SELECTIVE REDUCTION OF ALKYNES TO CIS-ALKENES BY HYDROMETALLATION USING [(Ph3P)CuH]6.

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Summary. Selective reduction of alkynes to the corresponding alkenes is reported using the stable, readily prepared copper(I) hydride reagent, [(Ph3P)CuH]6. Terminal alkynes are reduced at room temperature, unactivated internal alkynes react only at elevated temperature. Disubstituted alkynes with propargyl activation are also reduced, giving cis-olefins selectively. Protection of propargylic alcohol functionality is usually unnecessary, although fragmentation is sometimes competitive in sterically hindered cases. A tertiary propargyl acetate gave displacement to the allene exclusively.

Selective reduction of alkynes to the corresponding alkenes by hydrometallation (Eq. 1) provides

methodology complementary to catalytic hydrogenation,[1,2a] and can be realized using a variety of metal hydride

reagents, including aluminum, boron, silicon, tin, and zirconium.[2] More recently, alkyne hydrometallation using

$$R \!-\!\!\equiv\!\!-\! R' \xrightarrow{\quad L_nM-H \quad} \underset{R}{\diagup}\!\!\diagdown^{R'} \qquad Eq.\ 1$$

several *in situ* derived copper(I) hydride "ate" complexes has been reported,[3] typically giving the corresponding

cis-alkenes selectively.[4]

We have previously described the use of the thermally stable copper(I) hydride complex, [(Ph3P)CuH]6,[5] for

highly regioselective and chemoselective conjugate reductions of α,β-unsaturated carbonyl compounds.[6] In the

course of investigating the chemoselectivity of this reagent, selective reactivity toward alkynes was noted. Because

of the possibility that alkyne hydrometallation using [(Ph3P)CuH]6 might provide a vinyl copper species directly

for subsequent applications, a preliminary survey of the reactivity of this complex was undertaken. Although

many aspects of the reactivity toward alkynes appear complicated and not all of the relevant variables have as yet

been identified and controlled, we report here that [(Ph3P)CuH]6 selectively hydrometallates both terminal alkynes

and internal alkynes, leading to the formation of the corresponding *cis*-alkenes.[7] For some substrates, byproduct

formation is observed resulting from overreduction to the saturated compound or, for unprotected propargyl

alcohols, fragmentation of the starting material.

The results of this initial investigation are given in Table 1.[8] Unsubstituted terminal alkynes (Entries 1, 2)

are reduced in moderate to good yields to the corresponding alkenes in wet (5 equiv H2O) benzene at room

temperature; in one case some overreduction was detected. These reactions require 0.32 equiv of [(Ph3P)CuH]6

(2 hydride equiv) for complete consumption of starting material and the presence of water in the reaction medium

for optimal yields. Under these conditions, internal alkynes such as 4-octyne were not reactive, and

diphenylacetylene gave only trace conversion after 24 h. Both of these substrates, however, were reduced cleanly

to the *cis*-olefin in high yield at reflux (Entries 3, 4), although a full equivalent of the hydride hexamer was

required. No intermediate copper(I) vinyl species is detected, even in reactions conducted under rigorously aprotic conditions; preliminary labelling experiments using [(Ph₃P)CuD]₆ indicate that at least some of the presumed vinyl copper intermediate reacts with the copper hydride to form alkene,[9] even in the presence of water.

Terminal and internal alkynes with propargyl alcohol and ether substitution were selectively reduced by [(Ph₃P)CuH]₆, generally affording the corresponding alkene in good yield after isolation and purification (Entries 5-9). Highest yields are usually obtained at reflux in benzene in the presence of 5-10 equivs of H_2O; reactions run in THF, at room temperature, or with substantially more water present frequently did not go to completion.[10] Complete conversion typically requires approximately 0.5 equiv of the hexamer (3 hydride equiv) or more, again suggesting that a substantial percentage of the quenching "proton" may may originate from the reagent.[9] For internal alkynes, only products of *cis* stereochemistry are observed; none of the *trans* isomers are detected by high-field ¹H NMR spectroscopy. For some substrates (Entries 5, 6, and 11), overreduction to the saturated compound was observed as a byproduct; in general, overreduction was not eliminated at lower reaction temperature.

The oxygen functionality in the substrate may be protected or unprotected; however, the unprotected substrates are substantially more reactive.[11] There appears to be a complicated dependence of the reduction on both steric and electronic factors in the proximity of the triple bond; substantial variation in reaction rates and product yields and distributions are observed in structurally related substrates differing in the nature of the oxygen substitution. Unprotected tertiary propargyl substrates (Entry 10) and *some* secondary compounds (Entry 8) may undergo a competitive fragmentation reaction, leading to terminal alkyne and either a ketone or aldehyde. The terminal alkyne and aldehyde produced are subsequently reduced by remaining hydride to the corresponding alkene and alcohol, respectively. This cleavage is presumed to result from deprotonation of the starting propargyl alcohol, either by reaction with a hydridic complex[12] or quenching a vinyl copper intermediate. The resultant propargylic copper alkoxide can then undergo thermodynamically favorable fragmentation, giving the carbonyl and copper acetylide (Eq. 2),[13] which may react further. Consistent with this equilibrium, compared to the unsubstituted

Eq. 2
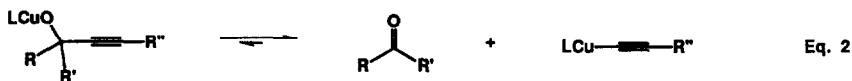
substrate 3-phenyl-1-butyn-3-ol in Entry 10, substitution of an electron-withdrawing bromine on the *para*-position of the aromatic ring resulted in significantly reduced fragmentation (anhydrous conditions: 75% reduction, 22% fragmentation) and substitution of an electron-donating methoxy group gave increased fragmentation (38% reduction, 60% fragmentation), and protection of the free alcohol as the benzyl ether suppressed the fragmentation completely (Entry 11).

Perhaps most interestingly, an acetylated tertiary propargyl alcohol (Entry 12) undergoes reductive displacement at room temperature, giving the sensitive 1,1-disubstituted allene exclusively. Under identical conditions, the acetate of 2-nonynol was unreactive.

Table 1. Hydrometallation of Alkynes Using [(Ph₃P)CuH]₆

Entry	Substrate	Reduction Conditions[a]	Time (h)	Product	Yield (%)[b]
1	Ph—≡	A	4	Ph⌒⌄	95[c]
2	≡⌒⌒OCOPh	A	4	⌒⌒⌒OCOPh	70[d]
3	C₃H₇—≡—C₃H₇	B[e]	1.5	C₃H₇⌒C₃H₇	96[c]
4	Ph—≡—Ph	B[e]	1.5	Ph⌒Ph	91
5	C₆H₁₃—≡⌒OH	B	1	C₆H₁₃⌒⌒OH	77[f]
6	Ph⌒O⌒O⌒≡	B	0.5	Ph⌒O⌒O⌒⌄	68[g]
7	Ph—≡ C(OH)C₆H₁₃	B	1	Ph⌒ C(OH)C₆H₁₃	76
8	C₆H₁₃—≡ C(OH)C₆H₁₃	B	1	H₁₃C₆⌒ C(OH)C₆H₁₃	42[h]
9	HO⌒≡⌒OEE	C	0.5	HO⌒⌒⌒OEE	84
10	C(CH₃)(OH)≡ (phenyl)	B[i]	1	C(CH₃)(OH)⌄ (phenyl)	59[j]
11	C(CH₃)(OCH₂Ph)≡ (phenyl)	B	1	C(CH₃)(OCH₂Ph)⌄ (phenyl)	64[k]
12	C(CH₃)(OAc)≡ (phenyl)	C	0.5	(isopropenyl phenyl)	81

[a] Reduction conditions; A: 0.50 equiv [(Ph₃P)CuH]₆, 5 equiv H₂O, C₆H₆ (0.75 mL/0.1 g hydride), RT; B: 0.50 equiv [(Ph₃P)CuH]₆, 5 equiv H₂O, C₆H₆, 80°C. C: 0.50 equiv [(Ph₃P)CuH]₆, C₆H₆, RT. On completion, the dark red-black solution is exposed to air and ether/pentane added with stirring (2h) to precipitate Cu-containing byproducts. Alternatively, after exposure to air, stirring over silica gel (0.25h) also precipitated the Cu byproducts. Depending on the polarity of the product, the remaining free Ph₃P can be removed directly by chromatography or after conversion to Ph₃P=O by oxidation with 5% aq. NaOCl and filtration through silica gel. [b] All yields refer to isolated products, after purification by chromatography, except as noted. [c] Yield determined by ¹H NMR integration at long pulse delay against benzyl alcohol or 3-methylanisole internal standard. [d] 7-8% saturated alcohol also isolated. [e] 1.0 equiv [(Ph₃P)CuH]₆ required. [f] 3% nonanol also isolated. [g] 13% saturated alcohol also isolated. [h] ~50% fragmentation observed. [i] Under anhydrous conditions at RT: 44% reduction, 50% fragmentation. [j] ~40% fragmentation observed. [k] 16% saturated alcohol also isolated.

Despite the complications discussed, the reduction of alkynes to *cis*-alkenes using [(Ph₃P)CuH]₆ should prove useful, particularly in multiply functionalized substrates where high chemoselectivity is required. Investigation into the scope and mechanism of this selective hydrometallation reaction is continuing, particularly with respect to the stabilization and utilization of the presumed vinyl copper intermediate and the suppression of overreduction and fragmentation.[14]

Footnotes and References

1. Review: Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*; Plenum: New York, 1984; Chapter 7.

2. Reviews: (a) Hutchins, R.O.; Hutchins, M.G.K. In *Supplement C: The Chemistry of Triple-Bonded Functional Groups*; Patai, S.; Rappoport Z., Eds.; Wiley: New York, 1983; Part 1, Chapter 14. (b) Hudrlik, P.F.; Hudrlik, A.M. In *The Chemistry of the Carbon-Carbon Triple Bond*; Patai, S., Ed.; Wiley: New York, 1978; Part 1, Chapter 7. (c) Negishi, E. *Organometallics in Organic Synthesis, Vol. 1*; Wiley: New York, 1980.

3. (a) Yoshida, T.; Negishi, E. *J. Chem. Soc. Chem. Commun.* **1974**, 762. (b) Crandall, J.K.; Collonges, F. *J.Org. Chem.* **1976**, 41, 4089. (c) Ashby, E.C.; Lin, J.J.; Goel, A.B. *J.Org. Chem.* **1978**, 43, 757. (d) Masure, D.; Coutrot, P.; Normant, J.F. *J. Organomet. Chem.* **1982**, 226, C55.

4. A closely related copper(I) species has been recently reported to reductively couple terminal alkynes to give diene products exclusively: Rao, S.A.; Periasamy, M. *J. Chem. Soc. Chem. Commun.* **1987**, 495.

5. (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) Simplified one-pot preparation: Brestensky, D.M.; Huseland, D.E.; McGettigan, C.; Stryker, J.M. *Tetrahedron Lett.* **1988**, 29, 3749.

6. (a) Mahoney, W.S.; Brestensky, D.M.; Stryker, J.M. *J. Am. Chem. Soc.* **1988**, 110, 291. (b) Brestensky, D.M.; Stryker, J.M. *Tetrahedron Lett.* **1989**, 30, 5677. (c) Koenig, T.M.; Daeuble, J.F.; Brestensky, D.M.; Stryker, J.M., submitted for publication. (d) Catalytic version: Mahoney, W.S.; Stryker, J.M. *J. Am. Chem. Soc.* **1989**, 111, 8818.

7. Conjugated alkynyl ketones are also reduced regioselectively by [(Ph₃P)CuH], typically giving the saturated ketone in the presence of at least 0.32 equiv of the reagent and water in benzene or THF at room temperature.[6] Under conditions of reductive silylation,[6] selective mono-reduction of the alkyne is obtained, resulting in the isolation of the α,β-unsaturated ketone on isolation: Daeuble, J.F.; Stryker, J.M., unpublished results.

8. All products were characterized by comparison to authentic materials, either commercially available or prepared by unambiguous synthesis. Previously unknown compounds gave satisfactory spectroscopic and mass spectral analysis.

9. Whitesides has shown that tributylphosphine stabilized vinyl copper complexes prepared *in situ* react with an unstabilized form of CuH to yield the alkene via a nonradical reductive elimination: Whitesides, G.M.; San Filippo, J., Jr.; Stredronsky, E.R.; Casey, C.P. *J. Am. Chem. Soc.* **1969**, 91, 6542.

10. These reactions proceed in the absence of water, although yields are generally lower.

11. For example, the substrate obtained by protection of Entry 7 with an ethoxyethyl group gave only a minor amount of reduced material, even at reflux using a full equivalent of the hydride hexamer.

12. While intact [(Ph₃P)CuH]₆ is known to be unreactive toward alcohol functionality and water,[5b] hydride deficient hexamers or smaller hydride fragments presumably present during the reaction are somewhat more hydridic.[6d]

13. Copper(I) t-butoxide is sufficiently basic to deprotonate phenyl acetylene quantitatively, consistent with the equilibrium shown in Eq. 2 being displaced essentially completely to the right: Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, 94, 658.

14. We thank Dave E. Huseland for some preliminary experiments, and the National Institutes of Health (GM 38068) for financial support.