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Copper(II)-Catalyzed Hydrosilylation of Ketones Using Chiral Dipyridylphosphane Ligands: Highly Enantioselective Synthesis of Valuable Alcohols

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Abstract: In the presence of $PhSiH_3$ as the reductant, the combination of enantiomeric dipyridylphosphane ligands and $Cu(OAc)_2{\cdot}H_2O$, which is an easy-to-handle and inexpensive copper salt, led to a remarkably practical and versatile chiral catalyst system. The stereoselective formation of a selection of synthetically interesting β-, γ- or δ-halo alcohols bearing high degrees of enantiopurity (up to 99.9% enantiomeric excess (*ee*)) was realized with a substrate-to-ligand molar ratio (S/L) of up to 10000. The present protocol also allowed the hydrosilylation of a diverse spectrum of alkyl aryl ketones with excellent enantioselectivities (up to 98% *ee*) and exceedingly high turnover rates (up to 50000 S/L molar ratio in 50 min reaction time) in air, under very mild conditions, which offers great opportunities for the preparation of various physiologically active targets. The synthetic utility of the chiral products obtained was highlighted by the efficient conversion of optically enriched β-halo alcohols into the corresponding styrene oxide, β-amino alcohol, and β-azido alcohol, respectively.

Keywords: alcohol · asymmetric catalysis · copper · enantioselectivity · hydrosilylation

Introduction

Discovery of truly efficient methods leading to enantiomerically enriched secondary alcohols, which constitute valuable intermediates for the preparation of structurally interesting and biologically active compounds, is a significant objective in organic synthesis.[1] The enantioselective hydrosilylation of ketones, as a desirable transformation towards chiral alcohols, has gained considerable attention due to the mild reaction conditions required and because of the operational simplicity.[2] Since the early reports that appeared three decades ago,[3] a variety of transition-metal catalysts, especially those based on rhodium,[4] ruthenium,[5] and iridium,[6] as well as some less expensive metals such as titanium,[7] zinc,[8] tin,[9] iron,[10,11] and cobalt,[12] have been exploited and applied in the asymmetric hydrosilylation of prochiral ketones. With respect to the stereoselective hydrosilylation mediated by chiral copper catalysts,[2f–h,13] a landmark work was described in 1984 by Brunner and Miehling[14] for which CuH-DIOP[15] asymmetric catalysis was used for the reduction of acetophenone with 38.8% *ee*. A significant breakthrough was accomplished by Lipshutz et al. in 2001,[13b–d] whereby an especially active $Cu^{I}Cl$/diphosphane (e.g., 3,5-xyl-MeO-BIPHEP[16] or DTBM-SEGPHOS[17])/*t*BuONa catalyst system was developed to effect highly enantioselective hydrosilylation of a broad assortment of prochiral ketones,[18] with substrate-to-ligand molar ratios (S/L) of up to 100000. Concomitant with Lipshutz's work in 2001, Riant and coworkers[19] disclosed an air-accelerated and base-free CuF_2/BINAP[20]/$PhSiH_3$ system that catalyzed the reduction of some alkyl aryl ketones with moderate to excellent enantioselectivities. Since then, a variety of effective copper catalysts that derive from enantiomerically pure diphosphanes (such as BINAP, DTBM-SEGPHOS or MeO-BIPHEP derivatives) and $Cu(OAc)_2{\cdot}H_2O$,[21] $[CuF(PPh_3)_3{\cdot}2MeOH]$,[22] CuCl[23] or some heterogeneous copper sources,[24] have been applied in the relevant hydrosilylation reactions. Additionally, some efficient copper catalysts bearing chiral monophosphane[25] or tetraoxazoline[26] ligands have also been developed for the hydrosilylation of simple ketones.

We have recently established a particularly efficacious asymmetric hydrosilylation system involving CuF_2, dipyridylphosphane (Scheme 1, P-Phos **1a** or Xyl-P-Phos **1b**),[27] and $PhSiH_3$, that rendered competitive levels of enantioinduction (up to 98% *ee*) and activity for the reduction of aryl

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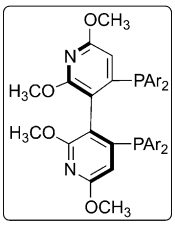
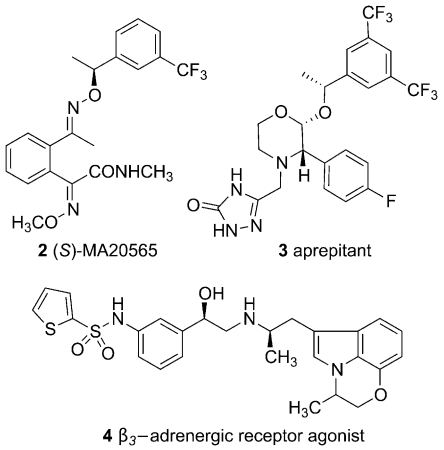


(*S*)-**1a**, Ar = C_6H_5, (*S*)-P-Phos
(*S*)-**1b**, Ar = 3,5-$(CH_3)_2C_6H_3$, (*S*)-Xyl-P-Phos

Scheme 1. Chiral dipyridylphosphane ligands.

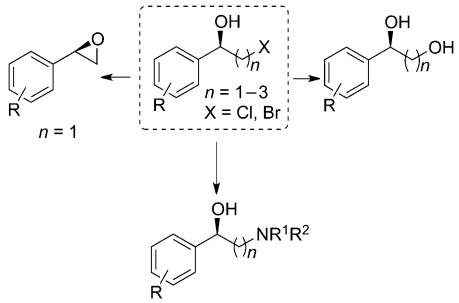
alkyl, diaryl, and hetero-aromatic ketones under ambient conditions.[28] The excellent practical potential of this catalyst system prompted us to further broaden its application scope. Particularly, we were very interested in the reduction of some ketonic substrates, the products of which could serve as key synthetic intermediates of some structurally versatile or physiologically active targets such as the wide-spectrum agricultural fungicide (*S*)-MA20565 (**2**),[29a] the NK-1 receptor antagonist aprepitant (**3**),[29b] and the β_3-adrenergic receptor agonist **4**[29c] (Scheme 2).

Optically active halo alcohols are especially significant structural elements for the formation of biologically active compounds, such as chiral epoxides, diols, and amino alcohols, due to the versatility conferred by the presence of the halogen that can readily act as a good leaving group



Scheme 2. Selected valuable bioactive targets derived from chiral alcohols.

(Scheme 3). Thus, a number of strategies for the asymmetric reduction of halo-substituted ketones to enantiomeric halo alcohols, such as hydroboration catalyzed by chiral oxazaborolidines,[30] transfer hydrogenation mediated by chiral Rh[31] or Ru catalysts,[32] and the Ru-catalyzed hydrogenation,[33] have been accordingly developed with good to excellent enantioselectivities. Nevertheless, non-precious-metal-catalyzed stereoselective hydrosilylation methods that can be used to generate these kinds of alcohols has received relatively little attention[7f,18c,34] and remain a challenge. In this contribution, it was of great interest to note that, in the



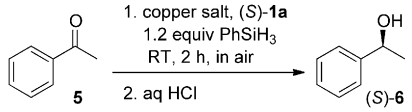
Scheme 3. Examples of synthetic applications of chiral β-, γ- or δ-halo alcohols.

presence of catalytic amounts of (*S*)-**1** plus an easy-to-handle and inexpensive copper salt, $Cu(OAc)_2{\cdot}H_2O$, a series of α-, β- and γ-halo substituted ketones were reduced quantitatively by employing $PhSiH_3$ as the hydride source with up to 99.9% *ee* (S/L up to 10000), which, to the best of our knowledge, represented the highest enantioselectivities achieved to date through hydrosilylation of such educts. The synthetic utility of the method was highlighted by the efficient transformation of representative optically enriched β-halo alcohols into the corresponding styrene oxide, β-amino alcohol, and β-azido alcohol, respectively. Furthermore, under ambient atmosphere and mild reaction conditions, the present catalyst system displayed good to excellent stereoselectivities (up to 98% *ee*) and extraordinarily high reactivities (S/L up to 50000 in 50 min reaction time on a 25 g substrate scale) for a diverse range of alkyl aryl ketones.

Results and Discussion

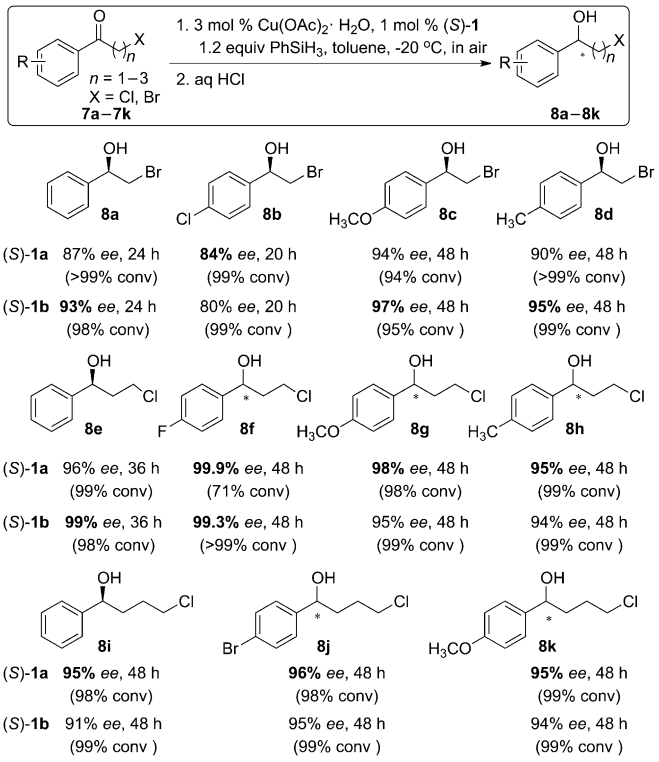
Optimization of the copper-catalyzed asymmetric hydrosilylation (Table 1): Previous studies on the copper-catalyzed hydrosilylation reactions indicated that the counter-ion of copper precursors often played a crucial role in the generation of an active catalyst.[19,22,28] This prompted us to further broaden the scope of the application of copper salts to find a more practical copper source with both higher efficacies and wider applications. In the initial study, multifarious copper precursors were tested in the reduction of the model substrate acetophenone **5** in air by utilizing 0.1 mol% (*S*)-**1a** ligand and 1.2 equivalents of $PhSiH_3$ as the reductant (Table 1). The results indicated that the extent of conversions or the enantioselectivities achieved varied considerably as a function of the counter-ion of copper salts. Similar to the results obtained under an N_2 atmosphere,[28a] both anhydrous and hydrated CuF_2 furnished (*S*)-1-phenylethanol **6** quantitatively after 2 h with 79 and 76% *ee* (Table 1, entries 1 and 2), respectively. Whereas all other copper(I)- or copper(II)-halides showed poor activities (Table 1, entries 3–7). Promising results were also obtained by applying CuOAc, $Cu(OAc)_2$, or $Cu(OAc)_2{\cdot}H_2O$ as the copper precursor (Table 1, entries 8–10). With respect to the other copper salts, including CuCN, $Cu(acac)_2$ (acac: acetylacetonate),

Table 1. Effects of counter-ions and solvents on the copper-catalyzed asymmetric hydrosilylation of **5**.[a]



	Copper salt (mol %)	S/L	Solvent	Conv [%][b]	*ee* [%][c]
1	CuF_2 (2)	1000	toluene	98	79
2	$CuF_2{\cdot}2H_2O$ (2)	1000	toluene	>99	76
3	CuCl (2)	1000	toluene	<5	76
4	CuI (2)	1000	toluene	<5	68
5	$CuCl_2$ (2)	1000	toluene	<5	64
6	$CuCl_2{\cdot}H_2O$ (2)	1000	toluene	<5	8
7	$CuBr_2$ (2)	1000	toluene	<5	48
8	CuOAc (2)	1000	toluene	>99	76
9	$Cu(OAc)_2$ (2)	1000	toluene	>99	75
10	$Cu(OAc)_2{\cdot}H_2O$ (2)	1000	toluene	>99	79
11	CuCN (2)	1000	toluene	<5	76
12	$Cu(acac)_2$ (2)	1000	toluene	19	76
13	$Cu(OCH_3)_2$ (2)	1000	toluene	11	34
14	$CuF(PPh_3)_3{\cdot}2EtOH$ (2)	1000	toluene	82	41
15	$Cu(CO_2CF_3)_2{\cdot}xH_2O$ (2)	1000	toluene	39	<5
16	$Cu(OAc)_2{\cdot}H_2O$ (4)	250	dioxane	99	77
17	$Cu(OAc)_2{\cdot}H_2O$ (4)	250	THF	25	13
18	$Cu(OAc)_2{\cdot}H_2O$ (4)	250	CH_2Cl_2	<5	51
19	$Cu(OAc)_2{\cdot}H_2O$ (4)	250	$CHCl_3$	<5	70
20	$Cu(OAc)_2{\cdot}H_2O$ (4)	250	CH_3CN	7	47
21[d]	$Cu(OAc)_2{\cdot}H_2O$ (4)	50	toluene	>99	91

[a] Reaction conditions: substrate (36–361 mg; substrate concentration = 0.3–0.5 mol L^{-1}). [b] The conversions were determined by NMR and GC analyses. [c] The *ee* values were measured by chiral GC analysis. The absolute configuration was determined by comparing the retention time with known data. [d] Reaction time: 24 h, reaction temperature: −20 °C.



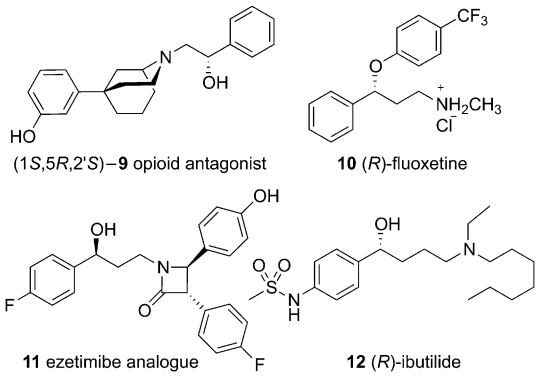
Scheme 4. Copper-catalyzed asymmetric hydrosilylation of halo-substituted ketones in air.

and $CuF(PPh_3)_3{\cdot}2EtOH$, among others, either poor activities or low selectivities were observed (Table 1, entries 11–15). In consideration of the practical applications, $Cu(OAc)_2{\cdot}H_2O$, which is inexpensive and stable towards both air and moisture, appeared to be the most preferable choice. This was also noted recently by Buchwald,[35] Yun,[21a] Lipshutz,[21b–c] and Beller et al.[25] In addition, the reaction was strongly solvent-dependent, and toluene was found to be the best choice (Table 1, entries 16–20 vs. entry 10). Although dioxane was also apparently much more conducive than other solvents to both reactivity and enantioselectivity (Table 1, entry 16), the high freezing-point limited its use at a lower temperature. Further examination demonstrated that lowering the reaction temperature facilitated a significant enhancement in enantioselectivity at the expense of reaction rate (Table 1, entry 21 vs. entry 10).

Asymmetric hydrosilylation of halo-substituted ketones (Scheme 4): An important exploration of the widespread application of the present catalyst system was in the synthesis of high-valued optically enriched alcohol intermediates for chiral pharmaceutical or agricultural targets. With the aforementioned preferred conditions in hand, we first set out to evaluate the efficiency of the present system for the catalytic asymmetric reduction of various halo-substituted ketones in air. Gratifyingly, as illustrated in Scheme 4, the present protocol allowed access to a variety of desirable β-, γ-, and δ-halo alcohols (**8a**–**k**) with good to excellent enantiopurities (84–99.9 % *ee*).

The coordinative α-bromo group of the substrates did not interfere with catalyst performance. Thus, with (*S*)-**1b** as the chiral ligand, α-bromoacetophenone (Scheme 4, **7a**) was quantitatively reduced to (*S*)-2-bromo-1-phenylethanol (**8a**) in 94 % *ee* within 24 h. The latter compound could be converted into the antinociceptive opioid antagonist (1*S*,5*R*,2′*S*)-**9** (Scheme 5).[36a] Introduction of the electron-withdrawing Cl group to the 4′-position of **7a** diminished the optical yield (**8b** vs. **8a**). However, replacement of the 4′-Cl with electron-donating CH_3 or CH_3O groups was beneficial and led to an enhancement in stereoselectivities (**8c** and **8d** vs. **8a**).

Unlike α-halo ketones, β- or γ-halo ketone substrates with either an electron-withdrawing or an electron-donating substituent on the aromatic ring (Scheme 4, **7e**–**k**) could be converted into the corresponding halo alcohols in good yields with over 95 % *ee* (**8e**–**k**). (*R*)-Fluoxetine **10** (Scheme 5), which is prescribed for the treatment of psychiatric disorders or some metabolic problems,[36b] had been synthesized by the group of Corey through the CBS reduction of β-chloropropiophenone **7e** as a key step.[37a] Utilizing $Cu(OAc)_2{\cdot}H_2O$ with (*S*)-**1b** as catalyst, the desired product **8e** was obtained in 97 % *ee* at −20 °C. Synthesis of the ezetimibe analogue **11** (Scheme 5), which possesses the potential of inhibiting cholesterol absorption,[36c] requires the synthesis of a γ-halo alcohol intermediate such as **8f**. To our delight, the enantioselective hydrosilylation of **7f** took place



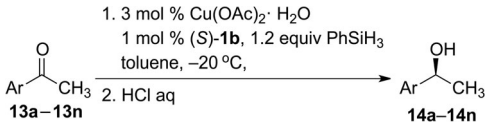
Scheme 5. Selected valuable bioactive targets derived from chiral halo alcohols.

smoothly in up to 99.9% *ee* by using the present system (Scheme 4). Furthermore, δ-chloroalcohol **8i** is the synthetic precursor of the potent class III antiarrhythmic agent (*R*)-ibutilide **12** (Scheme 5). The reduction of **7i** by phosphinamide-mediated hydroboration and rhodium-catalyzed hydrosilylation methods afforded **8i** in 75%[37b] and 88% *ee*,[34b] respectively. In this study, **8i** was provided neatly in 95% *ee* through the copper-catalyzed hydrosilylation of **7i** in the presence of (*S*)-**1a** ligand.

Asymmetric hydrosilylation of alkyl aryl ketones: Encouraged by the successful hydrosilylation of halo-substituted ketones, we then applied the present catalyst system to the enantioselective reduction of a wide range of aryl methyl ketones **13a**–**n** under a given set of conditions. As the findings in Table 2 indicate, the outcomes of the reactions largely depended on the position of the substituents on the aromatic ring of the ketone substrate, and use of the sterically encumbered ligand **1b** was beneficial to both higher optical yields and faster reaction rates in most cases. Substituents on either the *para*- (Table 2, entries 1–4) or *meta*- (Table 2, entries 5 and 6) position of acetophenone resulted in higher *ee* values (92–98%) than those obtained with *ortho*-substituted substrates (Table 2, entries 7 and 8). 2-Acetonaphthone (**13i**) was converted into the expected (*S*)-product with 96% *ee* (Table 2, entry 9).

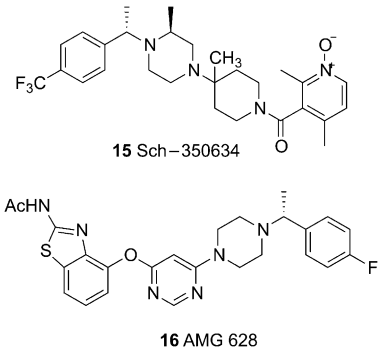
Aryl methyl substrates **13j**–**n** (Table 2, entries 10–14) were also examined in the reaction, the reduction products of which constitute key structural elements of some biologically active compounds. For example, (*S*)-MA20565 (**2**; Scheme 2), which is a potent agricultural fungicide with a new effective pharmacophore,[29a] could be synthesized from **14j**, and was conveniently furnished in 93% *ee* at −20 °C in air upon exposure of the corresponding ketone to (*S*)-**1b** ligated to copper hydride (Table 2, entry 10). With the hydrosilylation system developed here, **14k**, **14l**, and **14m** (Table 2, entries 11–13) were efficiently produced in as high as 96% *ee*. Compound **14k** is the crucial chiral building block for aprepitant **3** (Scheme 2), which is an NK-1 receptor antagonist for the treatment of chemotherapy-induced emesis.[29b] Product **14l** is a useful intermediate for the preparation of Sch-350634 (**15**; Scheme 6), which can inhibit the replication of HIV-1 through blockade of its entry into cells and thus could serve as a potential new target for antiviral therapy.[38] Optically active **14m** could be transformed into β_3-adrenergic receptor agonist **4** (Scheme 2), which is used for the treatment of obesity, noninsulin-dependent diabetes mellitus, and frequent urination.[29c] Additionally, an efficient route to AMG 628 (**16**; Scheme 6), which is a vanilloid receptor-1 antagonist, relies on access to a valuable nonracemic precursor **14n**,[39] which was furnished in 95% *ee* in this study (Table 2, entry 14).

Table 2. Asymmetric hydrosilylation of aryl methyl ketones **13a**–**n** in air.[a]



	Substrate	Ar	*t* [h]	Conv [%][b]	*ee* [%][c]
1	**13a**	4-$NO_2C_6H_4$	4	>99	98
2	**13b**	4-ClC_6H_4	12	98	95
3	**13c**	4-BrC_6H_4	12	98	97
4	**13d**	4-$CH_3C_6H_4$	24	98	94
5	**13e**	3-ClC_6H_4	12	>99	92
6	**13f**	3-$CH_3OC_6H_4$	12	98	95
7	**13g**	2-ClC_6H_4	12	99	77
8[d]	**13h**	2-$CH_3C_6H_4$	24	92	77
9	**13i**	2′-naphthyl	24	98	96
10	**13j**	3-$CF_3C_6H_4$	12	96	93
11	**13k**	3,5-$(CF_3)_2C_6H_3$	24	99	96
12	**13l**	4-$CF_3C_6H_4$	12	97	96
13	**13m**	3-$NO_2C_6H_4$	12	99	96
14	**13n**	4-FC_6H_4	12	99	95

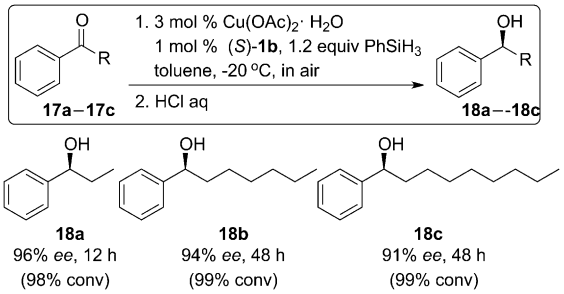
[a] Substrate (27–100 mg; substrate concentration = 0.3–0.8 mol L^{-1}) in toluene. [b] The conversions were determined by NMR and GC analyses. [c] The *ee* values were determined by chiral GC analysis. The absolute configuration was determined by comparing the retention time or optical rotation with known data. [d] Compound (*S*)-**1a** was used as a ligand.



Scheme 6. Selected valuable bioactive targets derived from chiral secondary alcohols.

To further investigate the general applicability of the present system, the hydrosilylation of a series of alkyl aryl ketones possessing different lengths of alkyl chains was systematically studied (Scheme 7, **17a**–**c**). When the methyl group of acetophenone (Table 1, **5**) was changed to an ethyl

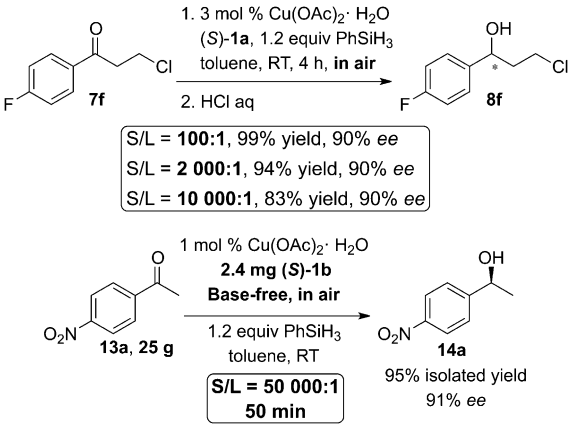
group (**17a**), the enantiopurity of the corresponding alcohol was found to increase from 91 (Table 1, entry 21) to 96% (Scheme 7, **18a**). Interestingly, further lengthening the alkyl chain gradually diminished the optical yield to 91% (**18b** and **18c** vs. **18a**).



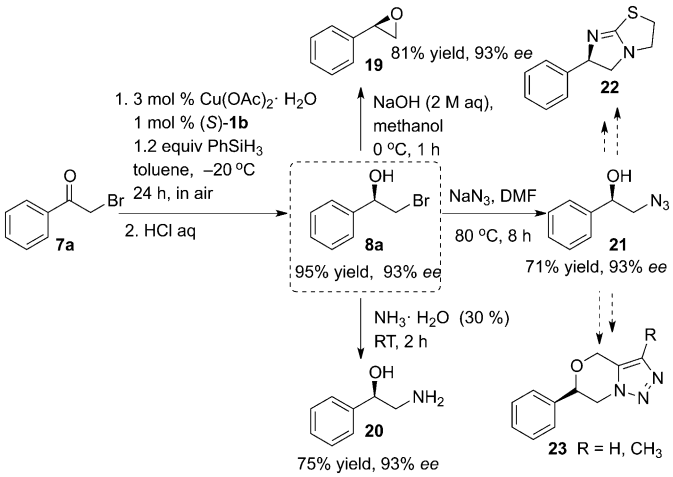
Scheme 7. Asymmetric hydrosilylation of alkyl aryl ketones **17a–c** in air.

Catalyst activities (Scheme 8): Although stereoselectivity is a major concern in asymmetric synthesis, the ability to conduct the reaction at a high substrate-to-catalyst ratio without loss of enantioselectivity is an important measure of the commercial feasibility of a reaction. The activity and air-stability of the present catalyst was therefore evaluated by conducting the reduction of 3-chloro-1-(4-fluorophenyl)propan-1-one (**7f**) at room temperature in air with an S/L ratio of 100 to 10000 (Scheme 8). The desired product **8f** was obtained cleanly in 90% *ee* after 4 h with an S/L ratio of 100. When the S/L ratio was increased to 10000, no substantial decrease of *ee* values was observed under otherwise identical conditions. To our excitement, further investigations indicated that the hydrosilylation of 4′-nitroacetophenone (**13a**) was completed in less than 1 h even when the S/L ratio was increased to 50000. As depicted in Scheme 9, when 25 g of **13a** was treated with only 2.4 mg of (*S*)-**1b**, 1 mol% $Cu(OAc)_2{\cdot}H_2O$, and 1.2 equiv of $PhSiH_3$ at room temperature in air, the reaction took place smoothly to afford product **14a** neatly with 91% *ee* after only 50 min.

Functionalization of optically enriched hydrosilylation products (Scheme 9): Chiral halo alcohols are important building blocks for the manufacture of a variety of structurally interesting and biologically active compounds. With the availability of a practical and economic catalytic method for the highly enantioselective synthesis of halo alcohols, a range of other optically enriched molecules becomes accessible. A convenient protocol, outlined in Scheme 9, allowed the conversion of β-halo alcohols into the corresponding styrene oxides, which are useful synthetic intermediates of various pharmaceuticals such as α_1-, β_2-, and β_3-adrenergic receptor agonists.[40] For instance, treatment of (*R*)-2-bromo-1-phenylethanol (**8a**; Scheme 4, 93% *ee*) with 2 M aqueous NaOH in methanol at 0°C gave chiral styrene oxide (*R*)-**19**[31a] (93% *ee*) in 81% isolated yield after 1 h. Another synthetically useful functionalization involved the facile transformation of **8a** into a valuable chiral β-amino alcohol (*R*)-**20**[41] in 75% yield by treating a methanol solution of **8a** with a large excess of 30% aqueous NH_4OH at room temperature for only 2 h. Moreover, **8a** was readily converted into β-azido alcohol (*R*)-**21**[33] in 71% isolated yield in the presence of 5 equiv NaN_3 in DMF at 80°C for 8 h under an N_2 atmosphere. Anthelmintic **22**, which is used to treat infections of parasitic worms, could be further prepared from β-azido alcohol.[42] Another reported noteworthy application of β-azido alcohols is the construction of heterocyclic compounds, such as triazolooxazine **23**.[43]



Scheme 8. Asymmetric hydrosilylation on large scales.



Scheme 9. Functionalization of optically active β-halo alcohol **8a**.

Conclusion

We have developed a remarkably effective and versatile copper-catalyzed asymmetric hydrosilylation system, which is generated in situ from the stable and inexpensive copper salt $Cu(OAc)_2{\cdot}H_2O$, chiral P-Phos ligand (*S*)-**1**, and the hydride donor $PhSiH_3$. The present system furnished excellent enantioselectivities (up to 98% *ee*) and exceedingly high turnover rates (S/L up to 50000 molar ratio in 50 min reaction time) in air, under very mild conditions, and could be used for the formation of a diverse spectrum of chiral alco-

hols, offering great opportunities for the preparation of various physiologically active compounds. In particular, the asymmetric synthesis of a vast array of valuable β-, γ- or δ-halo alcohols was realized with excellent stereocontrol (up to 99.9% *ee* and 10000 S/L ratio), which, to the best of our knowledge, represents the highest enantioselectivities observed for these substrates based on nonprecious-metal organocopper chemistry. The optically enriched β-halo alcohol products were efficiently transformed into the synthetically versatile chiral molecules, including styrene oxides, β-amino alcohols, and β-azido alcohols. Notably, the present protocol allows both catalyst and reactants to be handled in air without special precautions.

Experimental Section

General procedure for the asymmetric hydrosilylation in air (Table 1, entry 21): $Cu(OAc)_2{\cdot}H_2O$ (8.0 mg, 4.0×10^{-2} mmol) and (*S*)-P-Phos (**1a**; 13.0 mg, 2.0×10^{-2} mmol) were weighed under air and placed in a 25 mL round-bottomed flask equipped with a magnetic stirring bar. Toluene (1.0 mL) was added and the mixture was stirred at RT for 20 min. Phenylsilane (150 μL, 1.2 mmol) in toluene (0.5 mL) was added and the mixture was cooled to −20 °C. A solution of acetophenone (**5**; 120 mg, 1.0 mmol) in toluene (0.5 mL) was added under vigorous stirring, and the flask was stoppered. The reaction was monitored by TLC. Upon completion, the reaction mixture was treated with 10% HCl (2.0 mL) and the organic product was extracted with diethyl ether (3×3 mL). The combined extract was washed with water, dried with anhydrous sodium sulfate, filtered through a plug of silica gel, and concentrated in vacuo to give the crude product. The conversion and the enantiomeric excess of the product (*S*)-1-phenylethanol (**6**) were determined by ^{1}H NMR and chiral GC analyses to be more than 99 and 91%, respectively (Chirasil-DEX CB 25 m × 0.25 mm, Varian, carrier gas, N_2). The pure product was isolated by column chromatography (ethyl acetate/petroleum ether = 1:4).

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