetylene proceeded in the presence of CuCl (20 mol %) and tributylamine to produce **1b** in 74% yield (entry 1). Propargylic amine **1b** was obtained in 11% yield in the absence of base (Table S3 in the SI), suggesting that addition of base is essential for this alkyne substitution reaction. Among the copper(I) catalysts examined, CuCl gave the best yield (Table S4). In the case of *N,N*-dihexylpropargylamine (**1i**), using Na_2HPO_4 as the base was more effective, and the corresponding propargylic amine **6a** was obtained in 83% yield (entry 2). Although other bases, such as tributylamine and trioctylamine, were also effective, the choice of base strongly depended on the ease of separation between these trialkylamines and the products. A variety of alkynes **7**, such as 4-biphenylacetylene, 4-tolylacetylene, 4-methoxyphenylacetylene, 6-methoxy-2-naphthylacetylene, 4-(*N,N*-dimethylamino)phenylacetylene, and 4-tolacetylene, and various propargylic amines, including **1a** and **1i**−**l**, were employed in the alkyne substitution reaction to afford the corresponding propargylic amines (**6b**−**j**) in moderate to good yields (entries 3−11). The alkyne substitution reaction was also applied to alkynyl alcohol and ester. The reactions of **1a** with 2-phenyl-3-butyn-2-ol and ethyl propiolate gave **6k** and **6l** in 40 and 42% yield, respectively (entries 12 and 13). The propargylic amines **1k** and **1l**, which have a substituent at the propargylic position, also underwent the alkyne substitution reaction with phenylacetylene and 4-methoxyphenylacetylene to give the corresponding propargylic amines **6m**−**o** in

33−73% yield (entries 14−16). However, the propargylic amines having a substituent at the terminal position, such as **1b** and *N,N*-dicyclohexyl-2-butyn-1-ylamine, did not undergo the alkyne substitution reaction.

In conclusion, we have found that the substitution reactions of propargylic amines proceed in the presence of copper(I) catalysts. As described in the detailed mechanistic discussion in Scheme S2, C(sp)−C(sp³) bond cleavage assisted by the nitrogen lone-pair electrons is essential for the reaction, and the resulting iminium intermediates undergo amine exchange, aldehyde exchange, and alkyne addition reactions, although the possibility that the mechanism proceeds through copper allenylidene complexes[14] or propargylic cation intermediates[15,16] generated by C−N bond cleavage to give the amine-exchanged products cannot be excluded. Because iminium intermediates are key to aldehyde−alkyne−amine (A³) coupling reactions,[17−19] this transformation is effective not only for reconstruction of propargylic amines but also for chiral induction of racemic compounds in the presence of chiral catalysts.

Supporting Information Available: Experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 357.
(2) (a) De Vargas, E. B.; De Rossi, R. H.; Veglia, A. V. *J. Org. Chem.* **1986**, *51*, 1976. (b) Bujan, E. I.; Remedi, M. V.; Rossi, R. H. *J. Chem. Soc., Perkin Trans. 2* **2000**, 969.
(3) (a) Murahashi, S.-I.; Imada, Y.; Nishimura, K. *J. Chem. Soc., Chem. Commun.* **1988**, *1578*, 1579. (b) Murahashi, S.-I.; Imada, Y.; Nishimura, K. *Tetrahedron* **1994**, *50*, 453.
(4) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Synlett* **1991**, 91.
(5) (a) Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109. (b) Mitsudo, T.-a.; Zhang, S.-W.; Satake, N.; Kondo, T.; Watanabe, Y. *Tetrahedron Lett.* **1992**, *33*, 5533. (c) Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932. (d) Lemaire-Audoire, S.; Savignac, M.; Genêt, J. P.; Bernard, J.-M. *Tetrahedron Lett.* **1995**, *36*, 1267.
(6) Murahashi, S.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348.
(7) Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2000**, 1885.
(8) (a) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (b) Murahashi, S. I.; Komiya, N.; Terai, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6931.
(9) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.
(10) (a) Wei, C.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810.
(11) Li, Z.; Bohle, D. S.; Li, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928.
(12) (a) Nakamura, H.; Kamakura, T.; Ishikura, M.; Biellmann, J.-F. *J. Am. Chem. Soc.* **2004**, *126*, 5958. (b) Nakamura, H.; Onagi, S.; Kamakura, T. *J. Org. Chem.* **2005**, *70*, 2357. (c) Nakamura, H.; Tashiro, S.; Kamakura, T. *Tetrahedron Lett.* **2005**, *46*, 8333. (d) Nakamura, H.; Ishikura, M.; Sugiishi, T.; Kamakura, T.; Biellmann, J. F. *Org. Biomol. Chem.* **2008**, *6*, 1471.
(13) Nakamura, H.; Kamakura, T.; Onagi, S. *Org. Lett.* **2006**, *8*, 2095.
(14) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3777.
(15) Hattori, G.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3781.
(16) Lee, K. Y.; Lee, H. S.; Kim, H. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2008**, *29*, 1441.
(17) Leonard, N. J.; Leubner, G. W. *J. Am. Chem. Soc.* **1949**, *71*, 3408.
(18) (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (b) Wei, C.; Li, Z.; Li, C. J. *Synlett* **2004**, 1472.
(19) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

JA9109055