

Efficient Enantioselective Hydrosilylation of Ketones Catalyzed by Air Stable Copper Fluoride–Phosphine Complexes

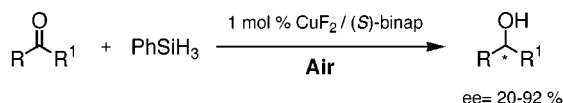
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ABSTRACT



Copper(II) fluoride–chiral diphosphine systems catalyze the hydrosilylation of several ketones with moderate to excellent enantioselectivities. An oxygen acceleration effect was observed and led to a practical protocol with low catalyst loading.

The selective reduction of unsaturated double bonds (C=O, C=N, C=C) catalyzed by homogeneous transition metal complexes is of great interest in organic synthesis.¹ Hydrosilanes, which are by themselves inert toward nonactivated carbonyl compounds, become suitable reductive agents for the hydrosilylation of these compounds in the presence of catalytic amounts of rhodium or titanium complexes.² However, in most cases, the cost of the catalysts as well as the rigorously anaerobic conditions required in those reactions have limited their use in the laboratory. More recently, new methods for the asymmetric hydrosilylation of prochiral ketones using inexpensive hydride sources such as PMHS (polymethylhydrosiloxane) and easily accessible catalysts based on titanium,³ zinc,⁴ and tin⁵ have opened a new pathway in this area in the view of practical applications.

The potential of copper for hydride delivery was recognized early, but it had mainly been used as a stoichiometric reducing agent. It was later shown that phosphine–copper-

(I) systems such as [CuH(PPh₃)]₆ or CuCl/PPh₃/Bu₄NF act as a catalyst for the hydrogenation as well as the 1,4-reduction of enones or enals in combination with silanes.⁶ Related work on copper(I)–phosphine systems has shown that highly enantioselective 1,4-reduction of α,β -unsaturated esters (80–92% enantiomeric excess (ee)) and cyclic enones (87–98% ee) can be achieved with a catalyst formed from CuCl/NaOtBu/chiral diphosphine (binap or BIPHEMP) and PMHS.⁷ Very recently, Lipshutz has also demonstrated the effectiveness of [CuH(PPh₃)]₆ for the hydrosilylation of aromatic and nonconjugated aldehydes and ketones.⁸ This report prompted us to display our own results on the

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asymmetric hydrosilylation of prochiral ketones by easy-to-handle copper-based catalysts.

We report here the asymmetric reduction of ketones by a copper-catalyzed hydrosilylation reaction. On a preliminary screening, various copper salts and ligands were combined and tested in hydrosilylation of acetophenone when using phenylsilane as a stoichiometric reducing agent (Figure 1).

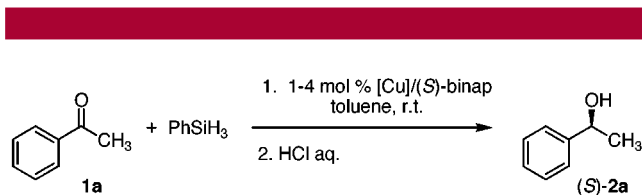


Figure 1. Asymmetric hydrosilylation of acetophenone catalyzed by modified copper fluoride catalysts.

A study on the reaction parameters led us to point out some special features (Table 1). First, it was shown that a

Table 1. Hydrosilylation of Acetophenone by Diphosphine-Modified Copper Fluoride Catalysts^a

entry	precursor (mol %)	atm.	time (h)	conv. (%) ^b	ee (%)
1	CuF ₂ /dppb (2)	Ar	8	90	
2	CuF ₂ /dppb (2)	air	2	99	
3	CuF ₂ /(S)-binap (4)	Ar	16	>99	79
4	CuF ₂ /(S)-binap (1)	air	2	98	78
	CuF ₂ /(S)-binap (0.5)		6	94	78
5	[CuF(PPh ₃) ₃ ·MeOH]/dppb (4)	Ar	2	90	
6	[CuF(PPh ₃) ₃ ·MeOH]/(S)-binap (4)	Ar	40	91	71
7	[CuF(PPh ₃) ₃ ·MeOH]/(S)-binap (2)	air	1	100	74
8	CuI/Ph ₃ SiF ₂ NBu ₄ /(S)-binap (1)	Ar	24	40	76
9	[PPh ₃ CuH] ₆ /(S)-binap (2)	Ar	16	95	80
10	CuF ₂ /(S)-binap (4) ^c	air	54	93	74
11	CuF ₂ /(S)-binap (4) ^d	air	24	94	76
12	CuF ₂ /(S)-binap (4) ^e	Ar	24	100	72

^a Reactions were conducted at room temperature with acetophenone (0.25 M), toluene, and PhSiH₃ (1.2–1.5 equiv) except when another silane is indicated. ^b Determined by GC. ^c PMHS (5 equiv) and acetophenone (1 M). ^d PMHS (5 equiv) and acetophenone (1M in THF). ^e Me(EtO)₂SiH (1.5 equiv).

fluoride ligand on the copper precursor was essential to generate an active catalyst. Thus, combinations of diphosphine ligands with either copper(II) or copper(I) fluoride precursors (CuF₂ or [CuF(PPh₃)₃]) gave short reaction times at low catalyst loadings. No reaction was observed when other copper halides were used. However, when copper(I) iodide was combined with binap and an anhydrous fluoride source (entry 8), some catalytic activity was restored. It was also noted that the use of a diphosphine ligand was crucial for the catalytic activity as monophosphine- and bidentate nitrogen-based ligands did not show any activity. Among the various diphosphines tested, the best results were obtained with dppb and binap. It should also be noted that the copper

fluoride sources used are stable to the atmosphere and can be either bought (CuF₂) or easily prepared ([CuF(PPh₃)₃]).⁹

At this stage, the role of the fluoride is still unclear, but some control experiments allowed us to think that it acts essentially in the initiation step of the catalytic cycle by activating the Si–H bond to generate a copper(I) hydride species. This hypothesis was supported by the fact that the combination of a copper hydride complex [CuH(PPh₃)]₆ and binap showed a significant catalytic activity, while no conversion was obtained when [CuH(PPh₃)]₆ was used alone (entry 9). However, this should be supported by some spectroscopic evidence of the generation of a copper hydride complex.

The most important feature of the present CuF₂/diphosphine/hydrosilane system is that experiments are preferably run in air. Not only is the system air stable, at least for the reaction time, but also the reactivity is highly enhanced when the reaction is carried out under oxygen instead of an argon atmosphere (entries 1–4). While 16 h were needed to reach complete conversion of acetophenone with 4 mol % CuF₂ and (S)-binap under argon (entry 3), a reaction carried out in air was complete after 2 h with only 1 mol % catalyst and without loss of the enantioselectivity (entry 4). This acceleration effect was even more pronounced when [CuF(PPh₃)₃·MeOH] was used as a copper source (entries 6–7). This observed reactivity contrasts the reported sensitivity of copper hydride to oxygen.^{7a,10} Although we are not able at the present time to explain this effect, it seems that oxygen plays a role in the formation of the precatalyst at the early stage of the catalytic cycle.¹¹

Finally, we have tried various silanes with almost no effect on the enantioselectivity. While the trihydrophenylsilane PhSiH₃ is the most active reducing agent with our catalytic system, two cheaper and readily available siloxanes can be employed, i.e., PMHS (entries 10 and 11) and methyldiethoxysilane, Me(OEt)₂SiH (entry 12), albeit with slower reaction rates.

After optimization, we were able to build up a practical and low-cost catalytic protocol for the asymmetric hydrosilylation of ketones. It should be noted that undried glassware and undistilled toluene can be used as the system is quite compatible with the presence of traces of water. Low catalyst loading (as low as 0.5 mol % CuF₂/binap) can be used in some cases (Table 1, entry 4). Several ketones could be converted in their corresponding secondary alcohols by using anhydrous CuF₂ and (S)-binap in toluene at room temperature, in the presence of phenylsilane (Figure 2, Table 2).¹²

(9) [CuF(PPh₃)₃·MeOH] is easily prepared from hydrated copper(II) fluoride: Gulliver, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, *52*, 153–159. The use of unmodified [CuF(PPh₃)₃·2EtOH] for the reduction of ketones by hydrosilanes was first reported by Mori in stoichiometric conditions: (a) Mori, A.; Fujita, A.; Nishihara, Y.; Hiyama, T. *Chem. Commun.* **1997**, 2159–2160. (b) Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573–4582.

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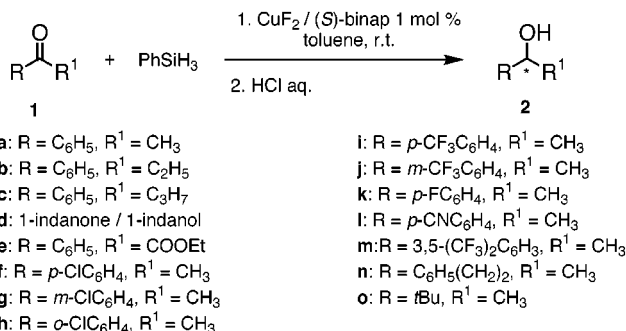


Figure 2. Asymmetric reduction of ketones.

Complete reduction of aromatic ketones proceeds in a few hours (2–14 h) with excellent enantioselectivities (ee up to 92%). In general, 1 mol % Cu was used for the complete reduction of the substrate. However, in some cases, complete conversion required an increase of the catalyst loading to 2 mol % (entry 4). Under the conditions used, several functional groups (e.g., ester, halides, cyanide, CF₃) remained unaffected. The reaction proceeds cleanly to give the corresponding aromatic alcohols after hydrolysis. Introduction of withdrawing para-substituents on acetophenone (**1f**, **1i**, **1k**, **1l**) produced a small amelioration of enantioselectivity (82–86% ee), while total conversion was reached in 3–8 h.

Different groups (Me, Et, Pr, COOEt, CF₃, cyclic chain) in an α -position to the carbonyl were also examined. The α -ketoester **1e** was selectively reduced to the corresponding α -hydroxyester **2e** with an excellent yield (100% in 3 h) but a very low ee (11%). Longer reaction times were required

(12) General procedure for the hydrosilylation of ketones in air: a 25 mL round-bottomed flask was charged with copper fluoride (2 mg, 0.02 mmol, 1 mol %) and (*S*)-binap (13 mg, 0.02 mmol, 1 mol %), and a stirring bar was added in air. Toluene (8 mL) was added, and the mixture was stirred for 5–10 min. Phenylsilane (0.30 mL, 2.4 mmol, 1.2 equiv) and acetophenone (0.235 mL, 2 mmol) were sequentially added under vigorous stirring, and the flask was stoppered. Conversion and ee determination were followed by gas chromatography performed on aliquots. Hydrolysis of the silyl ether by 1 N HCl and workup gave the crude alcohol. Bulb-to-bulb distillation gave analytically pure product (194 mg, 79% yield). GC analysis on a chiral column gave a 78% ee.

Table 2. Asymmetric Reduction of Ketones by PhSiH₃ Using CuF₂ and (*S*)-Binap, in Air^a

entry	substrate	time (h)	conversion (%) ^b	yield of 2 (%) ^c	ee (%) ^d
1	1a	2	98	79	78 (<i>S</i>)
2	1b	9	97	82	84 (<i>S</i>)
3	1c	8	100	80	92 (<i>S</i>)
4	1d	14 ^e	100	80	70 (<i>S</i>)
5	1e	3	100	99	11 (<i>R</i>)
6	1f	4	96	100 (7 h)	85 (<i>S</i>)
7	1g	8	63	97 (24 h)	75 (<i>S</i>)
8	1h	8	82	96 (20 h)	64 (<i>S</i>)
9	1i	3	100	89	86 (<i>S</i>)
10	1j	3	95	100 (6 h)	80 (<i>S</i>)
11	1k	4	100	100	82 (<i>S</i>)
12	1l	8	95	100 (16 h)	86 (–)
13	1m	3	100	88	85 (–)
14	1n	8	100	93	20 (<i>R</i>)
15	1o	29	75		20

^a Reactions were conducted at room temperature with substrate (2 mmol, 0.25M), toluene (8 mL), CuF₂ (1%), (*S*)-binap (1%), and PhSiH₃ (1.2 equiv).

^b Substrate conversion determined by GC. ^c Isolated yield (time in parentheses for 100% conversion). ^d Determined by GC using a chiral DEX CB column (25 cm × 0.25 mm × 0.25 μ m). Absolute configurations were determined by comparison of optical rotations with literature values. ^e CuF₂ (2%) and (*S*)-binap (2%).

for bulkier alkyl groups (entries 2–3), while the enantioselectivity was slightly affected. It should also be noted that dialkyl ketones can be reduced under these conditions, albeit with reduced enantioselectivities (entries 14 and 15).

In conclusion, a practical and efficient method has been developed that allowed the asymmetric reduction of ketones in aerobic and mild conditions. The catalyst could be activated by the hydrosilylating agent itself. Moreover, the system displays a high level of functional group compatibility. Studies to clarify the reaction mechanism are underway in our laboratory.

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