REGIOSELECTIVE CONJUGATE REDUCTION AND REDUCTIVE SILYLATION OF α,β-UNSATURATED ALDEHYDES USING [(Ph3P)CuH]6

Donna M. Brestensky and Jeffrey M. Stryker*[1]

Department of Chemistry
Indiana University
Bloomington, Indiana 47405

Summary: Regioselective conjugate reduction and reductive silylation of α, β-unsaturated aldehydes using the stable copper(I) hydride cluster, [(Ph3P)CuH]6, is reported. The reaction is general for a range of aldehyde substitution patterns, providing the saturated aldehyde, intermediate silyl enol ether, or completely reduced alcohol in high yield, depending on reaction conditions.
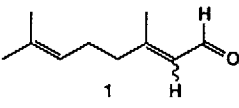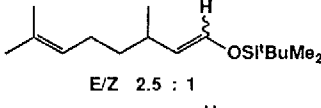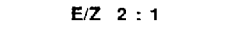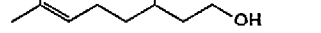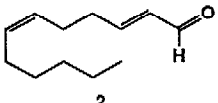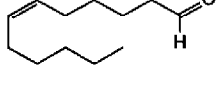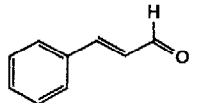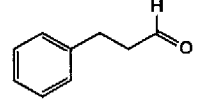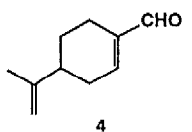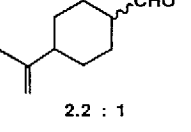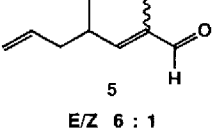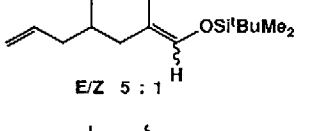
We recently reported that the well-characterized, thermally stable copper(I) hydride complex,

[(Ph3P)CuH]6[2], provides convenient and general methodology for the regioselective conjugate reduction of α,β-unsaturated carbonyl compounds.[3] This reaction proceeds at room temperature under inert atmosphere in either benzene or tetrahydrofuran solvent and is typically conducted in the presence of water or trimethylsilyl chloride, giving the saturated carbonyl or silyl enol ether, respectively, in high yield. The conjugate reduction is highly stereoselective and shows exceptional chemoselectivity, particularly with respect to reduction of simple carbonyl functionality. Most unusually, this hydride reduction is rendered catalytic in hydride when conducted under hydrogen pressure, although isolated double bonds are completely inert.[4]

The exceptional reluctance of this reagent to effect direct 1,2-reduction of unsaturated carbonyl functionality suggested that it might also provide regioselective conjugate reduction of α, β-unsaturated aldehydes, a significantly more demanding problem. While reduction of such double bonds can be accomplished selectively under catalytic hydrogenation conditions,[5] complementary methodology resistant to reaction with isolated alkenes is synthetically attractive, and a few methods of varying generality and convenience have been developed.[6]

Here we report that conjugate reduction of α,β-unsaturated aldehydes using [(Ph3P)CuH]6 proceeds with excellent regioselectivity, and offer general procedures for conjugate reduction, reductive silylation, and for some substrates, one-pot reduction to the saturated alcohol. Initial investigation focused on reduction of citral (1), a β,β-disubstituted ald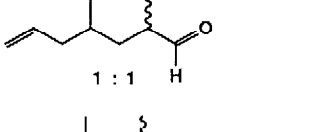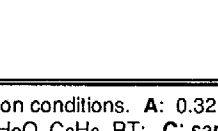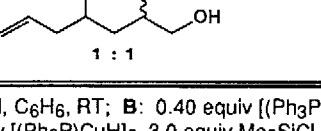ehyde considered to be a relatively rigorous test case. Treatment of citral in wet[7] deoxygenated benzene with approximately 0.2 equiv [(Ph3P)CuH]6[8] at room temperature gave the desired aldehyde accompanied by a small amount of fully reduced alcohol and a trace of the allylic alcohol from direct 1,2-addition of the hydride. While the regioselectivity of this reaction was readily apparent, some reduction of the initially formed aldehyde occurred competitively with conjugate reduction, even under hydride deficient conditions.[9,10]

A general solution to the problem of overreduction is found in the use of chlorotrialkylsilanes in place of water to trap the intermediate enolate (Table 1).[11] Typically, chlorotrimethylsilane is used, and the resultant

Table 1. Conjugate Reduction of α,β-Unsaturated Aldehydes Using $[(Ph_3P)CuH]_6$

Entry	Substrate	Reduction Conditions[a]	Time (h)	Hydrolysis Conditions[b]	Product[c]	Yield (%)[d]
1	1 E/Z 2 : 1	A	1.5	-	E/Z 2.5 : 1	78
2		A	1.5	F		83
3		B	32	-		74
4		C	24	-		90
5	2	D	<0.1	G		93
6	3	D	<0.25	H		81
7	4	E	3.5	F	2.2 : 1	77
8	5 E/Z 6 : 1	A	1.0	-	E/Z 5 : 1	93
9		D	1.0	F	1 : 1	75
10		B	36	-	1 : 1	81

[a] Reduction conditions. **A:** 0.32 equiv $[(Ph_3P)CuH]_6$, 2.5 equiv $^tBuMe_2SiCl$, C_6H_6, RT; **B:** 0.40 equiv $[(Ph_3P)CuH]_6$, 20 equiv H_2O, C_6H_6, RT; **C:** same as B, except THF solvent; **D:** 0.40 equiv $[(Ph_3P)CuH]_6$, 3.0 equiv Me_3SiCl, C_6H_6, RT; **E:** 0.50 equiv $[(Ph_3P)CuH]_6$, 3.5 equiv Me_3SiCl, C_6H_6, RT. [b] Hydrolysis conditions. **F:** $(^nBu)_4N^+F^-$, excess pH 7 phosphate buffer, THF, RT; **G:** 10% HCl, THF, RT; **H:** 5% AcOH in 7 : 1 THF/H_2O. [c] Stereochemical ratios by ^{1}H and ^{13}C NMR analysis, see supplementary material. [d] Yields refer to isolated products, after purification by chromatography.

sensitive silyl enol ether is hydrolyzed to the free aldehyde without purification. The use of sterically bulky silylating agents, however, allows the aldehyde silyl enol ether to be isolated and purified if desired (Entries 1,8). Under conditions of added chlorotrialkylsilane, no direct 1,2-reduction products can be detected, and unsaturated aldehydes with a variety of substitution patterns are reduced cleanly and in nearly quantitative yield to the silyl enol ether. Depending on the substrate, 0.33 to 0.50 equiv of the hydride hexamer (2-3 hydride equivs) is required for complete conversion of starting material.[12] Approximately one equivalent of the chlorosilane per hydride equiv is typically employed; under these conditions, any excess hydride eventually reacts with the chlorosilane, giving copper-containing material (presumably [(Ph$_3$P)CuCl]$_4$) which precipitates from the reaction mixture on addition of hexane, greatly simplifying reaction workup.[13]

Loss of material in the overall transformation to aldehyde can be attributed principally to difficulties encountered in the hydrolysis reaction for some substrates. As indicated in Table 1, conditions required for clean enol ether hydrolysis were strongly substrate dependent. While aldol side reactions were problematic for some acid or base sensitive substrates, oxidative degradations were also observed, particularly during the hydrolysis of the silyl enol ether from reduction of perillaldehyde 4.[14] In this case, highly variable yields of 4-isopropenyl-cyclohexanone were obtained from hydrolyses conducted in the presence of air. Thorough exclusion of oxygen largely suppressed this decomposition pathway. Hydrolysis conditions reported in Table 1 gave reasonably clean conversions, although rigorous optimization has not been undertaken. In this regard, among the substrates tested, hydrolyses of the silyl enol ethers derived from cinnamaldehyde (3, Entry 6) and 2,4-dimethyl-2,6-heptadienal (5, Entry 9) were most sensitive to reaction conditions.

For substrates not prone to complicating base-catalyzed side reactions, complete 1,4- plus 1,2-reduction can be realized on addition of excess hydride in the presence of water (Entries 3,10). Although benzene has been the solvent most used for conjugate reductions, the aldehyde reduction proceeds somewhat faster in THF (Entry 4).[15] It should be emphasized that not all unsaturated aldehydes undergo clean reaction under aqueous conditions; 2,6-dodecadienal (2, Entry 5), for example, gave completely intractable material under such conditions, although the reductive silylation and subsequent hydrolysis were straightforward.

Further investigations are in progress to probe the limits of the unusually high regioselectivity exhibited by [(Ph$_3$P)CuH]$_6$ in conjugate reduction reactions. Additionally, because the copper hydride hexamer is inert toward other carbonyl functionality,[3] direct reduction of saturated aldehydes using [(Ph$_3$P)CuH]$_6$ may find further application in complex organic systems demanding high chemoselectivity.[16]

Footnotes and References

1. Du Pont Young Faculty Awardee, 1988-1989. Union Carbide Innovation Recognition Program Awardee, 1989.

2. (a) Churchill, M.R.; Bezman, S.A.; Osborn, J.A.; Wormald, J. *Inorg. Chem.* **1972**, 11 1818. (b) Goeden, G.V.; Caulton, K.G. *J. Am. Chem. Soc.* **1981**, 103, 7354. (c) One-pot preparation: Brestensky, D.M.; Huseland, D.E.; McGettigan, C.; Stryker, J.M. *Tetrahedron Lett.* **1988**, 29, 3749.

3. Mahoney, W.S.; Brestensky, D.M.; Stryker, J.M. *J. Am. Chem. Soc.* **1988**, 110, 291.

4. Mahoney, W.S.; Stryker, J.M. *J. Am. Chem. Soc.*, in press.

5. (a) Pd^0: Hennis H.E.; Trapp, W.B. *J. Org. Chem.* **1961** 26, 4678. (b) $(Ph_3P)_3RhCl$: Jardine, F.H.; Wilkinson, G. *J. Chem. Soc. (C)* **1967**, 270. (c) $PdCl_2/NaBH_4$: Russell, T.W.; Duncan, D.M.; Hansen, S.C. *J. Org. Chem.* **1977**, 42, 551. (d) Cortese, N.A.; Heck, R.F. *J. Org. Chem.* **1978**, 43, 3985.

6. (a) R_2SiH_2, cat. Pd^0, $ZnCl_2 \cdot H_2O$: Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, 108, 7314. (b) R_3SnH, cat. L_nPd^0: Keinan, E.; Gleize, P.A. *Tetrahedron Lett.* **1982**, 23, 477. (c) DIBAH/HMPA/MeCu: Tsuda, T.; Satomi, H.; Hayashi, T.; Saegusa, T. *J. Org. Chem.* **1987**, 52, 439. (d) NaHTe: Ramasamy, K.; Kalyanasundaram, S.K.; Shanmugan, P. *Synthesis* **1978**, 545. Yamashita, M.; Kato, Y.; Suemitsu, R. *Chem. Lett.* **1980**, 847. (e) $NaHFe_2(CO)_8$: Collman, J.P.; Finke, R.G.; Matlock, P.L.; Wahren, R.; Komoto, R.G.; Brauman, J.I. *J. Am. Chem. Soc.* **1978**, 100, 1119, and references therein. (f) $K_3[Co(CN)_5H]$: Reger, D.L.; Habib, M.M.; Fauth, D.J. *J. Org. Chem.* **1980**, 45, 3860, and references therein.

7. Water (2 - 20 equiv) is added to provide rapid quenching of the highly reactive intermediate copper enolate, helping to suppress complicating aldol side reactions (see ref. 2). Typically, the benzene solution is saturated with deoxygenated water. In the reductive silylation procedure, the water is omitted.

8. As observed in the conjugate reduction of other α,β-unsaturated carbonyl compounds, complete consumption of starting material requires substoichiometric amounts of the hydride hexamer.

9. $[(Ph_3P)CuH]_6$ is known to reduce formaldehyde, catalyzing the Tishchenko reaction: see ref. 2b.

10. Reduction of benzaldehyde with $[(Ph_3P)CuH]_6$ is complete within 4 h, yielding benzyl alcohol in ca. 75-80% isolated yield.

11. All previously unknown products gave satisfactory ^1H NMR, ^{13}C NMR, IR, and HRMS analysis.

12. $[(Ph_3P)CuH]_6$ reacts slowly with Me_3SiCl in the absence of substrate, although the products of this reaction have not as yet been characterized fully. The silyl chloride appears to be somewhat more reactive toward other hydride-containing fragments which must be present during the course of the reduction reaction (see ref. 3). Because of this, excess hydride is required.

13. General experimental procedure, illustrated for **2** (Entry 5): Dodecadienal (0.203 g, 1.12 mmol), chlorotrimethylsilane (0.366 g, 3.37 mmol), and dry, deoxygenated benzene (2 mL) were combined in a 50 mL flask under nitrogen and stirred for 5 min. A solution of $[(Ph_3P)CuH]_6$ (0.804 g, 0.41 mmol, weighed quickly in air and placed under inert atmosphere) in dry, deoxygenated benzene (8 mL) was added via cannula and the reaction mixture stirred at room temperature until TLC analysis indicated complete reaction (3.5 h). The resultant dark solution was exposed to air and dry hexane (30 mL) was added to precipitate the copper-containing byproducts. The light yellow supernatant was filtered through celite and the solvent removed *in vacuo* to give an approximately 1 : 1 mixture of E- and Z-silyl enol ethers. The crude silyl enol ethers were dissolved in THF (10 mL), treated with 10 drops of 10% aq. HCl, and stirred at room temperature (0.5 h). The reaction mixture was partitioned between Et$_2$O and water, and the organic phase washed with water and saturated aqueous NaCl, and dried over anhydrous MgSO$_4$. After filtration and concentration *in vacuo*, purification by flash chromatography gave the saturated aldehyde (0.191 g, 93%).

14. Similar oxidative degradations of aldehydes have been previously noted. See, Chuit, C.; Foulon, J.P.; Normant, J.F. *Tetrahedron* **1980**, 36, 2305. Chuit, C.; Foulon, J.P.; Normant, J.F. *Tetrahedron* **1981**, 37 1385. Clive, D.L.J.; Farina, V.; Beaulieu, P.L. *J. Org. Chem.* **1982**, 47, 2572.

15. Tetrahydrofuran appears to be a generally acceptable solvent for conjugate reductions using the hydride hexamer, despite its reported instability in this medium (ref. 2a). For some substrates, improved yields have been obtained in this medium.

16. Financial support for this project from the National Institutes of Health (GM 38068) is gratefully acknowledged.