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(BDP)CuH: A "Hot" Stryker's Reagent for Use in Achiral Conjugate Reductions

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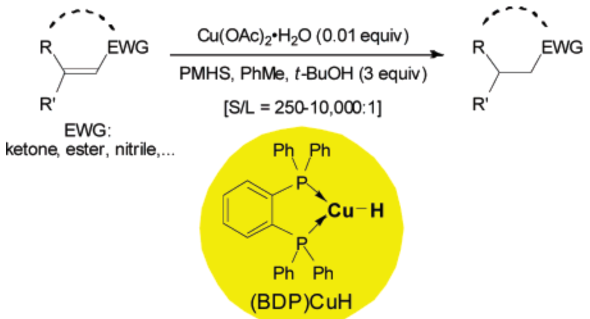
ABSTRACT

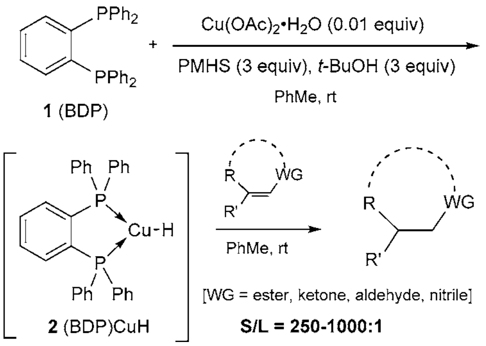


A ligand-modified, economical version of Stryker's reagent (SR) has been developed based on a bidentate, achiral bis-phosphine. Generated in situ, "(BDP)CuH" smoothly effects conjugate reductions of a variety of unsaturated substrates, including those that are normally unreactive toward SR. Substrate-to-ligand ratios typically on the order of 1000–10000:1 can be used leading to products in high yields.

Copper(I) hydride is a mild and selective reducing agent, whether used in stoichiometric or catalytic quantities. Among the most extensively studied and routinely used is the phosphine-stabilized hexameric complex $[(Ph_3P)CuH]_6$, commonly referred to as Stryker's reagent (SR).[1] It smoothly effects conjugate reductions of various α,β-unsaturated compounds[2] with considerable chemoselectivity. Originally, hydrogen gas was employed for its preparation and use as a stoichiometric reductant.[3] More recently, alternatives such as stannanes,[4] boranes,[5] and in particular, silanes have been developed as hydrogen equivalents in CuH chemistry.[6] Nonetheless, the reagent's inherent sensitivity to air, limited reactivity toward more challenging/hindered substrates, and high cost have encouraged us to find an alternative that addresses these issues. In this paper, we present a method for preparation of a new, "hot" Stryker's reagent capable of not only reducing sterically congested substrates but also doing so with exceptional substrate-to-ligand (S/L) ratios as well as in excellent isolated yields.

The potential for 1,2-bis(diphenylphosphino)benzene (**1**; *o*-BDPPB, shortened herein to "BDP"), a readily available, achiral bidentate ligand, to form a more reactive 16-electron complex with CuH was examined. Treatment of inexpensive Cu(OAc)$_2$•H$_2$O (directly from the bottle) at room temperature with excess polymethylhydrosiloxane (PMHS)[7] and one-tenth the amount of ligand relative to Cu(II) led to a yellow-colored solution in toluene (1.0 M; Scheme 1). The presumed in situ formed copper hydride complex **2**, (BDP)CuH,[8] was found to be especially reactive in subsequent

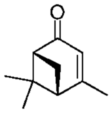
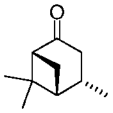
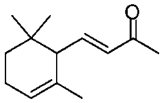
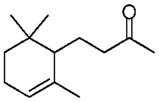
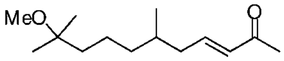
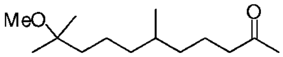
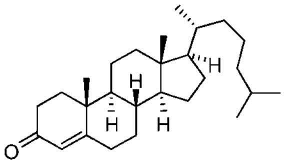
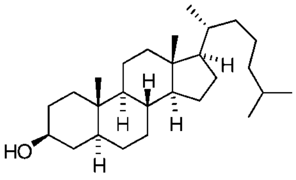
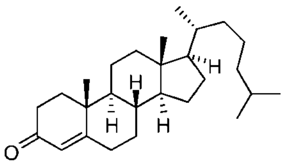
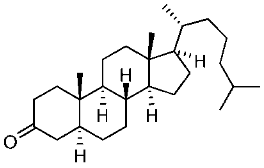
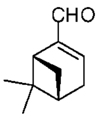
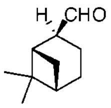
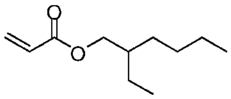
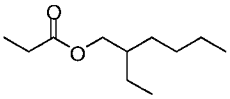
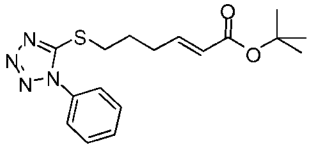
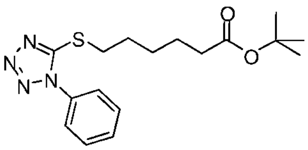
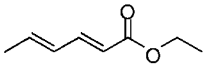
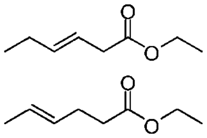
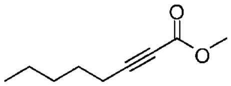
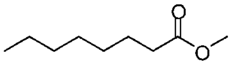
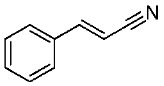
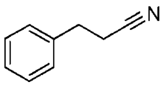
Scheme 1. Preparation and Use of (BDP)CuH (**2**)



10.1021/ol702689v CCC: $40.75

Table 1. Representative Reductions of α,β-Unsaturated Carbonyl Compounds

$$\textbf{Substrate} \xrightarrow[\text{PMHS (3 equiv), } t\text{-BuOH (3 equiv), PhMe, rt}]{\text{Cu(OAc)}_2\cdot\text{H}_2\text{O (1 mol \%), ligand } \textbf{1} \text{ (0.1 mol \%)}} \textbf{Product}$$

entry	substrate	S/L	time (h)	product	yield (%)[a]
1		1,000:1	3		96
2		1,000:1	3		96
3		1,000:1	3		89
4		1,000:1	5		86
5		1,000:1	4		82[b]
6		1,000:1	3		97
7		1,000:1	2		95
8		1,000:1	5		95
9		1,000:1	6		95[c]
10		1,000:1	3		90
11		100:1	19		91

[a] Isolated; purified by chromatography or Kugelrohr distillation. [b] Reaction run without t-BuOH. [c] Mixture (3:1) of inseparable isomers (see text).

conjugate reductions of both alkenes and alkynes activated by an ester, ketone, aldehyde, or nitrile. Solutions prepared in this fashion provide a S/L ratio of 1000:1 based on 1 equiv of substrate. Several representative examples are illustrated in Table 1. In most cases, limited amounts of *t*-BuOH (3 equiv) were used to achieve additional enhancements in reaction rates.[9]

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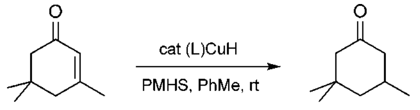
(1) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. (b) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818.

A direct comparison was made between Stryker's reagent and (BDP)CuH using isophorone, a particularly challenging test case given both β,β-disubstitution and the geminal methyl groups at C-5 (Scheme 2). While SR used at a S/L = 20 afforded only 7% conversion after 24 h, **2** led to quantitative reduction in less than 5 h with a S/L ratio of 1000:1. Increasing the S/L ratio to 10,000:1 lengthened the reaction time to 15 h (yield: 98%). Enhanced reactivity was not observed, nor was the extent of conversion improved, in the reaction of isophorone with SR in the presence of added triphenylphosphine (2 equiv relative to $(Ph_3P)CuH$). However, addition of only 0.1% BDP to SR (4 mol % relative to substrate) led to complete reduction of isophorone.

Scheme 2. Comparison of Reagents Using Isophorone



isophorone

$(Ph_3P)CuH$ ***S/L = 20:1***	7% (12 h)
$(Ph_3P)CuH$ + **1** ***S/L = 20:1***	>95% (12 h)[a]
(BDP)CuH ***S/L = 1,000:1***	99% (5 h)
(BDP)CuH ***S/L = 10,000:1***	98% (15 h)

[a] Ligand **1** (0.1 mol %) was combined with 5% SR; GC conversion.

The examples in Table 1 depict the versatility of this process. Other enones (entries 1−3) were also well-behaved toward (BDP)CuH. Cholestenone (entry 4) was found to over-reduce to the β-alcohol using **2** in the presence of *t*-BuOH, although exclusive conjugate reduction to the ketone could be realized in the absence of this additive (entry 5). By contrast, 4% SR gave a 1:1 mix of 1,2- and 1,4-adducts, along with ca. one-third of the starting material after 12 h. No over-reduction was observed in the case of myrtanal (entry 6). As expected, enoates reacted somewhat more slowly than enones (compare entry 3 vs 8), although an unhindered acrylate (entry 7) gave the corresponding ester within 2 h. Noteworthy is the case of *tert*-butyl enoate (entry 8) containing a distant tetrazolyl sulfide; no effect on the rate of hydrosilylation by these heteroatoms was seen (perhaps by competitive complexation with BDP for copper). Ethyl sorbate (entry 9) reacts with little regioselectivity to give an inseparable mixture of 1,4- and 1,6-reduction products (1:3, favoring 1,6- followed by α-protonation). No attempt was made to improve this ratio (e.g., by lowering the temperature). An acetyleneic ester (entry 10) reduces smoothly to the corresponding saturated derivative; no enoate intermediate could be observed in the course of this conversion. Cinnamylnitrile (entry 11) was slow to convert,[10] even at an S/L ratio of 100:1.

Attempts were made to mimic Stryker's use of hydrogen gas as a stoichiometric reductant in several reactions.[1b] Under our standard conditions, PMHS was replaced by hydrogen at pressures up to 50 psi. Surprisingly, no reduction of substrate was observed in any case. Perhaps the bidentate nature of BDP on copper(I), as opposed to monodentate Ph_3P in SR, prevents insertion of hydrogen to form the metal hydride.

The stability of toluene solutions of (BDP)CuH over time has also been examined (Scheme 3). Best results were obtained when only 1% copper was present, which relative to the amount of ligand present (0.1%) is still a 10-fold excess. Under these conditions, some of the excess copper precipitated out of solution, presumably as nonligated copper hydride. The trivial addition of triphenylphosphine (1 equiv relative to copper; 1%) prevents this occurrence and allows for a stock solution that can be stored indefinitely at room temperature under argon.[11] *tert*-Butyl alcohol was omitted from this formulation due to its tendency to decompose silanes over time.

Scheme 3. Room-Temperature Stability of (BDP)CuH

2 (BDP)CuH

Reaction times could be reduced by employing somewhat higher temperatures, conveniently achieved under microwave irradiation (Table 2). Sixty degrees was determined to be the upper limit for use of (BDP)CuH in conjugate reductions. Higher temperatures resulted in competitive reagent decomposition. In the specific case of isophorone, which requires

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(2) (a) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627. (b) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (c) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253. (d) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793. (e) Desrosiers, J.-N.; Charette, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5955.

(3) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749.

(4) Miao, R.; Li, S.; Chiu, P. *Tetrahedron* **2007**, *63*, 6737.

(5) Lipshutz, B. H.; Papa, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4580.

(6) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779.

(7) Lawrence, N. J.; Drew, M. D. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381.

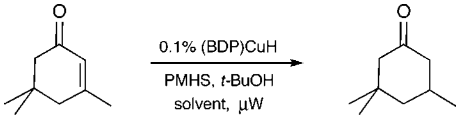
(8) ^1H NMR (benzene-d_6) δ 1.49. Treatment of Stryker's reagent (δ 3.55) with ligand **1** results in the total disappearance of the hydride signal with concommitant appearance of a peak at δ 1.49. The addition of PPh_3 to (BDP)CuH leads to no change in the spectrum for the hydride signal at δ 1.49.

(9) (a) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417. (b) Lipshutz, B. H.; Chrisman, W.; Noson, K. *J. Organomet. Chem.* **2001**, *624*, 367.

(10) Kim, D.; Park, B.-M.; Yun, J. *Chem. Commun.* **2005**, 1755.

(11) **Preparation of 10 mL of 1 M Stock Solution of (BDP)CuH.** In a flame-dried 50 mL amber vial which was cooled under argon were added $Cu(OAc)_2 \cdot H_2O$ (20.0 mg, 0.1 mmol), bis-diphenylphoshinobenzene (4.46 mg, 0.01 mmol), and triphenylphosphine (27.0 mg, 0.1 mmol). The reagents were dissolved in freshly distilled toluene (8.0 mL) and allowed to stir at room temperature for 1 h. Polymethylhydrosiloxane (PMHS) (2.0 mL, 30 mmol) was added dropwise to the stirring solution. There was an immediate color change from blue to red. The stock solution was thoroughly purged with argon and sealed. Storage in a refrigerator is recommended.

Table 2. Microwave-Assisted Reductions Using (BDP)CuH



time (min)	T (°C)	solvent	GC conversion (%)
15	60	toluene	76
15	60	Et_2O	60
15	60	THF	10
15	60	DMF	<5[a]
35	**60**	**toluene**	**100**[b]
35	60	Et_2O	81
35	60	2:1 toluene/THF	82

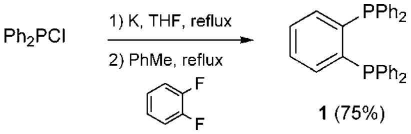
[a] No reduction due to the reaction between DMF and PMHS. [b] 92% isolated yield.

5 h to reach completion at room temperature (S/L = 1,000:1; see Scheme 2), 1,4-reduction could be accomplished in 35 min. Although toluene seems to be the favored solvent, clearly other selected media (e.g., Et_2O) are reasonable alternatives.

Finally, a new procedure was developed for the preparation of ligand **1**, further streamlining access to this otherwise relatively expensive precursor.[12] Thus, after considerable experimentation, it was found that *o*-difluorobenzene undergoes double displacement with potassium diphenylphosphide in refluxing toluene (Scheme 4). This approach can be used to obtain gram quantities of bis-phosphine **1**.

In summary, a new, economically attractive,[13] storable, and yet highly kinetically reactive source of catalytic copper hydride has been developed based on a readily available bis-phosphine ligand. This species, (BDP)CuH, is especially useful in 1,4-reductions of a variety of activated alkenes and alkynes, including hindered substrates.

Scheme 4. New Preparation of Ligand **1**



1 (75%)

Acknowledgment. Financial support provided by the NSF (CHE 05-50232) is warmly acknowledged.

Supporting Information Available: Characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) **Preparation of 1,2-Bis(diphenylphosphino)benzene.** A flame-dried 250 mL round-bottom flask cooled under argon was charged with freshly distilled THF (75 mL). Potassium (3.52 g, 90.0 mmol) was added in small pieces with stirring. The reaction flask was fitted with a reflux condenser under positive argon pressure, and chlorodiphenylphosphine (8 mL, 45.0 mmol) was added dropwise. The solution was then heated to reflux until potassium was consumed and the mixture had assumed a characteristic red color. To this refluxing solution was added *o*-difluorobenzene (2 mL, 20.0 mmol) via syringe followed by freshly distilled toluene (100 mL). The solution was refluxed for 24 h and then cooled to rt, and the volatiles were removed by rotary evaporation. The solution was redissolved in toluene, and 5 g of activated charcoal (Norit A) was added. The resulting mixture was hot filtered through a Celite pad and concentrated in vacuo, and the residue was recrystallized from toluene yielding 1,2-bis(diphenylphosphino)benzene (6.7 g, 75%) as a white crystalline solid: mp 185−186 °C (lit.[12b] mp 183−185 °C). (b) McFarlane, H. C. E. *Polyhedron* **1983**, *2*, 303.

(13) Based on prices quoted in the latest Sigma-Aldrich catalog, costs to reduce 1 mol of substrate employing (a) stoichiometric Stryker's reagent (SR) = $18,000; (b) using 5 mol % SR = $600. The same scale reduction using (BDP)CuH (0.1 mol %) would cost $20.