Copper(I)-Catalyzed Amination of Propargyl Esters. Selective Synthesis of Propargylamines, 1-Alken-3-ylamines, and (*Z*)-Allylamines

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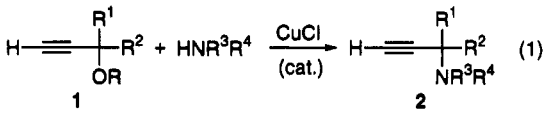
Summary: Copper(I)-catalyzed aminations of propargyl phosphates and acetates proceed under mild reaction conditions to give the corresponding propargylamines which are precursors of 1-alken-3-ylamines and (*Z*)-allylamines.

Propargylamines are synthetically and biologically important. Aliphatic propargylamines possess highly potent, irreversible, and selective inhibitory activity toward monoamine oxidase B (MAO B),[1] while *N*-benzylpropargylamines show aldehyde dehydrogenase inhibitory activity.[2] Furthermore, propargylamines are useful intermediates for the synthesis of various nitrogen compounds such as (*E*)-allylamines,[3] pyrroles,[4] β-lactams,[5] and pyrrolidines.[6] We wish to report that copper(I)-catalyzed amination of propargyl esters **1** gives propargylamines **2** highly efficiently (eq 1). This reaction has advantages



(1)

1 **2**

OR = $OP(O)(OEt)_2$, OAc

over previous methods which include the aminations of propargyl halides,[7] oxyphosphonium salts,[8] and triflates[9] and allenyl halides[10] because of easy availability of propargyl ester substrates **1**, selective formation of monoamination products, and mild reaction conditions.

First we examined the amination of propargyl phosphates because phosphates are excellent leaving groups toward transition metal catalysts.[11,12] The palladium-catalyzed amination of allyl phosphates gives (*E*)-allylamines efficiently;[11a] however, propargylamines could not be obtained by the similar palladium-catalyzed reaction of propargyl phosphates.[13] We found that copper chloride is an efficient catalyst for amination of propargyl phosphates under quite mild conditions. Typically, the reaction of 1-octyn-3-yl phosphate (**1a**) with 2 equiv of Et_2NH in the presence of 1 mol % of cuprous chloride in THF at 50 °C gave *N*,*N*-diethyl-1-octyn-3-ylamine (**2a**) in 91% isolated yield.[14] Cuprous chloride has been found to be the best catalyst among the catalysts examined. Other copper salts such as CuBr, CuI, $CuCl_2$, and $CuSO_4$ also gave propargylamine **2a** in good yields. The reaction did not proceed without a catalyst.

Representative results of the amination of propargyl phosphates are summarized in Table 1. Aliphatic, benzylic, and aromatic secondary amines react with propargyl phosphates to give tertiary propargylamines. When primary amines such as benzylamine and aniline (entry 5) are used, the corresponding secondary amines are obtained without contamination of bispropargylamines. Generally, the amination occurs highly regioselectively, and allenylamines could not be detected among the products. Amino alcohols such as *N*-methylethanolamine react chemoselectively (entry 6). It is noteworthy that *N*-propargylhydroxylamines (entry 7), which are the precursors of synthetically useful nitrones,[15] can be prepared simply upon treatment with *N*-monosubstituted hydroxylamines.

Importantly, the copper-catalyzed amination of propargyl acetates also proceeds to give the corresponding propargylamines. Thus, the reaction of 1-octyn-3-yl acetate (**1d**) with pipecoline in the presence of 5 mol % of CuCl in THF at reflux gave *N*-(1-octyn-3-yl)-2-methylpiperidine (**2h**) in 72% isolated yield. Representative results of the amination of propargyl acetates are summarized in Table 2. The amination of propargyl acetates is quite useful for the preparation of sterically hindered propargylamines (entries 2 and 3).

A terminal acetylenic proton is essential for the present copper-catalyzed amination reactions. 2-Octyn-1-yl phosphate did not undergo the amination even under severe conditions. The present copper-catalyzed amination can be rationalized according to Scheme 1. Copper acetylide complex **3** derived from the reaction of **1** with cuprous chloride in the presence of a base seems to be a key intermediate as indicated for the Glaser–Eglinton coupling reaction.[16] Elimination of the ester group from **3** gives

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(1) Yu, P. H.; Davis, B. A.; Boulton, A. A. *J. Med. Chem.* **1992**, *35*, 3705 and references cited therein.

(2) Shirota, F. N.; DeMaster, E. G.; Nagasawa, H. T. *J. Med. Chem.* **1979**, *22*, 463.

(3) (a) Hydrostannylation: Kende, A. S.; DeVita, R. J. *Tetrahedron Lett.* **1990**, *31*, 307. Corriu, R. J. P.; Bolin, G.; Moreau, J. J. E. *Tetrahedron Lett.* **1991**, *32*, 4121. (b) Carbocupuration: Corriu, R. J. P.; Bolin, G.; Iqbal, J.; Moreau, J. E.; Vernhet, C. *Tetrahedron* **1993**, *49*, 4603.

(4) Campi, E. M.; Jackson, W. R.; Nilsson, Y. *Tetrahedron Lett.* **1991**, *32*, 1093.

(5) Matsuda, I.; Sakakibara, J.; Nagashima, H. *Tetrahedron Lett.* **1991**, *32*, 7431.

(6) Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053.

(7) (a) Hennion, G. F.; Hanzel, R. S. *J. Am. Chem. Soc.* **1960**, *82*, 4908. (b) Kopka, I. E.; Fataftah, Z. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4616.

(8) Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* **1971**, 4368.

(9) Czernecki, S.; Valéry, J.-M. *J. Carbohydr. Chem.* **1990**, *9*, 767.

(10) Caporusso, A. M.; Geri, R.; Polizzi, C.; Lardicci, L. *Tetrahedron Lett.* **1991**, *32*, 7471.

(11) Palladium-catalyzed reactions: (a) Amination and alkylation: Tanigawa, Y.; Nishimura, K.; Kawasaki, A.; Murahashi, S.-I. *Tetrahedron Lett.* **1982**, *23*, 5549. (b) Azidation: Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292. (c) Hydroxylamination: Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Kodera, Y. *Tetrahedron Lett.* **1988**, *29*, 2973. (d) Carbonylation: Murahashi, S.-I., Imada, Y.; Taniguchi, Y.; Higashiura, S. *J. Org. Chem.* **1993**, *58*, 1538.

(12) Rhodium-catalyzed carbonylation: Imada, Y.; Shibata, O.; Murahashi, S.-I. *J. Organomet. Chem.* **1993**, *451*, 183.

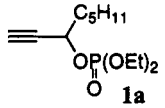
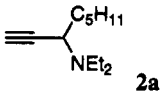
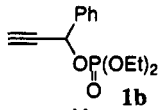
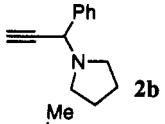
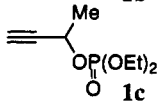
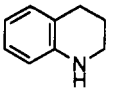
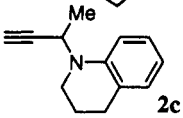
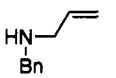
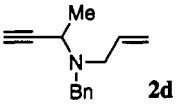
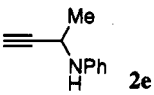
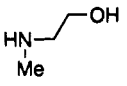
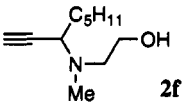
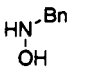
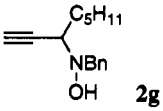
(13) Elimination of phosphoric acid takes place to give *cis*- and *trans*-3-octen-1-yne exclusively.

(14) Typical procedure. Preparation of propargylamine **2a**: A solution of **1a** (2.62 g, 10 mmol), Et_2NH (1.46 g, 20 mmol), and CuCl (0.010 g, 0.10 mmol) in THF (20 mL) was stirred under Ar at 50 °C for 2 h. The mixture was diluted with ether and extracted with 2 M HCl. The combined acidic layers were neutralized with NaOH and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, eluting with hexane:ethyl acetate = 7:3) afforded **2a** (1.65 g, 91% yield).

(15) Murahashi, S.-I.; Mitsui, H.; Watanabe, T.; Zenki, S. *Tetrahedron Lett.* **1983**, *24*, 1049 and references cited therein.

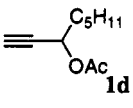
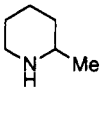
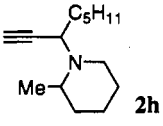
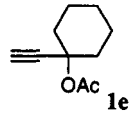
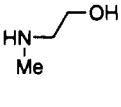
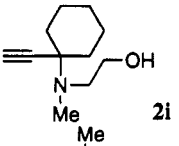
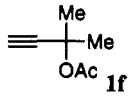
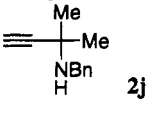
0022-3263/94/1959-2282$04.50/0

Table 1. Copper-Catalyzed Amination of Propargyl Phosphates[a]

entry	propargyl phosphate	amine	propargylamine	yield,[b] %
1	 **1a**	$HNEt_2$	 **2a**	91
2	 **1b**		 **2b**	75
3	 **1c**		 **2c**	85
4	**1c**		 **2d**	60
5	**1c**	H_2NPh	 **2e**	85
6	**1a**		 **2f**	84
7	**1a**		 **2g**	95

[a] The reaction of propargyl phosphates with amines (2 equiv) was performed in the presence of CuCl (1 mol %) in THF at 50 °C for 2 h. [b] Isolated yield.

Table 2. Copper-Catalyzed Amination of Propargyl Acetates[a]

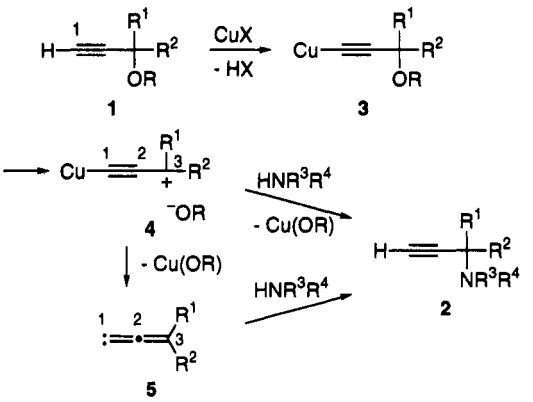
entry	propargyl acetate	amine	propargylamine	yield,[b] %
1	 **1d**		 **2h**	72
2	 **1e**		 **2i**	80
3	 **1f**	H_2NBn	 **2j**	62

[a] The reaction of propargyl acetates with amines (2 equiv) was performed in the presence of CuCl (5 mol %) in THF at reflux for 2 h. [b] Isolated yield.

zwitterion intermediate **4** and/or carbene intermediate **5**. Alcoholysis of propargyl halides in alkaline media is known to proceed *via* such zwitterion intermediates and/or carbene intermediates[17] derived from deprotonation followed by elimination of halides. Nucleophilic attack of amines at the C-3 position of the intermediate **4** or carbene **5** would give propargylamine **2** and copper(I) to complete catalytic cycle.

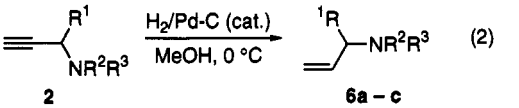
(16) Eglinton, G.; McCrae, W. *Adv. Org. Chem.* **1963**, *4*, 225.
(17) Shiner, V. J., Jr.; Wilson, J. W. *J. Am. Chem. Soc.* **1962**, *84*, 2402.

Scheme 1



The stereochemical course of the present reaction was examined for the amination of optically active propargyl phosphates. Typically, the treatment of (*S*)-**1a** ($[\alpha]^{22}_D$ −26.2° (*c* 1.22, $CHCl_3$), 98% ee)[18] with *N*-methylbenzylamine (0.7 equiv) in the presence of CuCl catalyst (1 mol %) in THF at 0 °C for 2 h gave racemic *N*-benzyl-*N*-methyl-1-octyn-3-ylamine (**2k**) in 24% yield along with recovered (*S*)-**1a** ($[\alpha]^{24}_D$ −25.9° (*c* 1.21, $CHCl_3$), 97% ee) (68%). These results support the intermediacy of **4** and **5**, which react with amine to give racemic propargylamine **2**.

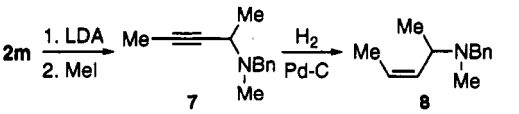
The propargylamines thus obtained are useful synthetic intermediates. A new strategy for synthesis of allylamines can be explored by the present copper(I)-catalyzed aminations. (*E*)-Allylamines can be prepared readily by palladium-catalyzed aminations of allylic esters;[11a] however, both 1-alken-3-ylamines and (*Z*)-allylamines are not easily accessible. Catalytic partial hydrogenation of propargylamines thus obtained affords 1-alken-3-ylamines **6** (eq 2). Typically, treatment of **2a** with 5% Pd–charcoal (0.5 mol%) in methanol under H_2 (1 atm) at 0 °C gave **6a** in 71% isolated yield.



(2)

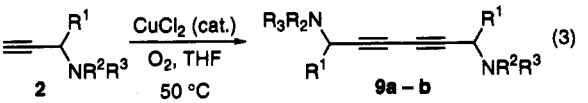
2a, **6a**; $R^1 = C_5H_{11}$, $R^2 = R^3 = Et$ Y; 71%
2l, **6b**; $R^1 = C_5H_{11}$, $R^2 = H$, $R^3 = Bn$ Y; 73%
2m, **6c**; $R^1 = Me$, $R^2 = Me$, $R^3 = Bn$ Y; 71%

Furthermore, α-substituted (*Z*)-allylamines can be obtained by alkylation and subsequent partial hydrogenation. Typically, methylation of **2m** (93%) followed by hydrogenation of **7** under the same conditions gave (*Z*)-*N*-benzyl-*N*-methyl-2-penten-4-ylamine (**8**) in 92% yield.



Copper-catalyzed dimerization of the product amines gives 1,6-diamino diynes **9** (eq 3), which are important precursors of polyconjugated nitrogen system. Thus, treatment of **2m** with $CuCl_2$ catalyst (10 mol %) under O_2 (1 atm) at 50 °C gave **9b** in 89% isolated yield.

(18) Phosphate (*S*)-**1a** was derived from (*S*)-1-octyn-3-ol ($[\alpha]^{23}_D$ −21.5° (*c* 1.15, ether), 98% ee) without loss of optical purity; Midland, M. M.; Graham, R. S. *Org. Synth.* **1985**, *63*, 57.



(3)

2a, **9a**; $R^1 = C_5H_{11}$, $R^2 = R^3 = Et$ Y; 75%

2m, **9b**; $R^1 = Me$, $R^2 = Me$, $R^3 = Bn$ Y; 89%

In summary, propargylamines can be prepared by copper(I)-catalyzed aminations of propargyl phosphates and acetates highly efficiently (eq 1). Moreover, 1-alken-3-ylamines and (*Z*)-allylamines can be obtained from propargylamines thus obtained selectively and conveniently.

Supplementary Material Available: Experimental procedures and spectral data for **1a–1f**, **2a–2m**, **6a–6c**, **7**, **8**, and **9a–9b** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.