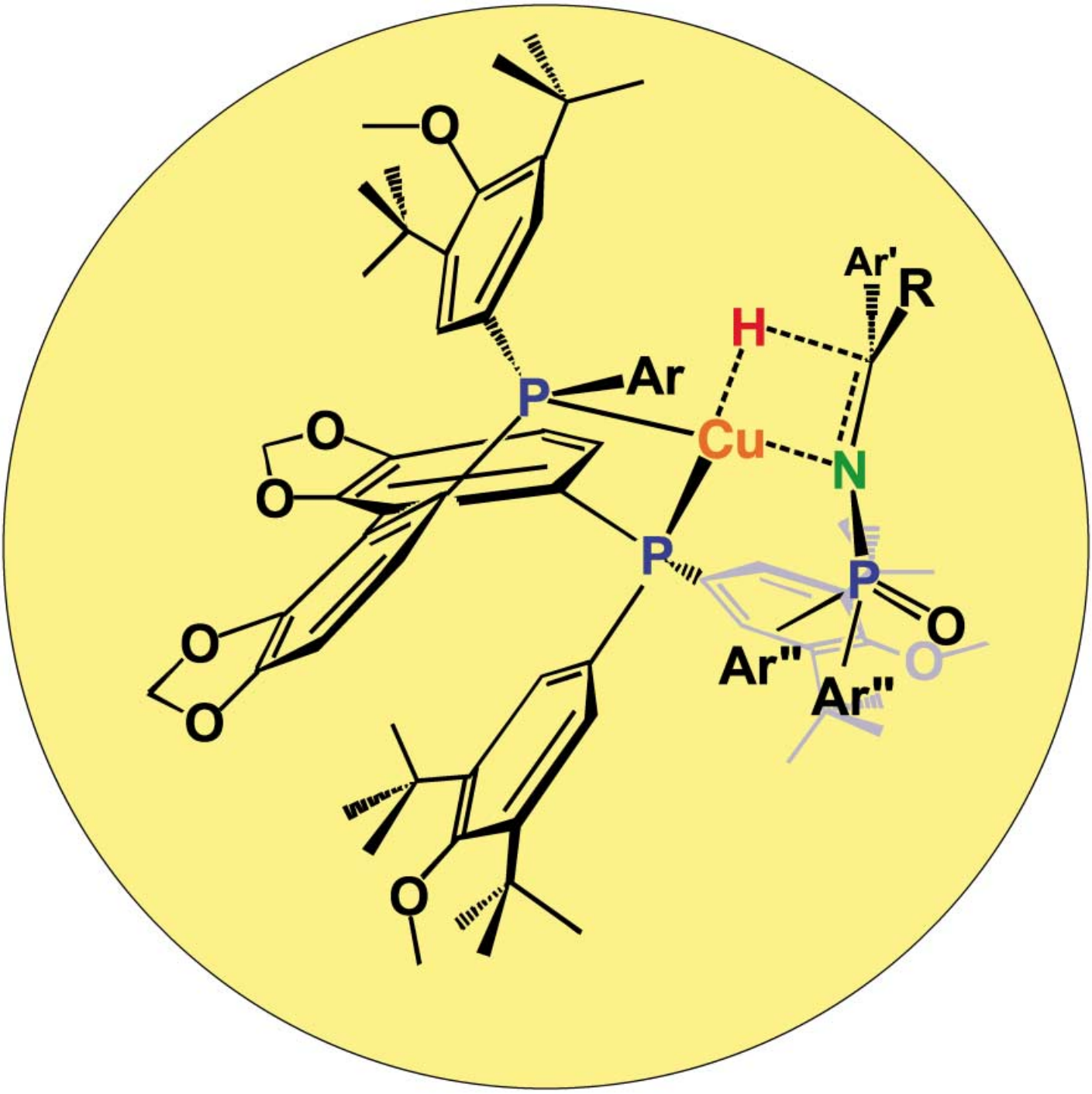
Communications



CuH, when coordinated by enantiopure SEGPHOS derivative, can reduce aryl ketimines catalytically at room temperature. This convenient route to enantio-enriched benzylic-like centers bearing a nitrogen atom is economically attractive as the starting materials and catalyst are inexpensive. For more information see the communication by B. H. Lipshutz and H. Shimizu on the following pages.

DOI: 10.1002/anie.200353294
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Asymmetric Synthesis

Copper(I)-Catalyzed Asymmetric Hydrosilylations of Imines at Ambient Temperatures**

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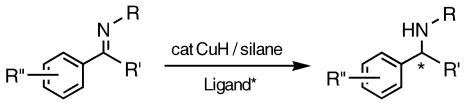
Catalytic asymmetric hydrosilylation of aryl-ketone-derived imines remains to this day a nontrivial, challenging reaction in organic synthesis that is highly valued in both industrial and academic circles.[1] Although considerably greater attention has been paid to the analogous asymmetric hydrogenation,[2] the use of safe and inexpensive silanes can be viewed as a highly desirable alternative. As is the case for hydrosilylations of aryl ketones,[3] catalysts derived from transition metals such as Rh,[4] Ru,[5] and Ti[6] predominate, although related chemistry based on Ir[7] has also been reported. Non-transition-metal-based processes in which induced chirality derives from a binaphthyl array[8] or proline derivatives[9] also show promise, although thus far *ee* values tend to be moderate.

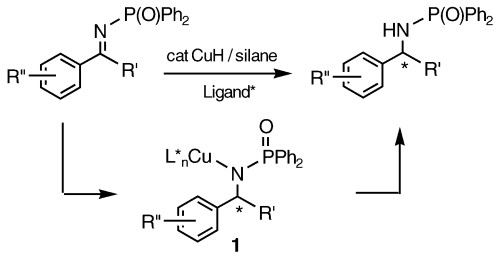
The problems we faced in developing new methodology, as others have noted previously, include the crucial choice of the substituent attached to nitrogen (R in Scheme 1).



Scheme 1. General reaction for asymmetric hydrosilylations of aromatic ketimines.

Opportunities for *E*/*Z* isomerism can play a pivotal role in the observed outcomes. Another variable of consequence can be the silane, the source of stoichiometric hydride. A general process that not only addresses these reaction variables but has no special reliance on temperature control and/or handling of imines, is efficient, and provides product amines of high *ee* values, is still lacking. In this contribution we describe unprecedented technology which relies on a base metal, copper. When in the form of $Cu^{I}H$ that is nonracemically ligated by a particular biaryl bisphosphane, a reagent results which gives rise to a straightforward, very efficient, and highly enantioselective hydrosilylation at room temperature.

The diphenylphosphinyl moiety was chosen first as the appendage on the nitrogen atom.[10] These derivatives are very commonly used and easily constructed, being obtained as a single (presumably *E*) isomer. Importantly, they can be readily hydrolyzed to the desired amines[10,11] without erosion of stereoechemical integrity in the newly formed product. Moreover, the nature of the phosphinyl residue was anticipated to be crucial in weakening an otherwise strong copper–nitrogen bond, the likely initial outcome from addition of the elements of Cu–H across the imine prior to any transmetalation event required for the regeneration of the metal catalyst (see compound **1**, Scheme 2).



Scheme 2. Presumed pathway for addition of CuH to a phosphinyl imine.

Initial experiments conducted at −25 °C in toluene by using ligated CuH prepared in situ[12] from CuCl, NaO–*t*Bu, DTBM–SEGPHOS,[13] and polymethylhydrogensiloxane (PMHS)[14] as hydride source led to low conversions (ca. 40 %) and modest *ee* values (ca. 70 %). Although previous hydrosilylations with CuH that involved carbonyl systems[15] indicated that the nature of the silane had little impact on levels of induction,[16] changing to tetramethyldisiloxane (TMDS)[17] dramatically increased the observed *ee* value (ca. 92 %), although the extent of conversion remained low. The key observation was then made that only one equivalent of MeOH[18] as additive and by using NaOMe in place of NaO–*t*Bu as base drove the reaction almost to completion in the presence of DTBM–SEGPHOS as ligand,[19] without erosion of the enantiomeric excess. When the reaction was warmed to room temperature, the *ee* value remained above the 80 % mark, which encouraged further optimization. By switching to the 3,5-dixylyl analogue[20] of the diphenylphosphinyl residue on nitrogen (Scheme 3), *ee* values on the order of >95 % were realized although the reactions took 2–3 days to reach completion. Ultimately, use of 2–3.3 equivalents of *t*BuOH in place of MeOH nicely improved the rates of these hydrosilylations while maintaining high levels of enantioselectivity.

Table 1 illustrates representative examples studied to date, all of which are based on DTBM–SEGPHOS-chelated CuH thereby documenting both versatility and elements of generality that is characteristic of this new method. Branching in the alkyl residue associated with the imine carbon did not adversely affect the *ee* values (compare entries 1–3). Imines derived from 1-indanone (entry 4) and α-tetralone (entry 5) behaved similarly, affording the corresponding nonracemic

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[**] We thank the NSF (CHE 0213522) for financial support, and Takasago for a research assistantship to H.S. We are also indebted to Dr. Takao Saito (Takasago), Drs. Rudolf Schmid and Michelangelo Scalone (Roche), Drs. Hans-Ulrich Blaser and Marc Thommen (Solvias) for supplying the SEGPHOS, BIPHEP, and JOSIPHOS ligands, respectively, used in this study.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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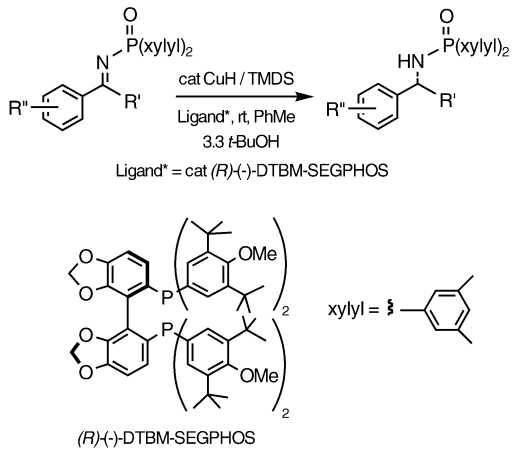
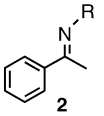
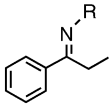
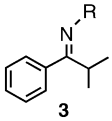
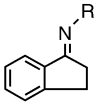
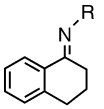
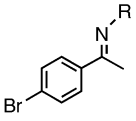
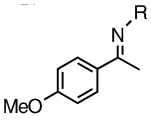
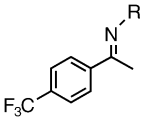


Scheme 3. Reagents and conditions used in these asymmetric hydrosilylations.

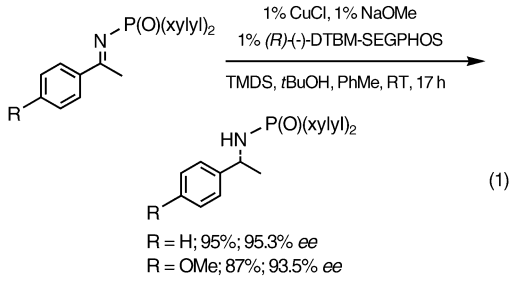
Table 1: Asymmetric hydrosilylations of imine derivatives using (*R*)-DTBM–SEGPHOS.[a]

entry	imine[b]	Yield [%][c]	*ee* [%][d]
1	 **2**	99 94	96.2 99.3
2		96	97.5
3	 **3**	90 93	94.3[f] 97.3[f]
4		93	98.4
5		93	97.6
6		95	96.1
7		98	94.2
8		94	97.3[g]

[a] Reactions were all run by using 6% CuCl, 6% NaOMe, 6% R-(−)-DTBM–SEGPHOS, 3 equiv TMDS, 3.3 equiv *t*BuOH in toluene at RT for 17 h unless specified otherwise. [b] R = P(O)(xylyl)$_2$. [c] Of isolated, chromatographically purified reduced material. [d] Determined by chiral HPLC unless noted otherwise. [e] Run at −25 °C. [f] Used 6 equiv TMDS. [g] Determined by chiral GC on the derived free amine.

products in high enantiomeric excess. Results from three substituted aromatic imine derivatives (entries 6–8) suggest that electronic perturbations are not significant at least insofar as yields and *ee* values are concerned. Most of these reactions were run at room temperature, although in the case of imines **2** (entry 1) and **3** (entry 3), cooling the reaction mixture to −25 °C increased the observed selectivity. Thus, it is assumed that higher *ee* values might follow, in general, at lower temperatures, a trend noted previously with aryl ketones by using a related reagent combination.[16]

While the examples in Table 1 were conducted at 0.14 M in toluene by using a convenient 6% of each catalyst precursor (i.e., CuCl, NaOMe, and DTBM–SEGPHOS), the level could be lowered to 1%, although reaction times increased (ca. 24 h). Raising the concentration (from 0.14 M to 0.5 M) led to an expected drop in reaction time [Eq. (1)].[21]



(1)

The sense of chiral induction engendered by *(R)*-DTBM–SEGPHOS was determined for all substrates by treating each isolated product with HCl in alcoholic media.[11] Basic workup led to the respective primary amines for which the rotation of each was measured and compared with literature values.[22] In all cases, the *(R)*-amine was clearly formed.[23]

In summary, a novel process for effecting asymmetric hydrosilylations of aryl ketimines based on catalytic amounts of copper hydride has been uncovered. This new technology offers convenience in the form of room temperature reactions, attractive economics due to reliance on catalytic quantities of a nonprecious metal, and an inexpensive silane. Efficiencies with regard to both chemical yields and enantioselectivities are high, and the resulting products are smoothly converted to their free-base forms upon mild hydrolysis. Further assessment of the scope and limitations of this method is underway, in particular regarding imines of dialkyl ketones.

Experimental Section

General procedure for the asymmetric hydrosilylation of phosphinyl imines at room temperature. (*R*)-*N*-(1-phenylethyl) bis(3,5-dimethylphenyl)phosphinamide (Table 1, entry 1). CuCl (3.7 mg, 0.038 mmol), NaOMe (2.0 mg, 0.038 mmol) and (*R*)-DTBM–SEGPHOS (44.3 mg, 0.038 mmol) were placed into a 25 mL round-bottomed flask (RBF). Toluene (1.0 mL) was added to the RBF and the resulting mixture was stirred at room temperature for 30–40 min. Meanwhile, *N*-(1-phenylethylidene) bis(3,5-dimethylphenyl)phosphinamide (235 mg, 0.626 mmol), *t*BuOH (0.20 mL, 2.1 mmol) and toluene (1.8 mL) were placed into a separate 5 mL pear-bottomed flask (PBF). The RBF was charged with tetramethyldisiloxane (TMDS; 0.33 mL, 1.9 mmol). The contents of the PBF were slowly added to the RBF

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by syringe and then the PBF was washed with additional toluene (1 mL). The reaction mixture was stirred at room temperature for 17 h. MeOH (1 mL) was slowly added and after 30 min 1N NaOH in MeOH (0.5 mL) was added. The mixture was stirred for a few hours, filtered through a plug of silica and concentrated under vacuum. Purification by silica gel chromatography (10% acetone in CH_2Cl_2) gave the corresponding phosphinyl amine (235 mg, 99% yield). HPLC analysis indicated 96.2% *ee*. (Daicel Chiralcel OD, hexane/isopropylalcohol 90/10, 1.0 mL min^{-1}, 220 nm; $R_t = 5.3$ min, (*R*), 7.3 min (*S*)).

Supporting Information available: Procedures and spectral data for all hydrosilylations.

Received: November 10, 2003 [Z53294]
Published Online: February 16, 2004

Keywords: copper · hydrides · hydrosilylation · P ligands · reduction

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[20] Made following a standard literature method[10c] by using chloro bis(3,5-dimethylphenyl)phosphane; T. V. RajanBabu, T. A. Ayers, G. A. Halliday, K. K. You, J. C. Calabrese, *J. Org. Chem.* **1997**, *62*, 6012.
[21] The increased concentration was achieved by decreasing the amount of toluene used. 1,1,3,3-tetramethyl disilazane (TMDS; 6 equiv) gave best results.
[22] See Supporting Information for details.
[23] As reported for BINAP, the (*S*)-enantiomer of DTBM–SEGPHOS is available by resolution following the protocol for the (*R*)-enantiomer, but with reliance on the opposite enantiomer of dibenzoyl tartrate; see H. Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, R. Noyori, *J. Org. Chem.* **1986**, *51*, 629.

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