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LETTERS

A Convenient, Efficient Method for Conjugate Reductions Using *Catalytic* Quantities of Cu(I)

Bruce H. Lipshutz,* John Keith, Patrick Papa, and Randall Vivian
Department of Chemistry
University of California, Santa Barbara, CA 93106 USA

[Fax: 805-893-8265; E-Mail: Lipshutz@chem.ucsb.edu]

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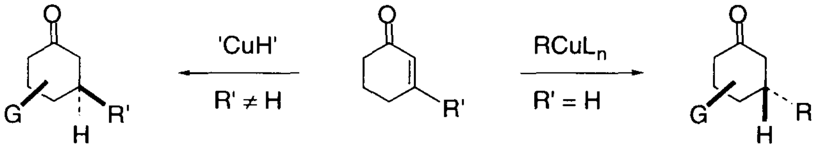
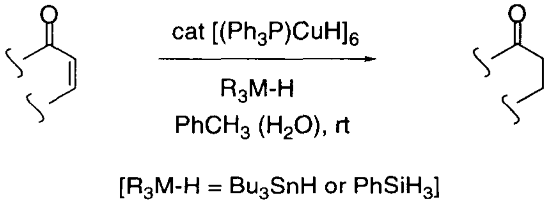
Abstract: Exposure of enones and enals to either Bu_3SnH or $PhSiH_3$ in the presence of $\leq$ 5 mol % $[(Ph_3P)CuH]_6$ leads to products of 1,4-hydride delivery in good yields.

1,4-Addition reactions to α,β-unsaturated carbonyl derivatives,[1] in particular with non-stabilized nucleophiles, remains primarily associated with organocopper chemistry.[2] Within this realm lies the unique potential for conjugate hydride delivery, which not only adds flexibility for arriving at a given target, but also provides an attractive entry to products of inverted stereochemistry (Scheme 1).



[**Scheme 1**]

In recognition of this important capability, several procedures have been developed over the past two decades,[3] although Stryker's reagent $[(Ph_3P)CuH]_6$ is perhaps the most widely used.[4] Unfortunately, as is characteristic of virtually all existing procedures,[5] this source of hydride is most effective as a stoichiometric reductant. It can be used catalytically; however, a hydrogen atmosphere at pressures around 1000 PSI is required.[6a] Under one atmosphere of hydrogen using *t*-butanol as co-solvent, over-reduction may still occur thus requiring careful monitoring.[6b] We now describe modified procedures that allow for this readily available copper species to be employed in 1,4-reductions with quantities as low as 0.5 mole percent.



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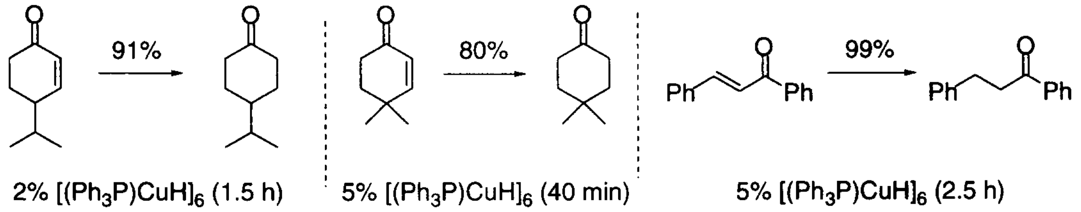
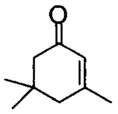
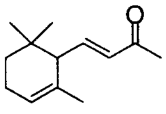
Initially, it was determined that the combination of 2-5 mol % $[(Ph_3P)CuH]_6$,[7] along with 1.1.-1.2 equivalents of Bu_3SnH, is sufficient to reduce conjugated ketones in good yields. Toluene containing small percentages of water[4] (5 equivalents relative to substrate) is an effective medium and products are realized in less than 3 h at reaction concentrations between 0.15 and 0.30 M. Three representative results are illustrated below.

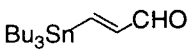


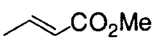
A more environmentally friendly method was envisioned where Bu_3SnH is replaced by an appropriate silyl hydride. $PhSiH_3$ was selected for study based on its tendency to donate hydride,[8] as well as the likelihood that it would not afford stable silyl enol ethers upon transmetalation with an initially formed copper enolate.[9] Treatment of an enone or enal with 5 mol % $[(Ph_3P)CuH]_6$[7] in the presence of this hydride source (1.5 equiv) in toluene (0.15-0.60 M) at room temperature affords products of 1,4-reduction in excellent yields. Table 1 offers a broad selection of substrates attesting to the issues of scope and generality. Particularly noteworthy is the finding that with increased levels of educt concentration, catalyst levels as low as 0.5 mol % are acceptable (entry 1). Other salient points to be made concerning the examples in Table 1 include: (1) only one isomer was observed in the case of entry 4, assumed to be the *cis*-3,5-dimethyl derivative; (2) while β-ionone reacts over time to regiospecifically afford the 1,4-adduct, α-ionone is unresponsive; (3) competing 1,2-addition of hydride under these conditions is not significant, most notably where enals are involved (*e.g.*, entry 10);[10] (4) by-products resulting from 1,4-reduction-aldol addition are not observed, suggesting transient enolate protection as intermediate silyl enol ethers.

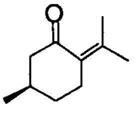
Of the substrates studied, those (shown below) which were found not to be amenable to this process include hindered (β,β-disubstituted) enones, β-alkyl-substituted enoates (although β-aryl enoates react well; *cf.* entry 9), and a β-stannylated enal. Also, no (substitution) reaction was observed with a β-triflyloxy-substituted enoate.

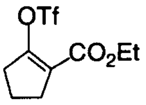








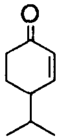
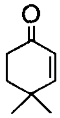
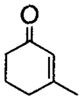
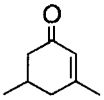
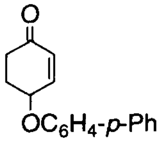
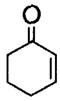
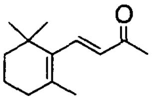
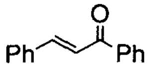
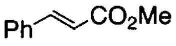
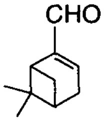
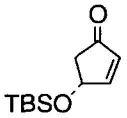




In summary, two methods[11,12] are disclosed which demonstrate the effectiveness of Cu(I) as a catalyst for effecting 1,4-hydride delivery. Both rely on commercially available hexameric $(Ph_3P)CuH$ as the source of copper, while either Bu_3SnH or $PhSiH_3$ provide the required hydride in stoichiometric amounts.[13] These reactions are especially convenient, being run at ambient temperatures and in common solvents. Further work on the development of other practical transition metal-catalyzed processes will be reported in due course.

Acknowledgement. Financial support of our programs provided by the NSF is warmly acknowledged with thanks.

Table 1. Copper-catalyzed 1,4-reductions using $[(Ph_3P)CuH]_6 + PhSiH_3$

Entry	Substrate	Cu (mole %)	Concentration (M)	Time	Yield (%)[a,b]
1		0.5	1.0	6 h	99
2		5	0.3	8 min	85
3		5	0.6	18 h	quant[c]
4		5	0.6	46 h	quant[c,d]
5		5	0.15	6 h[e]	97
6		5	0.3	7 min	quant[c]
7		5	0.3	47 h	96
8		5	0.3	10 min	96
9		5	0.3	20 min	95
10		5	0.3	5 h	80
11		5	0.3	10 min	70[f]

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[a] Of reduced carbonyl derivative. [b] Isolated, unless stated otherwise. [c] By quantitative gc. [d] One isomer. [e] Artificially long; product is difficult to follow by TLC. [f] Product is sensitive to chromatography; quant by gc.

References and Notes

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press, Tarrytown, N.Y., 1992.
2. Lipshutz, B.H.; Sengupta, S. *Org. React. (N.Y.)*, **1992**, *41*, 135.
3. For representative examples, see (a) Lipshutz, B.H.; Ung, C.; Sengupta, S. *Synlett*, **1989**, 64; (b) Semmelhack, M.F.; Stauffer, R.D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180; (c) Ashby, E.C.; Lin, J.J.; Goel, A.B. *ibid.* **1978**, *43*, 183; (d) Whitesides, G.M.; Filippo, J.S.; Stredronsky, E.R.; Casey, C.P. *J. Am. Chem. Soc.* **1969**, *91*, 6542; (e) Boeckman, R.K.; Michalak, R. *ibid.* **1974**, *96*, 1623.
4. Mahoney, W.S.; Brestensky, D.M.; Stryker, J.M. *J. Am. Chem. Soc.* **1988**, *110*, 291.
5. (a) A recent report by Hosomi[5b] suggests that CuH, generated from CuCl and $PhMe_2SiH$, can be used catalytically. However, all examples given, as recommended in the text, involve stoichiometric amounts of Cu(I); (b) Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 8887; (c) In the procedure sited above, DMI (N,N-dimethylimidazolidinone) is the recommended solvent.
6. (a) Mahoney, W.S.; Stryker, J.M. *J. Am. Chem. Soc.* **1989**, *111*, 8818; (b) Stryker, J.M.; Mahoney, W.S.; Daeuble, J.F.; Brestensky, D.M. In *Catalysis in Organic Synthesis*, Pascoe, W.E., Ed.; Marcel Dekker; New York, 1992, pp 29-44.
7. The amount of catalyst is based on copper for 1/6 $[(Ph_3P)CuH]_6$.
8. Hays, D.S.; Fu, G.C. *J. Org. Chem.* **1997**, *62*, 7070.
9. Using $PhMe_2SiH$, stable silyl enol ethers are the initial products as determined by GCMS. This could be used to advantage, *e.g.*, as in 3-component coupling reactions; Lipshutz and Keith, ongoing work.
10. This chemospecificity was anticipated based on earlier work by Stryker: Brestensky, D.M.; Stryker, J.M. *Tetrahedron Lett.* **1989**, *30*, 5677.
11. *General procedure for catalytic reductions using Bu_3SnH:* $[(Ph_3P)CuH]_6$ (2-5 mol %) is weighed into a round bottomed flask under an inert atmosphere. The copper complex is then dissolved in toluene so that the concentration will be 0.15-0.3 M relative to the substrate. The resulting red solution is then treated with 1.1-1.2 equivalents of Bu_3SnH, followed by 5 equivalents of water, and lastly the enone. The reaction is monitored by TLC, and when complete, is diluted with diethyl ether and washed with 10% KF (x 2), sat $NaHCO_3$ (x 1), and brine (x 2). Drying over anhydrous $MgSO_4$, vacuum filtration, and evaporation to dryness gives the crude product which is purified by Kugelrohr distillation or column chromatography on silica gel.
12. *General procedure for catalytic reductions using $PhSiH_3$:* $[(Ph_3P)CuH]_6$ (0.5-5.0 mol %) is weighed into a round bottomed flask under an inert atmosphere. The copper complex is then dissolved in toluene so as to give a concentration of between 0.15-1.0 M relative to substrate. Once the catalyst is in solution, the mixture is then treated with 1.5 equivalents of phenylsilane, followed by addition of the enone. The reaction is monitored by TLC. When complete, it is worked up by first diluting it with diethyl ether, and then washing with sat NH_4Cl (x 2), sat. $NaHCO_3$ (x 2), and brine (x 2). Drying over anhydrous $MgSO_4$, filtering, and evaporation to dryness gives the crude product which is purified by Kugelrohr distillation or column chromatography on silica gel.
13. The lifetime for the catalytic $[(PPh_3)CuH]_6$ / Bu_3SnH system under these conditions is only about 3 h, while that for the catalytic $[(PPh_3)CuH]_6$ / $PhSiH_3$ combination is on the order of several days.