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Tweaking Copper Hydride (CuH) for Synthetic Gain. A Practical, One-Pot Conversion of Dialkyl Ketones to Reduced Trialkylsilyl Ether Derivatives

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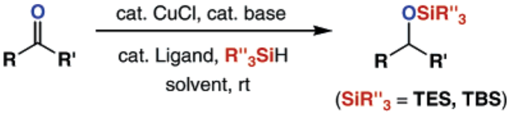
ABSTRACT



Variations in the reagents and stoichiometries used to generate CuH in situ, as well as the nature of the ligands present, have led to a very efficient and inexpensive method for effecting hydrosilylations of dialkyl ketones.

Hexameric $CuH \cdot Ph_3P$[1] was introduced by Stryker in 1988 as an excellent reagent for effecting conjugate reductions of α,β-unsaturated carbonyl compounds.[2] Its potential to reduce both aldehydes and ketones in a 1,2-sense, however, has only recently become of synthetic value.[3] Molecular hydrogen,[3a,b] Bu_3SnH,[3c] and various silanes[3d,e] can serve as stoichiometric sources of hydride, thereby allowing CuH to be used catalytically. The latter set of conditions (i.e., CuH·Ligand/silane) results in a net carbonyl hydrosilylation, which can be performed asymmetrically[4] in the presence of a nonracemic ligand (e.g., Roche's 3,5-xyl-MeO-BIPHEP[5] or Takasago's DTBM-SEGPHOS[6]) in the presence of excess PMHS at low temperatures.[7] Aryl silanes (e.g., $PhMe_2SiH$, Ph_2MeSiH), in addition to PMHS, readily participate in this process.[8] Unfortunately, both Et_3SiH (TES-H) and t-$BuMe_2SiH$ (TBS-H) lead, at best, to traces of the desired alcohol-derived silyl ethers, even in the case of aldehydes.[3e] Recently, Grubb's catalyst has been shown to activate silanes leading to hydrosilylations of ketones, although reactions with TES-H or TBS-H require heating.[9]

Because TBS is among the most valued of alcohol protecting groups,[10] we have endeavored to elucidate the experimental parameters that play a role in determining the extent of participation by a given silane. In this Letter we describe several new insights regarding the in situ generation of ligated "CuH"[11] and document that by control of stoichi-

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[1] Churchill, M. R.; Bezman, S. A.; Osborn, J. A.; Wormald, J. *Inorg. Chem.* **1972**, *11*, 1818. Churchill, M. R.; Bezman, S. A.; Osborn, J. A.; Wormald, J. *J. Am. Chem. Soc.* **1971**, *93*, 2063.

[2] Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. See also: Goeden, G. V.; Caulton, K. G. *J. Am. Chem. Soc.* **1981**, *103*, 7354.

[3] (a) Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153. (b) Chen, J.-X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789. (c) Lipshutz, B. H.; Ung, C. S.; Sengupta, S. *Synlett* **1989**, 64. (d) Brunner, H.; Miehling, W. *J. Organomet. Chem.* **1984**, *275*, C17. (e) Lipshutz, B. H.; Chrisman, W.; Noson, K. *J. Organomet. Chem.* **2001**, *624*, 367.

[4] Nishiyama, H.; Itoh, K. Asymmetric Hydrosilylation and Related Reactions. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 2.

[5] (a) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131. (b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schonholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.

[6] Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

[7] Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917.

[8] Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779.

[9] Maifeld, S. V.; Miller, R. L.; Daesung, L. *Tetrahedron Lett.* **2002**, *43*, 6263.

[10] (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991. (b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.

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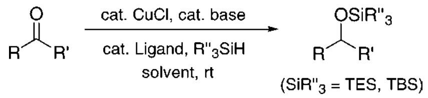
ometry a straightforward and effective method has been uncovered for converting dialkyl ketones to their TES and TBS ether derivatives at room temperature in high yields.



Previously, we have shown that both Roche's BIPHEP- and Takasago's SEGPHOS-type ligands are exceptional relative to Ph$_3$P for dramatically accelerating the reducing capabilities of in situ generated CuH.[7,8] An extensive study was undertaken to determine which mono- and/or bidentate phosphine ligands would impact the catalytic cycle such that TES ethers could readily be formed from ketones. Figure 1 shows several of the latter, which at S/L ratios of 200:1 gave complete conversion, including BIPHEP **1**, SEGPHOS **2**, Me-DuPHOS **3**,[12] BITIANP **4**,[13] and *o*-DPPB **5**.[14] Other monodentate (e.g., *n*-Bu$_3$P) or bidentate ligands (e.g., BINAP, Josiphos,[15] DIOP, and tetramethyl-BITIOP[16]) led to 0−43% conversion under otherwise identical conditions.

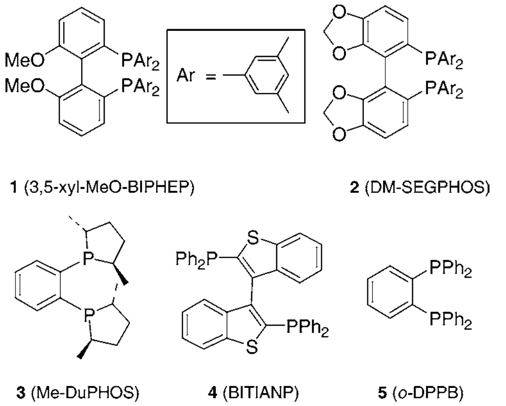


Figure 1. Effective ligands for the hydrosilylation of ketones with triethylsilane.

By lowering the amount of ligand further (to S/L = 2000: 1), only ligands **1**, **2**, and **5** led to full consumption of educt. This single modification in choice of ligand was sufficient, in the case of Et$_3$SiH,[17] to afford products of hydrosilylation on dialkyl ketones in excellent isolated yields. Figure 2 illustrates representative TES ethers formed from their precursor ketones using substrate-to-ligand ratios of 2000: 1. Decreasing the amount of silane from 5 to 1.5 equiv had essentially no impact on reaction efficiency.

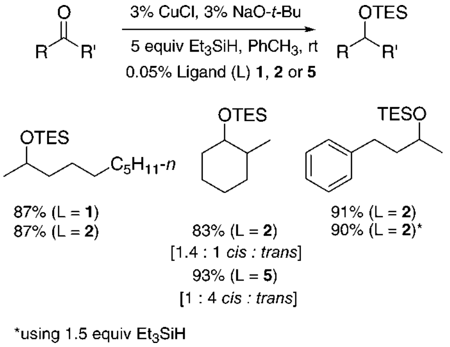
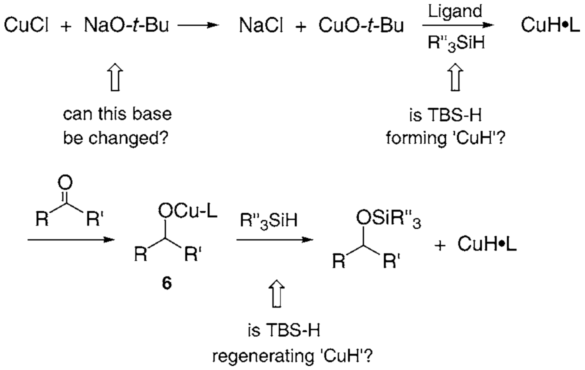


Figure 2. Representative hydrosilylations with triethylsilane.

Attempts to apply these conditions using TBS hydride (t-BuMe$_2$SiH)[18] in place of Et$_3$SiH were unsuccessful; with even greater amounts of copper (up to 5%) and ligand (up to 0.5%), only limited conversion took place. This encouraged us to question the extent of CuH formation both initially and in the catalytic cycle, since it is possible that the silane is too bulky to undergo hydride delivery either to [CuO-t-Bu]$_n$ or the initial product of ketone reduction (i.e., a copper alkoxide **6**; Scheme 1).[19] We also came to question the original prescription for generating CuH,[2] that is, what is the effect of changing the base to something other than *tert*-butoxide? With no guidance on this issue from the literature, commercially available, NaHMDS (0.6 M in toluene) was tested in combination with CuCl using benzylacetone (**7**) as educt (Scheme 2).

Scheme 1



Although the standard ratio (1:1 CuCl:base) led to 50% conversion, increasing the amount of NaHMDS to 2 equiv relative to copper drove the reaction to 96% completion. The switch to a nitrogenous base was predicated on the potential for added stabilization of copper by the amine and the well-

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(11) For an alternative set of conditions for generating and using CuH, see: Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* **2001**, *3*, 4111.

(12) Burk, M. J.; Feaster, J. E.; Nugent, W. A.;Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

(13) Benincori, T.; Brenna, E.; Sannicolo, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244.

(14) Commercially available from Aldrich, catalog no. 46, 027-3.

(15) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

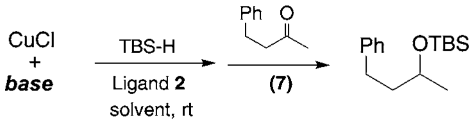
(16) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolo, F. *J. Org. Chem.* **2000**, *65*, 2043.

(17) Triethylsilane was obtained from Aldrich in a SureSeal bottle and used as received.

(18) TBS-H was purchased from Gelest and distilled prior to use.

(19) Chiu, P.;Li, Z.; Fung, K. C. M. *Tetrahedron Lett.* **2002**, *44*, 455.

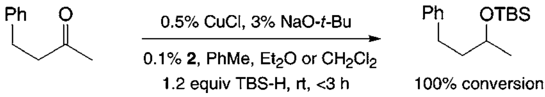
Scheme 2



base	*conversion*
1 equiv NaHMDS	43% (in Et_2O); 0% in DME)
2 equiv NaHMDS	96% (in Et_2O)

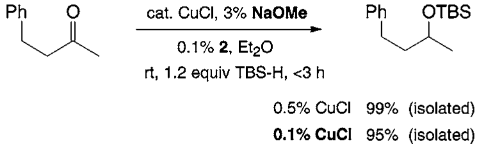
known activating and transition state stabilizing effect of silicon β to copper.[20]

In returning to NaO-*t*-Bu as base, however, with higher ratios vs CuCl, dramatic improvements were also observed, suggesting that the ratio of Cu(I) to base, rather than the nature of the base, is a key parameter. Ultimately, by lowering the percentage of CuCl (from 3% to 0.5%) while maintaining the level of base (NaO-*t*-Bu) at 3%, an essentially complete reaction was realized in only a few hours at ambient temperature (eq 1). Moreover, only 1.2 equiv of TBS silane were required, with the S/L ratio at 1000:1 (using DM-SEGPHOS, **2**). Solvents in which essentially identical rates were observed included toluene, ether, and methylene chloride. As expected, neither LiO-*t*-Bu or $LiN(TMS)_2$ in place of their sodio analogues led to an active reagent.[21]



(1)

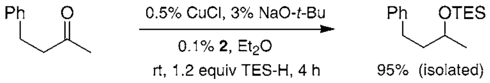
Even more remarkable was the observation that NaO-*t*-Bu could readily be replaced by commercial NaOMe. Using the same 1:6 ratio of CuCl to now NaOMe, without change of solvent (1.5 M, including the volume of silane) or S/L ratio (1000:1), complete conversion could be achieved in less than 3 h (eq 2). The amount of CuCl could also be reduced to 0.1% without impact.



(2)

Two additional examples run under these newly developed conditions on precursor ketones, which led to high isolated yields of reduced silyl ethers, are highlighted in Figure 3.

These conditions (using NaO-*t*-Bu) were also directly applicable to TES ether formation (eq 3).



(3)

Although these powerful ligands (1^5 and 2^6) are likely to be used extensively and hence become more accessible in the future, we have found that commercially available bisphosphine **5**[14] can be used in this context as long as the 1:6 ratio of CuCl to base is maintained (eq 4).

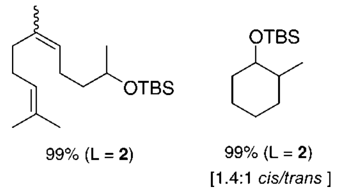
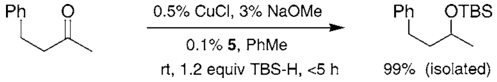


Figure 3. Representative hydrosilylations with TBS-H.



(4)

The impact of microwave irradiation on the rates of hydrosilylation of dialkyl ketones (cf. eq 4) was briefly examined. Conversions could be dramatically reduced to <15 min independent of whether reactions were run in solution or neat (Figure 4).

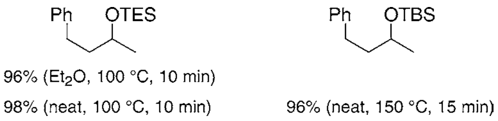
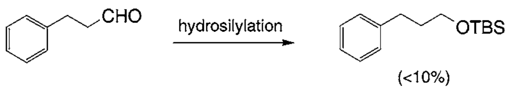
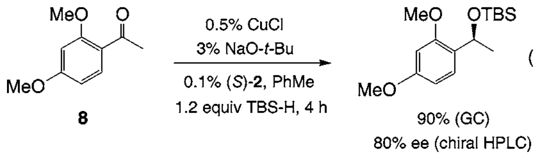


Figure 4. Representative hydrosilylations with microwave irradiation (isolated yields).

Attempts to apply these conventional solution conditions to the one-pot conversion of an aldehyde (e.g., hydrocinnamaldehyde) to the corresponding TBS-protected primary alcohol were completely unsuccessful; less than 10% yields were realized, along with considerable byproduct formation in large measure due to competing aldol-based events (eq 5). Likewise, asymmetric hydrosilylation of aryl ketone[7,8] **8** to afford a nonracemic secondary silyl ether could not be achieved at sufficiently low temperatures so as to maximize both conversion and ee; at ≥ −7 °C the ee was only 80% (eq 6).



(5)



(6)

In summary, a simple protocol has been developed for effecting the single-flask conversion of dialkyl ketones to

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[20] (a) Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43. (b) Eaborn, C. *J. Chem. Soc., Chem. Commun.* **1972**, 1255. (c) Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906.

their corresponding TES and TBS ethers based on an in situ generated, catalytic hydrido copper complex.[22] This method is competitive with the conventional two-pot approach involving metal hydride reduction followed by silyl halide/triflate protection. The unprecedented impact of the stoichiometry of base present on both the reactivity and stability of the reagent, along with the significant benefits of selected bidentate phosphine ligands, introduce new subtleties so often associated with organocopper chemistry.[24]

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

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

(22) **Representative Procedure for the Preparation of TBS Ethers from Ketones.** An oven-dried 10-mL round-bottomed flask (RBF) was equipped with a magnetic stir bar and purged with argon. Cu(I)Cl (3.0 mg, 0.03 mmol), NaOMe (9.7 mg, 0.18 mmol), and DM-SEGPHOS (5.1 mg, 0.006 mmol) were added as solids and stirred in diethyl ether (2.8 mL, 1.5 M) for 20 min. The RBF was then charged with *tert*-butyldimethylsilane (1.2 mL, 7.2 mmol, 1.2 equiv) followed by benzylacetone (0.9 mL, 6.0 mmol). The reaction was stirred at room temperature and monitored by TLC. Upon completion (3 h) the mixture was exposed to air for 20 min and then filtered through a pad of Celite and activated charcoal. The filter cake was washed three times with 10 mL of hexanes. The filtrate was concentrated in vacuo to afford 1.57 g (99%) of the known[23] product as a colorless oil.

(23) Pilcher, A. S.; DeShong, P. S. *J. Org. Chem.* **1993**, *58*, 5130.

(24) Individual control experiments designed to test the requirement for CuCl, base, and the ligand were conducted. In all cases, whether under conventional or microwave conditions, all three components were essential for hydrosilylation to occur.