

Zinc-Catalyzed Enantioselective Hydrosilylation of Imines

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Abstract: The highly enantioselective reduction of imines is achieved by employing chiral Zn/diamine catalysts. This new catalytic protocol offers attractive features such as use of a non-precious metal and an inexpensive silane, easy modification of chiral diamine ligands and provides ready access to chiral amines in good yields and with excellent enantioselectivities.

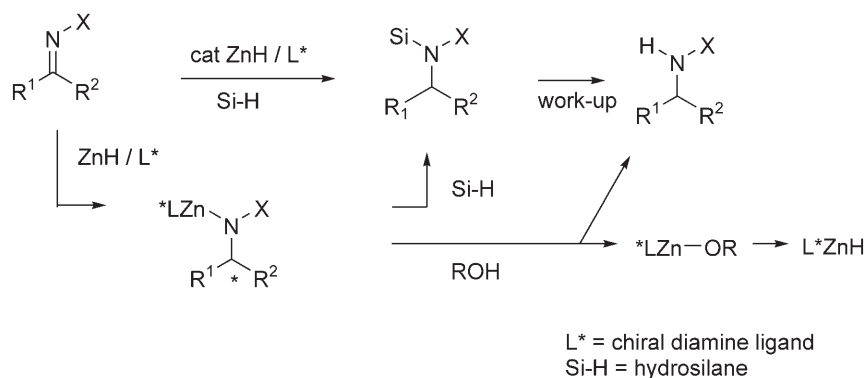
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The catalytic, enantioselective reduction of imines^[1] to produce chiral amines is of great importance due to the prevalence of chiral amines in natural products and pharmaceutical targets. Although greater attention has been paid to the asymmetric hydrogenation,^[2] asymmetric hydrosilylation employing safe and inexpensive hydrosilanes such as polymethylhydrosiloxane (PMHS) provides an alternative and attractive route to chiral amines. Catalysts derived from transition metals such as Ti,^[3] Rh,^[4] Ru,^[5] Cu,^[6] and recently Re^[7] were employed for enantioselective hydrosilylation of imines: with regard to Rh and Ru, only limited examples have been reported by rhodium

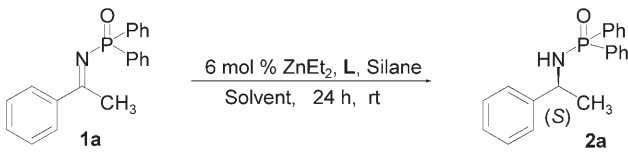
or ruthenium-chiral bisphosphine catalysts, and none of these reactions afforded amines with high enantioselectivity. Highly enantioselective reduction systems were developed with Ti, Cu, and Re, but either synthesis of complex catalysts (ligand-metal) or use of unusually modified substrates was necessary. Therefore, the development of more general and simpler catalyst systems for the reduction is required. Herein, we describe a highly enantioselective hydrosilylation of imines catalyzed by simple Zn-diamine catalysts.

Chiral diamine coordinated zinc catalysts for the enantioselective hydrosilylation of aromatic ketones first appeared in the literature in the late 1990s.^[8] However, asymmetric hydrosilylation of imines based on zinc remains undeveloped. Recently, Carpentier et al. included a few reduction examples of imines in their report on zinc-catalyzed hydrosilylation of ketones,^[9] but their system reduced imine substrates, particularly aromatic imines in very low yields and with poor enantioselectivities (0–4% *ee*).

The major problem in developing a new reduction methodology of imines based on zinc is that a strong zinc–nitrogen (Zn–N) bond^[10] formed by addition of Zn–H to the imine substrate during the catalytic cycle (Scheme 1). For optimal reactivity, this particular bond should be easily cleaved by an incoming hydrosilane without disturbing the interaction between the metal and the diamine ligand. Moreover, when a



Scheme 1. Presumed reaction pathway for Zn-catalyzed reduction of imines.

Table 1. Asymmetric hydrosilylation of **1a** under various conditions.


Entry	Ligand (L)	Silane (equivs.)	Solvent	Conversion [%]	ee [%] ^[a]
1	L1	PMHS (1.8)	toluene	41	65
2	L1	PMHS (1.8)	dioxane	33	66
3	L1	PMHS (1.8)	THF	67	68
4	L2	TMDS (4.0)	THF	31	-
5	L2	PMHS (4.0)	THF	92	90
6	L2	Ph ₂ SiH ₂ (1.2)	THF	100	90
7	L3	Ph ₂ SiH ₂ (1.2)	THF	100	94
8	L4	Ph ₂ SiH ₂ (1.2)	THF	88	84
9	L2	PMHS (4.0)	THF / MeOH ^[b]	100	98
10	L3	PMHS (4.0)	THF / MeOH ^[b]	100	94
11	L4	PMHS (4.0)	THF / MeOH ^[b]	100	94

^[a] Determined by chiral HPLC.^[b] THF:MeOH = 20:80 (v/v), [**1a**] = 0.37 M.

protic solvent is employed, the involvement of the free amine product as a ligand should be minimized for optimal enantioselectivity of each chiral ligand. Therefore, we thought that the choice of the substituent attached to the imine nitrogen was crucial. The diphenylphosphinyl moiety was chosen first as the substituent guided by the above requirements. The diphenylphosphinyl imine derivatives^[11] are obtained as a single isomer, tolerant to air and moisture, and can be readily hydrolyzed to the desired amines.^[12]

We initially examined the hydrosilylation of imine **1a** employing 6 mol % ZnEt₂, *N,N'*-ethylenebis(1-phenylethylamine) (ebpe, **L1**) as the ligand, and PMHS as the stoichiometric reducing agent in a range of solvents. Although the reactions were not complete within 24 h, promising enantioselectivities (65–68% *ee*)

were obtained (Table 1, entries 1–3). THF gave the highest conversion among the solvents screened and, thus, was chosen for further optimization.

In order to improve the enantioselectivity of the product, we prepared a series of ligands, **L2–L4** (Figure 1) from (*R,R*)-dpen (dpen = 1,2-diphenyl-1,2-ethanediamine). Diphenylsilane was more effective than tetramethylsilyloxane (TMDS) and PMHS (entries 4–6), resulting in complete conversion and yielding the desired amine product of >90% *ee* in THF with **L2** and **L3** (entries 6 and 7). The reaction using bulky ligand **L4** did not go to completion, giving only 88% conversion in 24 h (entry 8). We then focused on promoting rates of the reaction in which PMHS, a polymeric inexpensive silane, was employed. As reported in a few metal-catalyzed hydrosilylations by us and others,^[13a-c] alcohol additives greatly enhanced reaction rates of the zinc-catalyzed reduction of imines. The use of MeOH in combination with THF drove the reduction employing **L4** ligand and PMHS to completion within the reaction time (entry 8 vs. 11). In general, all **L2–L4** ligands offered good enantioselectivity, and the best value (98% *ee*) was obtained by employing **L2** and PMHS in THF/MeOH; these results are in contrast to the Zn-catalyzed ketone hydrosilylation for which the addition of alcohol additives produced alcohol products with lowered enantiomeric excess despite increased reaction rates.^[14] Particularly noteworthy is that unlike **L2** and **L4**, the **L3** ligand having extra coordinating methoxy groups provided the same level of enantioselectivity

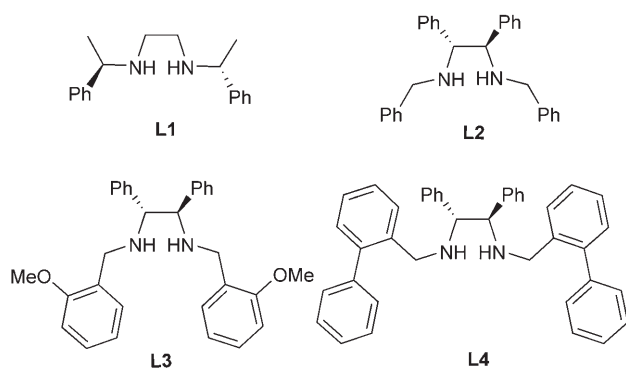
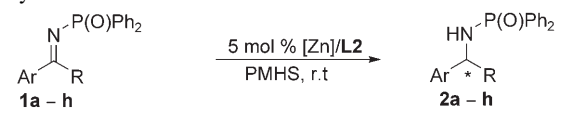
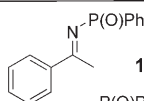
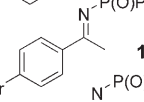
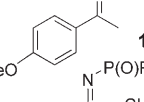
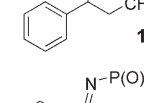
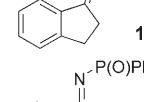
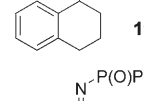
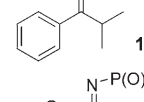
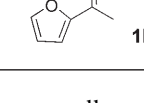
**Figure 1.** (*R,R*)-Ebpe (**L1**) and chiral diamine ligands (**L2–L4**) derived from (*R,R*)-dpen.

Table 2. Enantioselective hydrosilylation of *N*-diphenylphosphinylimines.^[a]

			
Entry	Imine	Yield [%]	ee [%] ^[b]
1		86	97
2		77	97
3		83	96
4		82	96
5		83	98
6		85	86
7		74	55
8		77	96

^[a] Reactions were all run by using 5 mol % ZnEt_2 , 5 mol % **L2**, and 3 equivs. PMHS in THF/MeOH (1 mL, 80:20 (v/v), [Imine] = 0.44 M) at room temperature for 12 h. Reaction time was not optimized.

^[b] Determined by chiral HPLC.

under the reaction conditions with or without MeOH (entries 7 and 10).

Having chosen **L2** as the best chiral ligand, various *N*-phosphinylimines were reduced by using 5 mol % catalyst, 3 equivs. of PMHS, and in MeOH/THF [20:80 (v/v)].^[15] The results are summarized in Table 2. Reduction of phenyl methyl ketimine **1a** afforded amine **2a** with good *ee* (97% *ee*).^[16] The reduction of phenyl methyl ketimine derivatives bearing electron-withdrawing (entry 2) and electron-donating groups (entry 3) on the aromatic ring yielded amines with high enantioselectivities. Ketimines derived from propiophenone and indanone were efficiently reduced, affording the corresponding amine products in high enantiomeric excess as well (entries 4 and 5). However, a further increase of the steric bulk of the alkyl side chain adversely affected the *ee* values (entries 6 and 7). Six-membered ring ketimine **1f** gave

the amine product in 86% *ee* and ketimine **1g** derived from isobutyrophenone was reduced with a low level of enantioselectivity (55% *ee*). Heteroaromatic ketimine substrate **1h** also reacted with excellent enantioselectivity (96% *ee*).

In conclusion, we have developed a highly enantioselective hydrosilylation of imines based on a chiral Zn/diamine catalyst. This new catalytic process offers attractive features such as use of a non-precious metal and an inexpensive silane, easy modification of chiral diamine ligands. Studies are underway to investigate the full scope and the mechanism of this methodology and to develop more efficient and enantioselective catalytic systems.

Experimental Section

General Procedure for the Enantioselective Hydrosilylation of *N*-Phosphinylimines (Table 2)

To a solution of ligand **L2** (8.6 mg, 0.022 mmol) in freshly distilled THF (0.4 mL), was added ZnEt_2 (0.02 mL, 1.1 M solution in toluene, 0.022 mmol) under nitrogen. The reaction mixture was stirred for 10 min, and a solution of phosphinylimine (0.44 mmol) in THF (0.4 mL), PMHS (0.08 mL, 1.32 mmol) and anhydrous MeOH (0.2 mL) was added successively. The resulting solution was stirred for 12 h at room temperature and the reaction was monitored by TLC. After completion of the reaction, MeOH (10 mL) and 1 N NaOH in MeOH (0.2 mL) were added. The mixture was stirred for 30 min, filtered through a pad of celite, and concentrated under vacuum. Purification by silica gel chromatography (10% acetone/ CH_2Cl_2) gave the corresponding phosphinylamines.

Acknowledgements

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- [10] For example, D (Zn–N) in $\text{Zn}[\text{N}(\text{TMS})_2]_2 = 209 \text{ kJ mol}^{-1}$, D (Zn–C) in $\text{Zn}[\text{CH}_2\text{CMe}_3]_2 = 157 \text{ kJ mol}^{-1}$, see: I. E. Gümrükçüoğlu, J. Jeffery, M. F. Lappert, J. B. Pedley, A. K. Rai, *J. Organomet. Chem.* **1988**, 341, 53.
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- [14] See refs.^[8b,9]
- [15] Mild bubbling occurred in this volume ratio and thus, this protocol using less MeOH was preferred over that employing 80 % MeOH.
- [16] Subtle changes in the *ee* values of **2a** were observed depending on the amount of MeOH added; for example, 10 % MeOH gave 95 % *ee* and 20 % MeOH 97 % *ee*. The effect of MeOH on the enantioselectivity needs further investigation in relation to mechanistic studies.