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(NHC)CuH-Catalyzed Entry to Allenes via Propargylic Carbonate S_N2'-Reductions

Carl Deutsch,[†] Bruce H. Lipshutz,[‡] and Norbert Krause*,[†]

Organic Chemistry, Dortmund University of Technology, Otto-Hahn-Strasse 6, D-44227 Dortmund, Germany, and Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106

norbert.krause@tu-dortmund.de

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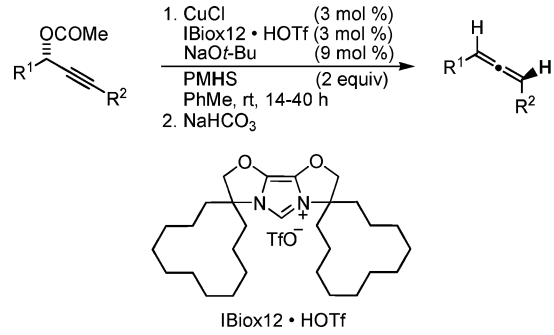
ABSTRACT



The copper hydride-catalyzed S_N2'-reduction of propargylic carbonates provides an efficient route to functionalized allenes. The method takes advantage of the stabilizing effect of NHC ligands on CuH and combines high reactivity and stereoselectivity with excellent tolerance toward reactive functionalities.

The combination of isolation of allenic natural products (e.g., bromoallene laurallene; Figure 1), industrial development of biologically active allenes (e.g., prostaglandin analogue enprostil),[1] and the potential use of highly reactive cumulated double bonds in synthesis have catapulted allenes into focus.[2] Their synthetic utility has been acknowledged by an abundance of regio- and stereoselective C−C and C−heteroatom bond-forming transformations now available, perhaps most noteworthy being their efficient transfer of allenic axial chirality to the creation of sp^3 stereogenic centers. New inroads for the syntheses of allenes that reflect their growing value continue to be disclosed, often taking advantage of copper-mediated or -catalyzed nucleophilic addition or substitution reactions.[2]

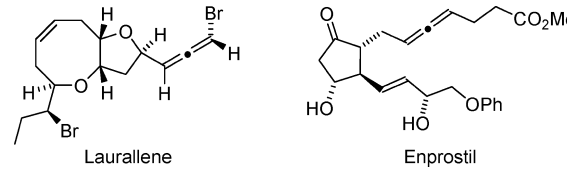


Figure 1. Naturally occurring and biologically active allenes.

One alternative to C−C bond construction is the synthesis of allenes through underutilized carbon−hydrogen bond formation. Other than two reports featuring allene syntheses

[†] Dortmund University of Technology.
[‡] University of California, Santa Barbara.

(1) Review : Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196–1216, and references cited therein.

(2) (a) *Cumulenes and Allenes*; Krause, N., Ed.; Science of Synthesis, Vol. 44; Thieme: Stuttgart, 2007. (b) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004. (c) Krause, N.; Belting, V.; Deutsch, C.; Erdsack, J.; Fan, H.-T.; Gockel, B.; Hoffmann-Röder, A.; Morita, N.; Volz, F. *Pure Appl. Chem.* **2008**, *80*, 1063–1069. (d) Brummond, K. M.; DeForest, J. E. *Synthesis* **2007**, 795–818. (e) Ma, S. *Pure Appl. Chem.* **2006**, *78*, 197–208. (f) Ma, S. *Chem. Rev.* **2005**, *105*, 2829–2871. (g) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671–11694.

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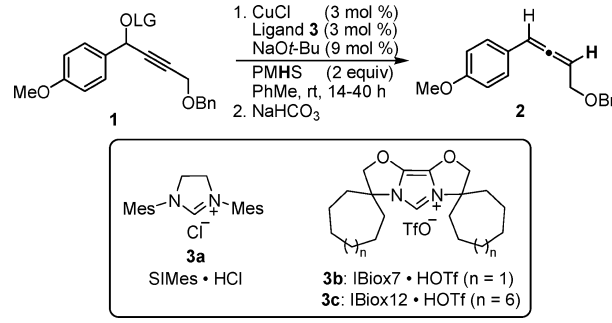
mediated by stoichiometric copper hydride[3] (Stryker's reagent [$(Ph_3PCuH)_6$][4]) on propargylic acetates,[5] there is only a single catalytic method[6] known leading to highly functionalized allenes involving in situ generation of CuH and reactions with propargylic oxiranes in the presence of polymethylhydridosiloxane (PMHS).[7] This shortage of synthetic methods stands in stark contrast to the rich and highly developed catalysis by CuH applied to both 1,2- and 1,4-reductions of carbonyl compounds.[3] While CuH-catalyzed S_N2'-reduction of propargylic oxiranes offers access to a variety of α-hydroxyallenes,[7] extension to other propargylic electrophiles would have advantages, such as (i) greater substrate reactivity, (ii) improved stereoselectivity, and (iii) better insight as to ligand effects in CuH catalysis. Importantly, the limitation of Stryker's reagent to S_N2'-reductions of *terminal* propargylic acetates[5] might be overcome.

To establish the optimal combination of leaving group and stabilizing ligand for the CuH catalyst, various propargylic electrophiles **1**[8] were treated in toluene at room temperature with a mixture of CuCl, NaO-*t*-Bu and NHC-carbene precursors **3a**−**c**[9] in the presence of PMHS as stoichiometric hydride source[10] (Table 1).

Whereas acetate **1a** and pivalate **1b** in the presence of IBiox12 (**3c**) afforded the desired allene **2** (albeit in a slow reaction that did not go to completion; entries 1, 2), no product was formed when **1b** was exposed to SIMes ligand **3a** (entry 3). Unexpectedly, more electron-deficient esters are not suitable for this S_N2'-reduction as well (entries 4 and 5). Best results were achieved with carbonates **1e** and **1f**, which afforded allene **2** in up to 95% isolated yield (entries 6−9). Again, the Glorius ligands **3b/c** performed in a far superior fashion to the Arduengo carbene **3a** (entries 6, 7, 9 vs 8). The bulkier IBiox12 carbene **3c**[11] relative to analogue **3b** gave a slightly higher yield of the allene (entry 6 vs 7).[12]

Table 1. Copper-Catalyzed S_N2'-Reduction of Propargylic Electrophiles **1**

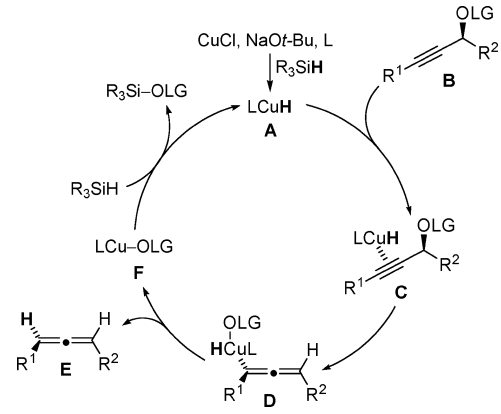


entry	**1**	LG	ligand	**1/2** (yield, %)
1	**a**	Ac	**3c**	35/40
2	**b**	Piv	**3c**	25/70
3	**b**	Piv	**3a**	0/0[a]
4	**c**	$ClCH_2CO$	**3c**	0/trace
5	**d**	$3\text{-}O_2NC_6H_4CO$	**3c**	60/20
6	**e**	MeOCO	**3b**	trace/88
7	**e**	MeOCO	**3c**	**0/95**
8	**f**	Boc	**3a**	25/33
9	**f**	Boc	**3c**	trace/75

[a] No conversion.

The proposed mechanistic model (Scheme 1) provides an explanation for the pronounced leaving group effect.

Scheme 1



Thus, the in situ formed copper hydride species **A** likely reacts with the propargylic electrophile **B** to form π-complex **C**, which is then converted into the σ-copper(III) species **D**.[13] Reductive elimination affords allene **E** and the copper salt **F**. The key to efficiency of the catalytic cycle is regeneration of the copper hydride catalyst **A** by reaction of **F** with PMHS. It has been shown that the rate of this transmetalation step depends strongly on the

(3) Reviews: (a) Lipshutz, B. H. Copper(I)-Mediated 1,2- and 1,4-Reductions. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 167−187. (b) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 498–504. (c) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927. (d) Lipshutz, B. H. *Synlett* **2009**, 509–524.

(4) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–293. (b) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749–3752.

(5) (a) Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 2397–2400. (b) Brummond, K. M.; Lu, J. *J. Am. Chem. Soc.* **1999**, *121*, 5087–5088.

(6) For a reductive allene synthesis using stoichiometric amounts of Schwartz's reagent, see: (a) Pu, X.; Ready, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 10874–10875. (b) For the synthesis of allenic hydrocarbons using catalytic CuH stabilized by phosphines, see: Zhong, C.; Sasaki, Y.; Ito, H.; Sawamura, M. *Chem. Commun.* **2009**, 5850−5852.

(7) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1650–1653.

(8) Substrates **1aa**−**ad**: Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569–583. Substrates **1ae** and **1af**: Mandai, T.; Matsumoto, T.; Tsujiguchi, Y.; Matsuoka, S.; Tsuji, J. *J. Organomet. Chem.* **1994**, *473*, 343–352.

(9) (a) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523–14534. (b) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49–54. (c) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.

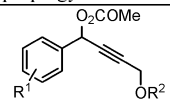
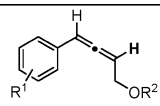
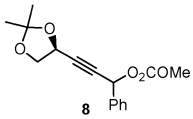
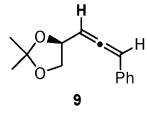
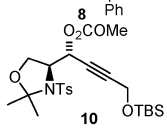
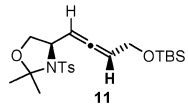
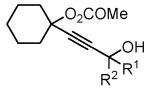
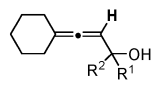
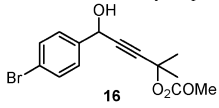
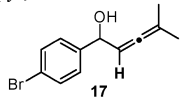
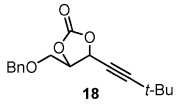
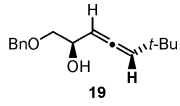
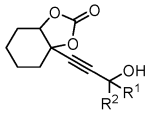
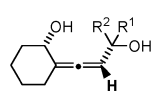
(10) Besides PMHS, also $(Me_2HSi)_2O$, Et_3SiH, and $(EtO)_3SiH$ were used as hydride source, but these silanes afforded diminished reactivities.

(11) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523–1533.

(12) Treatment of **1ae** with stoichiometric amounts of Stryker's reagent led to decomposition of the substrate.

(13) For a recent review on the mechanism of copper-mediate reactions, see: Gschwind, R. M. *Chem. Rev.* **2008**, *108*, 3029–3053.

Table 2. Copper-Catalyzed S_N2'-Reduction of Propargylic Carbonates[a]

entry	propargylic carbonate	allene	*dr*	yield/%
				
1	**1e**	R^1 = 4-MeO, R^2 = Bn	**2**		95
2	**4**	R^1 = 4-MeO, R^2 = THP	**5**		61
3	**6**	R^1 = 2-MeO/6-Me, R^2 = Bn	**7**		70
4[b,c]	 **8**	 **9**		50:50	96
5[c]	 **10**	 **11**		>95:5	75
					
6	**12**	R^1 = 4-MeOC_6H_4, R^2 = H	**13**		55
7	**14**	R^1 = cyclopropyl, R^2 = Me	**15**		70
8[d]	 **16**	 **17**			57
9[e]	 **18**	 **19**		>95:5	88
					
10	**20**	R^1 = 4-$F_3CC_6H_4$, R^2 = H	**21**	>95:5	59
11[e]	**22**	R^1 = 4-BrC_6H_4, R^2 = H	**23**	>95:5	69
12[e]	**24**	R^1 = cyclopropyl, R^2 = Me	**25**	>95:5	76

[a] Conditions: CuCl (3 mol %), **3c** (3 mol %), NaO-*t*-Bu (9 mol %), PMHS (2 equiv), rt, 8−24 h, workup with satd aq $NaHCO_3$. [b] **8** was used as a 1:1 mixture of diastereomers; **3b** was used instead of **3c**. [c] Substrate and product are enantiomerically pure. [d] 37% of starting material **16** recovered. [e] Relative configuration assigned by comparison with allenes obtained by S_N2'-reduction of propargyl oxiranes.[7]

basicity of the copper salt.[3] Thus, we assume that this step is slow for copper carboxylates, whereas a fast hydride transfer occurs with copper alkoxides which are presumably formed in situ from the corresponding carbonate.

The scope of this allene synthesis was explored by reacting various propargylic carbonates (Table 2) under the newly established optimal conditions (Table 1, entry 7). A wide variety of functional groups is tolerated in the substrate, such as electron-rich (Table 2, entries 1−3, 6) or electron-deficient aromatics (entries 8, 10, 11), free hydroxyl groups (entries 6−8, 10−12), silyl ethers (entry 5), acetals (entries 2, 4, 5), cyclopropanes (entries 7, 12), halogens (entries 8, 11), and CF_3 groups (entry 10). Moreover, the method also applies to cyclic carbonates (entries 9−12). In these S_N2'-reductions (as well as for chiral oxazolidine **10**, entry 5), each allene was obtained as a single diastereomer, indicating complete transfer of *axis-to-center chirality*. Comparison of the relative configuration of allenes **19**, **23**, and **25** with those obtained from propargylic oxiranes[7] reveals that propargylic carbonates react with S_N2' *anti*-stereoselectivity (as expected for the mechanism depicted in Scheme 1).[13] It is worth noting that allene **25** (entry 12) was obtained in diastereomerically pure form from carbonate **24**, while the corresponding oxirane led to only 86% *ds*.[7] Thus, the method presented herein offers the additional advantage of improved diastereoselectivity, as well as the opportunity to access enantiomerically enriched or pure precursors to propargylic carbonates, e.g., by Sharpless dihydroxylation.

In summary, we have developed a mild and efficient copper hydride-catalyzed S_N2'-reduction of propargylic carbonates which provides a highly chemo- and stereoselective route to functionalized allenes. Products of this type are valuable precursors for further transformations;[2] for example, Garner aldehyde-derived allene **11** can be used for the synthesis of derivatives of the antibiotic amino acid furanomycin by gold-catalyzed cycloisomerization.[14] We are continuing to expand the repertoire of CuH technology and to apply these methods to target-oriented synthesis.

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Supporting Information Available: Experimental procedures and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Erdsack, J.; Krause, N. *Synthesis* **2007**, 3741–3750, and references cited therein.