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New Chiral Bis(oxazolinyl)bipyridine Ligand (Bipymox): Enantioselection in the Asymmetric Hydrosilylation of Ketones

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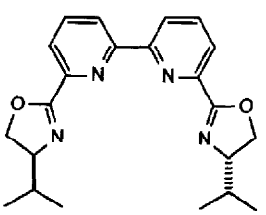
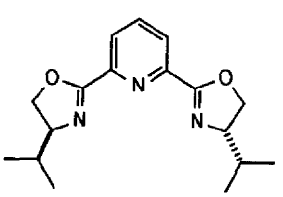
Abstract: A homochiral chiral 6,6'-bis(oxazolinyl)-2,2'-bipyridine ligand, *bipymox* (**1**), and its rhodium complex were synthesized to examine the enantioselectivity in the asymmetric hydrosilylation of ketones in comparison to other chiral oxazoline ligands such as bis-(oxazolinyl)pyridine, *pybox* (**2**), and mono(oxazolinyl)pyridine, *pymox* (**3**). The bipymox-rhodium catalyst gave the (*S*)-absolute configuration of the product 1-phenylethanol (90 %ee) in the reduction of acetophenone with diphenylsilane the same as the pybox-rhodium system but opposite to the pymox-rhodium system. The reduction of 4-tert-butylcyclohexanone was also described.

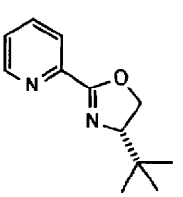
We have reported the homochiral terdentate bis(oxazolinyl)pyridine (*pybox*, **2**) and the bidentate mono-(oxazolinyl)pyridine (*pymox*, **3**) ligands for the enantioselective hydrosilylation of ketones.[1, 2-4] We have also disclosed the stereochemistry for the reduction of 4-tert-butylcylcohexanone and the remote electronic control of asymmetric hydrosilylation with 4-substituted pybox.[5,6] Our interests have focused on the difference of the stereo-chemical outcomes between the pybox system and the pymox system. Both systems gave more than 90 % ee in the hydrosilylation of ketones. However the pybox system produces the (*S*)-absolute configuration of the product secondary alcohols, while the pymox system gives the (*R*)-configuration. The difference in the stereochemical outcomes could be attributed to the chiral environments of their transition states. It can be assumed that the actual rhodium catalyst in the pybox system may contain only one pybox ligand,[1] while it is difficult to clarify whether the actual active pymox-rhodium catalyst has one or two pymox ligands. We disclose here a new chiral bipyridine ligand, bis(oxazolinyl)bipyridine (*bipymox*, **1**), its rhodium complex, and their application for the asymmetric hydrosilylation of ketones.[7] We are interested in how the dimeric pymox ligand **1** performed in the asymmetric induction especially in comparison to the pymox and pybox systems.



Bipymox-(S,S)-ip **1**



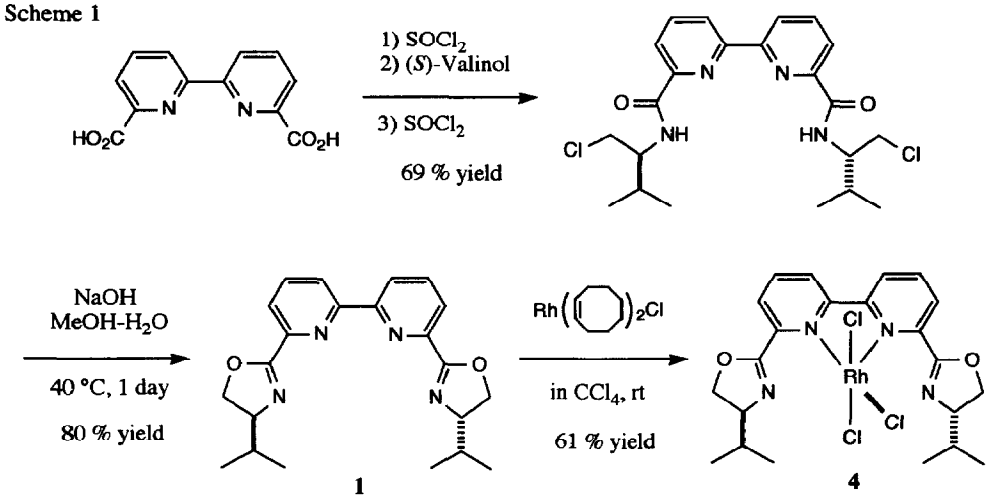
Pybox-(S,S)-ip **2**



Pymox-(S)-tb **3**

Bipymox **1** can be readily synthesized from 2,2'-bipyridine-6,6'-dicarboxylic acid[8] in several steps (Scheme 1). The corresponding bipymox-rhodium(III) trichloride complex **4** was obtained by an oxidation procedure by using $Rh(I)Cl(cyclooctene)_2/_2$ in CCl_4 solution according to our method previously reported.[9] The reaction of bipymox **1** and rhodium(III) chloride trihydrate in ethanol gave complicated polymeric products but did not give **4**. The ^1H NMR study indicates that the complex **4** has a C_2-symmetrical structure (Fig. 1) The proton signals of the pyridine and oxazoline rings are affected by coordination to the rhodium center. We could find no dynamic character due to coordination of the oxazoline rings of **4** in the range of -50 ° to 50 °C. Therefore, we concluded that *bipymox acts as a rigid bidentate bipyridine ligand with two free oxazoline rings.*

Scheme 1



Although, on the basis of a molecular modelling study, bipymox could be a terdentate ligand like pybox giving the corresponding rhodium complex, we preferentially obtained the bidentate bipymox-rhodium complex **4**. The model also indicates that the coordination site of bipymox is too open to allow a tetradentate coordination (Fig. 2).

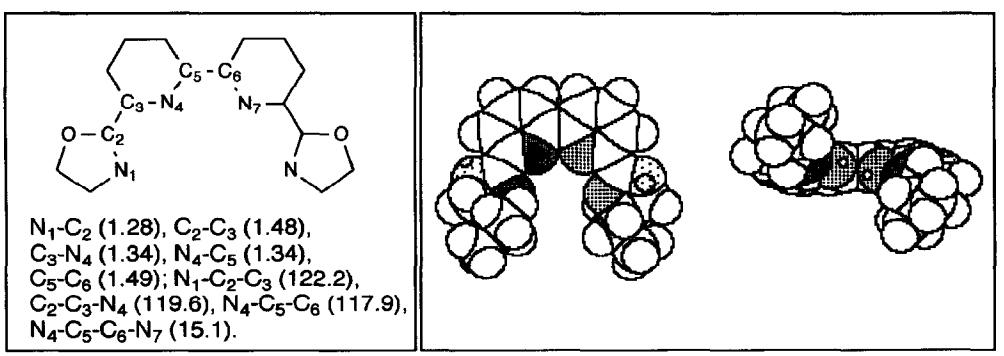


Fig. 2 The selected bond lengths (Å), bond angles (°), and the dihedral angles (°) of **1** by calculation and its space filling model (the top and front views).

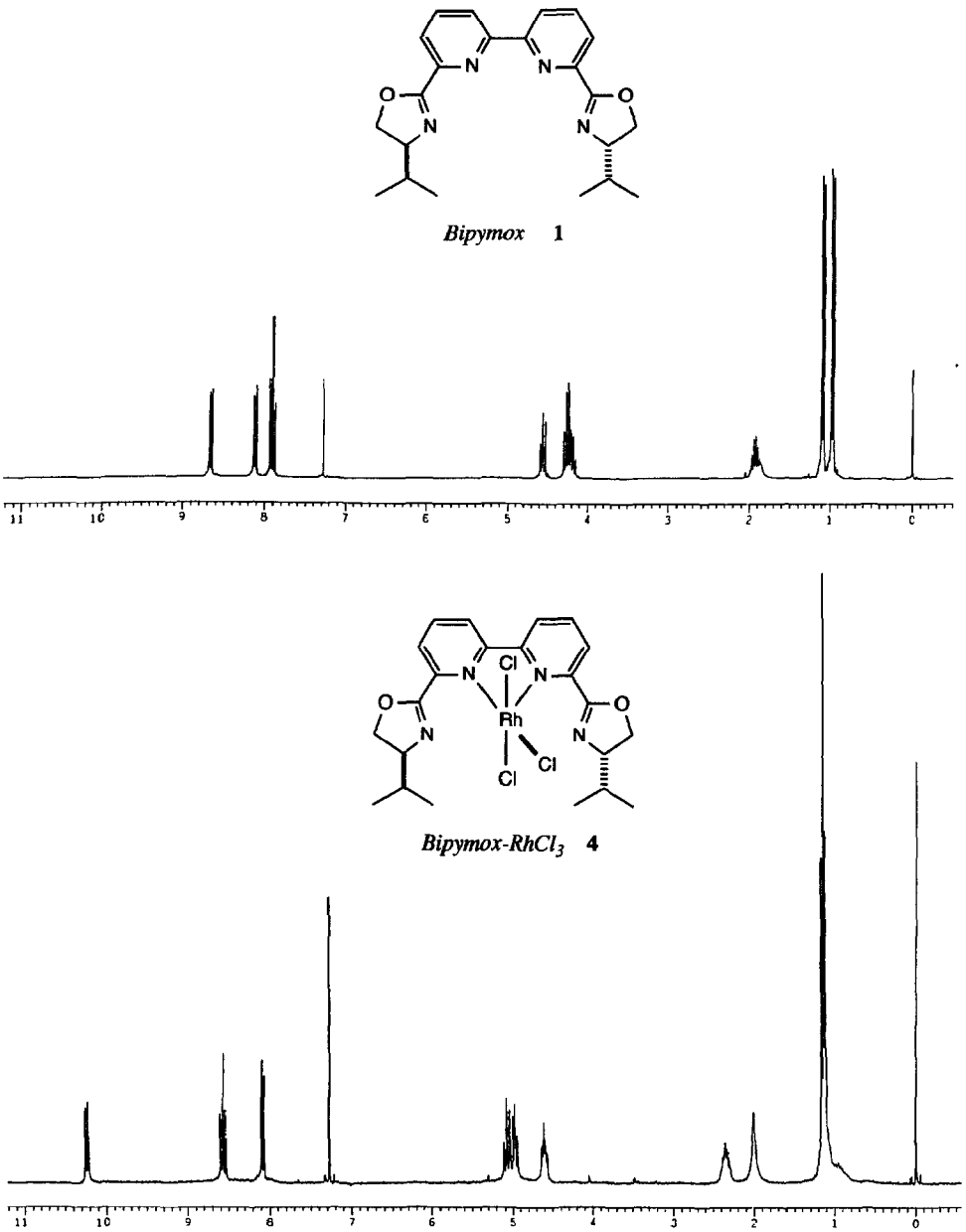
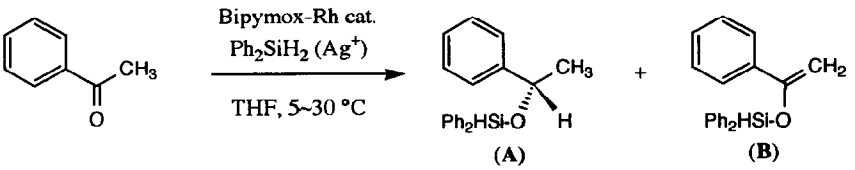


Fig.1 ^{1}H NMR spectra of Bipymox (**1**) (top) and Bipymox-$RhCl_3$ (**4**) (bottom).

We examined the hydrosilylation of acetophenone with diphenylsilane and the bipymox-rhodium catalysts (Table 1). The combination of Rh(cyclooctene)$_2$Cl (1.0 mol%) with bipymox (2 equiv) catalyzed the reaction to give the (*S*)-configuration of the product alcohol in 41 % ee (run 1). The reaction proceeded at a relatively higher temperature (20 °C) comparing to that with the pybox-rhodium catalysts (ca. 0 °C). Addition of $AgBF_4$ increased the enantioselectivity up to 70 % (run 3). However the product selectivities are not so high (57~68 %) because of the formation of the silyl enol ether as a by-product (32~39 %) (runs 1~4). In contrast, the use of the bipymox-$RhCl_3$ complex **4** as a catalyst drastically increased the selectivity (up to 98 %) as well as the enantioselectivity (up to 90 %) especially on addition of extra ligand (2 eq) and $AgBF_4$ (runs 5~9). Other ketones were also subjected to hydrosilylation with the bipymox-rhodium system, giving 97 % yield and 86 % ee (*S*) for 1-tetralone, 89 % yield and 92 % ee (*S*) for 1-acetylnaphthalene, 78 % yield and 72 % ee (*S*) for 4-phenyl-2-butanone, under similar reaction conditions as indicated in run 8 of Table 1, -5~10 °C, 2~18 h.

The enantioselectivities in the reduction of acetophenone with the oxazolinylpyridine systems are summarized in Table 2. The pybox-(*S,S*)-ip (**2**) gave the (*S*)-absolute configuration, while the pymox-(*S*)-tb (**3**) and pymox-(*S*)-ip gave the (*R*)-configuration. 6-Methyl derivatives of pymox **5**[3] and the phenanthroline derivative **6**[4] reverse the enantioselectivity. The bulkiness around 6-position of the pyridine skeletons could make the selectivity reverse. Therefore the introduction of the second chiral oxazoline group on the pyridine and bipyridine skeleton could make such a remarkable improvement for the enantioselection giving the (*S*)-configuration.

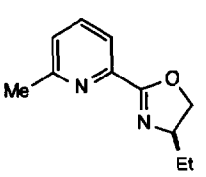


(A) **(B)**

Table 1. Asymmetric Hydrosilylation of Acetophenone with Bipymox-Rhodium Catalysts.*

run	cat	Ag salt	bipymox (eq to Rh)	condition (°C / h)	yield (A) / (B) (%)	% ee of (A) (*abs config*)
1	$Rh(cot)_2Cl$	-	2	20 / 2	68 / 32	41 (*S*)
2	"	AgOTf	2	15 / 3	64 / 33	43 (*S*)
3	"	$AgBF_4$	2	15 / 3	57 / 39	70 (*S*)
4	"	$AgBF_4$	4	15 / 3	67 / 32	68 (*S*)
5	$RhCl_3$(bipymox) **4**	-	0	30 / 2	78 / 22	24 (*S*)
6	"	-	2	25 / 2	86 / 14	75 (*S*)
7	"	$AgBF_4$	0	10 / 5	90 / 10	67 (*S*)
8	"	$AgBF_4$	3	5 / 4	98 / 2	90 (*S*)
9	"	$AgBF_4$	4	5 / 2	98 / 2	90 (*S*)

* Rh cat (1 0 mol%), cot = cyclooctene, Ag salt (2 eq to Rh), Ph_2SiH_2 (1 5 eq to ketone), Acetophenone (8.0 mmol), THF (2.0 ml). Conversion = 100 % checked by TLC. The yields (the ratio) of (**A**) and (**B**) were determined by chiral GLPC of the recovered ketone and the alcohol product.



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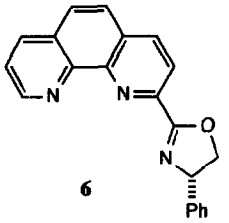

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Table 2. Enantioselection in the Hydrosilylation of Acetophenone with Oxazolinylpyridine-Rhodium Systems

ligand	1	2	3	5	6
abs. config. of the product alcohol*	*S*	*S*	*R*	*R*	*S*
(% ee)[ref]	(90)	(94)[1]	(91)[1](83)[2a]	(48)[2b]	(20)[2d]

‡ 2-Phenylethanl. **1**, bipymox-(*S,S*)-ip; **2**, pybox-(*S,S*)-tb; **3**, pymox-(*S*)-ip; **4**, 6-Me-pymox-(*R*)-et; 2-(4'-(*S*)-phenyloxazolin-2'-yl)phenanthroline **6**.

We have examined a tert-butyl derivative of the bipymox ligand, because a tert-butyl group on the oxazoline ring of pymox was the best choice for enantioselection.[1,2] However the tert-butyl-bipymox-rhodium catalyst showed no improvement giving low catalytic activity and low enantioselectivity for the hydrosilylation the same as the pybox system.

We have already reported that the hydrosilylation of 4-tert-butylcyclohexanone with the pybox-rhodium system shows a steric tolerance for production of the trans- and cis-alcohols, the same as the Wilkinson complex [RhCl-(PPh_3)$_3$],[10] in spite of the strong enantioselectivity.[5] We found similar selectivities by using the bipymox-rhodium system and also the pymox-rhodium system (Table 3). The ratio of trans- and cis-4-tert-butylcyclohexanol was 65:35 for the bipymox system. We found that the pymox system also gave a similar selectivity, 61:39 of the trans and cis ratio.

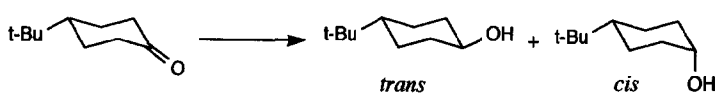
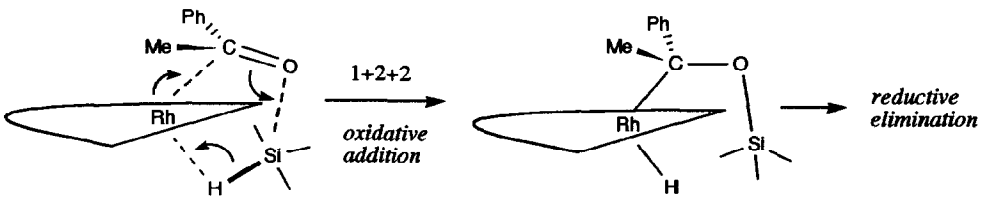


Table 3. Hydrosilylation of 4-tert-Butylcyclohexanone with Oxazolinylpyridine-Rhodium systems.*

ligand	1	2	3
ratio of tarns:cis	65 : 35	67 : 33	61 : 39
(yield, %)[ref]	(87)	(92)[5]	(74)

* Rh cat (1.0 mol%), tert-Butylcyclohexanone (8.0 mmol), Ph_2SiH_2 (1.5 eq to the ketone, THF (2.0 ml). Temp (°C), reaction time: 25°C, 4 h for **1**; 0°C, 1 day for **2**; 5 °C, 4 h for **3**.

Therefore we think that we can postulate a similar or a common transition state for the all oxazolinylpyridine-rhodium systems for the reduction of ketones. We have previously preferred the standard path; coordination of ketone on the H-Rh-Si species, migratory insertion of the ketone to the Rh-Si bond, then reductive elimination.[11] The concerted 3+2 mode of H-Rh-Si and C=O has also been hypothesized.[12] Here we introduce a new hypothetical path of the concerted 1+2+2 [Rh^+, C=O, and H-Si] type, to which a similar path is applied to explain a new hydrosilylation of olefins with a zirconium complex.[13] This mechanistic view is very attractive since it explains the prochiral face selection of ketones in the chiral environment of the bipymox and pybox-rhodium catalysts as in the following scheme.



We have thus found that bipymox ligand shows the *re-face selectivity* to give the (*S*)-alcohol in the rhodium catalyzed hydrosilylation of ketones the same as the terdentate ligand pybox system shows. These facts might indicate a similar chiral environment for the catalysts derived from pybox and bipymox, while the transition states for the pymox-rhodium system must be different. The active catalyst of the pymox system might be simple (pymox)Rh^+ species not (pymox)$_2Rh^+$ species.[3] New approaches are under way to clarify the reaction mechanism of the hydrosilylation of ketones with the oxazolinylpyridine systems.

Experimental Section

General. All reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran was distilled under nitrogen from sodium. ^1H (270 MHz) and ^{13}C (67.8 MHz) NMR spectra were recorded on a JEOL JNM-GX 270 spectrometer using tetramethylsilane as the internal reference. Infrared spectra were recorded on a JASCO A-3 spectrometer. Mass spectra were determined with a Hitachi M-80B mass spectrometer. Optical rotation was measured on a JASCO DIP-140 polarimeter. Microanalyses were performed with a Yanagimoto MT-3 CHN corder. Optical purity was determined by Shimadzu Capillary Gas Chromatograph 14A with a chiral capillary column (Astec Chiraldex G-TA , 20 m). Analytical tlc was performed on Merck (Art 5715) precoated silica gel plates (0.25 mm). Column chromatography was performed with silica-gel (Merck, Art 7734). Molecular modelling were carried with Chem3D-Plus (ver. 3) as an application by Macintosh (IIci) computer. 2,2'-Bipyridine-6,6'-dicarboxylic acid was synthesized according to the reported method.[8] Pymox-tb **3** was synthesized from picolinic acid by the similar steps to **1** via the following precursors: the acid chloride and the

amidochloride with (*S*)-2-amino-3,3-dimethyl-1-butanol obtained by reduction of L-(+)-tert-leucine. See ref 2 for another preparative method and chemical properties of **3**.

Synthesis of Bipymox, 6,6'-Bis(4-(*S*)-isopropyloxazolin-2-yl)-2,2'-bipyridine (1). 2,2'-Bipyridine-6,6'-dicarboxylic acid (4.0 g, 16.4 mmol) was treated with $SOCl_2$ (50 ml) at reflux temperature for 13 h. Excess $SOCl_2$ was removed under reduced pressure to give the acid chloride. To a solution of (*S*)-valinol (3.72 g, 36 mmol) and triethylamine (14 ml) in $CHCl_3$ (65 ml) was added a solution of the acid chloride in $CHCl_3$ (65 ml) at 0 °C. The mixture was stirred for 1 day at rt and then SOCl2 (15 ml) was added. After stirred for 3 h, the mixture was poured into ice-water (250 ml) and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4. Concentration gave white solid product which was purified by silica gel column chromatography with CH_2Cl_2-ether as eluent. The corresponding bis-amidochoride was obtained in 69 % yield (5.1 g, 11.3 mmol); white solids, mp 210 °C; TLC *Rf* = 0.8 (ethyl acetate); IR (KBr disk) 1660, 1520, 738 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.04 (d, J = 6.8 Hz, 6 H), 1.09 (d, J = 6.4 Hz, 6 H), 2.18 (m, 2 H), 3.83 (dd, J = 3.4, 11.7 Hz, 2 H), 3.90 (dd, J = 3.4, 11.7 Hz, 2 H), 4.21 (m, 2 H), 8.06 (t, J = 7.8 Hz x 2, 2 H), 8.29 (d, J = 7.8 Hz, 2 H), 8.35 (broad d, J = 9.3 Hz, 2 H), 8.53 (d, J = 7.8 Hz, 2 H) ppm; Anal. Calcd for $C_{22}H_{28}O_2N_4Cl_2$: C, 58.54; H, 6.25; N, 12.41. Found: C, 58.57; H, 6.25; N, 12.45.

To a solution of the bis-amidochloride (3.6 g, 8.0 mmol) in methanol (80 ml) was added aqueous NaOH (2.5 N, 20 ml). The mixture was stirred for 37 h at 40 °C. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by recrystalization with ethyl acetate and hexane to give **1** as white needles in 80 % yield (2.44 g, 6.4 mmol); mp 187 °C; TLC *Rf* = 0.5 (ethyl acetate); IR (KBr disk) 1630, 1560, 1420, 1355, 1065, 955, 810 cm^{-1}; $[\alpha]_D^{23}$ = -90.6 (c = 1.04, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (d, J = 6.8 Hz, 6 H), 1.09 (d, J = 6.8 Hz, 6 H), 1.93 (m, 2 H), 4.23 (m, 2 H), 4.24 (t, J = 8.0 Hz x 2, 2 H), 4.56 (t, J = 8.0 Hz x 2, 2 H), 7.91 (t, J = 7.8 Hz x 2, 2 H), 8.12 (d, J = 7.8 Hz, 2 H), 8.66 (d, J = 7.8 Hz, 2 H) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) 18.21, 19.10, 32.80, 70.78, 123.5, 124.4, 137.5, 146.4, 155.3, 162.6 ppm; MS *m/e* (relative intensity) 378 (M^+, 6), 335 (100), 249 (45), 221 (60), 194 (85), 180 (44), 153 (20); Anal. Calcd for $C_{22}H_{26}O_2N_4$: C, 69.82; H, 6.92; N, 14.80. Found: C, 69.84; H, 6.92; N, 14.81.

Synthesis of Bipymox-Rhodium Complex (4). To a mixture of bipymox (379 mg, 1.0 mmol) and Rh(cyclooctene)$_2$Cl (359 mg, 1.0 mmol) in THF (16 ml) was added CCl_4 (4 ml) under argon atmosphere. The mixture was stirred at rt for 1 day. Then the solvent was removed under reduced pressure. The residual solids were purified by silica-gel column chromatography with CH_2Cl_2-MeOH to give **4** as dark green solids in 61 % (358 mg, 0.61 mmol); mp > 300 °C; IR (KBr disk) 1575, 1410, 1390, 1255, 915 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.11 (t, J = 6.8 Hz, 12 H), 2.32 (m, 2 H), 4.60 (m, 2 H), 4.95 (t, 2 H), 5.05 (m, 2 H), 8.04 (d, J = 7.8 Hz, 2 H), 8.55 (t, J = 8.3 Hz x2, 2 H), 10.17 (d, J = 7.8 Hz, 2 H) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) 16.13, 18.84, 30.93, 69.14, 73.57, 127.3, 131.0, 143.2, 144.8, 157.5, 167.8 ppm; Anal. Calcd for Bipymox-$RhCl_3(CH_2Cl_2)$, $C_{23}H_{28}O_2N_4Cl_5Rh$: C, 41.07; H, 4.20; N, 8.33. Found: C, 41.20; H, 4.35; N, 8.34.

Typical Procedure of Asymmetric Hydrosilylation. The Reduction of Acetophenone with Bipymox-$RhCl_3$ and Diphenylsilane (run 8). A suspension of **4** (47 mg, 0.0 8 mmol), **1** (91 mg, 0.24 mmol), and $AgBF_4$ (31 mg, 0.16 mmol) in THF (2.0 mL) was stirred at rt for 1 h. After addition of acetophenone (0.93 mL, 8.0 mmol), diphenylsilane (2.2 g, 12 mmol) was added at -5 °C. The mixture was stirred at 5°C for 4 h and was treated with methanol and then hydrochloric acid (1.0 *N*) at 0°C. The product yield and the enantioselectivity were determined by GLPC analysis.

Hydrosilylation of 4-tert-Butylcyclohexanone. A suspension of **4** (47 mg, 0.0 8 mmol), **1** (91 mg, 0.24 mmol), and $AgBF_4$ (31 mg, 0.16 mmol) in THF (2.0 ml) was stirred at rt for 1 h. After addition of 4-tert-butylcyclohexanone (1.23 g, 8.0 mmol), diphenylsilane (2.2 g, 12 mmol) was added at -5 °C. After similar work-up described above, the product yield and the trans:cis ratio were determined by ^1H NMR of the recovered residue; for *H*-COH, δ 3.52 ppm for the trans alcohol and δ 4.04 ppm for the cis alcohol. For the reaction with pymox-tb **3**, $Rh(COD)Cl/_2$ (20 mg, 0.04 mmol), **3** (80 mg, 0.4 mmol), THF (2.0 ml), 4-tert-butylcyclohexanone (1.23 g, 8.0 mmol), and diphenylsilane (2.2 g, 12 mmol) were used.

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