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Remote Electronic Control in Asymmetric Cyclopropanation with Chiral Ru-Pybox Catalysts

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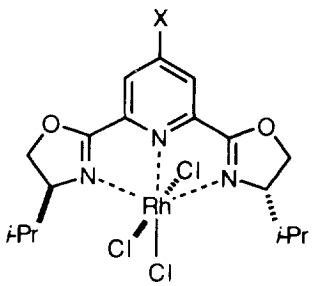
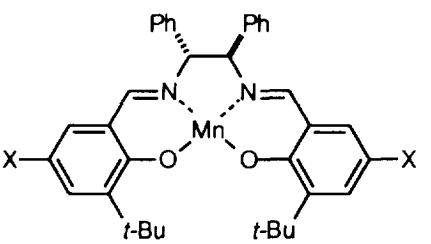
Abstract: Electronic control by remote substitents far from a catalytically active center was found in an asymmetric cyclopropanation of olefins and diazoacetates with the ruthenium catalysts of chiral 4-substituted bis(4'-isopropyloxazolinyl)pyridine, 4-X-pybox. It was found that electron-withdrawing groups increase the catalytic activity, but electron-donating groups decrease it. The enantiomer ratios of the product cyclopropanes with the electron-withdrawing groups, X = Cl and COOMe, are higher than those with the electron-donating groups, X = OMe and NMe_2. The enantiomer ratios of the ethyl and *l*-menthyl cyclopropanes were corelated toward Hammett's σ_{para} values to give positive ρ values, 0.365 for *trans*-ethyl ester, 0.486 for *cis*-ethyl ester, 0.517 for *trans-l*-menthyl ester, and 0.517 for *cis-l*-menthyl ester. However, the *trans:cis* ratios of the products were not affected by their substituents, ca. 90:10 for ethyl diazoacetate and ca. 96:4 for *l*-menthyl diazoacetate. Intramolecular cyclopropanation clearly gave a similar trend.

Introduction: Asymmetric induction with chiral metal-catalysts has been recognized to depend mainly on steric repulsion (i.e. nonbonding interaction) between an active metal-center decorated by chiral ligands and substrates. However, a concept of "*electronic control*" or "*electronic tuning*" in asymmetric catalytic reactions by substituents on chiral ligands remote from an active metal-center has been a few disclosed to very minutely regulate catalytic activity or enantioselectivty.[1] The concept can provide a new method how to optimize asymmetric reactions. In this respect, we have also demonstrated an electronic control in an asymmetric hydrosilylation of ketones with chiral 4-substituted bis(oxazolinyl)pyridine-rhodium catalysts **1**.[2] Another electronic control by remote substituents was reported by Jacobsen in an asymmetric epoxidation of olefins with chiral manganese-salen complexes **2**.[1a]



1



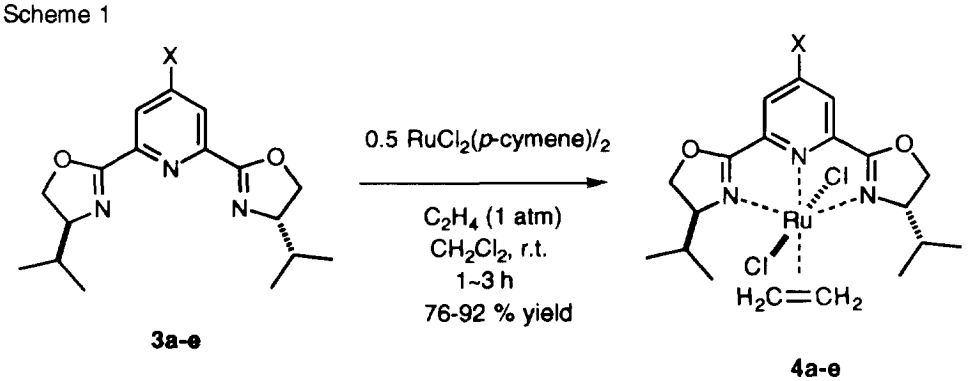
2

Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995

We have recently established a new asymmetric cyclopropanation of olefins with chiral *trans*-$RuCl_2$(pybox)(C_2H_4) complexes, [pybox = bis(oxazolinyl)pyridine], which posses an extremely high *trans*-selectivity (>90:10) with high enantioselectivity.[3] As an investigation on this line, we here disclose a fine electronic control in the asymmetric cyclopropanation with 4-substitued pybox-ruthenium catalysts **4a-e**: how do the remote substituents on pybox ligands affect the catalytic reaction?

Results and Discussion: Treatment of **3a-e** with $RuCl_2$(*p*-cymene)/$_2$ in dichloromethane at room temperature under ethylene atmosphere (1 atm) for 1-3 h produced *trans*-$RuCl_2$(4-X-pybox)(C_2H_4) **4a-e** in 76-93 % yields (X = Me_2N for **a**, MeO for **b**, H for **c** [3], Cl for **d**, CO_2Me for **e**). The complexes **4a-e** were purified at 0°C by silica-gel column chromatograpy with dichloromethane-methanol. Proton NMR spectra of **4** exhibit an interesting trend that the two signals of the coordinated ethylene moiety, H_α and H_β, shift with the electronic donating or withdrawing property of the substitutents at the 4-position of the pyridine skeletons of pybox; H_α, from δ 5.05 to 5.42 and H_β, from δ 4.73 to 5.12 ppm (Table 1). The electron-donating groups make the signals to uppper field, while the electron-withdrawing groups make them to lower field *vice versa*. Apparently the eletronic property by the substitutents influences toward the reverse *trans*-site on **4** through σ- or π-bonds of the pyridine-ruthenium skeleton.

Scheme 1



3a-e **4a-e**

[X: **a**, Me_2N; **b**, MeO; **c**, H; **d**, Cl; **e**, MeO_2C]

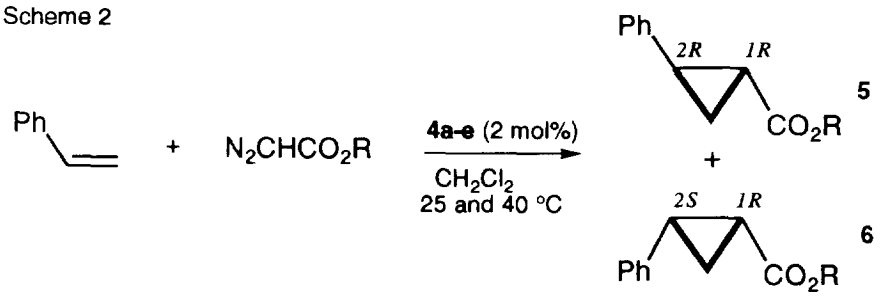
Table 1. Chemical shifts (δ) of protons of ethylene moiety of **4a-e**.

	4a	**4b**	**4c**	**4d**	**4e**
H_α	5.05	5.13	5.24	5.27	5.42
H_β	4.73	4.84	4.94	4.96	5.12

Asymmetric cyclopropanation with the complexes **4a-e** (2 mol%) was demonstrated by use of styrene (15 mmol) and ethyl and *l*-menthyl diazoacetates (3.0 mmol), which are commonly used substrates and reagents as a standard, in dichloromethane at 25-40 °C to give the *trans*- and *cis*-cyclopropanes **5** and **6** (Scheme 2). The

Me_2N catalyst **4a** did not show the catalytic activity at 25 °C with ethyl diazoacetate (run 1, Table 2). Most of ethyl diazoacetate remained unreacted in run 1, and even the dimerization of the diazoacetate giving a maleate and a fumarate was not observed. The MeO catalyst **4b** increased the reactivity slightly to 29 % yield (run 2). In contrast, H, Cl, and MeO_2C complexes **4c-e** catalyzed very smoothly to give 60-74 % yields (run 3-5). It is worth noting that the ratios of the *trans*- and *cis*-cyclopropanes **5** and **6** were not changed around ca. 90:10 for run 1-5. While, the enantiomeric excesses were influenced by the substituents to be higher with the electron-withdrawing groups and to be lower with the electron-donating groups. The enantiomeric excess reached up to 93% [(1*R*,2*R*):(1*S*,1*S*)] for the *trans*-isomers **5** and 87% [(1*R*,2*S*):(1*S*,2*R*)] for the *cis*-isomers **6** with MeO_2C catalyst **4e** (run 5), comparing to 53 with Me_2N catalyst **4a**, respectively.

Scheme 2



One question was left for us as to whether aggregation of the catalytst **4a** by the dimethyamino group might diminish the catalytic acitivity. When dimethylamiline (0.06 mmol) was added to the reaction mixture with H catalyst **4c** under the condition employed for run 3, the cyclopropanation smoothly proceeded to result in 68 % yield of **5** and **6** (ratio = 92:8, %ees: 88 for **5** and 79 for **6**). Therefore, we concluded that the dimethylamino group on **4a** can play a purely electronic action toward the catalytic center.

At 40 °C with ethyl diazoacetate, the reaction with Me_2N catalyst **4a** was improved to result in 45 % yield. Although the *trans-cis* stereoselectivity was not affected, the enantioselectivity slightly decreased for Me_2N and MeO complexes (run 6 and 7).

The reaction with *l*-menthyl diazoacetate was performed at 40 °C to give farely improved results of the yields, the *trans:cis* ratios, and the diastereomer ratios, which all have a similar trend to those for ethyl diazoacetate, better for the electron-withdrawing groups than for the electron-donating groups. Especially, MeO_2C complex **4e** gave an excellent result, 95% yield of **5** and **6**, 96:4 of the *trans:cis* ratio (the diastereomeric excess: 97 for **5** and 85 for **6**). The *trans:cis* ratios are around ca. 95:5 of the products **5** and **6** (run 10-15).

We can not demonstrate the kinetic study for the reaction with **4a-e**, because of slow addition of the diazoacetates to the reaction mixture by a syringe-pomp for ca. 8 h. Therefore, we should compare the catalytic activity by the yields, which stands for the selectivity between the cyclopropanation and the competing dimerization of the diazoacetates. In the case of the reactions at 40 °C for run 6-15, the diazoacetates were completely consumed and the rest of the desired cyclorpopanes were a mixture of the maleate and the fumarate as by-products.

Table 2. Cylcopropanation of styrene and diazoacetates with **4a-e.**

run	cat. **4-**	diazoacetate R =	temp (°C)	yield (%)	trans:cis	%ee (trans,cis)
1	**a**	Et	25	2	88:12	80,53
2	**b**			29	92:8	86,70
3	**c**			73	91:9	89,79
4	**d**			60	92:8	90,80
5	**e**			74	91:9	93,87
6	**a**	Et	40	45	90:10	78,55
7	**b**			66	90:10	84,68
8	**c**			90	93:7	89,82
9	**d**			84	90:10	87,72
10	**e**			81	90:10	85,68
11	**a**	*l*-ment	40	79	94:6	84,38
12	**b**			89	96:4	90,67
13	**c**			93	97:3	93,79
14	**d**			93	97:3	94,83
15	**e**			95	96:4	97,85

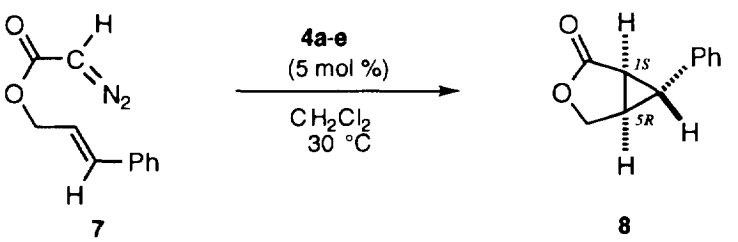
Table 3. Cyclization of **7** with **4a-e.**[a]

run	cat. **4-**	time (h)	yield (%)	%ee
1	**a**	41	67	52
2	**b**	12	73	78
3	**c**	2	83	86
4	**d**	2	80	85
5	**e**	0.33	72	89

[a] 30 °C, conversion 100 %.

Intramolecular cyclization of **7** was examined with **4a-e** (5 mol%) to give a similar phenomenum for the reaction rate and the enantioselectivity of **8** (Scheme 3) (Table 3). In this reaction, all of the diazoacetate **7** was added in the initial step.

Scheme 3



7 **8**

Hammett plots of the diastereoselectivity of the *trans*-product **5** and the *cis*-product **6** versus σ_{para} values with *l*-menthyl diazo-acetate (run 11-15 in Table 1) versus σ_{para} values are demon-strated in Figure 1 showing nice correlation, $\rho = 0.517$ ($R = 0.989$) for **5** and $\rho = 0.584$ ($R = 0.981$), respectively (Figure 1, **A**). The plot for **8** gave $\rho = 0.557$ ($R = 0.969$) of the enantiomer ratios and $\rho = 1.53$ ($R = 0.971$) of the relative reaction rate (Figure 1, **B** and **C**). In contrast, negative ρ values were reported for the asymmetric epoxidation with Mn-salen complexes.[1a]

We have already described that the cyclopropanation with the pybox-ruthenium system should proceeds concertedly via an attack of olefin to a hypothetical carbene-complex without no olefin-precoordination.[3] The fact, that the complex **4c** reacts smoothly with ethyl diazoacetate below 0 °C to give a mixture of dimerization products, can indicate that the rate determining step of the cyclopropanation with pybox-ruthenium catalysts may be the irreversible step of the carbene transfer to olefin. The carbene transfer is also the determinng step of the *trans:cis* ratios and the enantiomer ratios (diastereomer ratios for runs 11-15). It has been pointed out that a

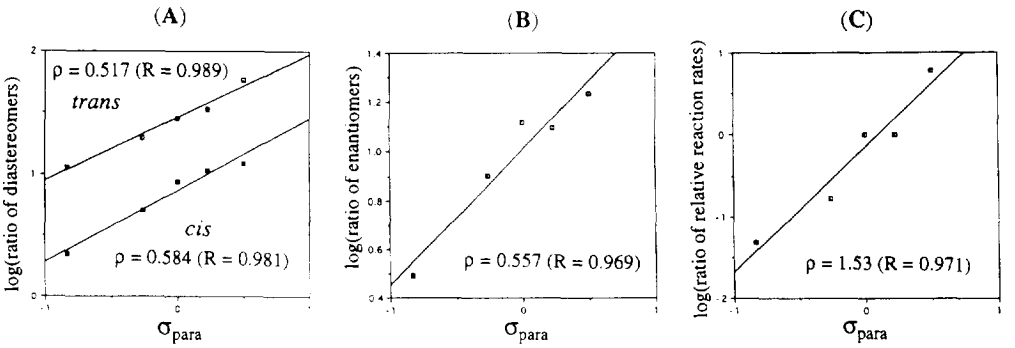


Figure 1. Hammett plots: σ_{para} vs (**A**) enantiomer ratios with *l*-menthyl diazoacetate (run 11-15. Table 1), (**B**) enantiomer ratios of **8** (Table 2), (**C**) relative reaction rates (Table 2).

shape and size of the ester moiety of the diazoacetates influence the both selectivities.[4] We found, as described above, that the substituents on **4** mainly alter the enantiomer ratios, not the *trans:cis* ratios. We think that the substituents of the complexes **4** electroncially affect the carbene carbon atom on the active species through the pyridine-ruthenium skeleton. The electron-withdrawing groups must increase the cationic property of the carbene carbon atom to increase the reactivity toward an olefin. On the contrary, the electron-donating groups deminish the cationic propety to decrease the reactivity. We can not correctly specify the origin of the deviation of the enantiomer ratios by electronic control of the substituents on **4**. However, we assume now that the deviation may be attributed to the change of inherent activity of the catalysts included in the rate-determining step.

Experimental Section

General: All reactions were carried out under nitrogen. Dichloromethane was distilled under nitrogen from phosphorus pentoxide. ^1H and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz, respectively, on a JEOL JNM-GX 270 spectrometer using tetramethylsilane as the internal reference in $CDCl_3$. Infrared spectra were recorded on a JASCO A-3 spectrometer. Microanalyses were performed with a Yanagimoto MT-3 CHN corder. Column chromatography was performed with silica gel (Merck, Art 7734). Analytical TLC was performed on Merck (Art 5715) precoated silica gel plates (0.25 mm). Optical purity was determined by Shimadzu Capillary Gas Chromatograph 14A with a chiral capillary column (Astec Chiraldex B-DA, 30 m). Optical rotation was measured on a JASCO DIP-140 polarimeter. Pybox derivatives, 2,6-bis[4-H-oxazolin-2'-yl]pyridine, **3a**, **3b**, **3c**, **3d**, were prepared by our method.[2] 4-Methoxycarbonyl pybox **3e** was prepared from pyridine-2,4,6-tricarboxylic acid trimethylester via the following three steps: 1) (*S*)-valinol (2 eq) in toluene at reflux temperature for 1 day, 14 % of 2,6-amidoalcohol (TLC, *Rf* = 0.48, CH_2Cl_2:MeOH = 10:1). 2) thionyl chloride (4 eq) in dichloromethane at room temperature for 1 day, 67 % of 2,6-amidochloride. 3) sodium hydride (4 eq) in tetrahydrofuran at 35 °C for 2 h, 75 % of **3e**: white solids, M.p. 136 °C; $[\alpha]^{20}_D$ = -85.9 (*c* = 0.85 in CH_2Cl_2); IR (KBr disk): 1725 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, TMS): δ = 0.96 (d, *J* = 6.8 Hz, 6H), 1.07 (d, *J* = 6.8 Hz, 6H), 1.88 (m, 2H), 3.99 (s, 3H), 4.20 (m, 2H), 4.26 (dd, *J* = 7.3 and 8.8 Hz, 2 H), 4.56 (dd, *J* = 7.3 and 8.8 Hz, 2H), 8.71 (s, 2H); $C_{19}H_{25}N_3O_4$ (359.4): calcd C 63.49, H 7.01, N 11.69; found C

63.44, H 7.07, N 11.51. *trans*-$RuCl_2$(4-H-pybox)(C_2H_4) **4c** was prepared with **3c** and [$RuCl_2$(*p*-cymene)]$_2$[5,3] *l*-Menthyl diazoacetate was prepared by the reported method described in the literature by Pfaltz.[1a]

Cinnamyl diazoacetate **7** was prepared by the reported method.[3b,6]

***trans*-$RuCl_2$(4-Me_2N-pybox)(C_2H_4) 4a.** A solution of 4-Me_2N-pybox **3a** (127 mg, 0.37 mmol) and [$RuCl_2$(*p*-cymene)]$_2$ (113 mg, 0.18 mmol) in dichloromethane (3 mL) was stirred at room temperature under ethylene atmosphere (1 atom) for 3 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography at 0 °C with dichloromethane and methanol (100:1) to give **4a** as dark-red solids in 83 % yield (168 mg, 0.31 mmol); dec. 68-72 °C; ^{1}H NMR (270 MHz, $CDCl_3$, TMS): δ = 0.79 (d, *J* = 6.8 Hz, 6H), 0.99 (d, *J* = 6.8 Hz, 6H), 2.48 (m, 2H), 3.26 (s, 6H, $N(CH_3)_3$), 4.39 (m, 2H), 4.70-4.85 (m, 2H of ethylene and (OCH_2x2)), 5.05 (m, 2H, ethylene), 7.15 (s, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$, TMS): δ = 14.2, 19.2, 29.5, 40.1, 67.2, 70.6, 71.6, 106.4, 145.3, 154.2, 163.5; $C_{21}H_{32}N_4O_2Cl_2Ru(H_2O)$ (562.5): calcd C 44.84, H 6.09, N 9.96; found C 45.05, H 5.89, N 9.68.

***trans*-$RuCl_2$(4-MeO-pybox)(C_2H_4) 4b.** A solution of 4-MeO-pybox **3b** (133 mg, 0.40 mmol) and [$RuCl_2$(*p*-cymene)]$_2$ (123 mg, 0.20 mmol) in dichloromethane (4 mL) was stirred at room temperature under ethylene atmosphere (1 atom) for 2 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography at 0 °C with dichloromethane and methanol (100:1) to give **4b** as dark-red solids in 79 % yield (169 mg, 0.32 mmol); dec. 75-80 °C; ^{1}H NMR (270 MHz, $CDCl_3$, TMS): δ = 0.79 (d, *J* = 6.8 Hz, 6H), 1.10 (d, *J* = 6.8 Hz, 6H), 2.50 (m, 2H), 4.07 (s, 3H, CH_3O), 4.42 (m, 2H), 4.77-4.90 (m, 2H of ethylene and 4H of (OCH_2x2)), 5.13 (m, 2H, ethylene), 7.47 (s, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$, TMS): δ = 14.4, 19.2, 29.6, 56.6, 68.9, 70.8, 71.8, 110.0, 146.7, 163.2, 165.7; $C_{20}H_{29}N_3O_3Cl_2Ru$ (531.5): calcd C 45.20, H 5.50, N 7.91; found C 45.17, H 5.78, N 7.59.

***trans*-$RuCl_2$(4-Cl-pybox)(C_2H_4) 4d.** A solution of 4-Cl-pybox **3d** (134 mg, 0.40 mmol) and [$RuCl_2$(*p*-cymene)]$_2$ (123 mg, 0.20 mmol) in dichloromethane (3 mL) was stirred at room temperature under ethylene atmosphere (1 atom) for 1 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography at 0 °C with dichloromethane and methanol (100:1) to give **4d** as dark-red solids in 76 % yield (162 mg, 0.30 mmol); dec. 115-120 °C; ^{1}H NMR (270 MHz, $CDCl_3$, TMS): δ = 0.76 (d, *J* = 6.8 Hz, 6H), 1.02 (d, *J* = 6.8 Hz, 6H), 2.47 (m, 2H), 4.43 (m, 2H), 4.82 (m, 2H, OCH_2), 4.89 (m, 2H of OCH_2), 4.96 (m, 2H, ethylene), 5.27 (m, 2H, ethylene), 7.87 (s, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$, TMS): δ = 14.4, 19.2, 29.6, 70.9, 71.8, 72.0, 123.4, 141.3, 146.4, 163.2; $C_{19}H_{26}N_3O_2Cl_3Ru$ (535.9): calcd C 42.59, H 4.89, N 7.84; found C 42.54, H 4.93, N 7.73.

***trans*-$RuCl_2$(4-MeO_2C-pybox)(C_2H_4) 4e.** A solution of 4-MeO_2C-pybox **3e** (125 mg, 0.35 mmol) and [$RuCl_2$(*p*-cymene)]$_2$ (106 mg, 0.17 mmol) in dichloromethane (3 mL) was stirred at room temperature under ethylene atmosphere (1 atom) for 1 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography at -20 °C with dichloromethane and methanol (100:1) to give **4e** as dark-red solids in 92 % yield (179 mg, 0.32 mmol); dec. 97-103 °C; ^{1}H NMR (270 MHz, $CDCl_3$, TMS): δ = 0.77 (d, *J* = 6.8 Hz, 6H), 1.02 (d, *J* = 6.8 Hz, 6H), 2.45 (m, 2H), 4.07 (s, 3H, CH_3O), 4.44 (m, 2H), 4.85 (m, 2H, OCH_2), 4.93 (m, 2H of OCH_2), 5.12 (m, 2H, ethylene), 5.41 (m, 2H, ethylene), 8.41 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$, TMS): δ = 14.5, 19.2, 29.7, 53.3, 70.7, 72.0, 74.0, 123.0, 133.4, 145.9, 163.8, 164.3; $C_{21}H_{29}N_3O_4Cl_2Ru(CH_2Cl_2)$ (644.4): calcd C 41.01, H 4.85, N 6.52; found C 41.08, H 4.74, N 6.66.

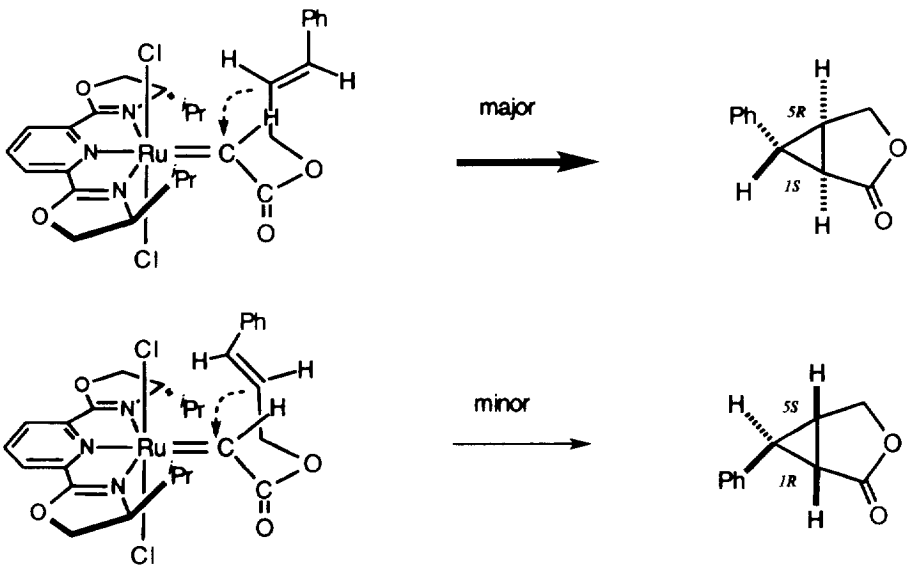
Cyclopropanation of styrene and diazoacetate with 4 as a typical reaction.

To a solution of *trans*-$RuCl_2$(4-X-pybox-*ip*)(ethylene) **4** (0.06 mmol) and styrene (1.7 mL, 15 mmol) in dichloromethane (2.0 mL) was added a dichloromethane solution of diazoacetate (3.0 mmol, ca. 1 *N*) through a microsyringe controlled by mechanical feeder (ca. 4 μL/drop, ca. 0.4 mL/h) for 8 h at 20~25 °C under argon atmosphere. After stirring for an additional 10 h, the mixture was concentrated under reduced pressure. The residual oil was subjected to silica-gel column chromatography with hexane-ether as eluent to give an oily mixture of *trans*-2-phenylcylopropane-1-carboxylate **5** and the *cis*-isomer **6**. After the products were converted to the corresponding methyl ester, their enantiomeric purities were measured by GLPC (Astec, Chiraldex B-DA, 30 m x 0.25 mm). See the detail in the reference 3b.

Intramolecular cyclopropanation with 7.

To a solution of *trans*-$RuCl_2$(4-X-pybox-*ip*)(ethylene) **4** (0.05 mmol) in dichloromethane (2.0 mL) was added a solution of *trans*-cinnamyl diazoacetate **7** (202 mg, 1.0 mmol) in dichloromethane (1.5 mL) at 30 °C under an argon atmosphere. After **7** was completely consumed, the reaction mixture was concentrated and purified by silica-gel column chromatography to give the desired product, (-)-[*1S,5R*-(1α,5α,6β)]-(-)-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one **8** as white solids: for spectroscopic data, see ref. 3b. The enantiomeric purity was measured by GLPC (Astec, Chiraldex B-DA, 30 m x 0.25 mm). See the detail in ref. 3b. The absolute configuration of (-)-**8** was erroneously described in ref 3b, as (*1R,5S*). In addition, the hypothetical transition state can be revised as shown in Scheme 4.

Scheme 4. Intramolecular cyclopropanation.



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