

Copper(0)-Induced Deselenative Insertion of *N,N*-Disubstituted Selenoamides into Acetylenic C–H Bond Leading to Propargylamines

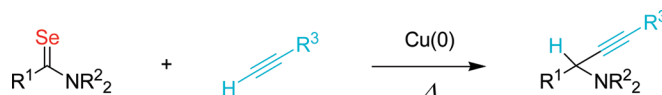
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Received January 30, 2009

ABSTRACT



Upon heating at 110 °C in the presence of copper(0) powder, terminal acetylenes undergo a novel deselenative C–H bond insertion reaction of *N,N*-disubstituted selenoamides, affording the corresponding propargylamines in good to excellent yields, selectively.

Carbenoid species, such as Fischer-type carbene complexes, Schrock-type carbene complexes, and other metal carbene complexes, have unique reactivity and properties; therefore, they have been often utilized as key intermediates in organic synthesis.^{1,2} Although alkoxycarbenes are widely studied and employed in many methods, there are many fewer examples

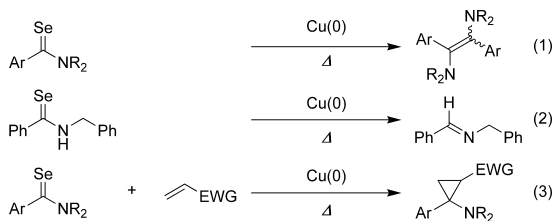
for aminocarbenes compared with alkoxycarbenes.³ Selenoamides, which have a C=Se bond adjacent to nitrogen, are relatively stable but still retain unique reactivity.⁴ They have been employed as precursors of synthetic reagents,⁵ intermediates of selenium containing heterocyclic compounds,⁶ and bioactive reagents.⁷ Recently, we have disclosed that selenoamides show the carbenoid-like reactivity upon treatment with copper(0) powder (Scheme 1): the

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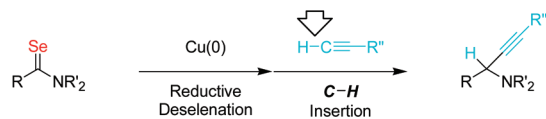
(2) For the transition-metal-catalyzed reaction of Fischer-carbene complexes, which C=M (M = Cr and W) bonds were activated by transition-metal complexes in mild conditions. For these reactions, see: (a) Meana, I.; Albéniz, A. C.; Espinet, P. *Organometallics* **2008**, *27*, 4193. (b) Barluenga, J.; Barrio, P.; Riesgo, L.; López, L. A.; Tomás, M. *Tetrahedron* **2006**, *62*, 7547. (c) Herndon, J. W. *Coord. Chem. Rev.* **2006**, *250*, 1889. (d) Gómez-Gallego, M.; Mancheño, M. J.; Sierra, M. A. *Acc. Chem. Res.* **2005**, *38*, 44. (e) del Amo, J. C.; Mancheño, M. J.; Gómez-Gallego, M.; Sierra, M. A. *Organometallics* **2004**, *23*, 5021. (f) Barluenga, J.; Barrio, P.; Vicente, R.; López, L. A.; Tomás, M. *J. Organomet. Chem.* **2004**, *689*, 3793. (g) Sierra, M. A.; Mancheño, M. J.; Sáez, E.; del Amo, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 6812.

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Scheme 1



Scheme 2



copper(0)-induced deselenative dimerization (eq 1),⁸ the copper(0)-induced intramolecular insertion reaction into N–H bond (eq 2),⁸ the copper(0)-induced cyclopropanation of alkenes (eq 3).⁹ Herein, we wish to report a novel intermolecular reductive insertion reaction of *N,N*-disubstituted selenoamides into acetylenic C–H bond induced by copper(0) (Scheme 2).

This deselenative C–H insertion reaction can lead to propargylamines. Propargylamines are synthesized by the reaction of organometallic reagents such as organo-lithium,¹⁰ -magnesium,¹¹ -zinc,¹² and -copper reagents,^{13,14} and they

are one of the important building blocks for pharmaceuticals and synthetic intermediates for *N*-heterocycles.^{15,16}

When *N*-(selenobenzoyl)piperidine (**1a**, 0.5 mmol) was treated with phenylacetylene (**2a**, 1 mL) in the presence of copper(0) (2.0 mmol) at 110 °C for 4 h, the reductive deselenation of **1a** and insertion reaction into C–H bond at

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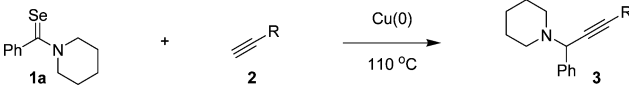
(12) For the synthesis of propargylamines using organozinc reagents, see, for example: (a) Ramu, E.; Varala, R.; Sreelatha, N.; Adapa, S. R. *Tetrahedron Lett.* **2007**, *48*, 7184. (b) Zani, L.; Alesi, S.; Cozzi, P. G.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 1558. (c) Lee, K. Y.; Lee, C. G.; Na, J. E.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 69. (d) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497. (e) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2003**, *44*, 6767. (f) Pinet, S.; Pandya, S. U.; Chavant, P. Y.; Ayling, A.; Vallee, Y. *Org. Lett.* **2002**, *4*, 1463.

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Table 1. Copper(0)-Induced Reaction of Selenoamide **1a** with Acetylenes **2**^a



entry	acetylene	product	yield ^b
1			99%
2			99%
3			99%
4			99%
5 ^c			84%
6 ^d			NR
7 ^e			61%
8			44%
9			59%
10			ND ^f

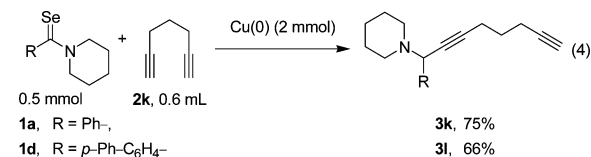
^a Reaction conditions: *N*-(selenobenzoyl)piperidine (**1a**, 0.5 mmol), acetylene (**2**, 1 mL), Cu(0) (2.0 mmol), 110 °C, 4 h. ^b Isolated yield. ^c **2e** (5.0 mmol) was employed. ^d **1a** (0.25 mmol) and **2f** (2.5 mmol) were employed. ^e Reaction was performed for 12 h. ^f Formation of 1,3,5- and 1,2,4-tri(ethoxycarbonyl)benzenes was observed by ¹H NMR and GC-MS.

the terminal position of **2a** were induced by copper(0), affording the corresponding propargylamine **3a** in 99% yield (Table 1, entry 1).

(16) For the recent review for the propargylamines, see, for example: (a) Kouznetsov, V. V.; Vargas Méndez, L. Y. *Synthesis* **2008**, 491. (b) Zani, L.; Bolm, C. *J. Chem. Soc., Chem. Commun.* **2006**, 4263. (c) Aschwanden, P.; Carreira, E. M. In *Acetylene Chemistry: Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tywinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005; p 101.

The results of the reaction using **1a** and several acetylenes **2** are summarized in Table 1. The same condition can be employed with both aromatic and aliphatic acetylenes **2** to give the corresponding propargylamines **3** as sole products. Functionalities such as methyl, pentyl, methoxy, and chloro substituents were tolerant of the C–H bond insertion reactions, forming the corresponding **3** in good to excellent yields (entries 2–5). In contrast, the acetylene **2f**, having an electron-deficient substituent such as the nitro group, did not react with **1a** (both **1a** and **2f** were recovered unchanged) (entry 6). Although the reaction of 1-octyne (**2g**) required longer reaction time, the corresponding propargylamine **3g** was obtained in 61% yield (entry 7). In the cases of acetylenes **2h** and **2i** containing heteroatom-containing functional groups (O or N), the reactions gave the corresponding propargylamines **3h** and **3i** in 44% and 59% yields, respectively (entries 8 and 9). In the case of ethyl propiolate (**2j**), however, the desired C–H insertion reaction did not take place, and instead, the formation of cyclotrimerization products of **2j** was observed by ¹H NMR and GC–MS (entry 10).¹⁷ This result suggests that Cu(I) or Cu(II) species may be formed in this reaction system.^{18,19} In the case of 1,6-heptadiyne (**2k**), the deselenative C–H bond insertion of selenoamides **1a** and **1d** took place at either alkynyl group of **2k** to give **3k** and **3l** in good yields, respectively (eq 4).

Next, we examined the reaction of several selenoamides



1 with **2a**, and the results were summarized in Table 2. Aryl selenoamides **1b**, **1c**, and **1d** having *p*-methyl, *m*-chloro, and *p*-phenyl substituents afforded the corresponding **3m**, **3n**, and **3o** in 98%, 80%, and 98% yields, respectively (entries 1–3). A selenoamide **1e** bearing a heterocycle such as pyridyl

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(18) In the cases of other acetylenes, trace amounts of enyne, diyne, and cyclotrimerization products were obtained. These results indicated that the Cu(I) or Cu(II) species was generated from copper powder in this reaction system, and these copper species afforded dimerization or cyclotrimerization products of acetylene.

(19) For the copper-catalyzed dimerization reaction of terminal acetylenes to give the corresponding diynes, see: (a) Alcaide, B.; Almendros, P.; Carrascosa, R.; Rodríguez-Acebes, R. *Eur. J. Org. Chem.* **2008**, 1575. (b) Setaka, W.; Kanai, S.; Kabuto, C.; Kira, M. *Chem. Lett.* **2006**, *35*, 1364. (c) Sharifi, A.; Mirzaei, M.; Naimi-Jama, M. R. *Monatsh. Chem.* **2006**, *137*, 213. (d) Tokita, Y.; Okamoto, A.; Nishiwaki, K.; Kobayashi, M.; Nakamura, E. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1395. (e) Deeming, A. J.; Hogarth, G.; Lee, M.-Y. V.; Saha, M.; Redmond, S. P.; Phetmung, H. T.; Orpen, A. G. *Inorg. Chim. Acta* **2000**, *309*, 109. The copper-catalyzed addition reaction of terminal acetylenes to give the corresponding enynes, see: (f) Nishiwaki, K.; Kobayashi, M.; Takeuchi, T.; Matuoto, K.; Osakada, K. *J. Mol. Catal. A - Chemical* **2001**, *175*, 73. (g) Ficini, J.; d'Angelo, J.; Falou, S. *Tetrahedron Lett.* **1977**, *18*, 1645. The copper-catalyzed cyclotrimerization reaction of unsaturated bonds, see: (h) Maazouz, A.; Texier, C.; Taha, M.; Alglave, H. *Compos. Sci. Technol.* **1998**, *58*, 621. (i) Spee, T.; Mackor, A. *J. Am. Chem. Soc.* **1981**, *103*, 6901. (j) Evers, J. T. M.; Mackor, A. *Tetrahedron Lett.* **1980**, *21*, 415.

Table 2. Copper(0)-Induced Reaction of Selenoamides **1** with Phenylacetylene (**2a**)^a

entry	selenoamide	product	yield ^b
1			98%
2			80%
3			98%
4			94%
5			76%
6 ^c			ND

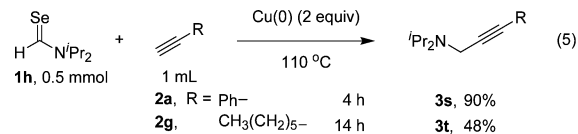
^a Reaction conditions: selenoamide (**1**, 0.5 mmol), phenylacetylene (**2a**, 1 mL), Cu(0) (2.0 mmol), 110 °C, 4 h. ^b Isolated yield. ^c 1-(*trans*-Phenylethynyl)piperidine (**4a**) was obtained in 63% yield as a sole product via an intramolecular C–H bond insertion reaction. This product was determined by ¹H NMR.

group could be also employed for this reaction to give **3p** in 94% yield (entry 4). In the case of selenoamide **1f** bearing acyclic amino group, the deselenative intermolecular C–H insertion reaction took place to provide **3q** in 76% yield (entry 5). Unfortunately, the reaction of **1g**, which has α -hydrogens to selenocarbonyl group, did not afford the desired propargylamine **3r**, and instead, 1-(*trans*-phenylethynyl)piperidine (**4a**) was obtained in 63% yield via an intramolecular C–H bond insertion reaction (entry 6).²⁰

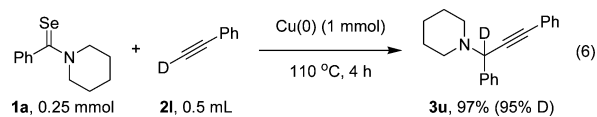
When the reaction was applied to selenoformamide **1h**, the C–H insertion reaction took place successfully, affording the corresponding propargylamines **3s** and **3t** in moderate to good yields, respectively (eq 5).

To elucidate the reaction pathway, we examined the reaction of **1a** with phenylacetylene-*d*¹ (**2l**). The reaction

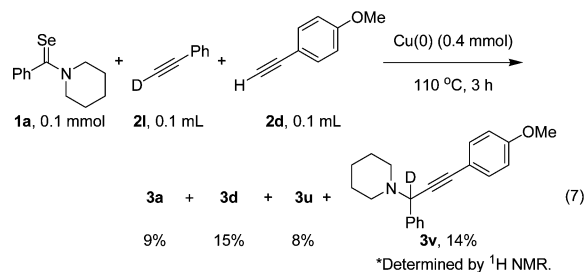
(20) The ¹H and ¹³C NMR spectra and chemical shift of **4a** were shown in this paper, see: Reddy, C.; Reddy, V.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2005**, *7*, 4427.



of **1a** with **2l** afforded the corresponding propargylamine-*d*¹ **3u**, successfully (eq 6).



When the same reaction of **1a** with **2l** was performed in the copresence of **2d**, the reaction provided a mixture of propargylamines **3a**, **3d**, **3u**, and **3v** (eq 7). In this reaction, 82% of phenylacetylene (54% D) and 85% of *p*-methoxyphenylacetylene (53% D) were also obtained. This result suggests that H/D scrambling took place between phenylacetylene and *p*-methoxyphenylacetylene. Recently, a copper-mediated H/D exchange of acetylenes has been reported.²¹ Hence, this C–H bond insertion reaction may include the formation of copper acetylide complex. However, the precise mechanistic pathway should wait for further detailed mechanistic studies.



In summary, we have developed novel copper(0)-induced deselenation of selenoamides and sequential insertion reaction into acetylenic C–H bond, affording the corresponding propargylamines successfully.

Acknowledgment. This work is supported by Grant-in-Aid for Scientific Research on Priority Areas (Area 444, No. 19020061) and Scientific Research (B, 19350095), from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Dr. Akihiro Nomoto (Osaka Prefecture University) for his helpful suggestion.

Supporting Information Available: General experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for propargylamines and selenoamides. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(21) The copper(I)-mediated H/D exchange reaction of terminal acetylene was reported, see: (a) Tachiyama, T.; Yoshida, M.; Aoyagi, T.; Fukuzumi, S. *J. Phys. Org. Chem.* **2008**, *21*, 510. (b) Tachiyama, T.; Yoshida, M.; Aoyagi, T.; Fukuzumi, S. *Chem. Lett.* **2008**, *37*, 38.