Enantioselective Reduction of Ketones by Polymethylhydrosiloxane in the Presence of Chiral Zinc Catalysts

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Received February 18, 1999

Abstract: Enantioselective reduction of ketones, particularly acetophenones, by polymethylhydrosiloxane (PMHS) to the corresponding secondary alcohols can be achieved with high yields and enantiomeric excesses (ee's) up to 88% in the presence of chiral zinc catalysts (eq 1). Two catalytic systems have been developed giving similar ee's: (i) *System A*: $ZnEt_2$ + chiral diimine or diamine **1**−**10**. (ii) *System B*: $Zn(carboxylate)_2$ + chiral diamine activated by Vitride. System B is inexpensive, stable, and ready to use in toluene, providing either (*R*) or (*S*) chiral secondary alcohols with 70−80% ee in the presence of (*S*,*S*)- or (*R*,*R*)-*N*,*N*′-ethylenebis-(1-phenylethylamine) (ebpe, **6**). The reduction has been carried out at the 1 kg scale without scale-up problems. The ligand is cheap and is recovered at the end of reaction by simple distillation from residues of the organic phase. Both precursors $ZnMe_2$·(*S*,*S*)-ebpe (**A**) and $Zn(dea)_2$·(*S*,*S*)-ebpe (**B**) for systems A and B, respectively, have been isolated and characterized by X-ray structure and exhibit the same catalytic properties and the same ee's for the reduction of acetophenone as the in situ prepared catalytic system. The complex $ZnEt_2$·(*S*,*S*)-ebpe) (**A**′) reacts with benzaldehyde to give the seven-membered ring dimer complex **La** in which benzaldehyde inserts into the Zn−N bond of complex **A**′. Acetophenone also reacts with **A**′ to give a similar seven-membered ring dimer complex **Lb**. Both **La** and **Lb** are catalysts for the enantioselective reduction of acetophenone by PMHS and gave activities and ee's similar to those of **A**′. Synthetic and mechanistic aspects of this new economical method are discussed in this paper.

Introduction

The search for economical methods of enantioselective reduction of ketones to secondary alcohols is a rewarding goal,[1] owing to the numerous applications in the fields of pharmaceuticals,[2] agrochemicals,[3] and flavor and fragrance.[4] Known industrial methods involve reduction by chiral hydride reagents such as Corey's oxazaborolidine,[5] Yamaguchi−Mosher reagent $LiAlH_4$ coordinated by BINAL-H[6] or Chirald,[2] Mukaiyama's reduction of ketones by $NaBH_4$ in the presence of chiral Co(II) complexes,[7] or Brown's chiral boranes such as Alpine-Borane.[8] Recently, asymmetric hydrogenation of ketones has been developed using ruthenium catalysts coordinated by chiral diamines[9a−d] or chiral amino alcohols.[9e] Asymmetric hydrosilylation of prochiral ketones as a method for enantioselective reduction has been known since the early 1970s, using rhodium catalysts coordinated by chiral phosphines[10] and later developed with rhodium and chiral nitrogen ligands,[11] titanium and chiral diamines[12] or binaphthol,[13] hypervalent chiral trialkoxysilanes,[14] and chiral ammonium fluoride.[15]

Polymethylhydrosiloxane (PMHS) is a safe and inexpensive polymer coproduct of the silicone industry, and its use as a

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(1) Reviews: (a) Itsuno, S. *Organic Reactions*; Paquette, A., et al., Eds.; John Wiley & Sons: New York, 1998; Vol. 52, p 395. (b) Harada, K.; Manegumi, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 8, p 139. (c) Nishizawa, M.; Noyori, R. *Ibid.*, p 159. (d) Singh, V. K. *Synthesis* **1992**, 605. (e) Brunner, H In *Houben-Weyl Methoden der Organischen Chemie*, 21st ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme Verlag: Stuttgart, Germany, 1996; Vol. 7, pp 3945−4197.

(2) Astleford, B. A., Weigel, L. O. In *Chirality in Industry II*; Collins, A. N., Ed.; Wiley: New York, 1997; p 99.

(3) Sheldon, R. A. *Chirotechnology*; Dekker: New York, 1993.

(4) (a) Rossiter, K. J. *Chem. Rev.* **1996**, *96*, 3201. (b) Boelens, M. *Perfum. Flavor.* **1993**, *18*, 2.

(5) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Industrial applications: Caille, J. C.; Bulliard, M.; Laboue, B. In *Chirality in Industry II*; Collins, A. N., Ed.; Wiley: New York, 1997; p 391.

(6) (a) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129. (b) Yamaguchi, S.; Mosher, S.; Pohland, A. *J. Am. Chem. Soc.* **1972**, *94*, 9254.

(7) (a) Nagata, T.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2145. (b) Nagata, T.; Sugi, K. D.; Yamada, T.; Mukaiyama, T. *Synlett.* **1996**, 1076.

(8) Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975 and references therein.

(9) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; lkariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (b) Ohkuma, T.; Ooka, H.; Yamakawa, M.; lkariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872. (c) Ohkuma, T.; Doucet, H.; Pham, T.; Mikami, K.; Korenaga, T.; Terada, M.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 1086. (d) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem Soc.* **1996**, *118*, 2521. (e) Alonso, D. A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2749.

(10) (a) Yamamoto, K.; Uramoto, Y.; Kumada, M. *J. Organomet. Chem.* **1971**, *31*, C9. (b) Ojima, I. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Ed.; Wiley: New York, 1989; Chapter 25, p 1479 and references therein.

(11) Brunner, H.; Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p 303 and references therein.

(12) Buchwald, S. L.; Gutierrez, A.; Grossman, R. B. *U.S. Patent 5,227,538* (July 13, 1993) to MIT.

(13) Imma, H.; Mori, M.; Nakai, T. *Synlett* **1996**, 1229.

(14) Reduction by $(RO)_3SiH$−Li(binaphthol): Shiffers, R.; Kagan, H. B. *Synlett* **1997**, 1175.

(15) Enantioselective reduction of acetophenones by PMHS in the presence of cinchona alkaloids ammonium fluorides (up to 60% ee): Drew, M. D.; Lawrence, N. J.; Watson, W.; Bowles, S. A. *Tetrahedron Lett.* **1997**, *38*, 5857.

10.1021/ja990522i CCC: $18.00
Published on Web 06/17/1999

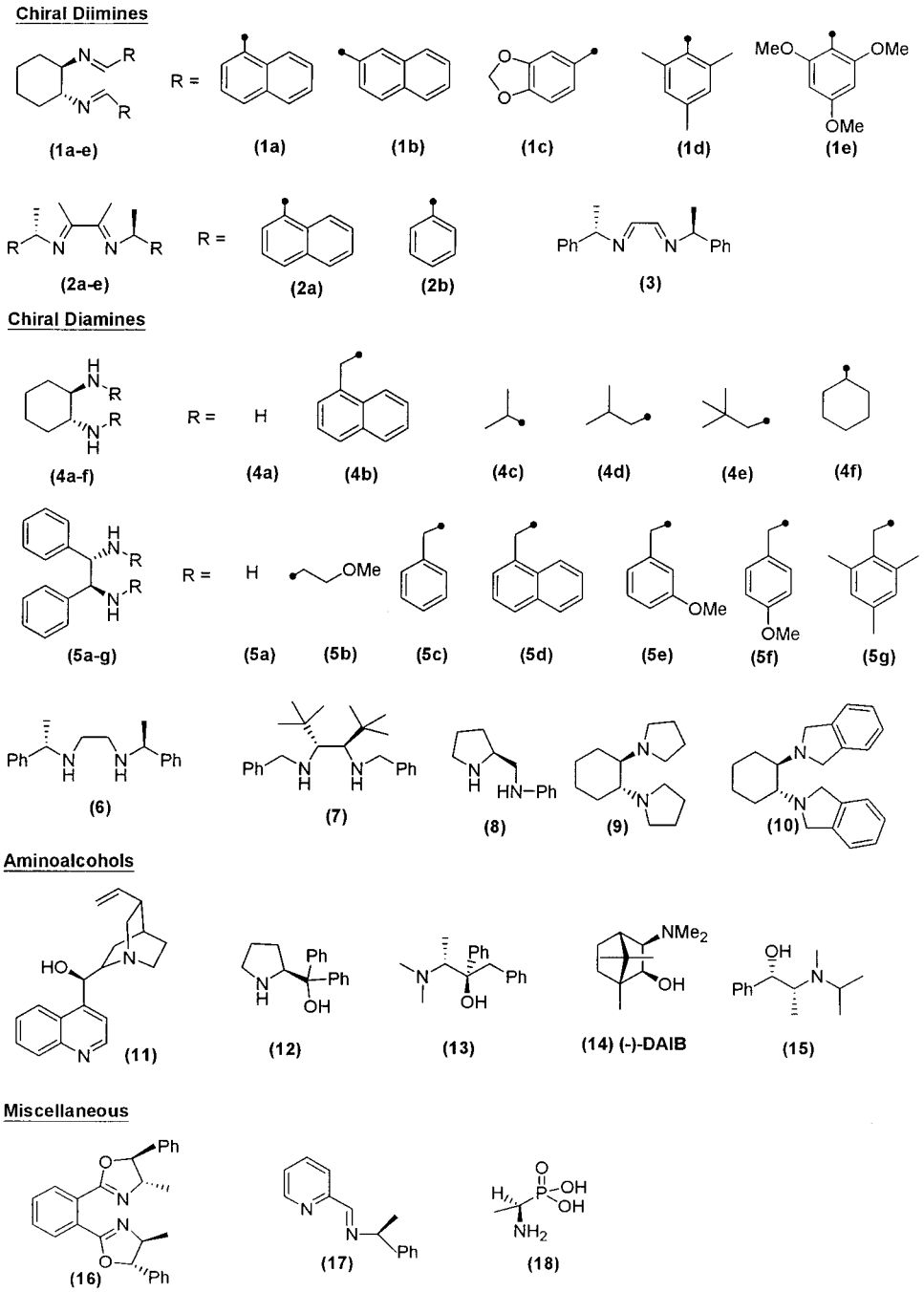


Figure 1. Representative ligands used in this study.

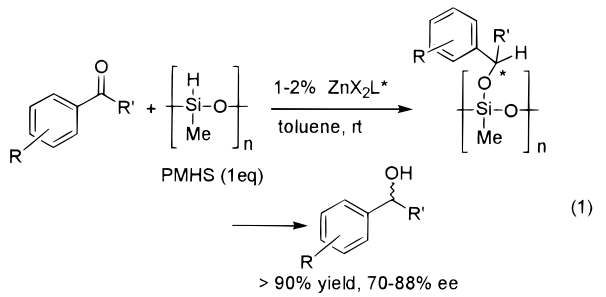
reducing silylating agent of ketones has been known since 1957.[16] Chiral titanocene catalysts activated by *n*-butyllithium have been used for the enantioselective reduction of acetophenones by PMHS with enantiometric excesses (ee's) up to 97%.[17]

In a previous paper,[18] we have shown that zinc hydride species, best generated from the reaction of zinc carboxylates with hydride reducing agents such as $NaBH_4$, are very effective catalysts for the selective hydrosilylation−reduction of carbonyl compounds, including esters, to the corresponding alcohols. Among the various catalytic systems, dialkylzinc activated by diamine ligands was found particularly effective for the hydrosilylation−reduction of carbonyl compounds. We thus checked for possible chiral recognition of the substrate using various bidentate optically active ligands and found that diethylzinc coordinated by inexpensive chiral diimines or diamines **1**−**10** catalyzes the enantioselective reduction of ketones by PMHS with >90% isolated yields and up to 88% ee (System A, eq 1). Further work allowed the design of inexpensive, ready-to-use (*R*)- and (*S*)-carbinol forming catalytic solutions made from soluble zinc carboxylates, chiral diamine ligands, and Vitride in toluene (System B, eq 1), which have been used on a 1 kg scale for the synthesis of various chiral alcohols.

(16) (a) Nitzche, S.; Wick, M. *Angew. Chem.* **1957**, *69*, 96. (b) Grady, G. L.; Kuivila, H. G. *J. Org. Chem.* **1969**, *34*, 2014. (c) Lipowitz, J.; Bowman, S. A. *Aldrichim. Acta* **1973**, *6*, 1. (d) Corriu, R. J. P.; Perz, R.; Réyé, C. *Tetrahedron* **1983**, *39*, 999. (e) Kobayashi, Y.; Takahisa, E.; Nakano, M.; Watatani, K. *Tetrahedron* **1997**, *53*, 1627. (f) Drew, M. D.; Lawrence, N. J.; Fontaine, D.; Sekhri, L.; Bowles, S. A.; Watson, W. *Synlett* **1997**, 989.

(17) Carter, M. B.; Schiott, B.; Guttierez, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11667.

(18) Mimoun, H. *J. Org. Chem.* **1999**, *64*, 2582. Patent WO 96/12694 to Firmenich S.A.



(1)

System A: 1% $ZnEt_2$ + chiral diamine or diimine

System B: 1% $Zn(RCO_2)_2$ + chiral diamine + vitride

Results and Discussion

The Catalytic Systems. Experiments were carried out using acetophenone as the substrate, various metal precursors (particularly zinc) at 2 mol % concentration with various ligands shown in Figure 1, and 1.1 mol equiv of PMHS in toluene at room temperature for 18 h. The results are shown in Table 1.

Whereas $ZnEt_2$ alone has no catalytic activity for reduction using PMHS,[18] it can be activated by ligands such as diamines which transform the linear C−Zn−C backbone into monomeric tetrahedral zinc complexes $ZnEt_2$(diamine) in which the diamine acts as a bidendate ligand.[19] This reaction thus belongs to the category of ligand-accelerated catalytic reactions,[5a,20] where the ligand can be used in a substoichiometric concentration with respect to the metal. In our case, 0.04 mol % ligand is enough to activate the 2 mol % $ZnEt_2$ used.

Activation of $ZnEt_2$ can be performed by chiral diimines (Table 1, entries 1−8) which allowed up to 75% ee with the bis(α-naphthyl)-(*R*,*R*)-cyclohexanediimine (**1a**). Chiral secondary diamines were found even more efficient than chiral diimines, with the best ee's (up to 88%) being reached so far by *N*,*N*′-dibenzyl-1,2-diphenyl-1,2 ethanediamine (**5c**) (entry 18). Chiral primary diamines such as **4a**, **5a**, and binaphthylamine (entries 9−11) were found to be inferior (24% ee max), as well as chiral tertiary diamines (55% ee max). Chiral amino alcohols prove ineffective as ligands, owing to the higher bond strength of the Si−O vs the Zn−O bond, resulting in the displacement of the ligand from zinc to PMHS.[18] This reaction is sensitive to steric effects, as shown by the low activity observed with the encumbered ligands **5g** and **7**. So far, the best ligands are those having a C_2 symmetry. (*S*)-2-(Phenylaminomethyl)pyrrolidine (**8**), cheaply made from glutamic acid, aniline, and $LiAlH_4$, gave only 8% ee.

Our attention was concentrated on the use of *N*,*N*′-ethylenebis(1-phenylethylamine) (ebpe, **6**), which, although not the most effective ligand, can be easily and inexpensively prepared on a kilogram scale in the (*R*,*R*)- or (*S*,*S*)-configuration from the reaction of 1,2-dichloroethane or 1,2-dibromoethane with 2 equiv of (*R*)- or (*S*)-α-phenylethylamine. This allowed the preparation of (*R*)- or (*S*)-carbinols from (*S*,*S*)- or (*R*,*R*)-**6**, respectively. The same general phenomenon was observed with the other diimines or diamines with C_2 symmetry, the (*R*,*R*)-ligand giving the (*S*)-carbinol and the (*S*,*S*)-ligand giving the (*R*)-carbinol.

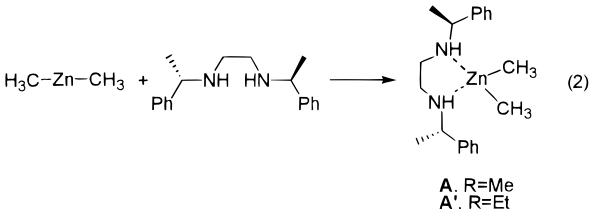
(19) (a) O'Brien, P.; Hursthouse, M. B.; Motevalli, M., Walsh, J. R.; Jones, A. C. *J. Organomet. Chem.* **1993**, *449*, 1. (b) Motevalli, M.; O'Brien, P.; Robinson, A. J.; Walsh, J. R.; Wyatt, P. B.; Jones, A. C. *J. Organomet. Chem.* **1993**, *461*, 5.

(20) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059. See also ref 5a for an earlier example of ligand-accelerated catalytic reaction.

Table 1. Enantioselective Reduction of Acetophenone by PMHS in the Presence of $ZnEt_2$ (2 mol %) and a Chiral Ligand (2 mol %) (toluene, 18 h, room temperature)

entry	ligands (see Figure 1)	conversion (%)	% ee
	Chiral Diimines		
1	**1a**	95	75 (*S*)
2	**1b**	97	74 (*S*)
3	**1c**	98	72 (*S*)
4	**1d**	95	70 (*S*)
5	**1e**	98	73 (*S*)
6	**2a**	98	56 (*S*)
7	**2b**	97	48 (*S*)
8	**3**	95	30 (*S*)
	Chiral Primary Diamines		
9	**4a**	98	18 (*S*)
10	**5a**	98	24 (*S*)
11	(*R*)-(+)-1,1′-bis(2-naphthylamine)	55	5 (*R*)
	Chiral Secondary Diamines		
12	**4b**	99	70 (*S*)
13	**4c**	95	52 (*S*)
14	**4d**	98	62 (*S*)
15	**4e**	97	63 (*S*)
16	**4f**	98	62 (*S*)
17	**5b**	95	47 (*R*)
18	**5c**	98	**88** (*R*)
19	**5d**	98	83 (*R*)
20	**5e**	98	84 (*R*)
21	**5f**	97	83 (*R*)
22	**5g**	15 (slow)	58 (*R*)
23	**6**	99	**75** (*R*)
24	**7**	20 (slow)	8 (*R*)
25	**8**	98	8 (*R*)
	Chiral Tertiary Diamines		
26	**9**	96	17 (*S*)
27	sparteine	60	19 (*R*)
28	**10**	98	55 (*S*)
	Amino Alcohols		
29	**11**	67	6 (*R*)
30	**12**	100	8 (*S*)
31	**13**	60	13 (*R*)
32	**14**	9	1 (*S*)
	Miscellaneous		
32	**16**	88	10 (*S*)
33	**17**	100	32 (*S*)
34	**18**	10	5 (*R*)

Complexation of $ZnMe_2$ by the diamine ligand (see eq 2) is exemplified by the isolation and X-ray characterization of the complex $ZnMe_2$·(*S*,*S*)-ebpe (**A**). The structure of the adduct **A**,



(2)

A, R=Me
A', R=Et

prepared in near quantitative yield by mixing the two reactants, is shown in Figure 2 with some significant bond lengths and angles.[21] The tetrahedral structure of this complex and its structural parameters are similar to those of $ZnMe_2$·(−)-sparteine[19b] and $ZnMe_2$·TMEDA[19a] [TMEDA = tetramethylethylenediamine] complexes, which contain tertiary diamines as ancillary ligands.

The isolated complex $ZnEt_2$·(*S*,*S*)-ebpe behaves similarly to the $ZnEt_2$ + (*S*,*S*)-ebpe mixture, as shown in Table 2 (compare

(21) Details on crystallographic and structural parameters are reported in the Supporting Information.

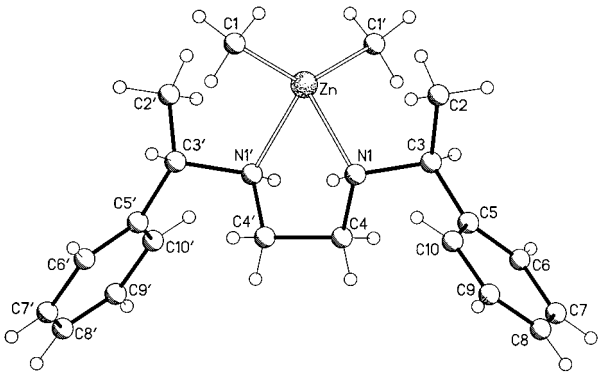
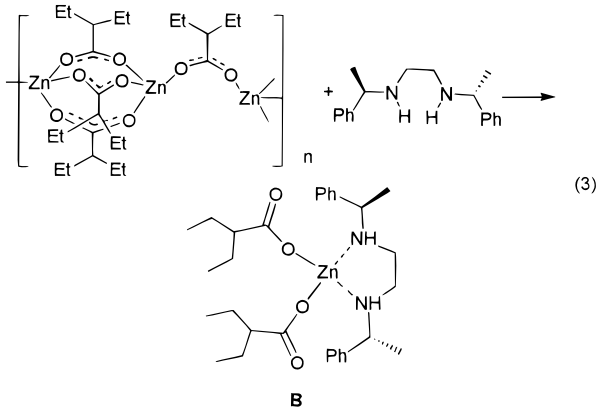


Figure 2. X-ray crystal structure of the complex $ZnMe_2$·(*S*,*S*)-ebpe (**A**). Selected bond distances (Å) and angles (deg): Zn−N1 = 2.230(3); Zn−N1′ = 2.230(3); Zn−C1 = 2.007(4); N1−C3 = 1.475(5); N1−C4 = 1.472(5); C1−Zn−N1′ = 108.0(2); C1−Zn−N1 = 106.2(2); N1−Zn−N1′ = 80.3(2). Primes denote the following symmetry operation: $-x, y, -z$.

entries 23 and 38). Other zinc precursors, such as $ZnMe_2$, ZnH_2, or PhZnH·Py, were found to be active as well for the enantioselective reduction of acetophenone (entries 7 and 35−37).

Soluble polymeric zinc carboxylates such as $Zn(2\text{-EH})_2$ [2-EH = 2-ethylhexanoate] or $Zn(dea)_2$ [dea = diethyl acetate or 2-ethylbutyrate] are inactive as such, but form monomeric active catalysts once coordinated by bidendate chiral secondary diamines such as ebpe (**6**). Thus, the reaction of zinc diethyl acetate with ebpe forms the adduct $Zn(dea)_2$·ebpe (**B**) in almost quantitative yield (eq 3).



The structure of complex **B** [$Zn(dea)_2$·(*S*,*S*)-ebpe] has been elucidated by X-ray crystal structure. The reaction occurs with the depolymerization[22] of the zinc carboxylate and the formation of the monomeric species, **B**, where the carboxylato group displays an η^1-O monodentate bonding mode. The depolymerization reaction can be monitored by the FT IR bands of the $[Zn(dea)_2]_n$ precursor [$\nu(CO_2)_{as}$ at 1630 (*syn-syn*), 1546 cm^{-1} (*syn-anti*), and $\nu(CO_2)_s$ at 1429 cm^{-1}], changing into $\nu(CO_2)_{as}$ at 1590 and $\nu(CO_2)_s$ at 1397 cm^{-1} bands of **B**.

The structure is shown in Figure 3 with some significant structural parameters. The η^1-O monodentate bonding mode of a carboxylato group is quite rare in Zn chemistry, except for the recently reported structure of $Zn(OAc)_2Py_2$.[23]

Table 2. Enantioselective Reduction of Acetophenone by PMHS in the Presence of Various Metal Derivatives (2 mol %), Ligands, and Activators (toluene, 18 h, room temperature)

entry	metal precursor	ligand	activator	conversion	% ee
7	$ZnEt_2$	**2b**		97	48 (*S*)
35	$ZnMe_2$	**2b**		99	48 (*S*)
36	ZnH_2	**2b**		96	48 (*S*)
37	PhZnH·Py	**2b**		95	49 (*S*)
23	$ZnEt_2$	**6**		99	75 (*R*)
38	$ZnEt_2$·ebpe **A**	**6** (included)		99	75 (*R*)
39	$Zn(dea)_2$	**6**		75	71 (*R*)
40	$Zn(dea)_2$·ebpe **B**	**6** (included)		70 (60 °C)	71 (*R*)
41	$Zn(dea)_2$	**6**	$NaBH_4$ (2%)	100	45 (*R*)
42	$Zn(dea)_2$	**6**	$LiAlH_4$ (1%)	100	67 (*R*)
43	$Zn(dea)_2$	**6**	Vitride (3%)	100	72 (*R*)
44	$Zn(dea)_2$	**6**	LiH (4%)	100	71 (*R*)
45	$Cd(dea)_2$	**6**		100	62 (*R*)
46	$Cd(dea)_2$	**5c**		100	81 (*R*)
48	$Co(dea)_2$	**6**		90 (60 °C)	58 (*R*)
49	$Cu(dea)_2$	**6**		0	
50	$Sn(2\text{-EH})_2$[a]	**6**		0	

[a] 2-EH = 2-ethylhexanoate.

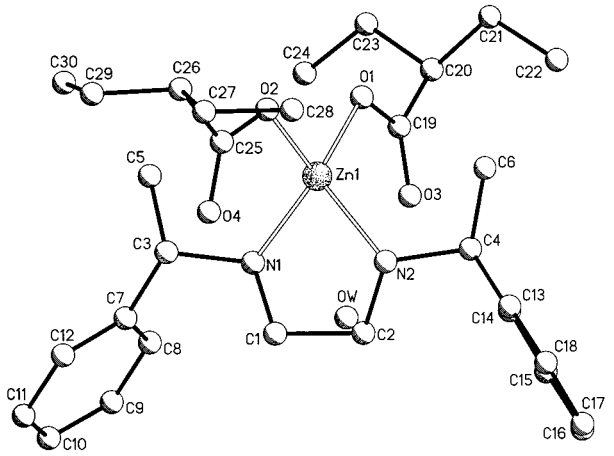


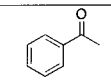
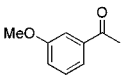
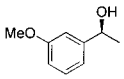
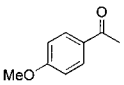
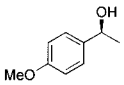
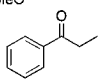
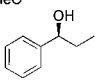
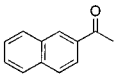
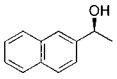
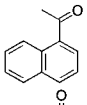
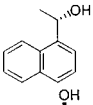
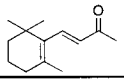
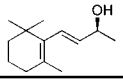
Figure 3. X-ray crystal structure of the complex $Zn(dea)_2$·(*S*,*S*)-ebpe·H_2O (**B**) (hydrogens have been omitted for clarity). Selected bond distances (Å) and angles (deg): Zn1−N1 = 2.076(3); Zn1−N2 = 2.070(2); Zn1−O1 = 1.964(2); Zn1−O2 = 1.947(2); O2−Zn1−O1 = 99.21(9); N2−Zn1−N1 = 87.4(1).

The zinc carboxylate, converted into the monomeric form **B** by the action of the bidentate amine, catalyzes the enantioselective reduction (Table 2, entry 40) of ketones using PMHS as a source of hydrido species. The activity of complex **B** can be enhanced by the addition of hydride reducing agents such as $NaBH_4$, $LiAlH_4$, LiH, or Vitride (entries 41−44).[24] The amount of Vitride necessary to activate the complex **B** was optimized to 1.5 mol equiv of $NaAlH_2(OR)_2$ per zinc atom. This allowed us to easily prepare homogeneous, ready-to-use, inexpensive (*R*)- or (*S*)-carbinol forming catalytic solutions in toluene containing $Zn(dea)_2$ (1 equiv, ca. 20 wt %), (*S*,*S*)- or (*R*,*R*)-ebpe (1 equiv), and Vitride (1.5 equiv), which can be stored for months without deactivation. These catalytic solutions were found more convenient to use than the diethylzinc catalyst, which is expensive and hazardous. The experimental procedure for the enantioselective reduction of ketones, which has been carried out on a kilogram scale thus conveniently consists of (i) adding PMHS (1.1 equiv) to the substrate containing the catalytic solution (2 mol % Zn), (ii) stirring the mixture at room temperature until completion of the reaction (ca. 12 h), (iii) hydrolyzing the reaction mixture with concentrated aqueous

(22) (a) Berkesi, O.; Dreveni, I.; Andor, J. A.; Mink, J. *Inorg. Chim. Acta* **1992**, *195*, 169. (b) Goldschmied, E.; Rae, A. D.; Stephenson, N. C. *Acta Crystallogr.* **1977**, *B33*, 2117. (c) Clegg, W.; Little, I. R.; Straugham, B. P. *J. Chem. Soc., Dalton Trans.* **1986**, 1283. (d) Gordon, R. M.; Silver, H. B. *Can. J. Chem.* **1983**, *61*, 1218.

(23) Singh, B.; Long, J. R.; Fabrizi de Biani, F.; Gatteschi, D.; Stavropoulos, P. *J. Am. Chem. Soc.* **1997**, *119*, 7030.

Table 3. Enantioselective Reduction of Various Ketones by PMHS in the Presence of $ZnEt_2$·(*R,R*)-ebpe (System A) and $Zn(dea)_2$·(*R,R*)-ebpe + Vitride (System B) (2 mol % Zn, 2 mol % ebpe, 3 mol % Vitride, toluene, room temperature)

Entry	Substrate	Product	%ee Syst.A	% ee Syst.B
51			76	74
52			76	73
53			76	72
54			77	81
55			80	76
56			71	66
57			75	72
58			67	64
59			66	68
59			20	15
60			18	20

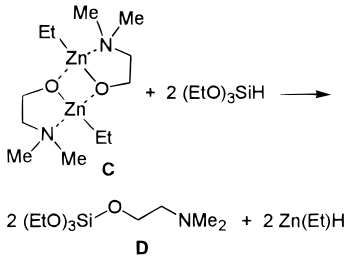
KOH or NaOH (1.2 equiv), and (iv) distilling the resulting chiral alcohol in vacuo. The ligand can be recovered in pure form and high yield by distillation from residues and reused for a next run.

The possibility to use other metal carboxylates, reported to be active in assisting the reduction with PMHS,[18] in the enantioselective reduction of acetophenone, has been explored (Table 2). Mn(II), Fe(II), Sn(II), Ni(II), and Cu(II) carboxylates or alkoxides,[25] in conjunction with ebpe and in the presence or absence of hydride activators, were found inactive and not enantioselective. Other metals showing an interesting catalytic activity were cadmium diethyl acetate (entries 45−46), which was also active in the absence of any hydrido species, though less enantioselective than $[Zn(dea)_2]$ (62 vs 75% ee with ebpe, 81 vs 88% ee with ligand **5c**), and cobalt diethyl acetate (entry 48) in the presence of ebpe (58% ee at 60 °C).

Both zinc catalytic systems **A** [$ZnEt_2$·ebpe] and **B** [$Zn(dea)_2$·ebpe + Vitride] were used for the enantioselective reduction of various ketones, giving similar yields and ee's, as shown in Table 3. As for most systems allowing enantioselective reduction of ketones,[1] the present zinc catalytic species are particularly well adapted for the reduction of acetophenones, acetonaphthones (entries 55 and 57), α-tetralone (entry 58), or acetylthiophene (entry 59), where the two substituents adjacent to the carbonyl moiety are well differentiated. Substrates such as cyclohexyl methyl ketone (entry 59) or *β*-ionone (entry 60) are reduced with much lower ee's. (<20%).

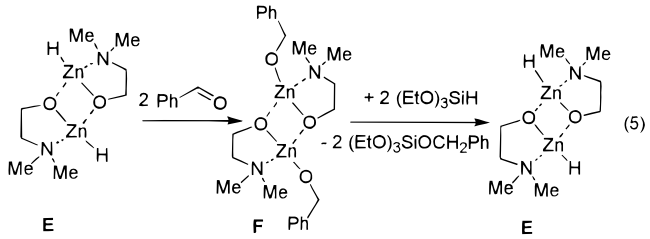
Mechanistic Studies. Is the Ancillary Ligand a Spectator or an Actor? In an attempt to clarify the mechanism of the enantioselective hydrosilylation of ketones using PMHS, we performed some model studies, looking at the reactivity of well-characterized zinc complexes in the presence of silanes.

Alkyl and Hydride Zinc Complexes with (Dimethylamino)ethanol (DMAE). Chiral amino alcohols such as DAIB (**14**) have been successfully used as auxiliary ligands for the enantioselective alkylation of carbonyl compounds by alkyl zinc species,[26] but their use in the present study was only marginally successful. Dimeric $[EtZn(DMAE)]_2$ (**C**) and $[HZn(DMAE)]_2$ (**E**) were prepared according to literature methods,[27] and their reactivity was briefly investigated (eqs 4 and 5). Complex **C** does not react with benzaldehyde but reacts with $(EtO)_3SiH$ in pentane to give a white solid, presumably EtZnH, which turns gray at room temperature and evolves hydrogen in contact with a protic source, together with the formation of $(EtO)_3Si(OCH_2CH_2NMe_2)$ (**D**). This latter compound, which has been characterized by ^1H NMR, results from anion exchange between zinc and silicon (eq 4).



(4)

The dimeric hydrido zinc complex **E** reacts with $(EtO)_3SiH$ to give ZnH_2 and $(EtO)_3Si(OCH_2CH_2NMe_2)$ (**D**). It also reacts with benzaldehyde to give a zinc alkoxy species with presumed structure, **F**, which upon reaction with 1 equiv of $(EtO)_3SiH$ gives a product exhibiting the same ^1H NMR pattern as the initial complex **E** (eq 5). Thus, the hydrido complex **E** appears as a possible model for the hydrosilylation catalyst, although the facile transfer of the alkoxo (dimethylamino)ethanol ligand from Zn to Si severely limits the catalyst life and the use of amino alcohols as ligands for the enantioselective hydrosilylation.



(5)

Alkyl and Hydride Zinc Complexes with Diamines. Since alkoxo ligands easily transfer from zinc to silicium, we investigated the use of chelating amido−amino and bis-amino ligands. The dimeric hydrido complex **G**[28] reacts very slowly with $(EtO)_3SiH$ to give insoluble ZnH_2 and the silazane **H** (eq

(24) Vitride is the trademark of $NaAlH_2(OCH_2CH_2OCH_3)_2$, conditioned as a 70 wt % solution in toluene.

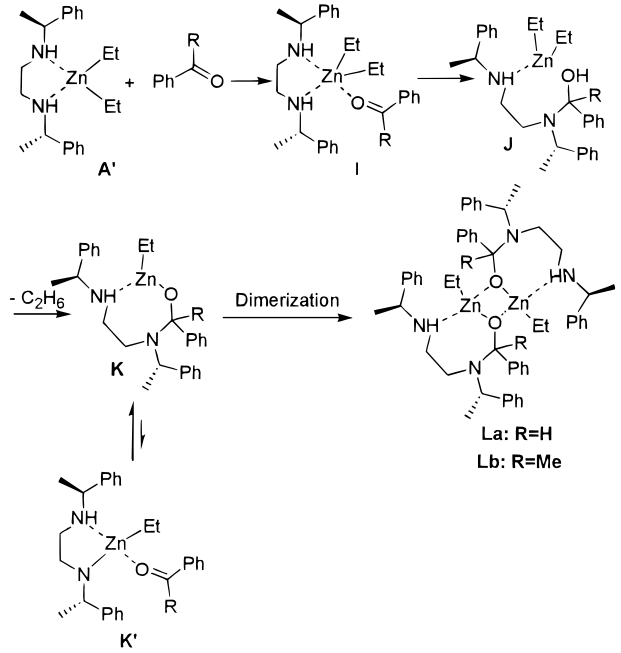
(25) The metal alkoxides were generated in situ from the reaction of metal chlorides with potassium *tert*-pentylate in THF.

(26) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49 and references therein.

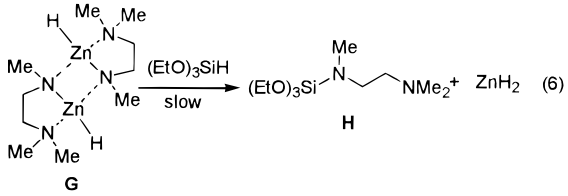
(27) (a) Bell, N. A.; Kassyk, A. L. *J. Organomet. Chem.* **1988**, *345*, 245. (b) Bell, N. A.; Kassyk, A. L. *Inorg. Chim. Acta* **1996**, *250*, 345.

(28) Bell, N. A.; Moseley, P. T.; Shearer, H. M. M.; Spencer, C. B. *J. Chem. Soc., Chem. Commun.* **1980**, 359. Complex **G** has been characterized by X-ray crystal structure, and recently shown to reduce ketones. (see ref 27b).

Scheme 1. Reduction of Carbonyl Compounds by $ZnEt_2$•ebpe and Evidence for a Metallacycle Intermediate



6), thus confirming that N-donor ligands are less labile than O-donor ligands and, therefore, more suitable for the hydrosilylation.



We have further investigated the reactivity of $ZnEt_2$•(*S*,*S*)-ebpe (**A′**) characterized by X-ray crystal structure (as the dimethyl analogue **A**), toward carbonyl compounds and silanes. Both **A** and **A′** are quite thermally stable and do not easily eliminate methane or ethane, respectively, at room temperature. Complex **A′** is conformationally fluxional, as shown by the fact that a single set of signals is observed by ^{1}H NMR, even when either $ZnEt_2$ or ebpe is used in excess. Concentrated solutions of $ZnEt_2$•ebpe slowly react with benzaldehyde or acetophenone to give products, **La** (R = H) and **Lb** (R = Me), respectively, with release of ethane (see Scheme 1). Both are characterized by rather complex ^{1}H NMR spectra, and no further study was undertaken to assign the signals. On the basis of the structure determined for **La**, we suggest a pathway leading to the dimeric structure and the seven-membered metallacycle (see Scheme 1). The coordination of the carbonyl functionality to **A′** (see **I**) is followed by the reaction of the amine with the carbonyl group, resulting in the formation of an amino alcohol **J**,[29] which is readily deprotonated by $ZnEt_2$ with loss of ethane and formation of the metallacycle **K**. The latter contains a three-coordinated zinc, which collapses to a dimer, in which zinc achieves the stable tetracoordination. The structure of **La** is displayed in Figure 4 with some relevant structural parameters.[21] The two zinc atoms are in a tetrahedral coordination environment, and they are bridged in a dimeric structure via the oxygen of the *gem*-aminoalkoxy group derived from the reaction of the ligand

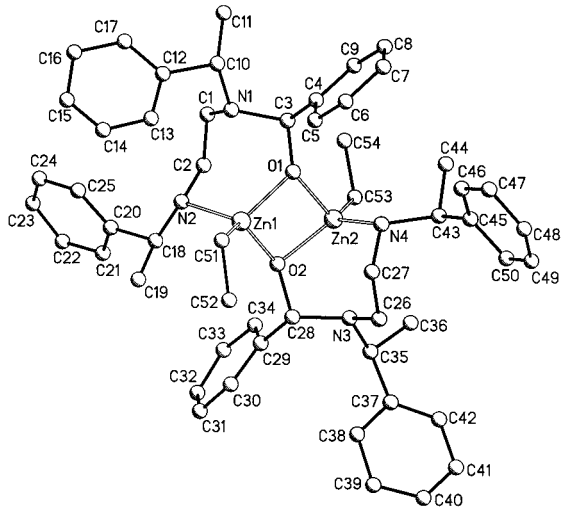


Figure 4. X-ray crystal structure of complex **La** (hydrogens have been omitted for clarity). Selected bond distances (Å) and angles (deg): Zn1−O1 = 2.02(2); Zn1−O2 = 1.96(2); Zn2−O1 = 2.05(2); Zn2−O2 = 2.02(2); Zn1−N2 = 2.17(2); Zn2−N4 = 2.14(2).

with the carbonyl functionality. The conformation of the seven-membered metallacycle is a slightly distorted boat. The absolute configurations of the chiral carbon atoms are as follows: C3, *R*; C10, *S*; C18, *S*; C28, *S*; C35, *S*; C43, *S*.[21] The conformations of C3, *R* and C28, *S* as from the structure of **La** reveal that we fished out in the solid state the *R*,*S* form rather than the active *R*,*R* or *S*,*S* species. It should be emphasized that the metal complexation stabilizes a quite unusual and unstable form of a *gem*-amino alcohol. The O2−C28 and N3−C28 bond lengths (1.47 and 1.55 Å, respectively) are not far from a typical O−C(sp^3) and N−C(sp^3). In addition, the sum of the dihedral angles for C28 (331°) clearly shows that it is sp^3 hybridized.

The same insertion of carbonyl group into the Zn−N bond also occurs with acetophenone, and the resulting complex **Lb** has similar NMR spectra and probably the same dimeric seven-ring structure.

Both complexes **La** and **Lb** have catalytic activities similar to that of $ZnEt_2$•ebpe complex **A′** and gave similar ee's (∼75%) in the reduction of acetophenone under standard conditions. Further, **Lb** reacts at room temperature with 1 equiv of PMHS to give (*R*)-methylphenylcarbinol with 78% ee after hydrolysis with aqueous NaOH. When **Lb** is used as catalyst (10 mol %) for the PMHS (1.2 equiv) reduction of propiophenone (1 equiv) in toluene, both (*R*)-ethylphenylcarbinol (100% yield, 80% ee) and (*R*)-methylphenylcarbinol (10% yield, 78% ee) were obtained after hydrolysis. This shows that both included and external ketone substrates are reduced with similar ee's[30] and suggests that an exchange may occur between the incorporated ketone and the external one through a reverse equilibrium between the amino alcoholate **K** and the zinc amide complex **K′** bearing the coordinated carbonyl substrate.[31]

This unprecedented mechanism is not only relevant to the present enantioselective hydrosilylation but could, eventually, be extended to nondeprotonable chiral diimines or tertiary diamine ligands.[32] Moreover, the proposed mechanism may shed some light on the recently reported Noyori's $RuCl_2$(phosphine)$_n$ + diamine system, which efficiently acts as a selective achiral and chiral ketone hydrogenation catalyst.[9]

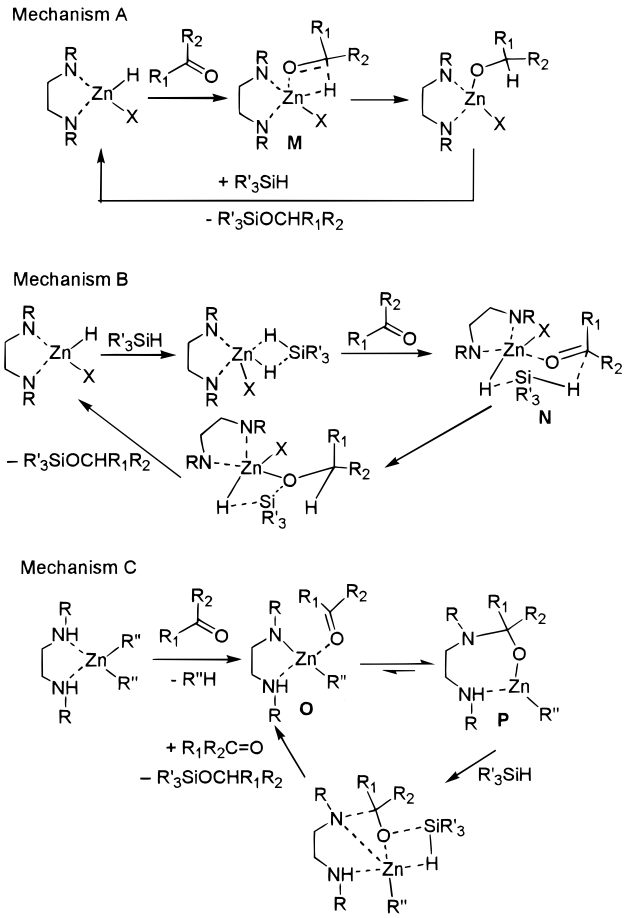
(29) Bergmann, E. D. *Chem. Rev.* **1953**, *53*, 309.

(30) We thank a reviewer for this pertinent suggestion.

(31) Arvidsson, P. E.; Davidson, O.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10*, 527.

(32) Cozzi, P. G.; Veya, P.; Floriani, C.; Rotzinger, F. P.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1995**, *14*, 4092 and references therein.

Scheme 2. Mechanisms to Interpret the Enantioselective Reduction of Ketones



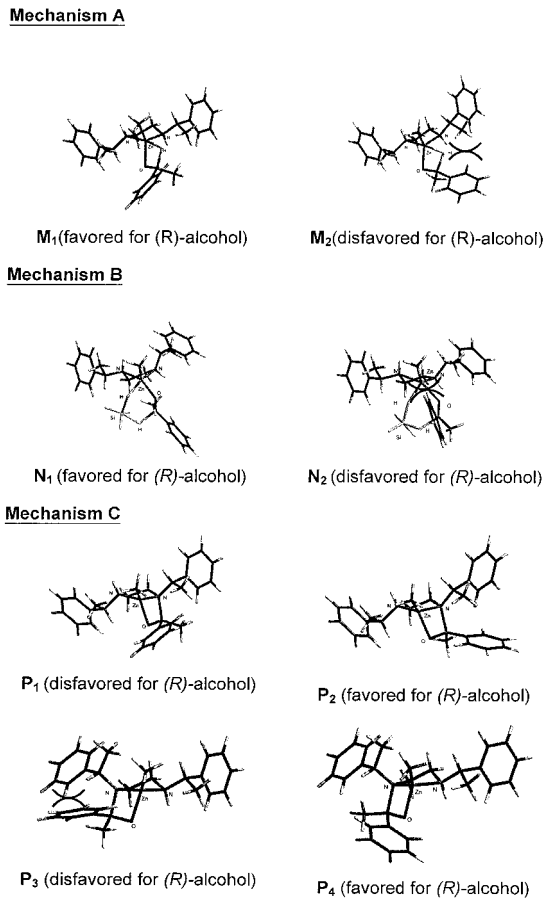


Figure 5. Modelization by PM3 of the transition states **M**, **N**, and **P** according to mechanisms A−C.

Mechanistic Considerations. On the basis of the experimental data so far available, we can suggest three different mechanisms, the former two being very closely related (Scheme 2):

Mechanism A. Hydrogen transfers from Zn−H to the carbonyl compound bonded to zinc in a fifth coordination site (transition state **M**). This reaction has been shown to occur with isolated zinc hydride complexes such as **E** and **G**[28b] and is confirmed in this study (eq 5).

Mechanism B. Zinc hydride forms an adduct with the silane in which SiH bonds are activated in a reactive pentavalent hydridosilicate associated to the zinc Lewis acid center. As for $LiAlH_4$ and $Zn(BH_4)_2$, hydrogen is transferred in a concerted way to the C═O coordinated to zinc in a six-membered ring transition state **N**. This mechanism has previously been suggested by us on the basis of steric effects of PMHS in comparison with monomeric silanes and of ester reduction.[18]

Mechanism C. The coordinated carbonyl compound inserts between zinc and a deprotonated coordinated secondary diamine (intermediate **P**) according to Scheme 2. In the latter case, the diamine, unlike in mechanisms A and B, not only is an ancillary ligand but is presumably involved in the substrate activation. Although speculative yet, the catalytic cycle shown in Scheme 2 may involve intramolecular displacement of an amido leaving group by hydride with retention of configuration at the carbinol carbon atom.[30] Alternatively, the amino alcoholate **P** may revert to the zinc amide **O** (see also **K** and **K′** in Scheme 1) with reformation of the carbonyl compound. In this case the reversible formation of the amino alcoholate only serves to put the carbonyl substrate in the right position to present the *si* face to the carbonyl moiety, giving the (*R*)-carbinol. Reduction of the carbonyl substrate could then occur by Zn−H or Si−H according to mechanism A or B.

The two hypothetical transition states **M** and **N** and the intermediate **P** can be visualized using semiempirical PM3 calculations[33] with constrained distances based on X-ray crystal structures of the (*S*,*S*)-ebpe complexes **A**, **B**, and **La** shown in Figures 2, 3, and 4, respectively. Acetophenone was chosen as the substrate for the three models. The tetrahedral zinc complexes **A** and **B** bearing (*S*,*S*)-ebpe ligand with a C_2 symmetry have two stereochemically equivalent sites occupied by alkyl or carboxylate groups. The two nitrogen atoms of the ligand play a key role in transmitting the chirality of the adjacent carbon atoms to the metal coordination sites. Chiral recognition of the substrate is controlled by the nitrogen substituents which create a classical asymmetric quadrant around the zinc atom. All three models can be used to interpret the chiral recognition of the substrate, with the (*S*,*S*)-ebpe ligand giving preferentially the (*R*)-carbinol.

In intermediate **M** representing the reaction of ZnMeH·(*S*,*S*)-ebpe with acetophenone, hydrogen transfer occurs in the empty quadrant (Figure 5). The two possible orientations of the ketone are represented in models $\mathbf{M_1}$ and $\mathbf{M_2}$. Intermediate $\mathbf{M_1}$, which gives the (*R*)-carbinol, is probably favored owing to a lower steric constraint of the methyl group of acetophenone with the ligand.

In intermediate **N** representing the reaction of ZnMeH·(*S*,*S*)-ebpe with SiH_4 and acetophenone, hydrogen transfers from pentavalent Si−H via a pseudo-chair conformation. Preference for the *si* face of acetophenone can be explained by the unfavorable pseudo-1,3-diaxial interaction of the substrate with

the methyl group coordinated to zinc. As shown in Figure 5, the model $\mathbf{N_1}$ gives the less unfavorable steric conformation for the formation of the (*R*)-carbinol.

In intermediate **P** representing the reaction of ZnMe·(*S*,*S*)-ebpe (deprotonated) with acetophenone, the chirality of the carbinol is determined by the attack of the deprotonated amido nitrogen atom on the ketone coordinated to zinc. Four conformations can be envisaged to model this transition state (Figure 5). The lowest energy transition state $\mathbf{P_4}$ allows the formation of the (*R*)-isomer from the (*S*,*S*)-ligand. As shown in Figure 5, $\mathbf{P_3}$ is probably disfavored by the highest steric constraint of the phenyl group of acetophenone with the ligand, while $\mathbf{P_1}$ and $\mathbf{P_2}$ have relative energies superior to 3.5 kcal/mol.[33]

Thus, all three mechanisms A−C are compatible with the observed enantioselectivity in the reduction of ketones by PMHS.

Conclusion

We have extended the PMHS technology to the enantioselective reduction of ketones using zinc catalysts activated by chiral diamines or diimines. The procedure is safe, inexpensive, simple, and gives carbinols in either (*R*)- or (*S*)-configuration with high yields and ee's. The procedure has been carried out on a 1 kg scale without scale-up problems. Moreover, the inexpensive ebpe ligand is recovered at the end of the reaction by simple distillation from residues and reused for a next operation. Thus, in terms of cost, the present enantioselective process is only slightly more expensive than the achiral one.[18] Further work is being carried out to further increase the ee's over 90% and to extend the scope of the reaction.

Experimental Section

General Procedure. Chemicals described in this study were all reagent grade purchased from Fluka or available in bulk quantities from Firmenich S.A. PMHS used in this study ($M_w = 2200$; specific gravity at 25 °C = 1; 1.55 wt % H) was obtained from Rhone Poulenc (trade name Rhodorsil Hydrofugeant 68), but PMHS from other suppliers (Aldrich, Hüls, Bayer) was found suitable as well. The molecular weight of PMHS was taken equal to 65 for stoichiometry calculation. Zinc, iron, manganese, tin, and cobalt 2-ethylhexanoates (metallic soaps) were commercially available from OMG-Vasset but can also easily be prepared from the reaction of metal oxide, carbonate, or acetate with 2-ethylhexanoic acid in toluene at 120 °C, with azeotropic distillation of water or acetic acid. Zinc diethyl acetate $Zn(dea)_2$ was prepared from the reaction of ZnO with diethylacetic acid (2 equiv) in toluene under reflux with azeotropic distillation of water. All compounds were characterized by GC−MS and ^{1}H and ^{13}C NMR. NMR spectra were recorded in $CDCl_3$ at 360 MHz with a Bruker AMX spectrometer. All ^{1}H NMR spectra are reported in δ units, parts per millions (ppm) downfield from tetramethylsilane. All ^{13}C NMR spectra are reported in ppm referenced to $CDCl_3$. Enantiomeric excesses (ee = $100(R - S)/(R + S)$) were determined by chiral GC analysis using a Chrompack CP-Chirasil-dex-CB 25 m capillary column.

Preparation of Ligands. Chiral cyclohexanediimines **1a**−**e** were easily prepared from the reaction of (*R*,*R*)-cyclohexanediamine tartrate[34] with the corresponding aldehyde; diimines **2a,b** and **3** were prepared from 2,3-butanedione and glyoxal, respectively, with α-phenylethylamine;[33] chiral diamines **4b**−**f**, **5a**−**g**, and **7** were kindly provided as samples by Prof. A. Alexakis (University Geneva);[36] ligand **8** was readily made from inexpensive glutamic acid and aniline, followed by $LiAlH_4$ reduction;[37] chiral tertiary diamines **9** and **10** were prepared according to the literature;[38] chiral amino alcohols (**11**−**15**) are commercial products, except (−)DAIB (**14**), which was kindly provided by Prof. Kagan (University Orsay); ligands **16** and **17** were prepared according to the literature.[39]

(*R*,*R*)-*N*,*N*′-Bis(1-naphthalenylmethylene)-1,2-cyclohexanediamine (1a). (*R*,*R*)-Cyclohexanediamine tartrate (7 g, 26.0 mmol) and solid K_2CO_3 (7.3 g) were dissolved in 35 mL of H_2O and 130 mL of ethanol. Then 1-naphthaldehyde (8.2 g, 52.0 mmol) was added, and the mixture was stirred for 3 h at room temperature. A white-cream solid precipitates, which is filtered, washed with EtOH−H_2O mixture, and then recrystallized in hot ethanol (75%).

Diimines **1b**−**g** were prepared according to the same procedure in good yields.[40]

(*R*,*R*)-*N*,*N*′-Ethylenebis(1-phenylethylamine) (ebpe, 6).[41] 1,2-Dibromoethane (170 g, 900 mmol) was added over 30 min with temperature control to (*R*)-α-phenylethylamine (440 g, 3630 mmol) heated to 130 °C. After cooling to 80 °C, the mixture was hydrolyzed with 283 g of aqueous KOH 45% to remove KBr. The organic phase was then distilled in vacuo to give first 9 g of recoverable starting amine, then 192 g of (*R*,*R*)-ebpe with a 98% purity (bp = 130 °C, 1 mbar, $[\alpha]_D = +65°$) (77%). The (*S*,*S*)-ebpe ligand was prepared in the same way from (*S*)-α-phenylethylamine.

(*R*,*R*)-2,2′-(1,2-Cyclohexylidene)diisoindole (10). This compound was prepared in the same way as described for ligand **9**.[38] (*R*,*R*)-Cyclohexanediamine (5 g, 43 mmol), dichloro-*o*-xylene (16 g, 90 mmol), and triethylamine (36 g) were mixed at 0 °C in CH_2Cl_2 (50 mL) over 1 h, then the mixture was refluxed at 60 °C for 7 h. After being cooled to 5 °C, the mixture was washed 3 times with H_2O (50 mL), then dried with Na_2SO_4. Addition of diethyl ether (20 mL) resulted in the precipitation of a white solid which was crystallized in a CH_2Cl_2−Et_2O mixture (60%).^{13}C NMR ($CDCl_3$, 25 °C): 20.91 (t), 24.63 (t), 57.05 (t), 62.60 (d), 122.30 (d), 126.60 (d), 140.08 (s). $[\alpha]_D = -63.2°$.

Preparation of Zinc Complexes. Zn(CH$_3$)$_2$[(*S*,*S*)-*N*,*N*′-ethylenebis(1-phenylethylamine)] (A). A toluene solution of $ZnMe_2$ (6.5 mL, 1.5 M, 9.7 mmol) was added to a solution of (*S*,*S*)-ebpe (**6**) (2.50 g, 9.33 mmol) in toluene (50 mL). A white precipitate forms before the end of the addition. Volatiles were removed in vacuo, then pentane (60 mL) was added to the residue. White complex **A** was collected and dried in vacuo (2.9 g, 85%). Crystals suitable for X-ray structure were grown in CH_2Cl_2/C_6H_6 at 9 °C. Anal. Calcd for $C_{20}H_{30}N_2Zn$: C, 66.02; H, 8.31; N, 7.69. Found: C, 66.7; H, 8.21; N, 7.73. ^{1}H NMR (CD_2Cl_2, 25 °C): δ 7.07 (m), 6.76 (m), 3.54 (m, 2H), 1.82 (m, 2H), 1.63 (m, 2H), 1.39 (d, 6H, $J = 6.8$ Hz), 1.23 (m, 2H), −0.29 (s, 6H).

Zn(C$_2$H$_5$)$_2$[(*S*,*S*)-*N*,*N*′-ethylenebis(1-phenylethylamine)] (A′). $ZnEt_2$ (1.43 g, 11.3 mmol) and (*S*,*S*)-ebpe (**6**) (3.0 g, 11.3 mmol) were mixed in toluene (80 mL). Volatiles were removed in vacuo, then pentane (50 mL) was added to the residue. The resulting suspension was cooled at −25 °C overnight, and finally **A′** was collected and dried in vacuo (3.16 g, 71%). Anal. Calcd for $C_{22}H_{34}N_2Zn$: C, 67.42; H, 8.74; N,

(33) All calculations were carried out on a SGI R10000 computer using the SPARTAN V5.0 program (Wavefunction, Inc., Irvine, CA, 1997). The geometries of the structures were obtained by PM3 energy calculations which incorporate parameters for Zn and Si. The lengths of the bonds involved in the mechanism were controlled by hypothetical distance constrains. The distances (in Å) were chosen as follows: Zn−O = 2.1, Zn−N = 2.1, Zn−H = 2.0, Si−H = 1.8, C−O = 1.4, C−N = 1.8, C−H = 1.8. Additional constraints were needed to control the geometries of $\mathbf{M_2}$, $\mathbf{N_1}$, and $\mathbf{N_2}$. Thus, this method cannot be considered as a "true" transition state calculation which is out of the scope of this paper. However, the geometry of the complexes obtained by this method can be used to discuss the three mechanisms. Energies of the complexes must be considered as less significant. Only the energy differences superior to 3.5 kcal/mol were considered in the discussion. PM3 energies (in kcal/mol) were as follows: $\mathbf{M_1}$, 86.7; $\mathbf{M_2}$, 85.0; $\mathbf{N_1}$, 117.3; $\mathbf{N_2}$, 122.8; $\mathbf{P_1}$, 74.4; $\mathbf{P_2}$, 79.2; $\mathbf{P_3}$,72.2; $\mathbf{P_4}$, 70.8.

(34) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939.

(35) Tom Dieck, H.; Dietrich, J. *Chem. Ber.* **1984**, *117*, 695.

(36) Alexakis, A.; Mangeney, P. *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Chapman & Hall: London, 1996, p 93 and references therein.

(37) Iriochijima, S. *Synthesis* **1978**, 684.

(38) Corey, E. J.; Sarshar, S.; Azimiora, M. D.; Newbold, R. C.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 7851.

(39) Brunner, H.; Reiter, B.; Riepl, G. *Chem. Ber*. **1984**, *117*, 1330.

(40) NMR spectra are reported in the Supporting Information.

(41) This is a modified procedure from the original method using 1,2-dichloroethane and α-phenylethylamine. Horner, L.; Dickerhof, K. *Liebigs Ann. Chem*. **1984**, 1240.

7.15. Found: C, 67.51; H, 8.74; N, 7.06. ^{1}H NMR (CD_2Cl_2, 25 °C): 7.07 (m), 6.76 (m), 3.54 (m, 2H), 1.82 (m, 2H), 1.63 (m, 2H), 1.39 (d, 6H, J = 6,8 Hz), 1.23 (m,2H), −0.29 (s,6H). IR (Nujol, ν_{max} cm^{-1}): 3283 (m). ^{1}H NMR (CD_2Cl_2, 25 °C, δ ppm): 7.36−7.23 (m, 10H), 3.75 (m, 2H), 2.45 (m, 2H), 2.23 (m, 2H), 1.85 (m, 2H), 1.50 (d, 6H, J = 6.8 Hz), 1.3 (t, 6H, J = 8.1 Hz), −0,04 (m, 4H).

Zn(Et$_2$CHCO$_2$)$_2$(*S*,*S*)-ebpe (B). To a solution of Zn(dea)$_2$ (3 g, 10 mmol) in diisopropyl ether (50 mL) was added (*S*,*S*)-ebpe (**6**) (3.1 g, 10 mmol). A white solid precipitates which was filtered, washed with pentane, and dried in vacuo (4.2 g, 73%). Crystals suitable for X-ray structure were grown in cyclohexane. ^{1}H NMR: δ 0.95 (tt, 12H, CH_3-CH_2), 1.55 (d, 6H, CH_3−CH), 1.6−1.7 (m, 8H, CH_2−CH), 2.3 (m, 2H, CH−C═O), 2.55−2.8 (m, 4H, CH_2−NH), 3.8 (m, 2H, CH−NH), 7.2−7.4 (m, 10H, arom). ^{13}C NMR (δ (ppm)): 12.37, 12.42 (q, CH_3), 23.36 (q, CH_3), 25.99 (t, CH_2), 46.42 (t, CH_2−NH), 51.15 (d, CH), 58.91 (d, CH), 126−129 (d,d,d), 141.19 (s), 184.9 (s, CO_2).

[ZnEt(OCH$_2$CH$_2$NMe$_2$)]$_2$ (C).[31] ZnEt$_2$ (18 mL, 1 M in hexane, 1.8 mmol) was added to a solution of 2-dimethylethanolamine (1.6 g, 1.8 mmol) in DME. Volatiles were removed in vacuo, and the residue was taken up in *n*-hexane (40 mL). After keeping the flask 24 h at −25 °C, **C** was collected as microcrystalline solid (1.7 g, 55%). Anal. Calcd for $C_6H_{15}NOZn$: C, 39.47; H, 8.28; N, 7.67. Found: C, 40.0; H, 8.69; N, 7.57. ^{1}H NMR (C_6D_6, 25 °C): δ 4.01 (b), 3.78 (m), 3.65 (b), 2.7 (b), 2.20 (bm), 2.08 (s), 1.73 (m), 1.55 (m).

Reaction of C with (EtO)$_3$SiH and Preparation of D. Complex **C** (4.43 g, 24.3 mequiv) was reacted with (EtO)$_3$SiH (4 g, 24.3 mmol) in DME (100 mL). ^{1}H NMR of the raw mixture (a sample was taken to dryness in vacuo in a glovebox and dissolved in C_6D_6) showed that the starting material had been consumed. ^{1}H NMR (C_6D_6, 25 °C): δ 3.89 (m), 3.45 (b), 2.45 (m), 2.21(s), 2.13 (s), 1.67 (t, 3H, J = 8.3 Hz), 1.87 (m), 0.48 (q, 2H, J = 8.3 Hz). After standing overnight at room temperature, some white solid formed; it was filtered off, volatiles were removed in vacuo, and pentane was added to the resulting grayish solid to give a white, sticky solid (**D**). ^{1}H NMR (C_6D_6, 25 °C): δ 3.88 (m, 9H), 2.42 (m, 2H), 2.09 (m, 9H), 1.68 (t, 3H, J = 8.3 Hz, 1.18 (m, 9H), 0.46 (q, 2H, J = 7.8 Hz).

[ZnH(OCH$_2$CH$_2$NMe$_2$)]$_2$ (E). Dimethylethanolamine (1.98 g, 22.2 mmol) was added to a suspension of ZnH_2 (1.5 g, 22.2 mmol) in THF, prepared from the reaction of ZnEt$_2$ with $LiAlH_4$. Hydrogen evolution was observed, and a white precipitate of **E** was collected and dried in vacuo. Anal. Calcd for $C_4H_{11}NOZn$: C, 31.09; H, 7.17; N, 9.06. Found: C, 31.15; H, 7.29; N, 8.79. ^{1}H NMR (C_6D_6, 25 °C): δ 4.28 (s), 3.88 (b), 2.13 (s), 0.49 (b).

Reaction of E with (EtO)$_3$SiH. (EtO)$_3$SiH (0.91 g, 5.5 mmol) was added to a solution of **E** (0.86 g, 5.56 mequiv) in THF (100 mL). The reaction mixture turned milky within minutes. ^{1}H NMR of the raw reaction mixture (a sample was taken to dryness and suspended in C_6D_6): δ 4.01 (t, 2H, J = 6.3 Hz), 3.89 (q, 6H, J = 6.8 Hz), 2.49 (t, 2H, J = 6.3 Hz), 2.13 (s, 6H, Me), 1.19 (t, 9H, J = 6.8 Hz).

Reaction of E with Benzaldehyde, then (EtO)$_3$SiH. PhCHO (0.66 g, 6.2 mmol) was added to a solution of **E** (0.95 g, 6.15 mequiv) in DME (100 mL). ^{1}H NMR of the raw reaction mixture (a sample was taken to dryness and suspended in C_6D_6): δ 7.66 (b), 7.28 (b), 7.05 (b), 5.26 (b), 4.27 (b), 3.87 (b), 3.63 (b), 2.22 (b), 1.89 (b). (EtO)$_3$SiH (1 g, 6.1 mmol) was added to the reaction mixture. ^{1}H NMR of the raw reaction mixture (a sample was taken to dryness and suspended in C_6D_6) δ 7.36 (m), 4.92 (s), 4.89 (s), 4.86 (s), 4.28 (bs), 3.87 (m), 2.13 (bs).

Reaction of ZnEt$_2$·(*S*,*S*)-ebpe A′ with Benzaldehyde. Synthesis of the Dimeric Complex La. ZnEt$_2$ (1.80 g, 14.6 mmol), (*S*,*S*)-ebpe (3.77 g, 14 mmol), and benzaldehyde (1.66 g, 15.6 mmol) were mixed in toluene to give a yellow solution which exhibited in ^{1}H NMR a spectra consisting of the superimposition of PhCHO and **A′**. After 1 day at room temperature, volatiles were removed in vacuo, pentane was added to the residue, the resulting suspension was cooled at −25 °C overnight, and finally **La** was collected and dried in vacuo (2.6 g, 40%). Anal. Calcd for $C_{27}H_{35}N_2OZn$: C, 69.15; H, 7.52; N, 5.97. Found: C, 68.95; H, 7.64; N, 5.76. ^{1}H NMR (C_6D_6, 25 °C): δ 9.64 (s, PhCHO), 7.9−6.9 (m), 6.27 (b), 5.68 (s), 5.60 (s), 4.0 (m), 3.54 (m), 3.3−2.5 (m), 1.93 (m), 1.83 (m), 1.33 (d), 1.23 (d), 1.19 (d), 1.13 (d), 1.05 (d), 0.90 (m), 0.67 (m), 0.5 (m). Crystals suitable for X-ray analysis were grown in pentane at −25 °C, which exhibited the same ^{1}H NMR spectra as the reaction mixture of **A′** and PhCHO, after standing for 24 h. When the reaction was carried out in an NMR tube in C_6D_6, evolution of ethane was observed (singlet at 0.80 ppm).

Reaction of ZnEt$_2$·(*S*,*S*)-ebpe A′ with Acetophenone. Synthesis of the Dimeric Complex Lb. ZnEt$_2$ (2.07 g, 16.7 mmol), (*S*,*S*)-ebpe (4.49 g, 16.8 mmol), and acetophenone (2.0 g, 16.6 mmol) were mixed in toluene to give a yellow solution. After 1 day at room temperature, volatiles were removed in vacuo, pentane was added to the residue to give a yellow oil which became a yellow powder after triturating with cold pentane (2.68 g, 5.56 mmol). Anal. Calcd for $C_{28}H_{36}N_2OZn$: C, 69.77; H, 7.53; N, 5.81. Found: C, 66.94; H, 6.74; N, 4.69. ^{1}H NMR (C_6D_6, 25 °C): δ 8.03 (m), 7.82 (m), 7.3−6.8 (m), 6.63 (m), 6.04 (s), 5.58 (m), 4−1.15 (b), 1.51 (J = 8.3 Hz), 1.36 (d), 1.21 (d), 0.41 (q, J = 8.3 Hz). When the reaction was carried out in an NMR tube in C_6D_6, evolution of ethane was observed (singlet at 0.80 ppm).

Enantioselective Reduction of Acetophenone. Method A. In a three-necked 1 L flask, ZnEt$_2$ (33.2 mL, 1 M in toluene, 33 mmol) and (*S*,*S*)-ebpe (**6**) (8.84 g, 33 mmol) were dissolved in 100 mL of toluene for the formation of complex **A′**. Then 200 g of acetophenone (1.66 mol) was added, and 130 g of PMHS (2 mol) was added to the mixture in 30 min, keeping the temperature between 25 and 30 °C. After 24 h at room temperature, all the acetophenone was consumed (GC control of an aliquot sample hydrolyzed by KOH 15%). The reaction mixture was poured cautiously on 375 g of KOH (45%) (*Caution: evolution of H_2!*) in ca. 30 min. The aqueous phase containing potassium polymethylsiliconate was discarded, and the organic phase was concentrated in vacuo, then methylphenylcarbinol was recovered by distillation in vacuo (190 g, 94% yield, 99% purity, 75% ee (*R*)). The same results were obtained using 4 times less (*S*,*S*)-ebpe (8.25 instead of 33 mmol).

Method B. In a three-necked 1 L flask, Zn(dea)$_2$ (2.95 g, 10 mmol) and (*S*,*S*)-ebpe (2.68 g, 10 mmol) were dissolved in toluene (100 mL) to form complex **B**. Then, a 70% solution of Vitride (2 g) in toluene was added. After the release of H_2 stops, 120 g of acetophenone (1 mol) was introduced, followed by 70 g of PMHS (1.08 mol). The reaction mixture was stirred 24 h at room temperature until complete consumption of the substrate. Then the mixture was cautiously poured on a 45% aqueous solution of KOH. After concentration of the solvent, methylphenylcarbinol was recovered by distillation (116 g, 95% yield, 99% purity, 75% ee (*R*)).

Acknowledgment. H.M. thanks MM Joël Pastori and Daniel Soares for their invaluable technical assistance. We thank also Prof. A. Alexakis (Geneva University) for providing samples of ligands **4b**−**f**, **5a**−**g**, and **7** and for helpful discussion.

Supporting Information Available: X-ray crystallography data, descriptions of the structures, tables of crystallographic data for **A**, **B**, and **La**, and NMR spectra of ligands and complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

JA990522I