Catalytic Hydrosilylation of Carbonyl Compounds with Zinc(II) Acetate: Asymmetric Induction Collaborated with N_2S_2 Ligands

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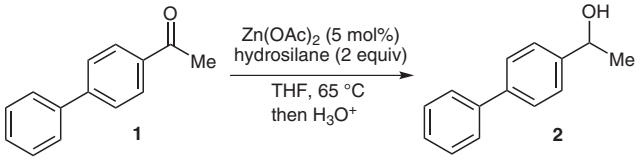
Abstract: Zinc acetate proved to be an efficient catalyst for hydrosilylation of ketones and aldehydes in the combination with $(EtO)_2MeSiH$, and a good to excellent asymmetric induction was observed in the presence of chiral N_2S_2 ligands.

Key words: reduction, hydrosilylation, zinc, asymmetric catalysis, chiral ligand

Reduction method of carbonyl compounds has been rapidly progressing as compatible with social demands such as environmetally benign and inexpensive procedures.[1] In this context, iron catalysts have been highlighted to show efficient activity including asymmetric induction with appropriate phosphine, nitrogen, or sulfur ligands.[2] In place of iron catalysts, biologically benign zinc-based catalyts can also be applied as one of alternatives. In 1999, actually, Mimoun et al. reported the excellent achievement of economical reduction method with zinc catalysts derived from Zn(2-ethylhexanoate)$_2$ (2-EH)/$NaBH_4$ or $ZnEt_2$/$Me_2N(CH_2)_2NMe_2$ (TMEDA) in the presence of inexpensive polymethylhydrosiloxane (PMHS) as a hydride donor.[3] The zinc-catalyzed reduction of ketones was followed by Carpentier,[4] Parrodi–Juaristi–Walsh,[5] Mikami,[6] and Riant,[7] to disclose asymmetric reductions. Recently, Bandini–Umani–Ronchi[8] applied their chiral diamine-bisthiophene ligands with $ZnEt_2$ for asymmetric reduction of ketones.[9] Here, we disclose that $Zn(OAc)_2$ can act as an efficient catalyst for hydrosilylation of ketones with $(EtO)_2MeSiH$ as hydride donor, and we show some examples for asymmetric induction by use of N_2S_2 ligands.

A system of Zn(2-EH)$_2$/PMHS reported by Mimoun needs $NaBH_4$ as a metal activator for hydrosilylation of ketones.[9] During our previous work for metal-catalyzed hydrosilylation,[10] we happened to find that a cheep zinc salt $Zn(OAc)_2$ by itself with $(EtO)_2MeSiH$ sufficiently works a reducing agent of ketones. The representative example is as follows: methyl biphenyl-4-yl ketone (**1**) (1.0 mmol) was treated in a THF (3.0 mL) solution at 65 °C for 12 hours with $Zn(OAc)_2$ (0.05 mmol, 5 mol%) and $(EtO)_2MeSiH$ (2.0 mmol). The hydrosilylation smoothly took place followed by hydrolysis to produce the corresponding secondary alcohol **2** in almost quantitative yield (Table 1, entry 1). The reaction proceeded very slowly at 30 °C; ca. 50% for 72 hours (entry 2). The catalyst loading of 1 mol% worked sufficiently to result in the almost the same result (entry 3). The PMHS in place of $(EtO)_2MeSiH$ did not work well under the above conditions, even in methanol-containing solution described by Mimoun (entry 4). Alkoxysilanes such as $(EtO)Me_2SiH$ and $(EtO)_3SiH$ gave good yields (entries 5 and 6), but alkylsilanes did not give the product alcohol (entries 7 and 8).

Table 1 Catalytic Hydrosilylation of **1** with $Zn(OAc)_2$ and Hydrosilanes[a]



1 2

Entry	Silane	Time (h)	Yield (%)
1	$(EtO)_2MeSiH$	12	99
2[b]	$(EtO)_2MeSiH$	72	49
3[c]	$(EtO)_2MeSiH$	18	98
4	PMHS	24	trace
5	$(EtO)Me_2SiH$	24	97
6	$(EtO)_3SiH$	18	98
7	Et_3SiH	24	no reaction
8	Me_2PhSiH	24	no reaction

[a] Reaction conditions: **1** (1.0 mmol), silane (2.0 mmol), THF (3.0 mL).
[b] At 30 °C.
[c] With $Zn(OAc)_2$ (1 mol%).

Under the conditions used in entry 1 of Table 1, representative aromatic and aliphatic ketones were subjected to the hydrosilylation to give the corresponding secondary alcohols in high yields 91–99% (Table 2, entries 1–9). In addition, hydrosilylation of the several aldehydes was also demonstrated to give the corresponding primary alcohols in high yields 91–99% (entry 10–13). Benzalacetone was reduced to exclusively give 1,2-reduction product (entry 14).

In the case of reduction of ester groups, Mimoun reported that the reduction of methyl benzoate to benzyl alcohol was readily promoted by Zn(2-EH)$_2$/$NaBH_4$/PMHS sys-

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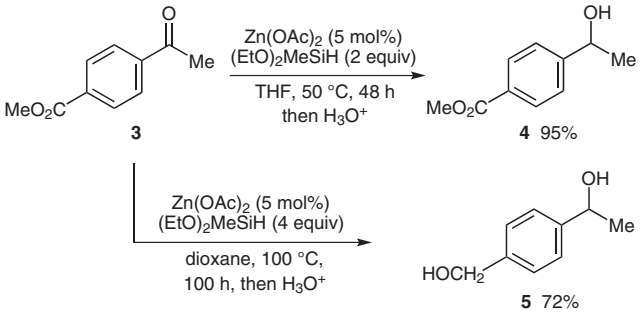
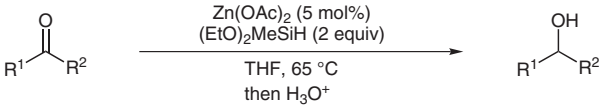
tem, while the reduction with $Zn(OAc)_2/NaBH_4$/PMHS resulted in a low yield 2%.[9] Therefore, we were interested in the reduction ability of our system with $Zn(OAc)_2$/$(EtO)_2MeSiH$ using 4-$MeOCOC_6H_4C(=O)Me$ (**3**) as a substrate (Scheme 1). Gratifyingly, the chemoselective hydrosilylation was realized at 50 °C on the ketone moiety to give the corresponding secondary alcohol **4** in 95 yield with small amount (ca. 5%) of the diol **5**. Furthermore, both of the ketone and the ester moiety were reduced at 100 °C in a dioxane solution to the diol **5** in 72% with 24% of **4**.



Scheme 1 Chemoselective reduction

Table 2 Catalytic Hydrosilylation of Other Ketones and Aldehydes with $Zn(OAc)_2$ and $(EtO)_2MeSiH$[a]

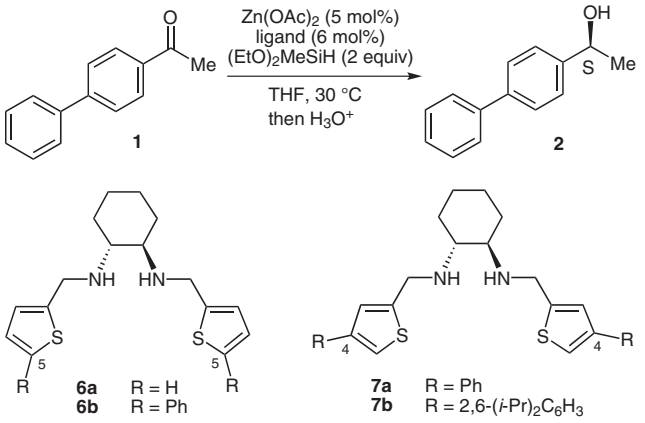


Entry	R^1	R^2	Yield (%)
1	Ph	Me	98
2[b]	4-$MeOC_6H_4$	Me	98
3	4-BrC_6H_4	Me	98
4[c]	4-$F_3CC_6H_4$	Me	91
5[b]	2,6-$(MeO)_2C_6H_3$	Me	95
6	2-Naph	Me	98
7	Ph	*n*-C_5H_{11}	99
8	$Ph(CH_2)_2$	Me	99
9	*n*-$C_{11}H_{23}$	Me	99
10[c]	4-PhC_6H_4	H	99
11[c]	4-NCC_6H_4	H	91
12[b,c]	4-MeOPh	H	99
13[c]	9-Anth	H	93
14[b]	PhCH=CH	Me	99

[a] Reaction conditons: carbonyl compound (1.0 mmol), THF (3.0 mL), 12 h.
[b] Work-up: KF (2 mmol), TBAF (TBAF, ca. 1 mL, 1 M in THF), 0 °C, 2 h.
[c] 24 h.

Bandini–Umani–Ronchi have recently developed chiral diamino-bis(thiophene) ligands of N_2S_2 type, including **6a** and **6b** to apply them to asymmetric hydrosilylation of several ketones with $ZnEt_2$ and PMHS.[8,11] We were interested in study on the matching of $Zn(OAc)_2$ and the N_2S_2-type ligands **6a** and **6b** in asymmetric hydrosilylation. In addition, we newly prepared 4-subsituted thiophene ligands **7a** and **7b** for this purpose. The hydrosilylation in the presence of **6a** and **6b** proceeded smoothly at 30 °C to result in 61% and 63% ee of **2** (*S*), respectively (Table 3, entry 1 and 2). It is noteworthy that the ligands **7a** and **7b** with substituents at 4-position of the thiophene skeletons were capable to increase the enantioselectivity up to 78–83% (entry 3 and 4). It was thus found that modification on the thiophene rings could give us change of enantioselectivity. The reaction with the ligand **7a** was accelerated to finish at 65 °C for 3 hours, but the ee decreased to 50%.

Table 3 Asymmetric Hydrosilylation of **1**[a]

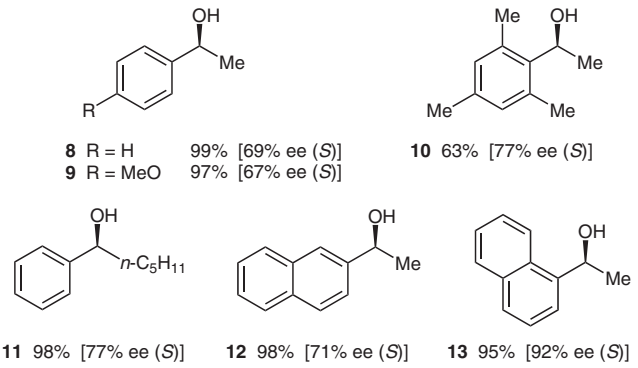


Entry	Ligand	Time (h)	Yield (%)	ee (%) (abs. config)
1	**6a**	24	99	61 (*S*)
2	**6b**	24	97	63 (*S*)
3	**7a**	24	98	83 (*S*)
4	**7b**	18	99	78 (*S*)

[a] Reaction conditons: **1** (1.0 mmol), **6** and **7** (6 mol%), THF (3.0 mL).

Some of ketone substrates (1.0 mmol) were examined for asymmetric hydrosilylation with $Zn(OAc)_2$ (5 mol%), $(EtO)_2MeSiH$ (2 mmol), and N_2S_2 ligand **7a** (6 mol%, Figure 1). Several substituted phenyl ketones were reduced in ca. 70% ee of **8**–**12**. Methyl α-naphthyl ketone successfully gave the corresponding alcohol **13** in 92% ee (*S*) with 95% yield.[12,13]

In conclusion, it was found that commercially available zinc acetate as a catalyst without any assistance of ligands could promote hydrosilylation of carbonyl compounds in the combination of diethoxymethylsilane. Although the asymmetric induction with chiral N_2S_2 ligands is still



8 R = H 99% [69% ee (*S*)]
9 R = MeO 97% [67% ee (*S*)]
10 63% [77% ee (*S*)]
11 98% [77% ee (*S*)] **12** 98% [71% ee (*S*)] **13** 95% [92% ee (*S*)]

Figure 1 Asymmetric reduction of several ketones

good to excellent, further experiments are now under way to reach high efficiency.

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(12) **Typical Procedure for Hydrosilylation of Methyl Biphenyl-4-yl Ketone (1)**
Zinc acetate (9.2 mg, 0.05 mmol; Wako 260-01881, lot LTM1219) and the ketone (196 mg, 1.0 mmol) were placed in a flask. Under an argon atmosphere, absolute THF (3.0 mL) was added at r.t. The mixture was stirred for 10 min at 65 °C, and $(EtO)_2MeSiH$ (320 μL, 2.0 mmol) was then added by a syringe. The mixture was stirred for 24 h at 65 °C. The reaction was monitored by TLC examination; the ketone was consumed, and the silyl ether product was observed. At 0 °C, aq HCl (2 N, 2 mL) was added to quench the reaction. After stirring for 1 h, the mixture was extracted with EtOAc (3 × 10 mL), and the extract was washed with brine and aq $NaHCO_3$ and dried over Na_2SO_4. After concentration, the residue was purified by silica gel column chromatography (hexane–EtOAc as eluent) to give the corresponding desired alcohol **2** (196 mg, 0.99 mmol) in 99%.
Asymmetric Hydrosilylation of Methyl α-Naphthyl Ketone
Under the same reaction conditions above described in the typical procedure, the ligand **7a** (27.4 mg, 0.06 mmol) and methyl α-naphthyl ketone (170 mg, 1.0 mmol) were used to obtain the alcohol **13** (163 mg, 0.95 mmol) in 95% and 92% ee (*S*); analysis, CHIRALCEL OJ-H [hexane–2-PrOH (95:5), 0.8 mL min^{-1}]; t_R (*S*) = 34.2 min, t_R (*R*) = 43.5 min.

(13) **Preparation of Ligands 7a and 7b**
A mixture of (1*R*,2*R*)-cyclohexane-1,2-diamine (116 mg, 1.0 mmol), 4-phenylthiophene-2-carbaldehyde (392 g, 2.1 mmol, commercially available), $MgSO_4$ (2.4 g) in THF (10 mL) was stirred at r.t. for 40 h. After diluted with EtOAc (10 mL), the mixture was filtered through Celite and was concentrated to give white solids (ca. 470 mg). A MeOH solution (15 mL) of the solids was treated with $NaBH_4$ (392 mg) at r.t. for 18 h. Then, H_2O (15 mL) was added, and the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. After concentration, the residue was purified by silica gel column chromatography with hexane–EtOAc to give white solids (265 mg, 0.58 mmol) in 58% yield.
Compound **7a**: mp 113–115 °C. IR (KBr): ν = 3100, 3056, 2927, 2853, 1451, 737, 688 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91–2.37 (m, 14 H), 3.90–3.94 (m, 2 H), 4.13–4.18 (m, 2 H), 7.24–7.39 (m, 8 H), 7.54–7.57 (m, 4 H). ^{13}C (75 MHz, $CDCl_3$): δ = 25.1, 31.6, 45.7, 60.4, 118.8, 123.4, 126.0, 126.7, 128.5, 135.8, 141.3, 145.7. Anal. Calcd (%) for $C_{28}H_{30}N_2S_2$: C, 73.32; H, 6.59; N, 6.11. Found: C, 72.91; H, 6.69; N, 6.01; $[\alpha]_D^{29}$ –17.0 (*c* 1.00, $CHCl_3$).
Synthesis of Compound 7b
Starting from 2,6-diisopropylaniline via 2,6-diisopropylphenyliodide, 2,6-diisopropylphenyl boronic acid was prepared. The mixture of the boronic acid (463 mg, 2.25 mmol), 4-bromothiophene-2-carbaldehyde (318 mg, 1.5 mmol, commercially available), $Pd(OAc)_2$ (3.4 mg), *S*-Phos (12.7 mg), K_3PO_4 (650 mg, 3.0 mmol) in toluene (3.0 mL) at 100 °C for 24 h. The mixture was diluted with EtOAc and filtered through Celite. After concentration, the residue was purified by silica gel column chromatography to give 4-(2′,6′-diisopropylphenyl)thiophene-2-carbaldehyde (354 mg, 1.3 mmol) in 87%. A mixture of (1*R*,2*R*)-cyclohexane-1,2-diamine (46 mg, 0.4 mmol), thiophene-2-carbaldehyde

(218 mg, 0.8 mmol, commercially available), and $MgSO_4$ (960 mg) in THF (5.0 mL) was stirred at r.t. for 24 h. After diluted with EtOAc, the mixture was filtered through Celite and was concentrated to give white solids. A MeOH solution (10 mL) of the solids was treated with $NaBH_4$ (151 mg) at r.t. for 24 h. Then, H_2O (10 mL) was added, and the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. After concentration, the residue was purified by silica gel column chromatography with hexane–EtOAc to give the desired amine **7b** (178 mg, 0.284 mmol) in 71% yield.

Compound **7b**: oil. IR (film): ν = 3055, 2959, 2927, 2861, 1459, 751, 673 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09–1.10 (m, 24 H), 1.15–1.40 (m, 6 H), 1.85 (m, 2 H), 2.23 (m, 2 H), 2.42 (m, 2 H), 2.83 (m, 4 H), 4.00 (d, *J* = 14.9 Hz, 2 H), 4.19 (d, *J* = 14.9 Hz, 2 H), 6.82 (s, 2 H), 6.93 (s, 2 H), 7.22–7.27 (m, 4 H), 7.38 (m, 2 H). ^{13}C (75 MHz, $CDCl_3$): δ = 24.2, 24.3, 24.5, 24.6, 25.1, 30.3, 30.4, 31.6, 45.5, 60.2, 121.0, 122.1, 126.9, 127.6, 134.4, 139.2, 144.0, 147.4. HRMS–FAB: *m/z* calcd for $C_{40}H_{55}Cl_2N_2S_2^+$ [M + H]: 627.3807; found: 627.3805. $[\alpha]_D^{29}$ –23.4 (*c* 1.00, $CHCl_3$).