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Asymmetric reduction of *ortho*-multisubstituted benzophenones catalyzed by diamine–Zn–diol complexes

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Abstract—The asymmetric reduction of benzophenones multisubstituted at the *ortho*-positions was achieved via hydrosilylation catalyzed by in situ generated chiral diamine–Zn–diol complexes under mild conditions, wherein polymethylhydrosiloxane (PMHS) served as a safe and inexpensive source of hydride.

The development of chiral catalysts, which transform prochiral molecules into optically active ones by propagation of chirality, has been recognized as one of the most important subjects in modern synthetic organic chemistry. Highly promising candidates for use as chiral catalysts are generally metal complexes that bear chiral and nonracemic organic ligands. The chiral metal catalysts are known to exhibit ligand-acceleration or asymmetric-activation catalysis.[1] Herein, we report on the asymmetric-activation approach to the asymmetric reduction of sterically demanding benzophenones catalyzed by Zn complexes composed of chiral diamines and achiral diols.

Benzhydrol is known as a basic skeleton for bioactive pharmaceuticals and the intermediates used in commercial drug synthesis.[2] While several trials of asymmetric reduction of monosubstituted benzophenones have been reported,[3] there has been no report on asymmetric reduction of benzophenones multisubstituted at the *ortho*-positions, that is, the 2, 6, and 2′ positions. We first attempted asymmetric reduction of 2,6-dimethylbenzophenone and 2,2′,4,6-tetramethylbenzophenone (**1**) through chiral borane or aluminate reagents,[4] enzymatic reduction,[5] and catalytic hydrogenation,[6] without success, apparently due to the steric shielding effect of the *ortho*-substituents. We then examined hydrosilylation using silanes or siloxanes. In general, reduction by silanes is achieved in the presence of a hard acid such as CF_3CO_2H or BF_3OEt_2.[7] In the presence of a nucleophile, on the other hand, reduction with siloxanes proceeds under mild conditions.[8] Among the siloxanes which are generally stable and hence less reactive than silanes,[9] polymethylhydrosiloxane (PMHS) is one of the most attractive reducing reagents, as it is inexpensive, nontoxic, and stable in air and moisture.[10,11]

Asymmetric hydrosilylation using a chiral zinc complex[12] prepared from chiral diamine **3a** and Et_2Zn has been reported by Mimoun and co-workers,[12a,b] who, however, did not report reduction of any benzophenone, particularly of the hindered **1**. When we used a stoichiometric amount of this complex for hydrosilylation of **1** at room temperature, a high yield was obtained (Table 1, entry 1). Using a stoichiometric amount of the zinc complex, moderate enantioselectivity (up to 84% ee) was achieved at −10 °C (entry 2). Lewis acidic ZnF_2 (entry 5) and $Zn(OTf)_2$ (entry 6) were unsuccessful. Although Mimoun postulated the involvement of ZnH in his catalytic hydrosilylation, the ZnH complex[13] was not effective in this hydrosilylation (entry 7). Toluene was the best solvent for these stoichiometric reactions (entries 1, 2, 8–12). However, the decrease in the amount of the diamine (**3a**)–Et_2Zn complex resulted in the decrease in enantioselectivity (entries 3 and 4).

We therefore searched for another Zn catalyst system in which an anion was not freely released, namely Zn-dialkoxide catalysts. In the context of asymmetric activation,[1c,14] we have already reported that BINOL–Zn–diamine catalysts are effective for alkylation of

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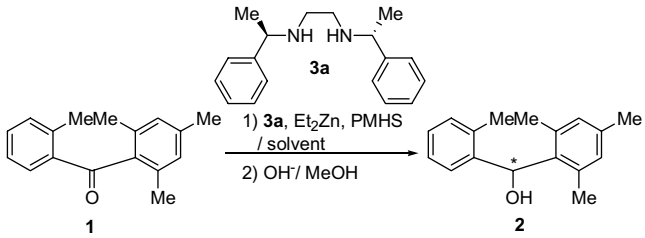
Table 1. Reduction of **1** by PMHS in the presence of diamine (**3a**)–zinc catalyst

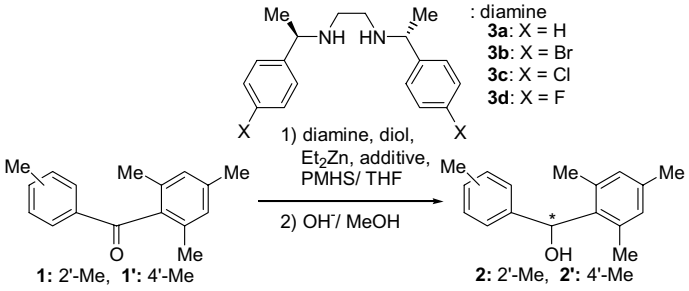


Entry	Catalyst		Reaction conditions			Selectivity[a]	
	Zn source	mol %	Solvent	Temp (°C)	Time (h)	Conv. (%)	ee (%)
1	Et_2Zn	100	Toluene	rt	3.5	>99	77
2	Et_2Zn	100	Toluene	−10	9	>99	84
3	Et_2Zn	20	Toluene	rt	28	>99	37
4	Et_2Zn	10	Toluene	rt	10	>99	5
5	ZnF_2	100	Toluene	rt	24	0	—
6	$Zn(OTf)_2$	100	Toluene	rt	24	0	—
7	ZnH_2	100	Toluene	rt	48	0	—
8	Et_2Zn	100	THF	0	6	>99	49
9	Et_2Zn	100	CH_2Cl_2	0	9	89	51
10	Et_2Zn	100	DMSO	rt	3.5	92	67
11	Et_2Zn	100	CH_3CN	0	6	>99	1
12	Et_2Zn	100	Hexane	0	6	>99	71

[a] By chiral HPLC analysis: CHIRALCEL OJ (Daicel Chemical Ind., Ltd., Japan): UV at 231 nm; hexane/2-PrOH = 9/1; 0.6 mL/min).

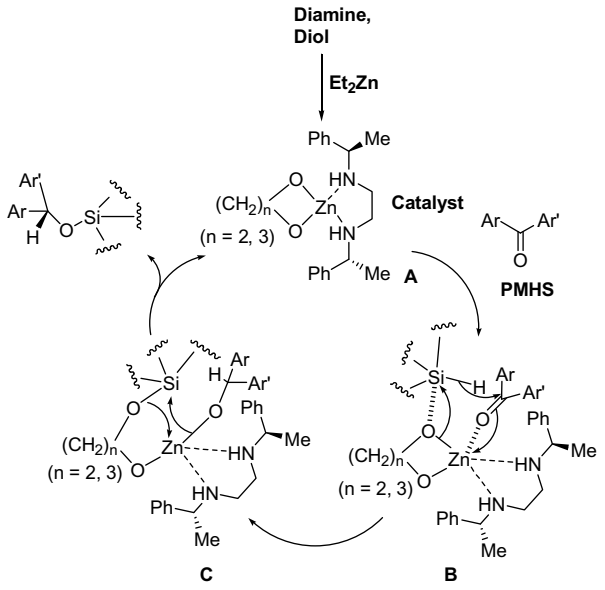
aldehydes and that reduction of aldehydes proceeds as a side reaction. Therefore, we examined the addition of diols to the diamine–Zn complex (Table 2), as several alkoxides had been employed as activators for silanes/sil-

Table 2. Reduction by chiral diamine–zinc–diol catalysts



Entry	Substrate	Catalyst				PMHS (equiv mol)	Additive	Reaction conditions			Selectivity[a]	
		Diamine	Zn source	Diol	mol %			Solvent	Temp (°C)	Time (h)	Conv. (%)	ee (%)
1	**1**	**3a**	Et_2Zn	(*S*)-BINOL	10	6	MS3A	THF	rt	48	97	74
2	**1**	**3a**	Et_2Zn	(*R*)-BINOL	10	6	MS3A	THF	rt	48	45	77
3	**1**	**3a**	Et_2Zn	HO⁄⁄OH	10	6	MS3A	THF	rt	9	>99	76
4	**1**	**3a**	Et_2Zn	HO⁄⁄OH	10	6	MS3A	Toluene	0	6	17	54
5	**1**	**3a**	Et_2Zn	HO⁄⁄OH	10	6	MS3A	THF	0	6	21	84
6	**1**	**3a**	Et_2Zn	HO⁄OH	10	6	MS3A	THF	rt	24	74	74
7	**1**	**3a**	Et_2Zn	HO⁄OH	10	6	—	THF	rt	8	1	—
8	**1**	**3a**	Et_2Zn	HO⁄OH	2	2	MS3A	THF	rt	48	70	77
9	**1′**	**3a**	Et_2Zn	HO⁄OH	2	2	MS3A	THF	5	24	68	83
10	**1**	**3b**	Et_2Zn	HO⁄OH	10	6	MS3A	THF	rt	24	68	85
11	**1**	**3c**	Et_2Zn	HO⁄OH	10	2.5	MS3A	THF	rt	24	98	90
12	**1**	**3d**	Et_2Zn	HO⁄OH	10	2.5	MS3A	THF	rt	24	97	96

[a] By chiral HPLC analysis (DAICEL CHIRALCEL OJ: UV at 231 nm; hexane/2-PrOH = 9/1; 0.6 mL/min). Detection of **2**: T_R 11.6 min (major enantiomer), 18.4 min (minor enantiomer) and substrate **1** was detected at 15.5 min. Detection of **2′**: T_R 15.5 min (major enantiomer), 24.1 min (minor enantiomer) and substrate **1′** was detected at 13.9 min.



Scheme 1. Proposed catalytic cycle.

oxanes.[15] Interestingly, the configuration of (*S*)/(*R*)-BINOL had little effect on the degree of enantioselectivity (entries 1 and 2). Furthermore, achiral diols such as 1,3-propanediol[16] (entries 3–5) and ethylene glycol (entries 6–12) gave almost the same degree of enantioselectivity. In these catalytic reactions, THF was the best solvent rather than toluene, which was the best in the stoichiometric reactions. The addition of MS3A also increased the conversion (entries 6 vs 7), as previously suggested[17] that MS3A could be effective for the ligand exchange or catalyst turnover. In sharp contrast to the Zn–diamine (**3a**) complex, essentially no change was seen in the degree of enantioselectivity (77% ee vs 74% ee) even by the decrease in the amount of the diamine–Zn–diol complex (entries 8 vs 6). Catalytic asymmetric reduction of 2,4,4′,6-tetramethylbenzophenone (**1′**) also gave a high degree of enantioselectivity (83% ee) (entry 9). Through derivation of diamines (Br: entry 10, Cl: entry 11, and F: entry 12), the *p*-F-diamine (**3d**)–Zn–diol complex gave the highest enantioselectivity (96% ee, 97%).

Et_2Zn is reported to form a number of oligomeric structures.[18] In a combination of bidentate ligands such as diamines and aminoalcohols, a monomeric species forms.[12f,g] Mimoun has demonstrated by X-ray crystallography that an intermediate composed of diamine **3a** and benzaldehyde forms a dimer in aprotic solvent.[12a] Carpentier has also reported that a dimeric Et_2Zn–dibenzylethylenediamine complex is changed to the monomeric complex by the addition of alcohol.[12c] In our diamine–Zn–diol complex (Scheme 1), Et_2Zn reacts with diol and diamine to give the diamine–Zn–diol complex (**A**).[19] As reported, Et_2Zn with diols immediately forms cyclic Zn-dialkoxide with the generation of ethane.[17f] Zn(II) has a d^{10} electron system and, according to the 18-electron rule, the coordination sites of Zn(II) are limited to a maximum number of four. Therefore, after the addition of ketones and PMHS, one Zn(II)-diol bond may be cleaved via the reduction of ketones with PMHS. PMHS, activated by one of the dialkoxide anions, would release hydrides for reduction of the substrate in a concerted fashion (**B**). In the final step, the new alkoxide anion, derived from the substrate, would attack the silylether (**C**) to afford the initial cyclic dialkoxide catalyst (**A**) and the silylether of the reduction product.

*Representative procedure for asymmetric hydrosilylation of benzophenone **1** catalyzed by the diamine (**3a**)–Et_2Zn–ethylene glycol (1:1:1) complex:* In an argon atmosphere, Et_2Zn (1 mol/L in hexane, 0.1 mL, 0.1 mmol) was added to a solution of diamine **3a** (26.8 g, 0.1 mmol) and ethylene glycol (6.2 mg, 0.1 mmol) in THF (2 mL) in the coexistence of dried MS3A (10 mg) and stirred for 10 min at 0 °C. To the solution, benzophenone **1** (238.6 mg, 1 mmol) and PMHS (390 mg, 6 mmol) were added successively with THF (1 mL), and the reaction mixture was warmed to room temperature with stirring. The stirring was continued for 24 h and quenched by the addition of 1 mol/L NaOH (ca. 1 mL) and MeOH (ca. 1 mL). The mixture was then extracted with AcOEt. The organic layers were then washed with brine and dried over Na_2SO_4. Evaporation of the organic solvent gave the reduction product **2**. Both the enantiomeric excess and the conversion were measured using chiral HPLC analysis.[20]

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19. We obtained almost the same enantioselectivity, irrespective of the order of addition of diamine, diol, and Et_2Zn. Case 1: addition of ethylene glycol to diamine–Et_2Zn complex; case 2: addition of Et_2Zn to ethylene glycol and diamine **3a** solution; case 3: addition of diamine to Zn–ethylene glycol complex. In all contacts of Et_2Zn with ethylene glycol, evolution of ethane gas was observed.
20. HPLC analysis condition, see: footnote in Table 2.