

New Applications for Copper-Hydride: Reductive Synthesis of Functionalized Allenes[†]

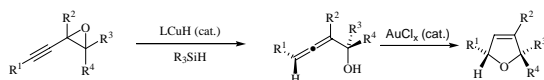


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Introduction

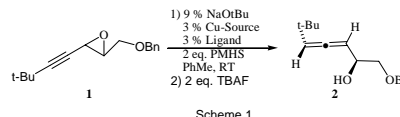
During the last decade the general point of view towards allenes changed from chemical curiosities to powerful intermediates in the target oriented synthesis¹. Especially α -hydroxyallenes came into the focus because they can not only be cyclized under axis-to-center chirality transfer into 2,5-dihydrofuranes², a motif that can be found in an abundance of natural products, but also converted under Mitsunobu-conditions into α -amino- and α -thioallenes and their derivatives³.

An elegant access to the required α -hydroxyallenes relies upon the S_N2' -ring opening reaction of propargylic epoxides with organometallic compounds, and in particular with organocuprates.



Although even functionalized Grignard-reagents which are transmetalated into the desired Gilman-cuprates can be used in the construction of complex α -hydroxyallenes⁴ the corresponding Cu(I)-mediated or catalyzed delivery of hydride had remained undeveloped.

Based on a work of Stryker⁵ we have established an unprecedented, mild and efficient copper-catalyzed diastereoselective S_N2' -reduction of propargyl oxiranes which provides, via hydrosilylation, a highly selective route to α -hydroxyallenes bearing various functional groups (ethers, esters, alcohols, etc.).



Scheme 1

Results

Since the early works of Stryker copper-hydride chemistry usually used for 1,2- and 1,4-reductions⁶ has evolved and besides bidentate phosphines N-heterocyclic carbenes (NHC)⁷ are frequently used for stabilizing the *in-situ* prepared CuH-species. These catalytic systems show usually a much higher reactivity than the so called Stryker's reagent itself.

During optimization studies (scheme 1) towards application in the S_N2' -substitution, best result were obtained by using the most frequently used combination of NaOtBu and CuCl generating *in situ* CuO/Bu which is converted into the reactive CuH-species. As stabilizing ligands, the NHC precursors, the so called IBiox system L1 developed by Glorius and co-workers⁹ and the imidazolium salt SiMes L2 which are both easily available in multi-gram scale^{8,9} yielded the α -hydroxyallenes in good yields under excellent center-to-axis chirality transfer while other precursors showed lower diastereoselectivities or yield.

In all cases PMHS was used for generating the active copper-catalyst. If other silanes like TMDS or (EtO)₃SiH are used, no complete conversion or lower selectivities are detected.

Encouraged by this we synthesized next a variety of functionalized propargylic oxiranes by epoxy acetylid addition to several ketones leading to a variety of oxiranes bearing different functionalities like enynes, ether or acetate-groups (Table 2)¹⁰.

We were delighted to observe a tremendous functional group tolerance towards ethers (entries 6,7), esters (entry 1), enynes (entry 7), cyclopropanes (entries 4,5), CF₃ groups (entries 6). Furthermore, the presence of primary (entry 2) or tertiary hydroxy groups (entries 3-7) also allows a complete and chemoselective S_N2' -reduction of the propargyl oxirane without noticeable hydrolysis of the silane or the copper hydride species.

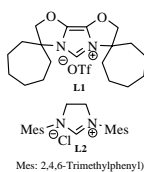


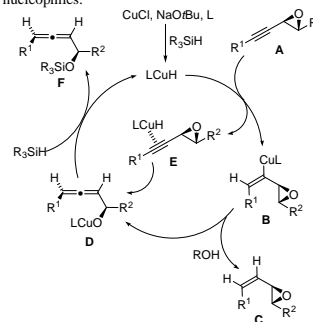
Table 1: copper-catalyzed S_N2' -reduction

| No | oxirane | allenol | L | t (h) | T(°C) | Yield (%) | ds |
|----|---------|---------|----|-------|--------|-----------|---------|
| 1 | | | L2 | 15 | 0...20 | 61 | >95 : 5 |
| 2 | | | L1 | 0.5 | 0 | 86 | >95 : 5 |
| 3 | | | L1 | 1 | 0 | 60 | >95 : 5 |
| 4 | | | L1 | 1 | 0 | 77 | >95 : 5 |
| 5 | | | L2 | 1 | 0 | 74 | 86:14 |
| 6 | | | L1 | 1 | 0 | 69 | >95 : 5 |
| 7 | | | L1 | 1 | 0 | 70 | >95 : 5 |

Reaction conditions: CuCl (3 mol%), L (3 mol%), NaOtBu (10 mol%), PMHS (2 Eq.), toluene; workup with *n*Bu₄F · 3H₂O (2 Eq.)

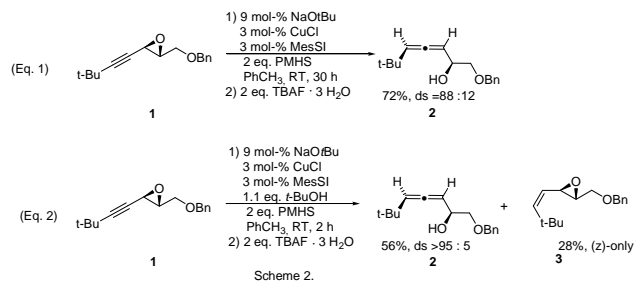
Although this method usually provides the desired α -hydroxyallenes under complete center to axis chirality transfer, the lowered selectivity in some cases (entry 5) can be explained by two competing mechanisms. The *in situ* prepared NHC-stabilized-copper-hydride species can form the σ -complex E which might be in equilibrium with a copper(III) species that, upon reductive elimination, would give the allene D with the experimentally observed *anti*-stereoselectivity. Transmetalation with the silane lead to the silyl ether F and the catalytically active copper hydride LCuH. Fluoride-mediated hydrolytic work up of F then furnished the α -hydroxyallene.

The other pathway would follow a hydrocupration-protodemetalation sequence involving *syn*-addition of the copper hydride to the triple bond of substrate A to afford vinylcopper intermediate B^[11]. A β -elimination of intermediate B might afford the α -alkoxyallenes D similar to a mechanistic model previously suggested by Alexakis *et al.*^[11] for the copper mediated S_N2' -substitution with carbon nucleophiles.



Indirect proof for the diminished selectivities following the hydrometalation-protodemetalation pathway was found by adding *tert*-Butanol to the reaction mixture (scheme 2).

While the aprotic reaction conditions furnished the desired allenol 2 in good yields and moderate selectivities, addition of the alcohol not only increased the selectivity but also lead to a byproduct, the (*z*)-vinylloxirane 3 obviously the result of a hydrocupration^[5].



Further work will be devoted to the application in natural product synthesis, studies towards the reaction mechanism, as well as expanding the existing procedure to other leaving groups than epoxides.

References

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