Hydride Reagents

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CuH in a Bottle: A Convenient Reagent for Asymmetric Hydrosilylations**

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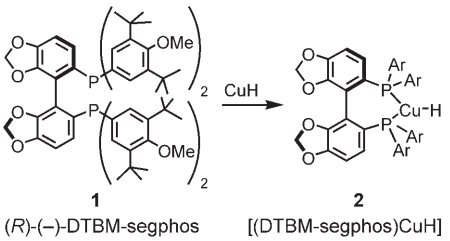
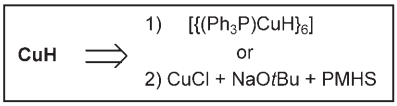
Copper hydride (CuH), when complexed by the Takasago ligand (*R*)-(−)-DTBM-segphos, (**1**),[1] as shown in Scheme 1





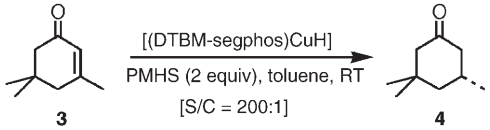
Scheme 1. Formation of [(DTBM-segphos)CuH].

(DTBM = 3,5-di-*tert*-butyl-4-methoxy), is a remarkably reactive yet selective reagent for effecting asymmetric hydrosilylations. Aromatic ketones,[2a] hindered cyclic enones,[2b] aryl imines,[2c] and selected α,β-unsaturated esters and lactones[2d] all react with [{(*R*)-(−)-DTBM-segphos}CuH] (**2**) in the presence of stoichiometric PMHS[3] to afford the corresponding products of asymmetric reduction with excellent *ee* values. Substrate-to-catalyst (S/C) ratios typical of asymmetric hydrosilylations (< 500:1) mediated by other metals (e.g., Rh, Ti, Ru)[4] can be increased substantially, while reaction rates are comparable in many cases, even at much lower temperatures.

Preparation of **2** typically follows either of two procedures: 1) addition of ligand **1** to preformed [{$(Ph_3P)CuH\}_6$] (i.e., Stryker reagent)[5] or 2) in situ formation[6] by using CuCl, NaO*t*Bu, and **1** in the presence of excess silane (PMHS). To simplify handling and to gauge reagent lifetime for potential storage and ease of use, alternatives to its preparation have been investigated. Herein, we report our findings, which suggest that complex **2** is, indeed, quite robust.

Several copper salts were screened as alternatives to CuCl. In particular, those with counterions that are already oxygen-based are, in principle, ready for direct transmetalation with PMHS to CuH. The 1,4-reduction of hindered enone isophorone was used as a test case; results from several experiments are illustrated in Table 1. Each reaction was performed under otherwise identical conditions, with a S/C ratio of 200:1. While the *ee* values for all but one case were > 96%, the extent of conversion over time varied considerably as a function of the counterion. In principle, the counterion should not play a major role, but these data suggest that rates can indeed be affected by this reaction variable. Cu-$(OAc)_2 \cdot H_2O$ (Table 1, entry 1) appears to be the best choice to date for several reasons (see below), as also noted recently by others.[7] Copper phenoxide (Table 1, entry 2) was roughly comparable in all respects, an unexpected result in light of prior work from Stryker and co-workers, who found that the replacement of NaO*t*Bu with NaOPh did not lead to a useful catalytic system.[8] The bulky phenoxide from BHT (Table 1, entry 11), on the other hand, in the form of Cu(BHT), led to a far less reactive albeit highly selective precursor to ligated CuH.

Table 1: Survey of copper salt precursors to [(DTBM-segphos)CuH].



3 4

Entry	Copper source[a]	*t* [h]	Conversion [%]	*ee* [%][b]
1	$Cu(OAc)_2 \cdot H_2O$	1	100	99
2	CuOPh	1.5	100	99
3	CuCl	2	100	99
4	CuOAc	2	100	99
5	$CuCl_2 \cdot H_2O$	20	17	98
6	$Cu(O_2CCF_3)_2 \cdot H_2O$	20	50	98
7	$Cu(OTf)_2$	20	25	97
8	[Cu(acac)$_2$]	20	44	99
9	[Cu(bzac)$_2$]	20	5	86
10	[Cu(TMHD)$_2$]	20	67	98
11	Cu(BHT)	20	81	99

[a] acac = acetoacetate; BHT = 2,6-di-*tert*-butyl-4-methylphenol; bzac = $PhC(O)CH_2C(O)CH_3$; Tf = trifluoromethanesulfonyl; TMHD = 2,2,6,6-tetramethyl-3,5-heptanedione. [b] By chiral capillary GC. [c] From CuCl + NaBHT.

The catalyst **2** derived from $Cu(OAc)_2 \cdot H_2O$ led to complete reduction of enone **3** to nonracemic ketone **4** in 1 h with > 99% *ee*. Given the room temperature conditions and high enantioselectivity, this observation encouraged investigation of reagent shelf life, but now with catalyst **2** at a S/C ratio of 1000:1 (vs. 200:1; see Table 1, entry 1). Thus, a 0.001M solution of **2** in toluene was prepared and stored in a bottle at room temperature. This stock solution stored in a refrigerator was monitored over time for yields of isolated product and levels of induction in the reaction of isophorone (1 mmol) added to **2** (1 mL). As shown in Table 2, over a 4-

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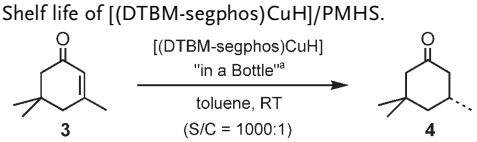
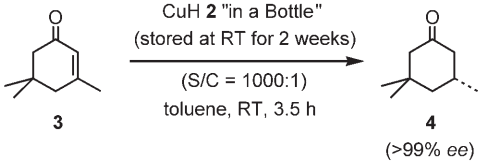
Table 2: Shelf life of [(DTBM-segphos)CuH]/PMHS.



t [days]	Yield [%][b]	*ee* [%]
1	88	99
5	87	99
9	88	98
28	86	96
60	87	94

[a] Stored at 4 °C. [b] Yield of isolated product.

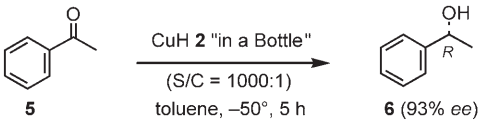
week period, the enantioselectivity dropped only slightly (from 99 to 96 % *ee*). After 2 months, the recorded enantioselectivity was still $\geq$ 94 % *ee*. To show that the decline in enantioselectivity was likely to be due to adventitious oxygen introduced over time as a result of normal use, a fresh solution of CuH was prepared and stored at room temperature for 14 days without puncturing the Sure/Seal. The CuH in a bottle was tested again on isophorone [Eq. (1)]; no loss in enantio-



(1)

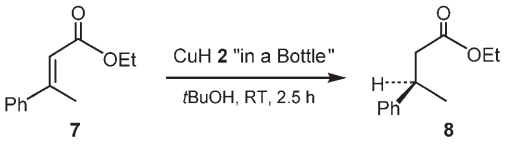
selectivity was observed. Thus, we have found that reagent degradation can be minimized by simply switching to a more efficient Oxford Sure/Seal Storage valve cap. With reagent integrity documented at room temperature for a 2-week period, prospects for routine storage and even commercialization now exist. Notably, whereas in prior applications the ratio of substrate-to-copper was about 100:1 (i.e., $\approx$1 % CuCl),[2b] in the case at hand the amount of copper present is equal to the quantity of ligand, thus significantly decreasing the extent of transition metal involved.

Treatment of an aryl ketone, acetophenone (**5**), with $Cu(OAc)_2$-derived reagent **2** [Eq. (2)] led to the alcohol **6** with 93 % *ee*, essentially identical to that seen previously when using freshly prepared [{(*R*)-(−)-DTBM-segphos}CuH] derived from CuCl.[2a]



(2)

Cinnamate **7** was also exposed to [(DTBM-segphos)CuH] (S/C 1000:1, room temperature). Initially, product ester **8** was obtained with 98 % *ee* [86 % yield of isolated product; Eq. (3)]. A second experiment under identical conditions (room temperature, 2.5 h) in the presence of reagent **2** that had been stored on the shelf at room temperature over a 2-week period afforded **8** with essentially the same enantioselectivity (99 % *ee*) and yield (85 %).

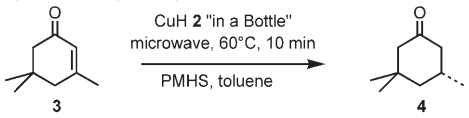


(3)

t_0: 86%, 98% *ee*
2 weeks at RT: 85%, 99% *ee*

Asymmetric hydrosilylations with CuH under microwave conditions are unprecedented in the literature, and are made all the more interesting given the limited thermal stability of this species. Nonetheless, the increased rates normally observed when using this technique might allow rapid conjugate reduction to occur. In the event, even at 1000:1 S/C ratios, reactions run within a microwave reactor at 60 °C are close to complete within 10 min without erosion in enantioselectivity (Table 3).[9]

Table 3: Asymmetric hydrosilylations under microwave irradiation.



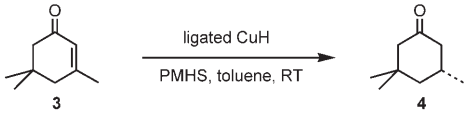
S/C	Conversion[a] [%]	*ee* [%]
500	98	99
1000	95	99

[a] By GC analysis.

The results of the reactions of enoates and cyclic enones at room temperature or above in the presence of the Stryker reagent as the catalytic source of CuH[2b,d] raises the question as to the impact of Ph_3P. Achiral [(Ph_3P)CuH] could potentially compete in a background reaction, thereby lowering the *ee* values. The addition of Ph_3P (1 equiv) to a solution of [(DTBM-segphos)CuH]/PMHS stored in a bottle caused the *ee* value of the product ketone **4** from the hydrosilylation of isophorone to drop from 99 to 96 % (Table 4, entry 2). Alternatively, the addition of ligand **1** (2 equiv) to preformed [(Ph_3P)CuH] led to further erosion in enantioselectivity to 95 % *ee* (Table 4, entry 3). Thus, the presence of Ph_3P has a small but finite effect that detracts from the inherent enantioselectivity imparted by the DTBM-segphos ligand.

Although ^{1}H NMR spectral information on the Stryker reagent is available,[10] the corresponding data for CuH

Table 4: Impact of Ph_3P on reactions of **3** with **2**.



Entry	Copper source	CuH/**1**	*t* [h]	*ee* [%]
1	[(segphos)CuH] in a bottle (**2**)	1:1	3	99
2	$Cu(OAc)_2 H_2O$ + **1** + Ph_3P (1 equiv)	1:1	5	96
3	[(Ph_3P)CuH] + **1** (2 equiv)	1:2	5	95

complexed by a nonracemic bisphosphine ligand has yet to be reported. The spectrum of $[\{(Ph_3P)CuH\}_6]$ in C_6D_6 shows the hydride at $\delta = 3.52$ ppm.[11] Individual spectra of PMHS (Figure 1a) and DTBM-segphos (Figure 1b) in this solvent are shown along with that of $Cu(OAc)_2 \cdot H_2O$ in the presence of this ligand (Figure 1c). Upon addition of PMHS, a new peak at $\delta = 2.55$ ppm appears (Figure 1d), which is presumed

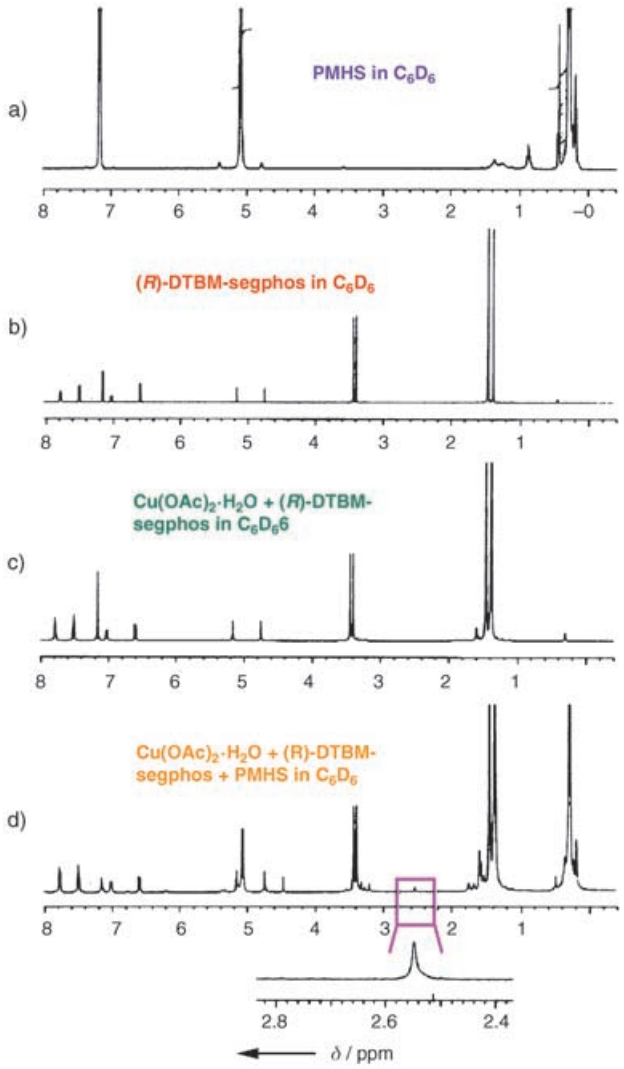


Figure 1. ^{1}H spectrum of [{(*R*)-DTBM-segphos)}CuH].

to correspond to the hydride in reagent **2**. The identical chemical shift is observed for the corresponding reagent complexed with a bitianp ligand (see the Supporting Information).[12] These spectra also show not only that a seemingly discrete species arises from the combination of CuH and DTBM-segphos (or bitianp), but that the presence of Ph_3P (as noted previously; see Table 4, entry 3, and the Supporting Information) in reactions at room temperature or above can alter enantioselectivities through competing background reactions that would not otherwise be observed in the presence of DTBM-segphos alone.

In summary, a powerful source of an asymmetric Stryker reagent, copper hydride complexed by Takasago's *(R)*-DTBM-segphos, has been prepared and documented to be a stable "CuH in a bottle" for easy access and use in asymmetric hydrosilylations.[13,14] Just as our "cuprate in a bottle" (i.e., (2-thienyl)Cu(CN)Li) introduced two decades ago[15] provides easy access to "higher-order" cuprate species, this reagent combination should encourage many future applications of ligand-accelerated asymmetric CuH chemistry.

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[1] T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, H. Kumobayashi, *Adv. Synth. Catal.* **2001**, *343*, 264.
[2] a) B. H. Lipshutz, K. Noson, W. Chrisman, A. Lower, *J. Am. Chem. Soc.* **2003**, *125*, 8779; b) B. H. Lipshutz, J. M. Servesko, T. B. Petersen, P. P. Papa, A. Lover, *Org. Lett.* **2004**, *6*, 1273; c) B. H. Lipshutz, H. Shimizu, *Angew. Chem.* **2004**, *43*, 2278; *Angew. Chem. Int. Ed.* **2004**, *43*, 2228; d) B. H. Lipshutz, J. M. Servesko, B. R. Taft, *J. Am. Chem. Soc.* **2004**, *126*, 8352.
[3] PMHS = polymethylhydrosiloxane; N. J. Lawrence, M. D. Drew, S. M. Bushell, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3381; we found that this silane, used as purchased from Lancaster, works well in all of the hydrosilylations reported by us to date. However, PMHS received from Acros, surprisingly, was totally ineffective in this CuH chemistry.
[4] For representative examples, see: Rh: D. A. Evans, J. S. Tedrow, K. R. Campos, *J. Am. Chem. Soc.* **2003**, *125*, 3534; B. Tao, G. C. Fu, *Angew. Chem.* **2002**, *41*, 4048; *Angew. Chem. Int. Ed.* **2002**, *41*, 3892; Ti: J. Yun, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 5640; Ru: a) G. Zhu, M. Terry, X. Zhang, *J. Organomet. Chem.* **1997**, *547*, 97; b) Y. Nishibayashi, I. Takei, S. Uemura, M. Hidai, *Organometallics* **1998**, *17*, 3420; Zn: H. Mimoun, J. Y. de Saint Laumer, L. Giannini, R. Scopelliti, C. Floriani, *J. Am. Chem. Soc.* **1999**, *121*, 6158. For a review, see: "Asymmetric Hydrosilylation and Related Reactions": H. Nishiyama, K. Itoh in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, chap. 2.
[5] a) W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291; b) D. M. Brestensky, J. M. Stryker, *Tetrahedron Lett.* **1989**, *30*, 5677; c) W. S. Mahoney, J. M. Stryker, *J. Am. Chem. Soc.* **1989**, *111*, 8818.
[6] D. H. Appella, Y. Moritani, R. Shintani, E. M. Ferreira, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9473.
[7] For the first reported uses of this alternative precursor to nonracemically ligated CuH, see: M. P. Rainka, Y. Aye, S. L. Buchwald, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5821; D. Lee, J. Yun, *Tetrahedron Lett.* **2004**, *45*, 5415.
[8] J. M. Stryker, W. S. Mahoney, J. F. Daeuble, D. M. Brestensky in *Catalysis in Organic Synthesis* (Ed.: W. E. Pascoe), Marcel Dekker, New York, **1992**, pp. 29–44.
[9] For a more detailed study on the use of microwave irradiation in reactions of ligated copper hydride, see: B. H. Lipshutz, B. A. Frieman, J. B. Unger, D. M. Nihan, *Can. J. Chem.* **2005**, *83*, 606.
[10] G. V. Goeden, K. G. Caulton, *J. Am. Chem. Soc.* **1981**, *103*, 7354.
[11] B. H. Lipshutz, W. Chrisman, K. Noson, P. Papa, J. A. Sclafani, R. W. Vivian, J. Keith, *Tetrahedron* **2000**, *56*, 2779.
[12] a) T. Benincori, E. Cesarotti, O. Piccolo, F. Sannicolo, *J. Org. Chem.* **2000**, *65*, 2043; b) T. Benincori, E. Brenna, F. Sannicolo, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin, T. Pilati, *J. Org. Chem.* **1996**, *61*, 6244.

[13] Preparation of [(DTBM-segphos)CuH] in a bottle (0.001M): An oven-dried poly-coated amber glass bottle equipped with a stirrer bar was purged under argon. Under an inert atmosphere (e.g., glove box), $Cu(OAc)_2 \cdot H_2O$ (10 mg, 0.05 mmol) and (*R*)-(−)-DTBM-segphos (59 mg, 0.05 mmol) were added followed by dry toluene (44 mL), and the reaction mixture was allowed to stir for 2 h at room temperature. PMHS (6 mL, 100 mmol) was added dropwise, and the mixture was allowed to stir for 30 min. The amber bottle was then sealed by using a standard Oxford Sure/Seal top and stored at 0 °C.

[14] Typical procedure (isophorone): A solution of [(DTBM-segphos)CuH] "in a bottle" (1 mL, 0.001M) was added to a 10-mL round-bottomed flask that had been flame dried and purged with argon. Isophorone (**3**, 150 μL, 1 mmol) was added neat and the reaction was stirred at room temperature until complete (monitored by TLC; 1 h; 4:1 hexanes/EtOAc). The reaction was diluted with THF (5 mL) and then quenched with aqueous NaOH (5 mL, 3M), after which the mixture was allowed to stir at room temperature for 2 h. After a standard extractive workup, the residue was purified by flash chromatography (4:1 hexanes/EtOAc) to afford the product ketone (*R*)-**4** (123.6 mg, 88%) as a clear oil. The product was analyzed by chiral GC (BDM-75), which indicated an *ee* value of 99%. The spectral data matched those previously reported.[2b]

[15] B. H. Lipshutz, J. A. Kozlowski, D. A. Parker, S. L. Nguyen, K. E. McCarthy, *J. Organomet. Chem.* **1985**, *285*, 437.

