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Copper-catalyzed asymmetric hydrosilylation of ketones using air and moisture stable precatalyst $Cu(OAc)_2{\cdot}H_2O$

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Abstract—Air and moisture stable copper(II) salts can be used to catalyze the hydrosilylation of aromatic ketones. The combination of catalytic amounts of copper(II) acetate or copper(II) acetate monohydrate and BINAP in the presence of organosilanes as the stoichiometric reducing agent generates an active catalyst for the reduction of ketones.

Asymmetric reduction of prochiral ketones by homogeneous transition metal complexes is of great interest in organic synthesis. Hydrosilylation reaction employing organosilanes as the stoichiometric reductant provides an attractive route to optically active secondary alcohols.[1] A variety of Rh complexes[1] since early 1970s, and recently with titanium complexes[2] and ligated zinc species[3] were studied in the enantioselective hydrosilylation of ketones.

Recently, the use of CuH complexes in hydrosilylation reactions became an interesting research field. The use of copper for hydride delivery was initially studied with Stryker's reagent, $[CuH{\cdot}PPh_3]_6$ as a stoichiometric reducing reagent in conjugate reduction of enones.[4] Later, the use of reductants such as hydrogen gas[4,5] and silanes[6] enabled the generation of a Cu–H complex in a catalytic fashion. Asymmetric reactions catalyzed by a Cu–H complex were also reported where an active catalyst was generated in situ from CuCl/NaO*t*-Bu and a chiral diphosphine ligand for the highly enantioselective reduction of α,β-unsaturated carbonyl compounds[7] and aromatic ketones.[8] In situ generation method of CuO*t*-Bu from CuCl/NaO*t*-Bu became favored due to inconveniences associated with extra steps in separation[9] and instability of CuO*t*-Bu.[10] However, in cases where the presence of NaCl inhibited the catalytic activity, the use of isolated CuO*t*-Bu was necessary.[11] Besides Stryker's reagent and copper alkoxides, only copper fluorides were reported as useful catalyst precursors in the Cu–H catalyzed hydrosilylation of ketones.[12] Therefore, we became interested in finding other easy-to-handle copper sources that can generate an active copper hydride catalyst with no formation of salts. We report here the use of air and moisture stable $Cu(OAc)_2{\cdot}H_2O$ in combination with a chelating diphosphine for the hydrosilylation of aromatic ketones.

In preliminary experiments, we focused on whether Cu(II) salts can be used instead of Cu(I) salts as a precursor. We tested and compared various reaction conditions by changing copper sources and silanes using (*S*)-BINAP[13] as ligand (Table 1). The combination of copper(II) chloride with NaO*t*-Bu (entry 2) was as effective as copper(I) chloride in the hydrosilylation of acetophenone. The methodology employing copper(I) or copper(II) chloride, however, requires NaO*t*-Bu for activation with the concomitant production of NaCl as a side product. We searched for other copper sources and were pleased to find that copper carboxylates, especially copper acetates could be activated with no additives in the presence of silanes. Both copper(I) acetate and copper(II) acetate were effective in the reduction of acetophenone (entries 3 and 4) and especially, the copper(II) acetate system showed comparable reactivity to the CuCl/NaO*t*-Bu or $CuCl_2$/NaO*t*-Bu systems. Furthermore, air and moisture stable $Cu(OAc)_2{\cdot}H_2O$ resulted in increased reaction rates leading the reaction to completion in 7 h (entry 6). We subsequently looked into variation of the silane component in the reaction. The use of different silanes did

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Keywords: Hydrosilylation; Copper(II) precursor; Cu–H.

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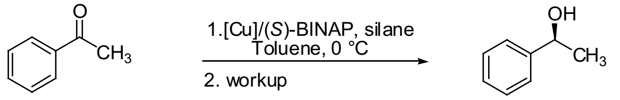
Table 1. Hydrosilylation of acetophenone using various copper precursors[a]



Entry	Cu precursor (mol%)	Silane (equiv)	Time (h)[b]	Yield (%)	Ee (%)[c]
1	CuCl (5)/NaO*t*-Bu (5)	PMHS (5)	24	87	75
2	$CuCl_2$ (3)/NaO*t*-Bu (9)	Ph_2SiH_2 (1)	12	96	80
3	CuOAc (3)	Ph_2SiH_2 (1)	21	96	80
4	$Cu(OAc)_2$ (3)	Ph_2SiH_2 (1)	10	92	80
5	$Cu(OAc)_2$ (3)	Ph_2SiH_2 (0.6)	30	81	80
6	$Cu(OAc)_2{\cdot}H_2O$ (3)	Ph_2SiH_2 (1)	7	94	79
7	$Cu(OAc)_2{\cdot}H_2O$ (3)	$PhSiH_3$ (1)	<1	90	80
8	$Cu(OAc)_2{\cdot}H_2O$ (3)	PMHS (5)	17	85	79
9[d]	$Cu(OAc)_2{\cdot}H_2O$ (3)	Ph_2SiH_2 (1)	2.5	85	82[e]

[a] Reactions were performed with acetophenone (1 mmol, 1 M), toluene, and 1 equiv Ph_2SiH_2 or 5 equiv PMHS.

[b] Time needed for complete conversion of substrate.

[c] Determined by chiral GC analysis using a Chiralsil-DEX CB column.

[d] (*R*)-*p*-Tol-BINAP (=2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl) was used instead of (*S*)-BINAP.

[e] (*R*)-1-Phenylethanol was obtained.

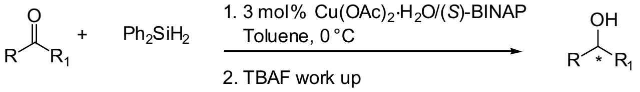
not affect the enantioselectivity of the procedure. While phenylsilane is the most active reductant (entry 7),[14] the inexpensive polymer siloxane PMHS can be employed (entry 8), albeit with slower reaction rates. In addition, the two H's of Ph_2SiH_2 could be used for the reduction successively with no effect on ee, but slow reaction rates were observed (entry 5).

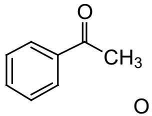
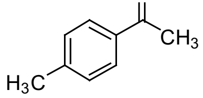
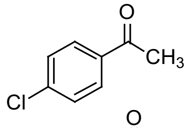
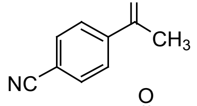
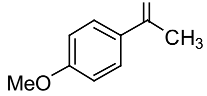
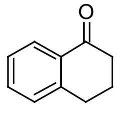
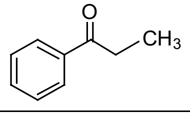
Several aromatic substrates were reduced to the corresponding secondary alcohols by employing a catalytic amount of $Cu(OAc)_2{\cdot}H_2O$ and (*S*)-BINAP in the presence of 1 equiv Ph_2SiH_2[15] in toluene at 0 °C, and the results are shown in Table 2.[16] In general, the $Cu(OAc)_2{\cdot}H_2O$ system performs better than the $Cu(OAc)_2$ system (entries 2 and 4 vs 3 and 5).[17] Aromatic ketones possessing an electron withdrawing substituent at the *para* position afforded the corresponding alcohol products in shorter reaction times with good levels of enantioselectivity (entries 4 and 6). Longer reaction times were required for electron-rich substrates (entry 7) and substrates bearing bulkier alkyl groups than methyl (entries 8 and 9[18]).

A proposed mechanism is shown in Scheme 1. We postulate that in the initiation step, σ-bond metathesis between $Cu(OAc)_2$ and the hydrosilylation reagent takes place, generating a copper hydride species. At this stage, we are not sure whether the active catalytic species is a copper(I) hydride or copper(II) hydride.[19] The resulting copper hydride species reacts with a ketone substrate, resulting in formation of a copper alkoxide that subsequently undergoes σ-bond metathesis with the organosilane to afford the silyl ether.[20] This mechanism is consistent with the observation that the type of organosilanes affects the reaction rates but not the enantioselectivity of products.

In summary, we have shown that the in situ generation protocol of Cu–H from CuCl/NaO*t*-Bu could be replaced by the copper(II) precursor, $Cu(OAc)_2{\cdot}H_2O$ for the asymmetric hydrosilylation of ketones. This conve-

Table 2. Asymmetric hydrosilylation of aromatic ketones using copper(II) acetate as a precursor



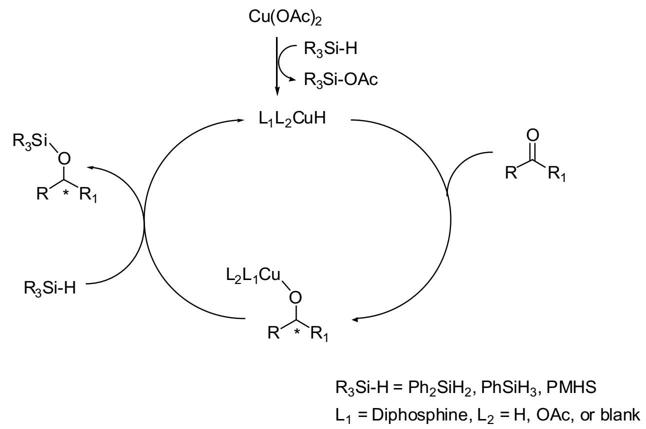
Entry	Substrate	Time (h)	Yield (%)[a]	Ee (%)[b]
1		7	94	79
2		8	93	85
3[c]		15	95	85
4		2	90	87
5[c]		12	96	86
6		2	83	89
7		22	81	86
8		31	96	81
9[d]		1	86	85

[a] Isolated yields.

[b] Determined by chiral GC using a Chiralsil-DEX CB column. All the alcohol products obtained with (*S*)-BINAP have the (*S*) configuration.

[c] $Cu(OAc)_2$ was used instead of $Cu(OAc)_2{\cdot}H_2O$.

[d] $PhSiH_3$ was used instead of Ph_2SiH_2 due to slow conversion of the ketone in the presence of Ph_2SiH_2.



Scheme 1.

nient and reliable Cu–H generation protocol is advantageous over the existing methods; the air and moisture stable precursor can be activated by the hydrosilylating reagent itself, and thus obviates the need to use alkoxide bases for catalyst activation and prevents the formation of salts in the reaction medium. Studies aimed at expanding the use of $Cu(OAc)_2 \cdot H_2O$ in Cu–H catalyzed reactions, especially to the ones that are inhibited by inorganic salts as well as examining mechanistic features of an active catalytic species generated from the copper(II) precursor are underway in our laboratory.

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References and notes

1. (a) Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 2; (b) Nishiyama, H. In *Comprehensive Asymmetric Catalysis*; Jacobson, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 6.3 and references cited therein.
2. (a) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640; (b) Halterman, R. L.; Ramsey, T. M.; Chen, Z. *J. Org. Chem.* **1994**, *59*, 2642; (c) Imma, H.; Mori, M.; Nakai, T. *Synlett* **1996**, *1229*.
3. Mimoun, H.; Laumer, J. Y.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158.
4. (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291; (b) Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 3237.
5. Chen, J.-X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789.
6. (a) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627; (b) Lipzhutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779.
7. (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473; (b) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797.
8. (a) Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917; (b) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779; (c) Lipshutz, B. H.; Lower, A.; Noson, K. *Org. Lett.* **2002**, *4*, 4045.
9. For the preparation of CuO*t*-Bu, see: Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 658.
10. Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749.
11. The inhibitory effect of inorganic salts was observed in the conjugate reduction of β,β-disubstituted nitroalkenes: Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793.
12. Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* **2001**, *3*, 4111.
13. The hydrosilylation of ketones catalyzed by a ligated Cu(I)–H complex belongs to the category of ligand-accelerated catalytic reactions.[8] (*S*)-BINAP (=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) was chosen because it is readily available although it is not the best ligand for the reaction.
14. See also entry 9 in Table 2.
15. Ph_2SiH_2 was chosen as the stoichiometric reducing agent because it is better for reactivity comparison of various ketone substrates than highly active $PhSiH_3$.
16. General procedure for the asymmetric hydrosilylation of ketones: $Cu(OAc)_2 \cdot H_2O$ (6.0 mg, 0.03 mmol) and (*S*)-BINAP (18.7 mg, 0.03 mmol) were placed in an oven-dried Schlenk tube and toluene (0.6 mL) was added under nitrogen. The resulting mixture was cooled to 0 °C, and then Ph_2SiH_2 (0.19 mL, 1 mmol) was added. The color of the resulting solution turned from blue to green in 5 min and the reaction was further stirred for 10–20 min. Ketone substrate (1 mmol) was added by syringe, followed by addition of toluene (0.4 mL) for washing. The reaction was stirred at 0 °C until no starting material was detected by TLC. Upon completion of the reaction, the reaction mixture was quenched with water and transferred to a round-bottom flask with an aid of Et_2O (10 mL), and then TBAF (1.0 M in THF, 1.2 mL) was added. The reaction mixture was stirred vigorously stirred for 0.5 h. The layers were separated and the aqueous layer was extracted with Et_2O (2×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel chromatography to afford the desired product.
17. The role of H_2O is unclear at this stage.
18. The reaction was incomplete even after 25 h when 1 equiv Ph_2SiH_2 was employed.
19. The same active catalytic species, Cu(I)–H might be generated from both copper(I) and copper(II) sources, judging from the fact that the same levels of enantioselectivity were obtained with both precursors. However, more studies to identify the exact nature of a catalytic species generated from the Cu(II) salt are necessary.
20. A similar mechanism was proposed for (NHC)Cu-complex-catalyzed hydrosilylation of ketones (NHC = *N*-heterocyclic carbene), see: Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2004**, *23*, 1157.