5
Copper(I)-mediated 1,2- and 1,4-Reductions

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5.1 Introduction and Background

Long before Kharasch’s seminal paper on copper-catalyzed additions of Grignard reagents to conjugated enones (1941) [1] and Gilman’s first report on formation of a lithiocuprate (Me₂CuLi; 1952) [2] appeared, Cu(I) hydride had been characterized by Wurtz as a red-brown solid [3]. Thus, “CuH” is among the oldest metal hydrides to have been properly documented, dating back to 1844. Although studied sporadically for many decades since, including an early X-ray determination [4], most of the initial ‘press’ on copper hydride was not suggestive of it having potential as a reagent in organic synthesis. In fact, it was Whitesides who demonstrated that this unstable material is often an unfortunate result of a β-elimination, which occurs to varying degrees as a thermal decomposition pathway of alkylcopper species bearing an available β-hydrogen (such as n-BuCu; Eq. 5.1) [5]. Stabilized forms of CuH, most notably Osborn’s hexameric [(Ph₃P)CuH]₆ [6], for which an X-ray structure appeared in 1972, for years saw virtually no usage in organic synthesis even in a stoichiometric sense, let alone a catalytic one. Several groups in the 1970s and early 80s, however, recognized the value of hydride delivery to α,β-unsaturated frameworks with the aid of copper complexes. This interest resulted in several hydrido cuprates of widely varying constitution, each intended for use as a stoichiometric 1,4-reductant.

\[
\text{Cu-P(n-Bu)₃} \rightarrow \text{(n-Bu₂P)CuH}
\] (5.1)

The mixed hydrido cuprate “R₅Cu[Li](H)”, designed to contain a nontransferable or ‘dummy’ group R₅ (such as 1-pentynyl, t-butoxide, or thiophenoxide) [7], was found by Boekeman et al. to effect conjugate reductions of enones in good yields [8]. The preferred ligand R₅ is the 1-pentynyl group, which is likely to impart a reactivity greater than that of the corresponding heteroatom-based mixed hydrido complex (Eq. 5.2). The reagents are made by initial treatment of CuI with DIBAL in toluene at −50 °C, to which the lithium salt of the dummy ligand is then added. Similar treatment of CuI with potassium tri-sec-butyborohydride has been suggested by
Negishi to give rise to "KCuH₂", which reduces ketones and other functional groups [9].

\[
\begin{align*}
\text{O} & \quad \begin{array}{c}
\text{C}_3\text{H}_7\equiv \text{Cu}[\text{H}]\text{Li} \\
\text{THF, HMFA, -20\°C, 24 h}
\end{array} \\
\text{O} & \quad \begin{array}{c}
\text{74\%}
\end{array}
\end{align*}
\] (5.2)

Reduction of "Me₃CuLi₂" with LAH was described by Ashby and co-workers as a means to produce the powerful reducing reagent "Li₂CuH₃" [10], which can be used in either THF or Et₂O at room temperature for conjugate reductions (Eq. 5.3). Strangely, the species analogous to Gilman’s reagent, "LiCuH₂", delivers hydride to an enone in THF in a predominantly 1,2-sense.

\[
\begin{align*}
\text{O} & \quad \begin{array}{c}
\text{Li}_2\text{CuH}_3 \\
\text{Et}_2\text{O, rt, 48 h}
\end{array} \\
\text{O} & \quad \begin{array}{c}
\text{93\%}
\end{array}
\end{align*}
\] (5.3)

Semmelhack et al. chose CuBr, together with either Red-Al or LiAl(OMe)₃H in a 1:2 ratio, to afford presumed hydrido cuprates, albeit of unknown composition [11]. In THF, both the former "Na complex" and the latter "Li complex" are heterogeneous (and of differing reactivities), yet each is capable of 1,4-reductions of unsaturated ketones and methyl esters (Eq. 5.4). Commins has used a modified version, prepared from lithium tri-t-butoxy-aluminium hydride and CuBr (in a 3:4.4 ratio), to reduce a 3-substituted-N-acylated pyridine regioselectively at the α-site [12].

\[
\begin{align*}
\text{O} & \quad \begin{array}{c}
\text{"Li complex"} \\
\text{THF, -20\°C, 1 h}
\end{array} \\
\text{O} & \quad \begin{array}{c}
\text{98\%}
\end{array}
\end{align*}
\] (5.4)

5.2 More Recent Developments: Stoichiometric Copper Hydride Reagents

While these and related reagents have seen occasional use, none has been the overwhelming choice over another, perhaps due to questions of functional group tolerance and/or a general lack of structural information. In 1988, however, Stryker et al. described (in communication form) results from a study on the remarkable tendency of the Osborn complex [(Ph₃P)CuH]₆ [6a, b] to effect highly regioselective conjugate reductions of various carbonyl derivatives, including unsaturated ketones, esters, and aldehydes [13]. The properties of this phosphine-stabilized reagent
(mildness of reaction conditions, functional group compatibility, excellent overall efficiencies, etc.) were deemed so impressive that this beautifully crystalline red solid was quickly propelled to the status of “Reagent of the Year” in 1991. It is now commonly referred to, and sold commercially, as “Stryker’s Reagent” [14].

Among its salient features, this copper hydride (written for simplicity from now on as the monomer (Ph₃P)CuH) can be prepared in multi-gram quantities from four precursor compounds (CuCl, NaO-t-Bu, PPh₃, and H₂) that are not only readily available but also very inexpensive (Eq. 5.5) [15]. It is also noteworthy that the by-products of formation (NaCl and t-BuOH) are especially “environmentally friendly”.

\[
\begin{align*}
\text{CuCl} + \text{NaO-t-Bu} + \text{PPh₃} + \text{H}_2 & \xrightarrow{\text{H}_2, \text{PPh₃}, \text{rt}} \text{[(Ph₃P)CuH]₆} + \text{NaCl} + \text{t-BuOH} \\
15-24 \text{ h} & \quad \text{(5.5)}
\end{align*}
\]

The quality of (Ph₃P)CuH can vary, depending upon the care taken in the crystallization step. An unknown impurity – that shows broad signals at δ 7.78, 7.40, and 7.04 in the ¹H NMR spectrum in dry, degassed benzene-d₆ – is usually present in all batches of the reagent, although small amounts are not deleterious to its reduction chemistry. The hydride signal, a broad multiplet, occurs at 3.52 ppm (Fig. 5.1). Proton NMR data reported by Caulton on the related [(tol)₃P]CuH include a “broad but structured multiplet centered on δ +3.50 in C₆D₆” [16].

Either hexane or pentane can replace acetonitrile to induce crystallization without impact on yield or purity. The hexamer can be weighed in air for very short periods of time, but must be stored protected under an inert atmosphere. Curiously, (Ph₃P)CuH as originally studied may occasionally be most effective when used in the presence of moist organic solvent(s), the water providing an abundant source of protons, some of which ultimately find their way into the neutral carbonyl adduct (Eq. 5.6). When TMSCl (= 3 equiv.) is present in place of water, in situ trapping of the presumed copper enolates results; on workup these afford carbonyl products directly [13, 16]. More hindered silyl chlorides (such as t-BuMe₂SiCl) produce isolable silyl enol ethers, as is to be expected [13b]. Unlike cuprates, the reagent is of low basicity. Reactions are highly chemoselective, with 1,4-reductions of enones proceeding in the presence of halides and sulfonates, as well as sulfide residues in the γ-position [17].

\begin{align*}
\text{O} & \xrightarrow{(\text{Ph₃P})\text{CuH}, \text{rt}, 28 \text{ h}} \text{O} & \xrightarrow{\text{isomer}} (85\%; 16-17:1) \\
\end{align*}

Preparation of [(Ph₃P)CuH]₆ [15]

Triphenylphosphine (100.3 g, 0.3825 mol) and copper(I) chloride (15.14 g, 0.1529 mol) were added to a dry, septum-capped 2 L Schlenk flask and placed under nitrogen. Benzene (distilled and deoxygenated, approximately
800 mL) was added by cannula, and the resultant suspension was stirred. The NaO-t-Bu/toluene suspension was transferred by wide-bore cannula to the reaction flask, washing if necessary with additional toluene or benzene, and the yellow, nearly homogeneous mixture was placed under positive hydrogen pressure (1 atm) and stirred vigorously for 15–24 h. During this period the residual solids dissolved, the solution turned red, typically within one hour, then dark red, and some gray or brown material precipitated. The reaction mixture was transferred under nitrogen pressure through a wide-bore Teflon cannula to a large Schlenk filter containing several layers of sand and Celite. The reaction flask was rinsed with several portions of benzene, which were then passed through the filter. The very dark red filtrate was concentrated under vacuum to approximately one-third of its original volume, and acetonitrile (dry and deoxygenated, 300 mL) was layered onto the benzene, promoting crystallization of the product. The yellow-brown supernatant was removed by cannula, and the product was washed several times with acetonitrile and dried under high vacuum to give 25.0–32.5 g (50–65%) of bright red to dark-red crystals.

The yields obtained by this procedure are roughly comparable to those obtained starting directly with purified (CuO-t-Bu)₄ and one atmosphere of hydrogen, although higher yields (ca. 80%) have been reported under 1500 psi of hydrogen pressure [16].

![Fig. 5.1. ¹H NMR spectrum of [(Ph₃P)CuH]₆ in C₆D₆. Chemical shifts: δ 7.67, 6.95, 6.74, and 3.52. Signals marked by • indicate impurities.](image-url)
Representative procedure for conjugate reduction of an enone [13]

\[\text{[(Ph}_3\text{P)}\text{CuH)}_6 \text{ (1.16 g, 0.82 mmol), weighed under inert atmosphere, and Wieland–Miescher ketone (0.400 g, 2.24 mmol) were added to a 100 mL, two-necked flask under positive nitrogen pressure. Deoxygenated benzene (60 mL) containing 100 } \mu \text{L of } \text{H}_2\text{O (deoxygenated by nitrogen purge for 10 min) was added by cannula, and the resulting red solution was allowed to stir at room temperature until starting material had been consumed (TLC monitoring; 8 h). The cloudy red-brown reaction mixture was opened to air, and stirring was continued for 1 h, during which time copper-containing decomposition products precipitated. Filtration through Celite and removal of the solvent in vacuo gave crude material which was purified by flash chromatography to afford the product in 85% yield.}

An insightful application of Stryker’s reagent can be found in efforts by Chiu aimed at the total synthesis of pseudolaric acid A (Fig. 5.2), where a conjugate reduction-intramolecular aldol strategy was invoked [18]. Treatment of precursor enone 1a with (Ph\(_3\)P)CuH (two equivalents) in toluene at sub-ambient temperatures quickly afforded the annulated aldol products 2 and 3 in a 2.4–3:1 ratio (Scheme 5.1). The same treatment in THF produced a higher percentage (6:1) of the undesired cis-fused isomer 2. Earlier attempts under basic conditions to form the required trans-fused aldol based on the saturated analog of 1b met with failure, the 10-membered skeleton 4 forming from second-stage decomposition of the initially derived mix of 2 and 3. The switch to copper hydride, used at uncharacter-
istically low temperatures (−23°C), ultimately provided entry to the bicyclic array by virtue both of the directed 1,4-hydride delivery to enone 1a, and also of the relatively non-basic nature of the intermediate copper alkoxide.

Soon after the appearance of the series of papers from the Stryker labs [13, 15, 17, 19a], an alternative method for the presumed generation of stoichiometric halohydrido cuprate “XCu(H)Li” (X = Cl or I) was reported (Scheme 5.2) [20]. It relies on a transmetalation between Bu₃SnH and CuI/LiCl, the inorganic salts combining to form a mixed dihalocuprate (5) [21], which may then undergo a ligand exchange with the tin hydride to afford halohydrido species 6.

![Scheme 5.2. In situ generation of hydrido cuprates.](image)

Selective 1,4-reduction of unsaturated aldehydes and ketones by 6 occurs smoothly in THF between −25 °C and room temperature within a few hours (Eq. 5.7). Particularly noteworthy is the realization that phosphines are noticeably absent from the reaction medium. The analogous combination of CuCl/Bu₃SnH in N-methyl-2-pyrrolidinone (NMP) or DMF does not behave identically [22], failing to react with the hindered substrate isophorone, whereas a 72% yield of the corresponding reduced ketone is formed with reagents XCu(H)Li/Bu₃SnH. Nonetheless, a form of “CuH” is being generated in this more polar medium, effectively utilized by Tanaka to arrive at 3-norcephalosporin 8 upon reaction with allenic ester 7 (Scheme 5.3).

![Scheme 5.3. Conversion of allenyl ester 7 to 3-norcephalosporin 8.](image)
Representative procedure for Bu₃SnH/CuI/LiCl conjugate reduction [20]

(E,E)-8-Acetoxy-2,6-dimethyl-2,6-octadienal (80 mg, 0.391 mmol) was added at −60 °C to a solution of CuI (190.4 mg, 1.00 mmol) and LiCl (100.8 mg, 2.38 mmol) in THF (4.5 mL), followed by Me₃SiCl (0.27 mL, 2.09 mmol). After 10 min, Bu₃SnH (0.30 mL, 1.10 mmol) was added dropwise, producing a cloudy yellow slurry. The reaction mixture was then allowed to warm gradually to 0 °C over 2 h. A concurrent darkening to a reddish-brown color was observed. Quenching was carried out with 10% aq. KF solution (3 mL), resulting in an orange precipitate. The organic layer was filtered through Celite and evaporated, and the residue was rapidly stirred with additional quantities of 10% KF for ca. 30 min before diluting with ether. The organic layer was then washed with saturated aq. NaCl solution and dried over anhydrous Na₂SO₄. The solvent was then removed in vacuo and the material was chromatographed on silica gel. Elution with EtOAc/hexanes (10:90) gave 82 mg (100%) of (E)-8-acetoxy-2,6-dimethyl-6-octenal as a colorless oil; TLC (15% EtOAc/hexanes) Rf 0.22.

Interestingly, the CuCl/PhMe₂SiH reagent pair was reported by Hosomi and co-workers to generate what was presumed to be CuH, also uncomplexed by phosphine [23]. The choice of solvent is critical, with ligand exchange occurring at room temperature in DMF or DMI (1,3-dimethylimidazolidinone), but not in THF, CH₂CN, or CH₂Cl₂, suggesting a stabilizing, Lewis basic role for the solvent in place of phosphine. Neither CuCN nor Cul are acceptable replacements for CuCl. When ratios of 4:2 silane:CuCl are used, along with one equivalent of substrate, excellent yields of 1,4-adducts may be anticipated (Eq. 5.8).

\[
\text{CuCl, PhMe}_2\text{SiH} \\
\text{DMI, rt, 22 h}
\]

Although unhindered enones and enoates work well, attempted 1,4-reduction of acrylonitrile afforded α-silylated product 9 (Scheme 5.4). Presumably this unexpected product results from a 1,4-reduction/α-anion trapping by the PhMe₂SiCl present in solution. Curiously, there was no mention of any similar quenching of intermediate enolates on either carbon or oxygen when unsaturated ketones or esters were involved.

Scheme 5.4. 1,4-Reduction/α-silylation of acrylonitrile.
On the basis of the identical O–Cu to O–Si transmetalation, Mori and Hiyama examined alternative Cu(I) salts in the presence of Michael acceptors [24, 25]. This study produced the finding that PhMe₂SiH/CuF(PPh₃)₃/2EtOH (1.5 equivalents) in DMA (N,N-dimethylacetamide) is effective for conjugate reductions (Eq. 5.9). Triethylsilane could also be employed in place of PhMe₂SiH, but other silyl hydrides gave either undesired mixtures of 1,4- and 1,2-products (with Ph₃SiH₂ and (EtO)₃SiH, for example) or no reaction (with PhCl₂SiH, for example). Hindered enones, such as isophorone and pulegone, were not reduced under these conditions. Most efforts at trapping intermediate enolates were essentially unproductive, aside from modest outcomes when D₂O and allyl bromide were used [25].

\[
\text{PhMe}_2\text{SiH} / \text{CuF(PPh}_3\text{)}_3 / 2\text{EtOH (1.5 equivalents)} \quad \text{(rt, DMA)} \quad (91\%)
\]

The successes described above notwithstanding, synthetic chemistry in the 1990s was in large measure characterized by ‘catalysis’, which encouraged development of organocopper processes that were in line with the times. The cost associated with the metal was far from the driving force; that was more (and continues to be) a question of transition metal waste. In other words, proper disposal of copper salt by-products is costly, and so precludes industrial applications based on stoichiometric copper hydrides.

### 5.3 1,4-Reductions Catalytic in Cu(I)

Prior to the advent of triphenylphosphine-stabilized CuH [6a, b, 13], Tsuda and Saegusa described use of five mole percent MeCu/DIBAL in THF/HMPA to effect hydroalumination of conjugated ketones and esters [26]. The likely aluminium enolate intermediate could be quenched with water or TMSCl, or alkylated/acylated with various electrophiles (such as MeI, allyl bromide, etc.; Scheme 5.5). More
highly conjugated networks, such as in 10, were reduced in a 1,6 fashion, with the enolate being alkylated at the expected \( \alpha \)-site.

t-BuCu has been used extensively in place of MeCu en route to synthons (such as 11) of value in the construction of the D vitamins (Eq. 5.10) [27]. Very recently, replacement of t-BuCu by a more stable silyl analogue, PhMe\(_2\)SiCu, has been reported:

(1) to minimize the amount of copper required for this reductive bromination (6.5 versus 20 mol%; Eq. 5.11),
(2) to afford enhanced regioselectivity (>19:1 ratio for 1,4-reduction versus 1,2-addition to the isolated keto group),
(3) to produce higher overall yields (70 versus 57%), and
(4) to be readily usable in large scale reactions [28].

\[
\text{\textbf{(5.10)}}
\]

Not long after Stryker’s initial report on (Ph\(_3\)P)CuH [13], that group discovered that it was possible to establish a catalytic cycle in which molecular hydrogen serves as the hydride source [19]. Although yields are very good, very high pressures (ca. 500–1000 psi) are unfortunately needed, at which products of overreduction are occasionally noted in varying amounts (Eqs. 5.12, 5.13). Addition of PPh\(_3\) stabilizes the catalyst, although turnover appears to be slowed. The inconveniently high pressures can be avoided by the introduction of t-BuOH (10–20 equiv./copper), which promotes clean hydrogenation at one atmosphere of hydrogen, presumably by protonolysis of the unstable copper(I) enolate intermediate to give the more stable copper t-butoxide complex (vide infra).

\[
\text{\textbf{(5.12)}}
\]
The continued search for methods to effect 1,4-reductions using catalytic quantities of CuH produced several reports late in the last decade. The basis for these new developments lies in an appreciation for the facility with which various silyl hydrides undergo transmetalation with copper enolates. Thus, a limited amount of (Ph3P)CuH (0.5–5 mol%) in the presence of PhSiH3 (1.5 equivalents relative to substrate) reduces a variety of unsaturated aldehydes and ketones in high yields (Eq. 5.14) [29]. Limitations exist with respect to the extent of steric hindrance in the educt. Similar results can be achieved using Bu3SnH in place of PhSiH3, although the latter hydride source is the appropriate (albeit expensive) choice from the environmental perspective.

An alternative, in situ source of (Ph3P)CuH can be fashioned from CuCl/PPh3/TBAF and PhMe2SiH (1.2 equivalents) in DMA, initially made at 0°C with the reaction then being run at room temperature [25]. Unhindered acyclic enones require 20 mol% of CuCl, PPh3, and TBAF for best results (Eq. 5.15). Cyclic examples are more demanding, with substituted cyclohexenones such as carvone undergoing reduction when excess reagents are present (1.6 equivalents). Acetylcyclohexene was unreactive to the catalytic conditions above.

Use of the Stryker protocol (CuCl + NaO-t-Bu under H2) for generating a copper hydride, but replacing PPh3 with p-tol-BINAP and H2 with four equivalents of polymethylhydrosiloxane (PMHS) [30], is presumed to produce the corresponding reagent bearing a nonracemic bidentate phosphine ligand, (p-tol-BINAP)CuH. This species, derived in situ and first described by Buchwald, is capable of delivering hydride to β,β-disubstituted-α,β-unsaturated esters, with control over the absolute stereochemistry at the resulting β-site (Eq. 5.16) [31]. Likewise, conjugated cyclic enones can be reduced with asymmetric induction by the same technique [32], although either (S)-BINAPCuH or Roche’s [(S)-BIPHEMP]CuH can be em-
ployed here as well as \(\text{(p-tol-BINAP)}\text{CuH}\) (Eq. 5.17) [33]. In both methods, PMHS functions as the stoichiometric source of hydride, which participates in a transmetalation step involving the likely copper enolate to regenerate the copper hydride catalyst [34]. Enoates require ambient temperatures, excess PMHS (4 equivalents), and reaction times of the order of a day, while enones react at 0 °C and require only 1.05 equivalents of silyl hydride, to prevent overreduction. The ee values obtained range from 80–92% for the newly formed esters, while those for ketones are generally higher (92–98%).

\[
\text{CO}_2\text{Et} \quad \overset{[(S)-p-tol-BINAP]}{\text{CuH}} \quad \text{PMHS, rt, PhCH}_2, 22 \text{ h} \quad \rightarrow \quad \text{CO}_2\text{Et} \quad (89\%) \quad 92\% \text{ ee}
\]

\[
\text{Ph} \quad \overset{[(S)-p-tol-BINAP]}{\text{CuH}} \quad \text{PMHS, 0°, PhCH}_2, 4 \text{ d} \quad \rightarrow \quad \text{Ph} \quad (82\%) \quad 96\% \text{ ee}
\]

**General procedure for asymmetric conjugate reduction of \(\alpha,\beta\)-unsaturated esters** [31]

\((S)-p\text{-tol-BINAP} (10 \text{ mg}, 0.162 \text{ mmol})\) was placed in a flame-dried Schlenk flask, and dissolved in toluene (6 mL). The solution was degassed by briefly opening the flask to vacuum, then backfilling with argon (this degassing procedure was repeated 3 more times). The Schlenk flask was transferred into an argon-filled glovebox. \(\text{NaO-t-Bu} (8 \text{ mg}, 0.083 \text{ mmol})\) and \(\text{CuCl} (8 \text{ mg}, 0.081 \text{ mmol})\) were placed in a vial, and dissolved in the reaction solution. The resulting mixture was stirred for 10–20 min. The Schlenk flask was removed from the glovebox, and PMHS (0.36 mL, 6 mmol) was added to the reaction solution under an argon purge. The resulting solution turned a reddish-orange color. The \(\alpha,\beta\)-unsaturated ester (1.5 mmol) was added to the reaction solution under argon purging and the resulting solution was stirred until reaction was complete, as monitored by GC. The Schlenk flask was then opened and ethanol (0.3 mL) was added dropwise to the reaction (CAUTION! Rapid addition of ethanol caused extensive bubbling and foaming of the solution). The resulting solution was diluted with ethyl ether, washed once with water and once with brine, and back-extracted with ethyl ether. The organic layer was then dried over anhydrous MgSO₄ and the solvent removed in vacuo. The product was then purified by silica column chromatography.

**General procedure for the asymmetric reduction of \(\alpha,\beta\)-unsaturated ketones** [32]

A chiral bis-phosphine (\((S)-p\text{-tol-BINAP}, (S)\text{-BINAP}, \text{or (S)-BIPHEMP}) (0.05 \text{ mmol})\) was placed in a flame-dried Schlenk tube and dissolved in toluene (2 mL). The Schlenk tube was transferred to a nitrogen-filled...
glovebox. In the glovebox, NaO\textsubscript{t-Bu} (5 mg, 0.05 mmol) and CuCl (5 mg, 0.05 mmol) were weighed into a vial. The toluene solution of the chiral bisphosphine was added by pipette to the vial to dissolve solids and the resulting solution was then transferred back into the Schlenk tube. The Schlenk tube was removed from the glovebox, the solution was stirred for 10–20 min, and PMHS (0.063 mL, 1.05 mmol) was added to the solution with argon purging. The resulting solution turned reddish orange in color. The solution was then cooled to the specified temperature. The \(\alpha,\beta\)-unsaturated ketone (1.0 mmol) was added to the reaction mixture with argon purging and the resulting solution was stirred at room temperature (18–27 h). Consumption of the \(\alpha,\beta\)-unsaturated ketone was monitored by GC. When the reaction was complete, the Schlenk tube was opened and water (1 mL) was added. The resulting solution was diluted with diethyl ether, washed once with water and once with brine, and back-extracted with diethyl ether. TBAF (1 mmol, 1 M in THF) was added to the combined organic extracts and the resulting solution was stirred for 3 h. The solution was then washed once with water and once with brine, back-extracted with diethyl ether, and the organic layer was dried over anhydrous MgSO\textsubscript{4}. The solvent was then removed in vacuo and the product was purified by silica column chromatography. In order to determine the \(er\), the product was converted into the corresponding \((R,R)\)-2,3-dimethylethylene ketal and then analyzed by GC analysis (Chiraldex G-TA) for the diastereomeric ketals.

Intermediate silyl enol ethers can be trapped and isolated from initial conjugate reductions of enones with Stryker’s reagent, or they may be used directly in Mukaiyama-type aldol constructions (i.e. in 3-component constructions; 3-CC) [35]. Thus, in a one-pot sequence using toluene as the initial solvent and 1–5 mol\% \((\text{Ph}_3\text{P})\text{CuH}\) relative to enone, any of a number of silyl hydrides (such as PhMe\textsubscript{2}SiH, Ph\textsubscript{2}MeSiH, tetramethyldisiloxane (TMDS), or PMHS) can be employed to produce the corresponding silyl enol ether. Dilution with CH\textsubscript{2}Cl\textsubscript{2} without isolation, followed by cooling to \(-78^\circ\text{C}\) and introduction of an aldehyde, followed by a Lewis acid (TiCl\textsubscript{4} or BF\textsubscript{3}OEt\textsubscript{2}) results in good yields of aldol adducts (Eq. 5.18). Unfortunately, there is no acyclic stereocontrol (\(\text{syn}\) versus \(\text{anti}\) selectivity) in these 3-CC reactions [34b].

\[
\begin{align*}
\text{O} & \quad \text{1. cat (PPh}_3\text{CuH, PhMe}_2\text{SiH, PhCH}_2\text{H, rt)} \\
\text{CHO} & \quad \text{OCH}_2\text{Cl}_2, \text{TICl}_4 \\
\text{O} & \quad \text{78° to rt} \\
\end{align*}
\]

\((82\%)\) 1:1 \(\text{syn:anti}\)

Representative procedure for conjugate reduction-aldol 3-CC: 2-{Hydroxy-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-methyl}-4,4-dimethylcyclohexanone [35]

Dimethylphenylsilane (0.23 mL, 1.5 mmol, 1.5 equiv.) was added dropwise to a homogeneous, red solution of \([\text{CuH(PPPh}_3]_6\) (16.0 mg, 0.008 mmol, 5 mol\% Cu) in toluene (2.0 mL) and the solution was stirred at room temperature for ca. 5 min. 4,4-Dimethylcyclohexanone (0.13 mL, 1.0 mmol) was
added dropwise to the resulting red solution, which was stirred at room temperature. After ca. 7 min, the solution had darkened to a heterogeneous brown/black. Monitoring of the reaction by TLC showed that the enone had been consumed after 3 h, forming the corresponding silyl enol ether. The solution was diluted with CH2Cl2 (5.0 mL) and added by cannula to a solution of N-tosyl-indole-3-carboxaldehyde (0.45 g, 1.5 mmol, 1.5 equiv.) and TiCl4 (1.5 mL of 1.0 M solution in CH2Cl2, 1 equiv.), in CH2Cl2 (7.0 mL) at −78 °C. Stirring was continued for 1 h and the reaction was quenched with saturated NaHCO3 solution (6.0 mL) at −78 °C, and allowed to warm to room temperature. A blue precipitate was filtered using a Buchner funnel, and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic portions were washed with brine (2 × 50 mL) and dried over anhydrous Na2SO4, and the solvent was removed in vacuo. Purification by flash chromatography (1:9 EtOAc/PE to 1:4 EtOAc/PE) afforded diastereomers as a yellow oil (combined yield 0.35 g, 82%).

5.4 1,2-Reductions Catalyzed by Copper Hydride

Reductions of non-conjugated aldehydes and ketones based on copper chemistry are relatively rare. Hydrogenations and hydrosilylations of carbonyl groups are usually effected by transition metals such as Ti [36], Rh [37], and Ru [38], and in one case, Cu [39]. An early report using catalytic [(tol)_3P]CuH in reactions with formaldehyde, in which disproportionation characteristic of a Tishchenko reaction took place, is indicative of a copper(I) alkoxide intermediate [16]. Almost two decades later, variations in the nature of the triphenylphosphine analogue (Stryker’s reagent), principally induced by introduction of alternative phosphine ligands, have resulted in remarkable changes in the chemoselectivity of this family of reducing agents [40, 41]. Although not as yet fully understood, subtle differences even between alkyl substituents on phosphorus can bring about dramatic shifts in reactivity patterns. Changes in the composition of [(Ph_3P)CuH]_6 caused by ligands such as tripod (1,1,1-tris(diphenylphosphinomethyl)-ethane), which forms a dinuclear bidentate complex (Fig. 5.3) [42], have been used by Stryker to great advantage to reduce ketones in a 1,2-fashion.

Both conjugated and non-conjugated ketones, as well as conjugated aldehydes, undergo 1,2-addition in the presence of CuH modified by Me_2PhP (Eq. 5.19). Ketones react under an atmosphere of hydrogen over a roughly 24 hour period. The presence of t-BuOH (10–20 equiv./copper) is important for increasing catalyst life-
time, as in the corresponding cases of 1,4-reductions (vide supra), presumably by conversion of the initially formed copper alkoxide to the alcohol product in exchange for a thermally more stable \([\text{Cu(O-t-Bu)}]_4\). This complex is then hydrogenolyzed to reform the copper hydride catalyst. In most cases, isolated olefins are untouched, as is true for dienes, esters, epoxides, alkynes, and acetals. Rates are slower in substrates bearing free alkenes, probably a consequence of \(d-\pi^*\) interactions with the metal. Acyclic conjugated enones afford a high degree of control for generation of allylic alcohol products, with only small percentages of over-reduced material formed when using PhMe_2P-modified reagent. The corresponding PhEt_2P-altered Stryker’s reagent, however, does not function as a catalyst for this chemistry (this is also the case with the novel biaryl P,O-ligand 12, the dimethylphosphino analog of MOP) [43], while the mixed dialkylphenyl case Me(Et)PPh is unexpectedly effective (e.g., for \(\beta\)-ionone, 13: >50:1; 95% yield; Eq. 5.20).

\[
\text{(5.19)}
\]

\[
\text{(5.20)}
\]

With these new levels of appreciation of the nuances associated with CuH-phosphine interactions, considerable fine-tuning of Stryker’s reagent is now possible. One case in point involves enone 14, which can be converted predominately into any one of three possible products (Scheme 5.6) [40].

\[
\text{Conditions} \\
\text{No added phosphine, 10h} \\
(\text{A}) 16\% \text{ (PPPh}_3\text{)CuH} \\
1000 \text{ PSI H}_2 \\
(\text{B}) 16\% \text{ (PPPh}_3\text{)CuH} \\
1700 \text{ PSI H}_2 \\
(\text{C}) \text{ Me}_2\text{PPPh} (6 \text{ equiv / Cu}) 18 \text{ h} \\
5\% \text{ (PPPh}_3\text{)CuH} \\
500 \text{ PSI H}_2
\]

\[
\text{yield (\%)}
\]

<table>
<thead>
<tr>
<th>Conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No added phosphine, 10h</td>
<td>91</td>
</tr>
<tr>
<td>(A) 16% (PPPh)_3CuH, 1000 PSI H_2</td>
<td>0</td>
</tr>
<tr>
<td>(B) 16% (PPPh)_3CuH, 1700 PSI H_2</td>
<td>0</td>
</tr>
</tbody>
</table>

\[
\text{Scheme 5.6. Selective reductions as a function of phosphine.}
\]
General procedure for reduction of saturated ketones using [(Ph₃P)CuH]₆ and Me₂PPh

[40]

In a glovebox, [(Ph₃P)CuH]₆ (1–10 mol% Cu), Me₂PPh (6 equiv./Cu), and t-butanol (10–20 equiv./Cu) were combined in a Schlenk flask and dissolved in benzene. A solution of the substrate (10–100 equiv./Cu) in benzene (0.4–0.8 M in substrate) was added to this solution. The flask was sealed, removed from the drybox and, after one freeze-pump-thaw degassing cycle, placed under a slight positive pressure of hydrogen. The resulting yellow-orange homogeneous solution was allowed to stir until completion, as monitored by TLC. The reaction mixture was exposed to air, diluted with ether, and treated with a small amount of silica gel. This mixture was stirred in air for ≥0.5 h, filtered, concentrated in vacuo, and purified by flash chromatography. If the polarity of the product was similar to that of the residual phosphine, the crude mixture was treated with sodium hypochlorite (5% aqueous solution) and filtered through silica gel/MgSO₄ prior to chromatography.

General procedure for reduction of saturated ketones using (PhMe₂P)CuH produced in situ

[40]

Under an inert atmosphere, a solution of the substrate in benzene was added to a slurry of freshly purified CuCl (5 mol%), Me₂PPh (6 equiv./Cu), and t-butanol (10 equiv./Cu) in benzene (final concentration: 0.4–0.8 M in substrate). After degassing with one freeze-pump-thaw cycle, the suspension was placed under a slight positive pressure of hydrogen and allowed to stir until completion, as monitored by TLC. The product was isolated and purified as described above.

Further alterations in the above reaction conditions, notably the replacement of H₂ with various silanes as the hydride source, results in a net hydrosilylation of non-conjugated aldehydes and ketones [44]. The catalytic (PPh₃)CuH/excess R₃SiH combination is highly effective at converting aldehydes directly into protected primary alcohols, with silanes ranging from PhMe₂SiH – which produces a relatively labile silyl ether – to Hanessian's especially hydrolytically stable t-BuPh₂Si derivatives [45], all from the corresponding precursor silanes (Eq. 5.21). Levels of CuH used tend to be in the 1–3 mol% range, although from the few cases studied to date, one tenth as much may be sufficient to drive the reaction to completion. The more reactive PMHS [30] appears to be the ideal choice of silane for catalyst usage in the <1 mol% category, although the use of this polymeric hydride source necessitates workup under basic conditions.

\[
\text{CHO} \xrightarrow{\text{cat} \ (\text{PPh₃})CuH, \ Ph₃MeSiH} \text{PhCH₃, rt, 2 h} \xrightarrow{\text{Ph}} \text{Ph} \cap \text{O-Si-Me} \text{Ph} \ (\text{98%})
\]  

(5.21)
Representative 1,2-reduction/silylation of an aldehyde, giving (2-bromobenzoyloxy)diphenylmethylsilane [44]

A dried 25 mL flask with a rubber septum top was flushed with argon and charged with \([\text{PPh}_3(\text{CuH})]_6\) (53 mg, 0.162 mmol), as a red solid. Toluene (5.4 mL) was added, followed by neat diphenylmethylsilane (1.4 mL, 7.0 mmol), resulting in a homogeneous red solution. In a second dry, argon-flushed vessel (10 mL), fitted with a rubber septum, 2-bromobenzaldehyde (0.63 mL, 5.4 mmol) and toluene (4 mL) were mixed together, and the solution was transferred by cannula, with stirring, into the solution (at room temperature) of copper reagent and silane. The reaction mixture was monitored by TLC (elution with 5% diethyl ether/hexane, \(R_f = 0.74\)); the aldehyde was consumed after 30 min. The reaction was filtered through a pad of Celite/charcoal, washed with EtOAc (2 × 15 mL), and the filtrate concentrated to an oil in vacuo. Kugelrohr distillation (168 °C, 0.2–0.3 Torr) yielded the title compound as a colorless oil (1.98 g, 95%).

Ketones take considerably longer to reduce than aldehydes (10–24 h), although yields are not compromised. Differences in reactivity toward aldehydes and ketones can be used to advantage, with highly chemoselective reduction occurring at the aldehyde in the presence even of a methyl ketone (Eq. 5.22) [44].

\[
\begin{align*}
\text{O} & \quad + \quad \text{CHO} \\
\text{CuH}_{19} & \quad + \quad \text{cat (PhH)}_{12}\text{CuH} \\
\text{PMHS, PhCH}_3 & \quad \text{not observed} \\
\text{Kugelrohr distillation (168 °C, 0.2–0.3 Torr)} & \quad \text{yielded the title compound as a colorless oil (1.98 g, 95%).}
\end{align*}
\]

In situ production of phosphine-free CuH from CuCl or CuOAc (0.3–1.0 equivalents), in the presence of an excess of PhMe₂SiH in DMI at room temperature, displays a remarkable preference for reductions of aryl ketones (e.g., 15) over aliphatic ones such as 16 (Eq. 5.23) [46]. Reactions require a day or more to reach completion, concentrations of 0.5 M notwithstanding, but yields have been uniformly good (77–88%) for the few cases examined. Aldehydes, however, show no such selectivity and are reduced to the corresponding primary alcohols, albeit in high yields.

\[
\begin{align*}
\text{O} & \quad + \quad \text{O} \\
\text{Ph} & \quad \text{Bu} \\
\text{CuCl, PhMe₂SiH} & \quad \text{DMF, rt, 26 h} \\
\text{Ph} & \quad \text{Bu} \\
\text{Bu} & \quad \text{Bu} \\
\text{(95%) } & \quad \text{(90%)} \\
\text{(0%)} & \quad \text{(0%)} \\
\end{align*}
\]

5.5 Heterogeneous CuH-Catalyzed Reductions

Catalysts such as copper chromite, first prepared and utilized for carbonyl 1,2-reductions back in 1931 [47], have given way to more modern reagents for effecting
related transformations under heterogeneous conditions. Ravasio first described Cu/Al₂O₃ in steroid reductions (steroid-4-en-3-ones), examining the regioselectivities, stereoselectivities, and chemoselectivities of this supported reductant at 60 °C under a hydrogen pressure of one atmosphere [48]. A follow-up study by that group, described in 1996, promotes the more generally useful Cu/SiO₂ [48]. Under an atmosphere of H₂ at 90 °C in toluene, this catalyst effects 1,4-reductions of conjugated enones while leaving isolated olefins intact. Although the preparation of the catalyst is fairly involved (cf. the procedure below), the method results in excellent levels of conversion, and high yields of the corresponding ketones. The featured example in this work is that of β-ionone, from which the desired keto product, reflecting reduction of the α,β-site, was provided with high levels of regiocontrol (Eq. 5.24). Removal of the catalyst by filtration, followed by reactivation at 270 °C, essentially did not result in any change in selectivity after four consecutive cycles. These reactions are believed to involve CuH, generated on the surface of pyrogenic silica.

\[ \text{Beta-ionone (13) \rightarrow (98\%)} \]

\[ \text{Cu/SiO}_2, \text{H}_2 \]

PhCH₂, 90°, 2.5 h

**Catalyst preparation [49]**

Concentrated NH₄OH was added to a solution of Cu(NO₃)₂·3H₂O (25 mL, 160 g/L) until pH = 9 was reached, the support (silica, 10 g) was then added, and the mixture was slowly diluted to 3 L in order to allow hydrolysis of the Cu[NO₃]₄²⁻ complex and deposition of the finely dispersed product to occur. The solid was separated by filtration, washed with water, dried overnight at 120 °C, and calcined in air at 350 °C for 3 hours. In this way, 8% Cu samples, 308 m²/g BET surface area, were obtained. The catalyst was reduced with H₂ at 270 °C at atmospheric pressure, the water formed being removed under reduced pressure, before the hydrogenation reaction.

**Experimental conditions**

The substrates (2 mmol) were dissolved in toluene (12 mL) and the solution was transferred under H₂ into a glass reaction vessel in which the catalyst (0.3 g) had been reduced previously. Reactions were carried out at 90 °C and at atmospheric pressure, with magnetic stirring, the final charge of hydrogen being adjusted to 1 atm with a mercury leveling bulb, and monitored by withdrawing 20 μL samples through a viton septum and analyzing them by capillary GLC. After completion, the catalyst was filtered off, the solvent removed, and the reaction mixture analyzed by NMR. Superatmospheric pressure (1.5–5 atm) could conveniently be used to speed up the reaction without loss in selectivity when higher substrate/Cu ratios were used. For the recycling tests, the catalyst was washed with diethyl ether, dried, and reactivated at 270 °C.
A fascinating study on the surface science of copper hydride on SiO₂, as well as on Al₂O₃, ceria (cerium oxide), and ZnO, has appeared [50]. Pure, yet thermally unstable, CuH can be precipitated as a red-brown solid from aqueous cupric sulfate and hypophosphorous acid in the presence of H₂SO₄, and has been characterized by powder X-ray diffraction (PXRD) (Eq. 5.25). Transmission electron microscopy (TEM) data suggest that it is most stable when deposited on acidic SiO₂.

\[
\text{4Cu}^{2+} + 6\text{H}_2\text{PO}_2^- + 6\text{H}_2\text{O} + \text{H}^+ \rightarrow \text{4CuH}_\text{sat} + 6\text{H}_3\text{PO}_4^- + 8\text{H}^+ \quad (5.25)
\]

### 5.6 Overview and Future Developments

Although many variations on reagents bearing hydride ligated to copper(I) have been developed, it was the advent of Stryker’s reagent that provided a well defined, easily handled, and crystalline source of CuH. This hexameric copper hydride, [(Ph₃P)CuH]₆, has been enthusiastically embraced by the synthetic community as a highly reliable means of effecting fundamental conjugate reductions of unsaturated aldehydes, ketones, and esters. Unlike the procedures previously in use, in which presumed ate complexes of CuH required manipulations of multiple reagents and gave rise to highly basic species, (Ph₃P)CuH is relatively non-basic and is available commercially, or can be readily prepared in multigram quantities. Moreover, when stored under an inert atmosphere, it can last for months without significant decomposition. That (Ph₃P)CuH derives from readily accessible and inexpensive precursors is a bonus, and as it is regarded as a base metal catalyst, in association with either molecular hydrogen or silanes as sources of stoichiometric hydride, the economics involved in its use are highly favorable. Also not to be overlooked among the virtues of (Ph₃P)CuH is its tolerance to moisture, as well as many to functional groups – including isolated, unsaturated carbon-carbon bonds – which otherwise preclude normal modes of catalytic hydrogenation. The noteworthy impact exerted by various achiral monodentate and bidentate phosphine ligands on CuH reactions can be used to tremendous advantage in controlling resulting regioselectivities and chemoselectivities. Replacement of the PPh₃ in Stryker’s reagent with selected chiral, nonracemic bidentate phosphines has enabled enantioselective 1,4-reductions to be achieved. Still more recently, the 1,2-addition mode of Stryker’s reagent has been evolving rapidly. These reactions have similarly proven to be quite effective under conditions catalytic in CuH. Further recognition and greater appreciation of such elements of reactivity and selectivity, associated with both the 1,2- and the 1,4-reduction patterns of (Ph₃P)CuH, are likely to give rise to future improvements, new methodologies, and synthetic applications.
An aldimine reduction already “in the pipeline” has been tested using catalytic Stryker’s reagent along with various silanes, the preliminary data suggesting that such 1,2-additions do indeed take place, albeit far more slowly that those on the corresponding carbonyl derivatives (Eq. 5.26) [51]. In line with observations made concerning the effects of phosphines on CuH [40, 41], a remarkable rate enhancement has also been noted in ketone hydrosilylations under the influence either of racemic BINAP or DPPF (bis(diphenylphosphino)ferrocene). Thus, while 4-t-butylcyclohexanone takes a day to be reduced when catalytic (PPh₃)CuH is used with either H₂ [40, 41] or PMHS [44], simple addition of either of these bidentate ligands results in complete conversion in less than one hour at identical concentrations (Scheme 5.7) [44]. This key observation has generated considerable enthusiasm for development of a highly effective method for asymmetric hydrosilylations of aryl ketones using catalytic CuH ligated by a nonracemic bidentate phosphine (Roches’ 3.5-xyl-MEO-BIPHEP) [53]. It thus seems reasonable to conclude that the story of reductions by CuH in organic synthesis, whether under homogeneous or heterogeneous conditions, is far from complete.

Scheme 5.7. Effect of DPPF on reductions with Stryker’s reagent.

References

186 5 Copper(I)-mediated 1,2- and 1,4-Reductions

14 Listed as “hydrido (triphenylphosphine) copper(I) hexamer”; Aldrich catalog # 36497-5.
51 B. H. Lipshutz, A. B. Reed, K. Noson, unpublished work.