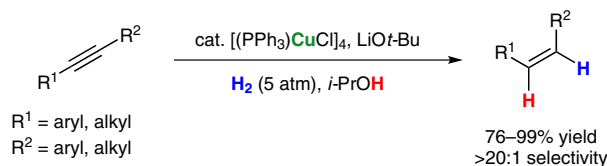


Copper-Catalyzed Semihydrogenation of Alkynes to Z-Alkenes

Kazuhiko Semba*^aRyohei Kameyama^aYoshiaki Nakao*^{a,b}

^a Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-Ku, Kyoto 615-8510, Japan
semba.kazuhiko.5n@kyoto-u.ac.jp
nakao.yoshiaki.8n@kyoto-u.ac.jp

^b CREST, Japan Science and Technology Agency (JST), 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan



Received: 16.12.2014

Accepted after revision: 20.01.2015

Published online: 26.01.2015

DOI: 10.1055/s-0034-1379896; Art ID: st-2014-r1032-c

Abstract Copper-catalyzed semihydrogenation of internal alkynes has been developed. The reaction proceeds under an atmosphere of hydrogen (5 atm) at 100 °C in the presence of a readily available $[(\text{PPh}_3)\text{CuCl}]_4$ catalyst to give various Z-alkenes stereoselectively.

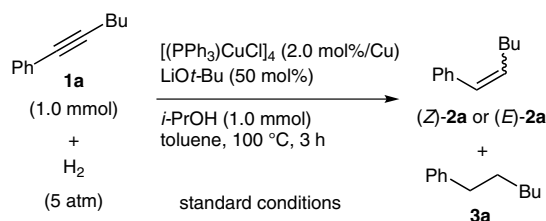
Key words alkynes, alkenes, catalysis, copper, hydrogenation

Much attention has been paid to develop copper-catalyzed reduction of unsaturated compounds such as carbonyls, imines, Michael acceptors, and alkynes due to low cost and abundance of copper as well as high chemo-, regio-, and stereoselectivities associated with copper catalysis.^{1,2} Usually, hydrosilanes are employed as a stoichiometric reducing reagent. In contrast, copper-catalyzed reduction using H_2 (hydrogenation) is rare, although it is more atom-efficient than the use of hydrosilanes. Hydrogenation of polar multiple bonds such as aldehydes, ketones, and Michael acceptors has been relatively well-studied with copper catalysis,³ whereas that of nonpolar multiple bonds such as alkynes is limited. To the best of our knowledge, Cu_2O -catalyzed semihydrogenation of terminal alkynes under an atmosphere of H_2 (20 atm) has been the only precedent.⁴

Semihydrogenation of internal alkynes is an efficient method to prepare Z-alkenes, which are versatile building blocks in organic synthesis and often found in biologically active compounds. A variety of heterogeneous catalysts have been developed for this transformation.⁵ Especially, the Lindlar catalyst is a well-established and effective catalyst for semihydrogenation of alkynes.⁶ Nevertheless, it often suffers from Z/E isomerization, shift of double bonds, and overhydrogenation to give alkanes. Thus, uptake of H_2 must be accurately monitored to control the hydrogenation. To overcome such difficulties, homogeneous catalysts such as rhodium, chromium, palladium, ruthenium, vanadium, and niobium have been developed.⁷ Here, we report that $[(\text{PPh}_3)\text{CuCl}]_4$,⁸ a readily available copper complex, efficiently catalyzes semihydrogenation of internal alkynes to give Z-alkenes in a highly stereoselective manner under an atmosphere of H_2 (5 atm).

First, we optimized the reaction conditions employing 1-phenyl-1-hexyne (**1a**) as a model substrate (Table 1). After screening a variety of reaction parameters, semihydrogenation of **1a** gave (Z)-1-phenyl-1-hexene [(Z)-**2a**] selectively in high yield without formation of (E)-1-phenyl-1-hexene [(E)-**2a**] and hexylbenzene (**3a**) under the standard conditions: $[(\text{PPh}_3)\text{CuCl}]_4$ (2.0 mol%/Cu), LiOt-Bu (50 mol%), and *i*-PrOH (1.0 mmol) in toluene at 100 °C for 3 hours under an atmosphere of H_2 (5 atm) (Table 1, entry 1).

Table 1 Semihydrogenation of **1a** with Various Copper Catalysts



Entry	Variation from the standard conditions	Conv. of 1a (%) ^a	Yield of (Z)- 2a + (E)- 2a + 3a (%) ^b	Ratio of (Z)- 2a /(E)- 2a / 3a (%) ^b
1	none	>99	99 (80) ^c	99:<1:<1
2	run for 12 h	>99	95	94:2:4
3	$\text{CuCl}/\text{Ph}_3\text{P}$ instead of $[(\text{PPh}_3)\text{CuCl}]_4$	>99	95	99:<1:<1
4	$\text{CuCl}/\text{P}(o\text{-tol})_3$ instead of $[(\text{PPh}_3)\text{CuCl}]_4$	<5	–	–

Table 1 (continued)

Entry	Variation from the standard conditions	Conv. of 1a (%) ^a	Yield of (Z)- 2a + (E)- 2a + 3a (%) ^b	Ratio of (Z)- 2a /(E)- 2a / 3a (%) ^b
5	CuCl/PCy ₃ instead of [(PPh ₃)CuCl] ₄	>99	90	54:4:42
6	CuCl instead of [(PPh ₃)CuCl] ₄	<5	–	–
7	without [(PPh ₃)CuCl] ₄	<5	–	–
8	without LiOt-Bu	<5	–	–
9	without <i>i</i> -PrOH	<5	–	–
10	under N ₂ instead of H ₂	<5	–	–
11	under H ₂ (1.0 atm)	<5	–	–
12	Cu ₂ O instead of [(PPh ₃)CuCl] ₄ , LiOt-Bu, and <i>i</i> -PrOH	<5	–	–

^a Determined by GC analysis with *n*-tridecane as an internal standard.

^b Determined by ¹H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard.

^c Isolated yield.

Notably, the selectivity is better than that reported using the Lindlar catalyst [(Z)-**2a**]/[(Z)-**2a** + (E)-**2a** + **3a**] = 91%.^{6d} Compound (Z)-**2a** was isolated in 80% yield after medium-pressure column chromatography on silica gel (Table 1, entry 1). Prolonging the reaction time to 12 hours slightly decreased the selectivity (Table 1, entry 2). [(PPh₃)CuCl]₄ generated in situ from CuCl and Ph₃P showed reactivity comparable to an isolated one (Table 1, entry 3). CuBr was similarly effective as CuCl. In contrast, other copper(I) salts such as CuI, CuOAc, and CuCN showed activity far less than CuCl. The effects of phosphine ligands are summarized in entries 4–6 (Table 1). The hydrogenation did not proceed with tri(*o*-tolyl)phosphine [P(*o*-tol)]₃ as a ligand or without any ligands (Table 1, entries 4 and 6). In the case of tricyclohexylphosphine (PCy₃), a considerable amount of **3a** was observed (Table 1, entry 5). When the reactions were performed in the absence of [(PPh₃)CuCl]₄, LiOt-Bu, or *i*-PrOH, no products were obtained (Table 1, entries 7–9). The reaction did not proceed under an N₂ atmosphere instead of H₂ (Table 1, entry 10), indicating that *i*-PrOH did not act as a hydride source. Under an atmosphere of H₂ (1.0 atm), the products were not formed (Table 1, entry 11). Cu₂O, which was reported to serve as a catalyst for semihydrogenation of terminal alkynes,⁴ was ineffective under the present reaction conditions (Table 1, entry 12). Even in the presence of Ph₃P, LiOt-Bu, and *i*-PrOH, Cu₂O was not a good catalyst.

The scope of substrates was investigated under the optimized reaction conditions (Table 2).⁹ In the case of 1-phenyl-1-propyne (**1b**), (Z)-1-phenyl-1-propene [(Z)-**2b**] was obtained in high yield with a small amount of (E)-1-phenyl-1-propene [(E)-**2b**] and propylbenzene (**3b**) (Table 2, entry 1). The reduction of 1-phenyl-2-trimethylsilylacetylene (**1c**) did not proceed (Table 2, entry 2). Diphenylacetylene derivatives **1d–g** were efficiently semihydrogenated to give the corresponding Z-alkenes (Table 2, entries 3–6). Electron-donating and electron-withdrawing substituents on the phenyl group did not affect the yields and selectivities

(Table 2, entries 4–6). The catalytic system was also effective for semihydrogenation of aliphatic alkynes **1h** and **1i**, giving the corresponding Z-alkenes (Z)-**2h** and (Z)-**2i** selectively (Table 2, entries 7 and 8). On the other hand, ynoate **1j** and terminal alkyne **1k** were not competent substrates. The reaction of **1j** afforded a complex mixture (Table 2, entry 9), whereas **1k** was not converted at all under the present conditions (Table 2, entry 10). With 5,7-dodecadiyne (**1l**), (Z)-5-dodecene was obtained selectively (Table 2, entry 11).

A plausible reaction mechanism is depicted in Scheme 1. Copper hydride **5** is generated from heterolytic cleavage of H₂ by copper alkoxide **4** (step a).¹⁰ According to the literature, *syn* addition of **5** across an alkyne gives alkenyl copper **6** in a stereoselective manner (step b).¹¹ Compound **6** is protonated by alcohol to afford (Z)-**2** and regenerate **4** (step c).¹² To gain insights into the proposed reaction mechanism, semihydrogenation of **1a** was performed using *i*-PrOH

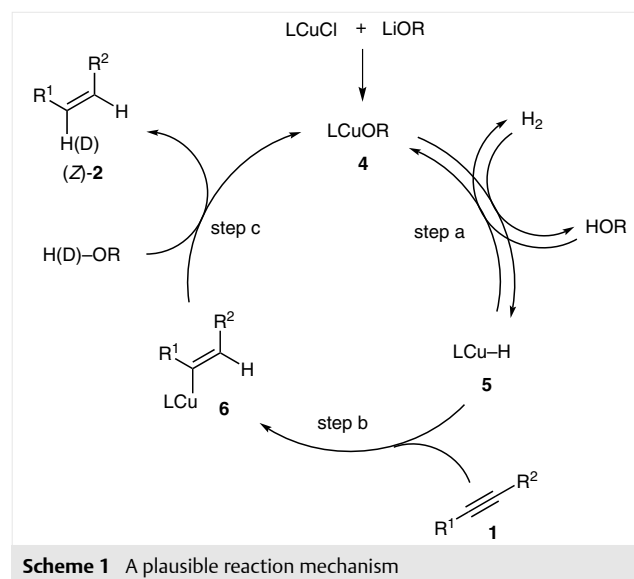


Table 2 Semihydrogenation of Various Alkynes **1**

Entry	Alkyne	Conv. of 1 (%) ^a	Yield of (Z)- 2 + (E)- 2 + 3 (%) ^b	Ratio of (Z)- 2 /(E)- 2 / 3 (%) ^c
1		>99	(78)	96:2:2
2		<5	-	-
3 ^d		>99	91	96:3:1
4	$R^1 = R^2 = \text{Me}$ (1e)	>99	99	98:<1:2
5	$R^1 = R^2 = \text{F}$ (1f)	>99	95	98:1:1
6 ^{e,f}	$R^1 = \text{C(O)O}i\text{-Pr}$, $R^2 = \text{H}$ (1g)	>99	52 (95)	>99:<1:<1
7		>99	76	>99:<1:<1
8		>99	(93)	>99:<1:<1
9		>99	complex mixture	-
10		<5	-	-
11 ^f		>99	(78) ^g	-

^a Determined by GC analysis with *n*-tridecane as an internal standard.

^b Isolated yield. Yields determined by ¹H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard are given in parentheses.

^c Determined by ¹H NMR analysis of a crude product.

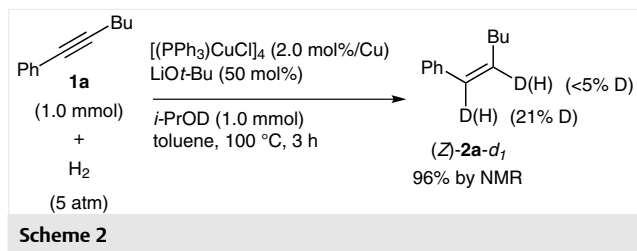
^d Run at 60 °C for 3 h.

^e Run at 80 °C for 3 h.

^f Run in 0.30 mmol scale.

^g (Z)-5-Dodecene was obtained selectively.

(Scheme 2). Monodeuterated alkene (*Z*)-**2a-d₁** was obtained regioselectively albeit with low deuterium incorporation. This result supports that *i*-PrOH serves as a source of hydrogen and that the addition of copper hydride **5** across **1a** (step b) proceeds regioselectively. Reversibility of step a should be responsible for contamination of *i*-PrOH under the reaction conditions of Scheme 2 and thus the observed low deuterium content in (*Z*)-**2a-d₁**.¹³



In conclusion, we have established the copper-catalyzed semihydrogenation of internal alkynes. The present transformation is catalyzed by a readily available copper complex under an atmosphere of H₂ (5 atm), giving *Z*-alkenes in high yields and selectivities. This simple catalytic system employing inexpensive metal catalyst can be an alternative to known protocols using a noble-metal catalyst such as the Lindlar catalyst.

Acknowledgment

This work was supported by a Grant-in-Aid for Young Scientists (B) (26810058) from MEXT and the Japan Science and Technology Corporation (CREST, 'Establishment of Molecular Technology towards the Creation of New Functions' Area).

Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0034-1379896>.

References and Notes

- (1) (a) For reviews on copper-catalyzed reduction of carbonyl compounds and Michael acceptors, see: Rendler, S.; Oestreich, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 498; and references cited therein. (b) Díez-González, S.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 349; and references cited therein. (c) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916; and references cited therein. (d) Lipshutz, B. H. *Synlett* **2009**, 509; and references cited therein.
- (2) For references on copper-catalyzed semireduction of alkynes, see: (a) Semba, K.; Fujihara, T.; Xu, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2012**, *354*, 1542. (b) Whittaker, A. M.; Lalic, G. *Org. Lett.* **2013**, *15*, 1112. (c) Wang, G.-H.; Bin, H.-Y.; Sun, M.; Chen, S.-W.; Liu, J.-H.; Zhong, C.-M. *Tetrahedron* **2014**, *70*, 2175. (d) Cao, H.; Chen, T.; Zhou, Y.; Han, D.; Yin, S.-F.; Han, L.-B. *Adv. Synth. Catal.* **2014**, *356*, 765. For the semireduction of alkynes

- using a stoichiometric amount of [(PPh₃)CuH]₆, see: (e) Daeuble, J. F.; Mcgettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 2397.
- (3) (a) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818. (b) Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153. (c) Chen, J.-X.; Daeuble, J. F. *Tetrahedron* **2000**, *56*, 2789. (d) Shimizu, H.; Igarashi, D.; Kuriyama, W.; Yusa, Y.; Sayo, N.; Saito, T. *Org. Lett.* **2007**, *9*, 1655. (e) Junge, K.; Wendt, B.; Addis, D.; Zhou, S.; Das, S.; Fleischer, S.; Beller, M. *Chem. Eur. J.* **2011**, *17*, 101.
 - (4) Sokol'skii, D. V.; Ualikhanova, A. *Russ. J. Phys. Chem.* **1977**, *51*, 886.
 - (5) (a) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226. (b) Brunet, J.-J.; Gallois, P.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 1937. (c) Brunet, J.-J.; Caubere, P. *J. Org. Chem.* **1984**, *49*, 4058. (d) Choudary, B. M.; Sharma, G. V. M.; Bharathi, P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 465. (e) Choi, J.; Yoon, N. M. *Tetrahedron Lett.* **1996**, *37*, 1057. (f) Alonso, F.; Osante, I.; Yus, M. *Tetrahedron* **2007**, *63*, 93. (g) Mizugaki, T.; Murata, M.; Fukubayashi, S.; Mitsudome, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.* **2008**, 241.
 - (6) (a) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446. (b) Lindlar, H.; Dubuis, R. *Org. Synth.* **1966**, *46*, 89. (c) Marvell, E. N.; Li, T. *Synthesis* **1973**, 457. (d) Rajaram, J.; Narula, A. P. S.; Chawla, H. P. S.; Dev, S. *Tetrahedron* **1983**, *39*, 2315.
 - (7) (a) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2143. (b) Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1985**, *50*, 1149. (c) van Laren, M. W.; Elsevier, C. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3715. (d) Sprengers, J. W.; Wassenaar, J.; Clement, N. D.; Cavell, K. J.; Elsevier, C. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 2026. (e) Belger, C.; Neisius, N. M.; Plietker, B. *Chem. Eur. J.* **2010**, *16*, 12214. (f) La Pierre, H. S.; Arnold, J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 3900. (g) Gianetti, T. L.; Tomson, N. C.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2011**, *133*, 14904. (h) Chernichenko, K.; Madarász, Á.; Pápai, I.; Nieger, M.; Leskelä, M.; Repo, T. *Nat. Chem.* **2013**, *5*, 718. Transfer semihydrogenation of alkynes was also reported, see: (i) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1989**, *30*, 4657. (j) Hauwert, P.; Maestri, G.; Sprengers, J. W.; Catellani, M.; Elsevier, C. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3223. (k) Hauwert, P.; Boerleider, R.; Warsink, S.; Weigand, J. J.; Elsevier, C. J. *J. Am. Chem. Soc.* **2010**, *132*, 16900. (l) Hua, J. L. R.; Liu, T. J. *Org. Chem.* **2010**, *75*, 2966. (m) Hua, J. L. R. *Chem. Eur. J.* **2011**, *17*, 8462. (n) Shen, R.; Chen, T.; Zhao, Y.; Qiu, R.; Zhou, Y.; Yin, S.; Wang, X.; Goto, M.; Han, L.-B. *J. Am. Chem. Soc.* **2011**, *133*, 17037.
 - (8) Churchill, M. R.; Kalra, K. *Inorg. Chem.* **1974**, *13*, 1065.
 - (9) **General Procedure for the Copper-Catalyzed Semihydrogenation**
In a glove box, [(PPh₃)CuCl]₄ (7.2 mg, 5.0 μmol), toluene (1.0 mL), LiOt-Bu (40 mg, 0.50 mmol), and *i*-PrOH (60 mg, 1.0 mmol) were added to a vial in this order. After being stirred for 1 min at r.t., alkyne **1** (1.0 mmol) and toluene (2.0 mL) were added to the resulting mixture. The vial was placed in an autoclave, and the autoclave was taken out of the glove box. An N₂ atmosphere in the autoclave was purged by positive pressure of H₂. Then, the mixture was stirred at 100 °C for 3 h under H₂ (5 atm). After being cooled to r.t., H₂ was released, and the mixture was diluted with EtOAc. The conversion of alkynes was determined by GC analysis with *n*-tridecane as an internal standard. The resulting solution was filtered through a pad of silica gel, and the filtrate was concentrated. The residue was purified by medium-pressure column chromatography on silica gel to give (*Z*)-**2**.

Representative data:

(Z)-2d: The reaction of **1d** (180 mg, 1.0 mmol) at 60 °C followed by purification by MPLC (16 g of silica gel and Biotage® SNAP Ultra 10 g; *n*-hexane) gave the corresponding product (160 mg, 0.91 mmol, 91%) as a mixture of **(Z)-2d**,^{14a} **(E)-2d**,^{14b} and **3d**^{14c} [(**Z**)-**2d**/**(E)-2d**/**3d** = 95:5:<1 determined by ¹H NMR analysis] as a colorless oil; *R*_f = 0.53 (hexane). ¹H NMR (CDCl₃, 400 MHz): δ = 7.28–7.16 (m, 10 H), 6.60 (s, 2 H); ¹³C NMR (CDCl₃, 101 MHz): δ = 137.2, 130.2, 128.8, 128.2, 127.1. All the resonances of ¹H and ¹³C NMR spectra were consistent with reported values.^{14a}

(Z)-2g: The reaction of **1g** (79 mg, 0.30 mmol) at 80 °C in toluene (0.80 mL) followed by purification by MPLC (16 g of silica gel and Biotage® SNAP Ultra 10 g; *n*-hexane–EtOAc, 99:1 to 93:7) gave the corresponding product **(Z)-2g** (42 mg, 0.16 mmol, 52%) as a pale yellow oil; *R*_f = 0.35 (*n*-hexane–EtOAc, 95:5). ¹H NMR (CDCl₃, 400 MHz): δ = 7.90 (d, *J* = 8.5 Hz, 2 H), 7.30 (d, *J* = 8.5 Hz, 2 H), 7.25–7.20 (m, 5 H), 6.71 (d, *J* = 12.2 Hz, 1 H), 6.61 (d, *J* = 12.2 Hz, 1 H), 5.24 (sept, *J* = 6.1 Hz, 1 H), 1.36 (d, *J* = 6.1 Hz, 6 H); ¹³C NMR (CDCl₃, 101 MHz): δ = 165.9, 141.8,

136.7, 132.1, 129.4, 129.31, 129.28, 128.8, 128.7, 128.3, 127.4, 68.3, 21.9. HRMS–APCI (+): *m/z* [M + H]⁺ calcd for C₁₈H₁₉O₂: 267.1380; found: 267.1375

- (10) [(PPh₃)CuH]₆ was synthesized from Cu(*O**t*-Bu) and Ph₃P, see: (a) Goeden, G. V.; Caulton, K. G. *J. Am. Chem. Soc.* **1981**, *103*, 7354. For catalytic activation of H₂ by copper salts, see (b) Halpern, J. *J. Phys. Chem.* **1959**, *63*, 398.
- (11) *syn*-Addition of copper hydride across internal alkynes was reported, see: (a) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369. (b) Fujihara, T.; Xu, T.; Semba, K.; Terao, J.; Tsuji, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 523.
- (12) For a reference on protonation of an alkenyl copper with an alcohol, see ref. 2a.
- (13) H–D exchange between copper hydride and alcohols was reported, see ref. 2b and: Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352.
- (14) (a) Yan, M.; Jin, T.; Ishikawa, Y.; Minato, T.; Fujita, T.; Chen, L.-Y.; Bao, M.; Asao, N.; Chen, M.-W.; Yamamoto, Y. *J. Am. Chem. Soc.* **2012**, *134*, 17536. (b) Chen, Z.; Luo, M.; Wen, Y.; Luo, G.; Liu, L. *Org. Lett.* **2014**, *16*, 3020. (c) Kantam, M. L.; Kishore, R.; Yadav, J.; Sudhakar, M.; Venugopal, A. *Adv. Synth. Catal.* **2012**, *354*, 663.