Copper Hydride Catalysis

DOI: 10.1002/anie.200603739

Small but Effective: Copper Hydride Catalyzed Synthesis of α-Hydroxyallenes**

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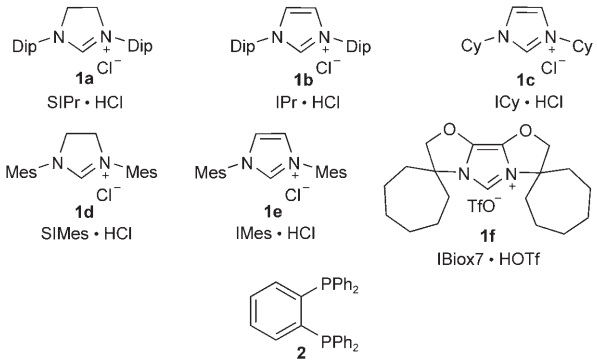
In recent years, allenes have developed from chemical curiosities into highly valuable intermediates for target-oriented synthesis mainly because they can undergo various transformations with high levels of chirality transfer.[1] Among functionalized allenes, α-hydroxyallenes play a particular role since they can be converted under mild conditions into 2,5-dihydrofurans[2] and other hetero-substituted allenes.[3] Owing to their importance, various methods for the synthesis of α-hydroxyallenes have been developed, often taking advantage of copper-mediated or -catalyzed nucleophilic addition or substitution reactions.[4] It is remarkable, however, that the smallest nucleophile, the hydride anion, has so far only played a minor role in this chemistry.[4a]

The only examples of allene syntheses mediated by copper hydride in S_N2' substitutions were reported by Stryker et al.[5] and by Brummond and Lu,[6] who treated terminal propargyl acetates with the hexameric copper hydride complex $[\{(Ph_3P)CuH\}_6]$ (Stryker's reagent[7]). In contrast to this, copper hydride chemistry has been used extensively for 1,4-[8,9] and 1,2-reductions[8,10] of various substrates. To render these reductions environmentally friendly, a variety of protocols using catalytic amounts of copper, as well as bidentate phosphine[8–10] or N-heterocyclic carbene (NHC)[11] ligands in the presence of a stoichiometric hydride donor (often a silane), have been developed. Interestingly, these catalytic systems usually display even higher reactivity than Stryker's reagent. Given our interest in the synthesis and transformations of α-hydroxyallenes, we have concentrated on propargyl oxiranes as the electrophile. To stabilize the copper hydride catalyst, we employed various NHC ligands (formed from the imidazolium salts **1**),[12,13] as well as the bisphosphine **2**, which shows a high reactivity in 1,2-reductions[10g] (Scheme 1).

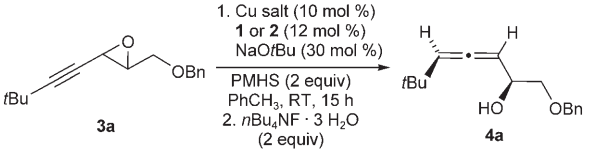
The imidazolium salts were deprotonated in situ by the base sodium *tert*-butoxide to afford the corresponding carbene. The results of a screening of the ligand and the copper salt, using propargyl oxirane **3a**[14] and polymethylhydridosiloxane (PMHS) as the stoichiometric hydride source, are summarized in Table 1.



Scheme 1. Carbene precursors **1a–f** and bisphosphine **2**. Dip: 2,6-diisopropylphenyl; Cy: cyclohexyl; Mes: 2,4,6-trimethylphenyl.

When CuCl was used in the absence of a stabilizing ligand, the S_N2'-reduction product **4a** was heavily contaminated with impurities which prevented the determination of the diastereoselectivity (entry 1, Table 1). The presence of NHC ligands led to a much cleaner reaction, and both the conversion of the substrate and the chirality transfer were found to strongly depend on the ligand and the copper salt. After 15 h at room temperature, the highest yields of **4a** were observed with ligand precursors **1c**, **1d**, and **1f** (entries 4, 5, and 10, Table 1), whereas precursors **1a**, **1b**, and **1e** gave inferior results

Table 1: Copper-catalyzed S_N2' reduction of propargyl oxirane **3a**.[a]



Entry	Cu salt	Additive	Yield [%] (**4a**/**3a**)	d.r. (**4a**)
1	CuCl	–	56[b]/0	–
2	CuCl	**1a**	12/36	95:5
3	CuCl	**1b**	41/25	70:30
4	CuCl	**1c**	70/20	90:10
5	CuCl	**1d**	70/20	88:12
6	$CuCl_2$	**1d**	60/37	86:14
7	CuF_2	**1d**	51/36	86:14
8	$Cu(OAc)_2 \cdot H_2O$	**1d**	63/36	86:14
9	CuCl	**1e**	12/80	70:30
10	CuCl	**1f**	75/3	93:7
11	$Cu(OAc)_2 \cdot H_2O$	**2**	70/0	60:40

[a] Bn = benzyl. [b] Contained uncharacterized impurities.

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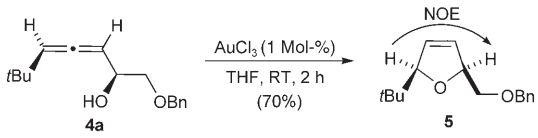
[**] Financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie (to N.K.), and the National Science Foundation (CHE-0550232, to B.H.L.) is gratefully acknowledged. We thank Prof. Dr. F. Glorius (University of Marburg) for providing a sample of carbene precursor **1f**, and Dr. A. Hoffmann-Röder (University of Mainz) for fruitful discussions.

(entries 2, 3, and 9, Table 1). When different copper salts were tested with carbene precursor **1d**, the highest yield of **4a** was found for CuCl (entry 5, Table 1), and lower yields were obtained with $CuCl_2$, CuF_2, and $Cu(OAc)_2{\cdot}H_2O$ (entries 6–8, Table 1). The best diastereoselectivity was observed with the IBiox ligand introduced by Glorius et al.[13] (entry 10, Table 1). In contrast to this, use of bisphosphine **2** gave a good yield of 70% but dismal diastereoselectivity (entry 11, Table 1). Besides PMHS, also $(Me_2HSi)_2O$, Et_3SiH, and $(EtO)_3SiH$ were used as the hydride source, but the latter three silanes afforded diminished reactivities and stereoselectivities.[15]

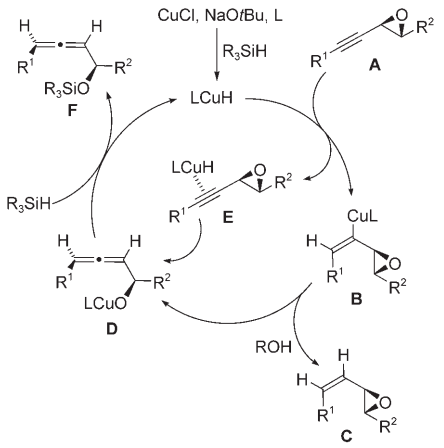
The relative configuration of the major diastereomer of α-hydroxyallene **4a** was determined by gold-catalyzed cycloisomerization to give the 2,5-dihydrofuran **5**, which is known to occur with complete chirality transfer (Scheme 2).[2a,b] NOE experiments revealed a *cis* configuration for **5** and hence a relative configuration for **4a** that is the result of an *anti*-selective S_N2' reduction. The same sense of chirality transfer is usually observed for copper-mediated S_N2'-substitution reactions of propargylic electrophiles with carbon nucleophiles.[16]



Scheme 2. Determination of the relative configuration of **4a**.

Encouraged by these results, we decreased the catalyst loading to 3 mol% and applied these conditions to a variety of functionalized propargyl oxiranes formed by addition of epoxy acetylides to aldehydes and ketones[17] (Table 2). We were delighted to observe a noteworthy functional-group tolerance towards ethers (entries 1, 2, 5, 6, 8, and 12, Table 2), esters (entry 3, Table 2), enynes (entry 12, Table 2), cyclopropanes (entry 10, Table 2), and CF_3 groups (entry 11, Table 2), as well as electron-rich (entries 6 and 8, Table 2) and electron-deficient aromatic rings (entries 5 and 7, Table 2). Furthermore, the presence of primary (entry 4, Table 2), secondary (entries 5–8, Table 2), or tertiary hydroxy groups (entries 9–12, Table 2) also allows complete and chemoselective S_N2' reduction of the propargyl oxirane without noticeable hydrolysis of the silane or the copper hydride species. Rather, the alcohol functionality strongly accelerates the reaction such that full conversion is observed after 30–60 min at 0°C (entries 4–12, Table 2) instead of 15 h (entries 1–3, Table 2). Interestingly, a similar effect is observed upon addition of *tert*-butyl alcohol to the reaction mixture. In the presence of 1.2 equivalents of this alcohol, substrate **3a** afforded hydroxallene **4a** in a yield of 58% after just 1 h at 0°C; however, this is accompanied by 30% of the *cis* vinyl oxirane formed by reduction of the triple bond of **3a**. Small amounts of this side product were also observed with other substrates (entries 4, 10, and 11, Table 2) but not for the highly unsaturated propargyl oxirane used in entry 12.

Formation of vinyl oxirane **C** in the presence of an alcohol can be rationalized by a hydrocupration–protodemetalation sequence involving *syn* addition of the copper hydride to the triple bond of substrate **A** to afford the vinylcopper intermediate **B**[18] (Scheme 3). A β elimination of intermediate **B** might afford the α-alkoxyallene **D**, which is converted into silyl ether **F** and the catalytically active copper hydride LCuH by reaction with the stoichiometric hydride source PHMS. Fluoride-mediated hydrolytic workup of **F** then furnishes the α-hydroxyallene.



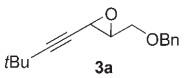
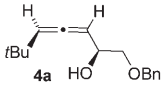
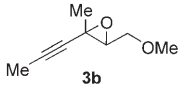
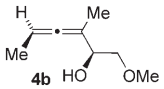
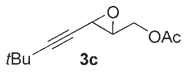
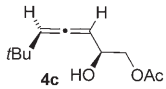
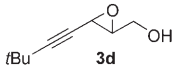
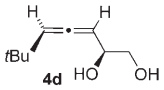
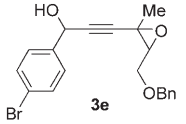
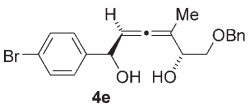
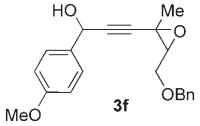
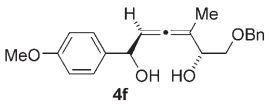
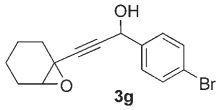
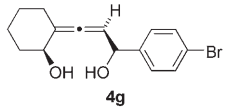
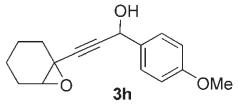
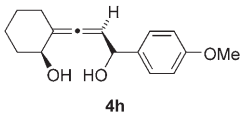
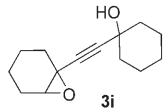
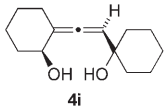
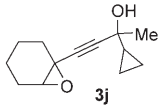
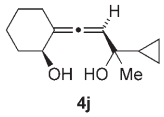
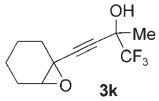
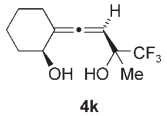
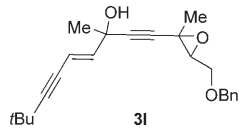
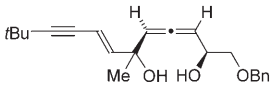
Scheme 3. Mechanistic model for the copper-catalyzed S_N2' reduction of propargyl oxiranes.

Although a similar *syn*- or *anti*-selective addition–elimination pathway has previously been suggested by Alexakis et al.[16] for the S_N2' substitution of propargyl oxiranes with carbon nucleophiles, it seems difficult to explain the high *anti* stereoselectivity observed experimentally with this mechanistic model. An alternative is the formation of the π complex **E** which might be in equilibrium with a σ copper(III) species that, upon reductive elimination, would give the allene **D** with the observed *anti* stereoselectivity. This pathway is very similar to that generally accepted for the copper-mediated S_N2' substitution of allylic electrophiles.[19] The diminished diastereoselectivity observed in some cases may be a result of competition between the two putative routes to intermediate **D**.

The functionalized α-hydroxyallenes formed by copper-catalyzed S_N2' reduction of propargyl oxiranes are highly valuable synthetic intermediates, and many substitution patterns accessible by our method have no precedent. To give an example for the utility of these products, we have treated the α,α′-dihydroxyallene **4h** (1:1 mixture of diastereomers with regard to the benzylic center) with catalytic amounts of gold(III) chloride and pyridine (Scheme 4).[2a,b] Much to our delight, an unprecedented regioselective cycloisomerization to give the spiro compound **6** took place; in other words, of the two secondary hydroxy groups, the one in the benzylic position participated in cyclization.

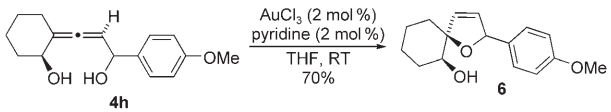
In summary, we have established an unprecedented, mild, and efficient copper-catalyzed diastereoselective S_N2' reduction of propargyl oxiranes which provides, by means of hydrosilylation, a highly selective route to α-hydroxyallenes bearing various functional groups (ethers, esters, alcohols,

Table 2: Copper-catalyzed S_N2' reduction of propargyl oxiranes **3** to give α-hydroxyallenes **4**.[a]

Entry	3	4[b]	1	t [h]	T [°C]	Yield [%]	d.r.[c]
1[b]	 **3a**	 **4a**	**1f**	15	0→20	76	93:7
2	 **3b**	 **4b**	**1f**	15	0→20	65	>95:5
3	 **3c**	 **4c**	**1d**	15	0→20	61	>95:5
4	 **3d**	 **4d**	**1d**	0.5	0	86	>95:5
5	 **3e**	 **4e**	**1f**	1	0	61	85:15
6	 **3f**	 **4f**	**1d**	1	0	73	>95:5
7	 **3g**	 **4g**	**1f**	1	0	73	>95:5
8	 **3h**	 **4h**	**1d**	0.5	0	64	>95:5
9	 **3i**	 **4i**	**1f**	1	0	60	>95:5
10	 **3j**	 **4j**	**1d**	1	0	74	86:14
11	 **3k**	 **4k**	**1d**	0.5	0	50	>95:5
12	 **3l**	 **4l**	**1d**	1	0	70	>95:5

[a] Conditions: CuCl (3 mol%), **1** (3 mol%), NaO*t*Bu (0.1 equiv), PHMS (2 equiv), toluene; workup with nBu$_4$NF·3 H$_2$O (2 equiv). [b] The relative configuration was assigned on the basis of the conversion of **4a** to **5** (Scheme 2). [c] Refers to the relative configuration of the hydroxyallene generated in the reduction.

etc.). Further work will be devoted to the application of the method in target-oriented synthesis, as well as to mechanistic studies and the fine-tuning of the stereoselectivity by using chiral carbenes or phosphines.



4h **6**

Scheme 4. Gold-catalyzed cycloisomerization of α,α′-dihydroxyallene **4h**.

Experimental Section

In a Schlenk flask, CuCl (4 mg, 0.039 mmol), NaO*t*Bu (11 mg, 0.12 mmol), and **1d** (13 mg, 0.039 mmol) were suspended under argon in dry, degassed toluene (2 mL). The mixture was heated to

100 °C for 2 min (or to 40 °C for 1 h) and then allowed to cool to room temperature over 1 h. PHMS (0.21 mL, 3.26 mmol) was added, and the mixture was stirred for 5 min at room temperature and then cooled to 0 °C. After addition of *trans*-2,3-epoxy-6,6-dimethylhept-5-yn-1-ol (250 mg, 1.63 mmol), the mixture was stirred at 0 °C for 30 min (complete consumption of the substrate determined by tlc). It was then poured into a cold (0 °C) solution of nBu$_4$NF·3 H$_2$O (1.03 g, 3.26 mmol) in THF (caution: foaming!), and the stirred mixture was warmed up to room temperature over 2 h. After addition of aqueous NH_4Cl solution and extraction with Et_2O, the combined organic layers were filtered through a short column of silica gel, charcoal, and Celite. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (SiO_2, cyclohexane/ethyl acetate, 4:1 to 2:1); yield: 215 mg (86 %) of 6,6-dimethylhepta-3,4-diene-1,2-diol as a pale yellow oil.

Received: September 12, 2006
Published online: January 15, 2007

Keywords: allenes · carbenes · chirality transfer · copper · reduction

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