# Rh-Catalyzed Enantioselective Hydrosilylation of Aromatic Ketones Using (*S,S*)-Phos-Biox as a Chiral Ligand

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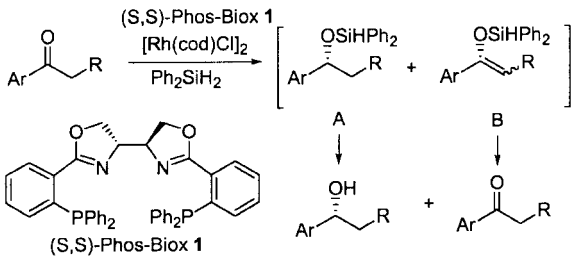
The transition metal-catalyzed asymmetric hydrosilylation of ketones using chiral ligand, followed by hydrolysis of the resulting silyl ethers provides an effective route to optically active alcohols.[1] The stereochemical course of metal-catalyzed reactions can be effectively controlled by an appropriate chiral ligand attached to the metal center. Therefore, the search for chiral ligands continues apace and a wide variety of chiral ligands have been developed for Rh, Ir, Ru or Ti-catalyzed asymmetric hydrosilylation of prochiral ketones.[2-5] Previously, we reported a new type of $C_2$-symmetric bis-phosphinobioxazoline, [(*S,S*)-Phos-Biox **1**], as a chiral ligand for asymmetric catalysis.[6] In a preliminary application of (*S,S*)-**1** as a chiral ligand for Rh-catalyzed asymmetric hydrosilylation of *p*-substituted acetophenones, it has been found that while other substituents (H, $CH_3$, Cl) afforded optically active alcohols in high enantioselectivities (91-97% ee), the *p*-methoxy substituent dramatically decreased the enantioselectivity (21% ee).[6a] We describe here an extension of these studies to a series of prochiral aromatic ketones using [(*S,S*)-Phos-Biox **1**] as a chiral ligand, with the aim of ascertaining how variations in the structure of the ketones, especially bearing methoxy substituent, affect the optical purity of the products (Scheme 1).

## Results and Discussion

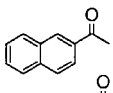
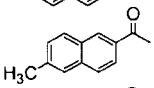
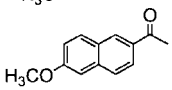
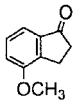
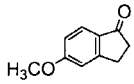
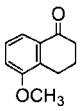
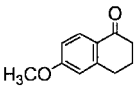
The hydrosilylation reactions were carried out with diphenylsilane in THF solvent in the presence of 0.5 mol% catalyst, which was prepared *in situ* from 0.25 mol% of $[Rh(cod)Cl]_2$ and 0.5 mol% of (S,S)-**1**, and the results are summarized in Table 1.

As shown in Table 1, the size of the alkyl groups in phenyl alkyl ketones did not effect at all on the enantioselectivities (entries 1-3). Thus, the enantiomeric excess value obtained from hydrosilylation of sterically bulkier isobutyrophenone (97% ee, entry 3) is the same or higher than those obtained from the sterically less demanding acetophenone (97% ee, entry 1) and propiophenone (92% ee, entry 2). The 2-aceto-




**Scheme 1**

**Table 1**. Enantioselective Hydrosilylation of Ketones using [(*S,S*)-Phos-Biox **1**]

| entry[a] | ketone | temp. (°C) | time (h) | yield (%)[b] | % ee (conf.)[c] |
|---|---|---|---|---|---|
| 1[d] |  | 0 | 7 | 98 | 97 (*R*) |
| 2 |  | 20 | 2.5 | 95 | 92 (*R*) |
| 3 |  | 20 | 3 | 93 | 97 (*R*) |
| 4[e] |  | 20<br>0 | 2<br>7 | 97<br>92 | 96 (*R*)<br>91 (*R*) |
| 5[e] |  | 20<br>0 | 4<br>8 | 95<br>90 | 94 (*R*)<br>85 (*R*) |
| 6 |  | 20<br>0 | 1<br>5 | 99<br>99 | 92 (*R*)<br>72 (*R*) |
| 7 |  | 20<br>0 | 3<br>10 | 96<br>91 | 52 (*R*)<br>68 (*R*) |
| 8 |  | 20<br>0 | 2<br>10 | 99<br>97 | 87 (*R*)<br>88 (*R*) |
| 9 |  | 20<br>0 | 2<br>10 | <3<br><3 | nd<br>nd |
| 10 |  | 0 | 10 | 97 | 81 (*R*) |
| 11 |  | 0 | 10 | 84 | 79 (*R*) |
| 12 |  | 0 | 10 | 94 | racemic |

[a]All reactions were carried out in THF in the presence of 0.25 mol% $[Rh(cod)Cl]_2$, 0.5 mol% (*S,S*)-Phos-Biox **1** and 1.6 eq. of diphenylsilane. [b]Isolated yield. [c]Determined by Chiral HPLC using Daicel Chiralcel OB column. [d]Result from reference 6a. [e]Determined by Chiral GC using Chiraldex CB column.

naphthones were also hydrosilylated at 20 °C with high enantioselectivities (entries 4-6). Interestingly, in these reactions, the enatioselectivities were decreased as lowering the reaction temperature. For example, the hydrosilylation of 6-methoxy 2-acetonaphthone at 20 °C exhibited 92% ee whereas 72% ee at 0 °C (entry 6). Moreover, in contrast to 4-methoxy acetophenone (21% ee),[6a] the methoxy group in 6-methoxy 2-acetonaphthone (92% ee) did not much effect negatively on the enantioselectivity. However, a dramatic "*p*-methoxy effect" has been observed in indanone and tetralone moieties. Hydrosilylation of unsubstituted indanone at 0 °C afforded (*R*)-1-indanol in 68% ee (entry 7). Introduction of the methoxy group at 4-position on indanone, the enantioselectivity was increased to 88% ee (0 °C) (entry 8). Very surprisingly, hydrosilylation of 5-methoxyindanone afforded mostly enolsilylether (B in Scheme 1), which was converted to the starting ketone after hydrolysis (entry 9). No alcohol product can be isolated. In striking contrast with 5-methoxyindanone, the 6-methoxytetralone was converted to silylether (A in Scheme 1) without enantioselectivity, thus, afforded *racemic* 6-methoxy-1-tetralol in 94% yield (entry 12). Unsubstituted tetralone itself was hydrosilylated in 97% yield with 81% ee (entry 10), but both of the yield (84%) and enantioselectivty (79% ee) were slightly decreased with 5-methoxy tetralone (entry 11). These results clearly indicate that the substitution position of the methoxy group effects largely on the enantioselectivity in acetophenones and teteralones and on the ratio of silylether (A)/enolsilylether (B) in indanones. Brunner[2a] and Kagan[7] with the use of pyridinethiazoline and DIOP as chiral ligands, respectively have also observed similar methoxy group effects on the enantioselectivity in Rh-catalyzed hydrosilylation of acetophenones and tetralones. Unfortunately, at present time, it is hard to explain how the "methoxy group effect" came into play on the selectivity and remained as unsolved problem in Rh-catalyzed hydrosilylation of aromatic ketones. Nevertheless, it seems clear that the methoxy effects on enantioselectivity may largely be related with metal instead of chiral ligands employed since this kind of effects was not observed in Ti-catalyzed hydrosilylation of *p*-methoxy acetophenones.[5]

In summary, rhodium-catalyzed hydrosilylation of various aromatic ketones using a $C_2$-symmetric bisphosphinobioxazoline ligand, [(*S*,*S*)-Phos-Biox **1**], has been investigated, and afforded optically active alcohols with high enantioselectivities (up to 97% ee). The enantioselectivities and yields are highly dependent on the substitution positions of the methoxy group on the aryl ring in indanones and tetralones.

## Experimental Section

**Typical procedure for the rhodium-catalyzed hydrosilylation of acetophenone derivatives**: A solution of ketone (1 mmol), $[Rh(cod)Cl]_2$ (1.2 mg, $0.25 \times 10^{-2}$ mmol), and (*S*,*S*)-Phos-Biox **1** (3.3 mg, $0.5 \times 10^{-2}$ mmol) was degassed, and then stirred for 1 h at room temperature under argon atmosphere. After addition of diphenylsilane (0.3 mL, 1.6 mmol) at 0 °C, the reaction mixture was stirred at 20 °C (or 0 °C) until all ketones disappeared by TLC analysis. The reaction was quenched with methanol (5 mL), and then 1 N hydrochloric acid (10 mL) at 0 °C. After stirring the solution for 1 h at 0 °C, organic layer was extracted with methylene chloride (10 mL × 4). The combined organic layer was washed with saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$, filtered and concentrated to give yellowish oil. The residue was purified by chromatography on silica column. The enantioselectivity has been determined by chiral HPLC using Chiralcel OB column or chiral GC using Chirasildex CB column.

**1-Phenylethanol** (entry2): Chiralcel OB, (*i*-propanol/*n*-hexane, 10/90; 0.5 mL/min; Retention time, (*S*)-10.74 min, (*R*)-12.32 min.

**2-Methyl-1-phenylpropanol** (entry 3): Chiralcel OB, (*i*-propanol/*n*-hexane, 1/99; 0.5 mL/min; Retention time, (*S*)-10.74 min, (*R*)-12.32 min.

**1-(2-Naphthyl)ethanol** (entry 4): Chirasildex CB, injection temp. 250 °C, oven temp. 140 °C isothermal, Retention time, (*R*)-15.85 min, (*S*)-17.35 min.

**1-(6-Methyl-2-naphthyl)ethanol** (entry 5): Chirasildex CB, injection temp. 250 °C, oven temp. 150 °C isothermal, Retention time, (*R*)-15.3 min, (*S*)-16.45 min.

**1-(6-Methoxy-2-naphthyl)ethanol** (entry 6): Chiralcel OB, (*i*-propanol/*n*-hexane, 10/90; 1 mL/min; Retention time, (*S*)-21.25 min, (*R*)-24.30 min.

**1-Indanol** (entry 7): Chiralcel OB, (*i*-propanol/*n*-hexane, 10/90; 1 mL/min; Retention time, (*S*)-8.62 min, (*R*)-6.05 min.

**4-Methoxy-1-indanol** (entry 8): Chiralcel OB, (*i*-propanol/*n*-hexane, 10/90; 1 mL/min; Retention time, (*S*)-10.70 min, (*R*)-7.92min.

**1-Tetralol** (entry 10): Chiralcel OB, (*i*-propanol/*n*-hexane, 10/90; 1 mL/min; Retention time, (*S*)-8.12 min, (*R*)-5.66 min.

**5-Methoxy-1-tetralol** (entry 11): Chiralcel OB, (*i*-propanol/*n*-hexane, 10/90; 1 mL/min; Retention time, (*S*)-11.84 min, (*R*)-9.25 min.

**6-Methoxy-1-tetralol** (entry 12): Chiralcel OB, (*i*-propanol/*n*-hexane, 10/90; 1 mL/min; Retention time, (*S*)-18.66 min, (*R*)-10.72 min.

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## References

1. For reviews, see: (a) Brunner, H.; Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric* Synthesis; Ojima, I., Ed.; VCH Publisher Inc.: New York, 1993; Chapter 6.
2. For Rh-catalyzed hydrosilylation of ketones, selected papers: (a) Brunner, H; Kürzinger, A. *J. Organomet. Chem.* **1988**, *346*, 413. (b) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846. (c) Brunner, H.; Brandl, P. *Tetrahedron: Asymmetry* **1991**, *2*, 919. (d) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**,

*10*, 500. (e) Hayashi, T.; Hayashi, C.; Uozumi, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2503. (f) Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 111. (g) Langer, T.; Janssen, J.; Helmchen, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1599. (h) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron:Asymmetry* **1996**, *7*, 2453. (i) Sudo, A.; Yoshida, H.; Saigo, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3205. (j) Brunner, H.; Störiko, R.; Nuber, B. *Tetrahedron: Asymmetry* **1998**, *9*, 407.

3. Ir-catalyzed hydrosilylation of ketones. (a) Faller, J. W.; Chase, K. J. *Organometallics* **1994**, *13*, 989. (b) Kinting, A.; Kreuzfeld, H. J.; Abicht, H. P. *J. Organomet. Chem.* **1989**, *370*, 343. (c) Nishibayashi, Y.; Segawa, K.; Takada, H.; Ohe, K.; Uemura, S. *Chem. Commun.* **1996**, 847.
4. Ru-catalyzed hydrosilylation of ketones. Zhu, G.; Terry, M.; Zhang, X. *J. Organomet. Chem.* **1997**, *547*, 97.
5. Ti-catalyzed hydrosilylation of ketones. (a) Carter, M. B.; Schiøtt, B.; Gutiérrez, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11667. (b) Imma, H.; Mori, M.; Nakai, T. *Synlett* **1996**, 1229. (c) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640.
6. (a) Lee, S.-g.; Lim, C. W.; Song, C. E.; Kim, I. O. *Tetrahedron: Asymmetry* **1997**, *8*, 4207. (b) Lee, S.-g.; Lim, C. W.; Song, C. E.; Kim, K. M.; Jun, C. H. *J. Org. Chem.* **1999**, *64*, 4445.
7. Peyronel, J. F.; Fiaud, J. C.; Kagan, H. B. *J. Chem. Res.* **1980**, 4057.