Asymmetric Hydroformylation of Heterocyclic Olefins Catalyzed by Chiral Phosphine−Phosphite−Rh(I) Complexes

Toshihide Horiuchi, Tetsuo Ohta,† Eiji Shirakawa, Kyoko Nozaki,* and Hidemasa Takaya‡

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-01, Japan

Received December 30, 1996⊗

Asymmetric hydroformylation of heterocyclic olefins catalyzed by phosphine−phosphite−Rh(I) complexes has been investigated. Hydroformylation of symmetrical heterocyclic olefins such as 2,5-dihydrofuran, 3-pyrroline derivatives, and 4,7-dihydro-1,3-dioxepin derivatives afforded the optically active aldehydes as single products in 64−76% ee. Unsymmetrical substrates such as 2,3-dihydrofuran and *N*-(*tert*-butoxycarbonyl)-2-pyrroline gave a mixture of regioisomers. From *N*-(*tert*-butoxycarbonyl)-2-pyrroline was obtained *N*-(*tert*-butoxycarbonyl)pyrrolidine-2-carbaldehyde in 97% ee. The hydroformylation products from 2,5-dihydrofuran and *N*-(*tert*-butoxycarbonyl)-3-pyrroline have the opposite configurations to those from 2,3-dihydrofuran and *N*-(*tert*-butoxycarbonyl)-2-pyrroline, respectively, with the same catalyst. The new phosphine−phosphite ligand (*R*,*S*)-3,3′-Me_2-BINAPHOS [= (*R*)-2-(diphenylphosphino)-1,1′-binaphthalen-2′-yl (*S*)-3,3′-dimethyl-1,1′-binaphthalene-2,2′-diyl phosphite] was prepared and its hydridorhodium complex was characterized by NMR spectroscopy. Using (*R*,*S*)-3,3′-Me_2-BINAPHOS as a ligand, the enantioselectivity was improved for some substrates. In addition, higher catalytic activity was observed with this ligand for most of the substrates employed.

Introduction

A number of compounds possessing the tetrahydrofuran, tetrahydropyran, thiophene, and pyrrolidine moiety display a wide range of biological activity, such as antitumor and antibacterial. For this reason, a great deal of effort has been devoted to synthesizing these compounds.[1] Hydroformylation of heterocyclic olefins would provide a potential synthetic tool for preparing these compounds. There have been, however, only a few reports on hydroformylation of heterocyclic olefins, most of these concerning the reaction of five-membered cycles such as oxazoline and pyrroline derivatives, and dihydrofurans.[2−4]

For hydroformylation of internal heterocyclic olefins, regioselectivity is of special interest because it is different from that of the corresponding acyclic olefins in many cases. For example, the regioselectivity of hydroformylation of cyclic vinyl ethers depends on the reaction conditions and the nature of the catalyst,[4] while the reaction of acyclic vinyl ethers generally affords the branched aldehydes in high selectivity.[5] Hydroformylation of cyclic enamides gave α-amido aldehydes in complete selectivity.[3] In contrast, a mixture of regioisomers was obtained from acyclic *N*-vinylamides.[3] Cyclic allyl ethers and allylamides are reported to easily isomerize into the corresponding vinyl ether and enamides, respectively.[4a,6] This fact would affect the regioselectivity of the hydroformylation of these substrates. By modification of the reaction conditions and the ligand employed, Claver et al. succeeded in the selective introduction of a formyl group on the 2- or 3-position of the tetrahydrofuran, starting from 2,3- or 2,5-dihydrofuran, respectively.[4a]

To the best of our knowledge, no report has appeared on the successful asymmetric hydroformylation of heterocyclic olefins. From the asymmetric hydroformylation of 2,5-dihydrofuran, the maximum optical purity of the product, tetrahydrofuran-3-carbaldehyde, was less than 10%.[7] Stille reported the asymmetric hydroformylation of *N*-(*tert*-butoxycarbonyl)-2-pyrroline catalyzed by RhH(CO)(PPh_3)$_3$/DIPHOL system [DIPHOL = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(5*H*-benzo[*b*]phosphindolyl)-butane].[3] However, the optical yield was disappointing (<1%).

We have developed the phosphine−phosphite ligands, (*R*,*S*)-BINAPHOS [= (*R*)-2-(diphenylphosphino)-1,1′-binaphthalen-2′-yl (*S*)-1,1′-binaphthalene-2,2′-diyl phosphite] [(*R*,*S*)-**1a**][8a] and (*R*,*S*)-BIPHEMPHOS [= (*R*)-3,3′-dichloro-6-(diphenylphosphino)-2,2′,4,4′-tetramethyl-

* To whom correspondence should be addressed. Phone: 81 (Japan) -75-753-5545. Fax: 81 (Japan) 75-761-8846. E-mail: Nozaki@npc05.kuic.kyoto-u.ac.jp.

† Present address: Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University, Tanabe, Kyoto 610-03, Japan.

‡ Deceased on October 4, 1995.

⊗ Abstract published in *Advance ACS Abstracts,* June 1, 1997.

(1) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press Ltd: Oxford, 1984; Vol. 1.

(2) Kollár, L.; Sándor, P. *J. Organomet. Chem.* **1993**, *445*, 257.

(3) Becker, Y.; Eisenstadt, A.; Stille, J. K. *J. Org. Chem.* **1980**, *45*, 2145.

(4) (a) Polo, A.; Claver, C.; Castillón, S.; Ruiz, A.; Bayón, J. C.; Real, J.; Mealli, C.; Masi, D. *Organometallics* **1992**, *11*, 3525. (b) Lapidus, A. L.; Priudze, I. G.; Korneyeva, G. A.; Vartanyan, M. M.; Rodin, A. P.; Slivinskii, Y. V.; Dolidze, A. V.; Loktev, S. M. *Neftekhimiya* **1993**, *33*, 102; *Petrol. Chem.* **1993**, *33*, 91.

(5) (a) Lazzaroni, R.; Bertozzi, S.; Pocai, P.; Troiani, F.; Salvadori, P. *J. Organomet. Chem.* **1985**, *295*, 371. (b) Amer, I.; Alper, H. *J. Am. Chem. Soc.* **1990**, *112*, 3674. (c) Lazzaroni, R.; Settambolo, R.; Uccello-Barretta, G. *Organometallics* **1995**, *14*, 4644.

(6) (a) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139. (b) Amino, Y.; Nishi, S.; Izawa, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 620.

(7) (a) Botteghi, C.; Branca, M.; Micera, G.; Piacenti, F.; Menchi, G. *Chim. Ind. (Milan)* **1978**, *60*, 16. (b) Gladiali, S.; Faedda, G.; Marchetti, M.; Botteghi, C. *J. Organomet. Chem.* **1983**, *244*, 289.

(8) (a) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033. (b) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395. (c) Higashizima, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron Lett.* **1994**, *35*, 2023. (d) Nanno, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron: Asym.* **1995**, *6*, 2583. (e) Horiuchi, T.; Ohta, T.; Nozaki, K.; Takaya, H. *Chem. Commun.* **1996**, 155. (f) Nozaki, K.; Li, W.; Horiuchi, T.; Takaya, H.; Saito, T.; Yoshida, A.; Matsumura, K.; Kato, Y.; Imai, T.; Miura, T.; Kumobayashi, H. *J. Org. Chem.* **1996**, *61*, 7658. (g) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.*, in press.

S0022-3263(96)02405-X CCC: $14.00

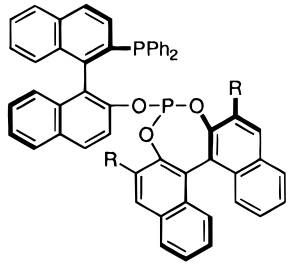
Table 1. Hydroformylation of Five-Membered Heterocyclic Olefins 4[a]

run	substrate	ligand	temp, °C	press., atm	time, h	% conv[b] (**5**/ **7**)	% ee of **5** (config)[c]
1	**4a**	(*R,S*)-**1a**	60	100	18	75 (100/0)	57 (*R*)
2	**4a**	(*R,S*)-**1b**	60	100	18	99 (100/0)	61 (*R*)
3	**4a**	(*R,S*)-**1a**	40	100	48	63 (100/0)[d]	62 (*R*)
4	**4a**	(*R,S*)-**1b**	40	100	41	93 (100/0)	63 (*R*)
5	**4a**	(*R,S*)-**1b**	40	20	24	>99 (100/0)	64 (*R*)
6	**4a**	(*R,S*)-**1b**	40	1	24	>99 (72/28)	41 (*R*)
7[e]	**4a**	(*R,S*)-**1b**	40	1	6	36 (97/3)[f]	68 (*R*)
8	**4b**	(*R,S*)-**1a**	60	100	72	98 (100/0)	47 (*R*)
9	**4b**	(*R,S*)-**1b**	60	100	72	99 (100/0)	73 (*R*)
10	**4c**	(*R,S*)-**1a**	60	100	71	92 (100/0)	66 (−)
11	**4c**	(*R,S*)-**1b**	60	100	72	97 (100/0)	65 (−)

[a] Reactions were carried out with the substrate **4** (4−5 mmol), $Rh(acac)(CO)_2$ (0.25 mol %) and (*R,S*)-**1** (4 equiv to Rh) in benzene (0.7−1.5 mL) under a 1:1 mixture of H_2 and CO. [b] Conversion into aldehydes. Determined by ^1H NMR spectroscopy. [c] The sign of optical rotation is given, when the absolute configuration has not been determined. [d] Substantial amount of unidentifiable impurity was detected in ^1H NMR. [e] Substrate/Rh ratio was 800. [f] 14% into 2,3-dihydrofuran.

biphenyl-2′-yl (*S*)-1,1′-binaphthalene-2,2′-diyl phosphite],[8c] and successfully applied them to the enantioselective hydroformylation of a variety of olefins such as arylethenes,[8a,c,g] vinyl carboxylates,[8a,c,g] 1,2-disubstituted olefins,[8b,c,g] sulfur-[8d] and fluorine-containing[8g] olefins, and some types of conjugated dienes.[8e] The outstanding enantioselectivity and the absence of side reactions in the above asymmetric hydroformylation prompted us to investigate the asymmetric hydroformylation of heterocyclic olefins as the next target.

Herein, we wish to report the asymmetric hydroformylation of oxygen- or nitrogen-containing internal cyclic olefins catalyzed by phosphine−phosphite−Rh(I) complexes. In addition, since subtle modifications in structures and electronic properties of chiral ligands often significantly influence their efficiencies in the catalytic reactions,[9] we also synthesized a new phosphine−phosphite ligand (*R,S*)-3,3′-Me_2-BINAPHOS [(*R,S*)-**1b**].

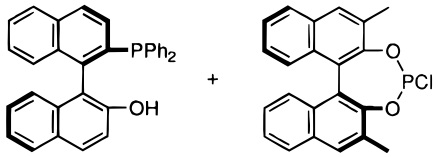


(*R,S*)-**1a**: R = H [(*R,S*)-BINAPHOS]
(*R,S*)-**1b**: R = Me [(*R,S*)-3,3'-Me_2-BINAPHOS]

Results and Discussion

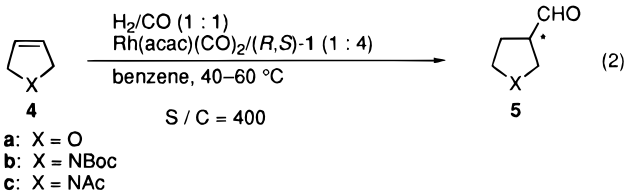
Preparation of (*R,S*)-3,3′-Me_2-BINAPHOS. Enantiomerically pure (*R,S*)-**1b** was easily prepared from (*R*)-**2** and (*S*)-**3**, similar to the synthesis of (*R,S*)-**1a** (eq 1).[8a,g] The proton-decoupled ^{31}P NMR spectrum of (*R,S*)-**1b** in $CDCl_3$ shows a signal due to the phosphine moiety at δ −13.6 (J_{P-P} = 22.9 Hz), almost the same value as that of (*R,S*)-**1a** (δ −13.3, J_{P-P} = 29.0 Hz).[8a] The resonance due to the phosphite moiety was observed at δ 141.8, a slightly upfield shift from that of (*R,S*)-**1a** (δ 146.2). Two methyl groups have different chemical shifts (δ 1.68 and 2.29) in the ^1H NMR spectrum.

Asymmetric Hydroformylation of Five-Membered Heterocyclic Olefins. First, the hydroformylation of 2,5-dihydrofuran (**4a**) was investigated (eq 2 and Table 1).



(*R*)-**2** (*S*)-**3**

$\xrightarrow[Et_2O]{NEt_3}$ (*R,S*)-**1b** (1)



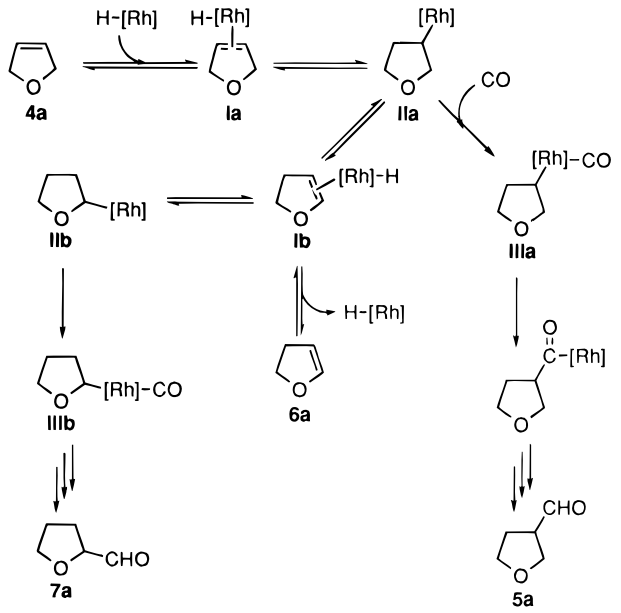
4 **5** (2)

a: X = O
b: X = NBoc
c: X = NAc

Next, the effect of the total pressure was examined using (*R,S*)-**1b** as a ligand. In all runs, no hydrogenation product was observed. At 20 atm, the reaction has proceeded much faster than at 100 atm without serious change in the selectivity (run 5). On the other hand, a mixture of **5a** and tetrahydrofuran-2-carbaldehyde (**7a**) was obtained from the reaction at 1 atm (run 6). In addition, the ee of **5a** has dropped to 41%. A similar dependence of the pressure on the regioselectivity was reported by Claver et al. using $[Rh_2(\mu\text{-}S(CH_2)_3NMe_2)_2(cod)_2]/PPh_3$ system as a catalyst.[4a] The formation of **7a** suggests the existence of the isomerization of **4a** to **6a** via β-hydride elimination from the alkylrhodium intermediate **IIa** to form **Ib** (Scheme 1).[4a] Indeed, **6a** was observed when the reaction was stopped after a partial

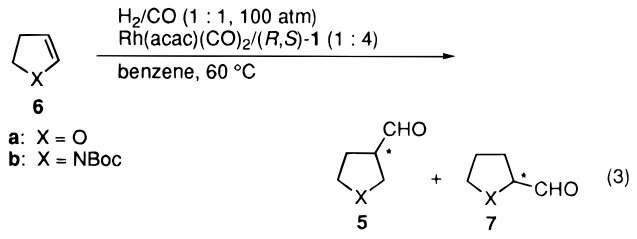
(9) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers, Inc.: New York, 1993; Chapter 1, p 1.

Scheme 1



conversion of **4a** (run 7). The slow coordination of CO to **IIa** at a low CO partial pressure should be responsible for the isomerization of **4a** because β-elimination can compete with the coordination of CO and the following CO insertion in this case. Therefore, a high CO pressure would be necessary to suppress this isomerization.

The hydroformylation of 2,3-dihydrofuran (**6a**) catalyzed by Rh(acac)$(CO)_2$/(*R*,*S*)-**1b** ([**6a**]/[Rh] = 400, 60 h) afforded an about 1:1 mixture of (*S*)-**5a** (38% ee) and **7a** in 77% conversion (eq 3). The ee and absolute configuration of **7a** have not been determined. The isomerization of **6a** into **4a** was not observed. It is noteworthy that the absolute configuration of the predominant enantiomer of **5a** obtained from **6a** is *S*, opposite to that from **4a**. This result shows that the absence of isomerization of the substrate is important to achieve high enantioselectivity from the reaction of **4a**. Indeed, the ee of **5a** has dropped when the isomerization of **4a** took place (Table 1, run 6). Due to the lower reactivity of **6a** compared to **4a**, the formation of **7a** was suppressed by stopping the reaction before the accumulation of **6a** dominates (run 7). As expected, the enantioselectivity was improved to 68% ee in this case, which is slightly higher than that observed at 100 atm (63% ee, run 4).



The hydroformylation of *N*-(*tert*-butoxycarbonyl)-3-pyrroline (**4b**) was carried out at 60 °C (eq 2). The reaction was almost completed in 72 h with both ligands to give (*R*)-**5b** as a single product (Table 1, runs 8 and 9). Again, the hydrogenation and isomerization of the substrate were not observed, though cyclic allylamides easily isomerize to enamides.[6] For this substrate, the enantioselectivity was much higher with (*R*,*S*)-**1b** than with (*R*,*S*)-**1a**. Notably, a bulky substituent *tert*-butoxycarbonyl group caused a higher enantioselectivity compared to other substrates, using (*R*,*S*)-**1b** as a ligand. A similar trend has been observed for the hydroformylation of sulfur-containing olefins[8d] catalyzed by the (*R*,*S*)-**1a**−Rh(I) complex.

Table 2. Hydroformylation of *N*-(*tert*-Butoxycarbonyl)-2-pyrroline (6b)[a]

run	ligand	time, h	% conv[b] (**5b**/**7b**)	% ee of **5b** (config)	% ee of **7b** (config)
1	(*R*,*S*)-**1a**	72	>99 (33/67)	71 (*S*)	97 (*S*)
2	(*R*,*S*)-**1b**	72	>99 (37/63)	22 (*S*)	88 (*S*)

[a] Reactions were carried out with **6b** (3 mmol), Rh(acac)$(CO)_2$ (0.5 mol %), and (*R*,*S*)-**1** (4 equiv to Rh) in benzene (1.0 mL) under a 1:1 mixture of H_2 and CO (total 100 atm) at 60 °C. [b] Determined by ^{1}H NMR spectroscopy.

The hydroformylation of *N*-(*tert*-butoxycarbonyl)-2-pyrroline (**6b**) was completed in 72 h at 60 °C (eq 3). In contrast to Stille's result in which **7b** was obtained as an exclusive product,[3] an about 1:2 mixture of (*S*)-**5b** and (*S*)-**7b** was obtained using the (*R*,*S*)-**1**−Rh(I) complexes as catalysts (Table 2). The steric bulkiness of (*R*,*S*)-**1** may be a reason for the lower regioselectivity. Indeed, the regioselectivity to **7b** was slightly lower with the more bulky ligand (*R*,*S*)-**1b** (run 2). With this substrate, (*R*,*S*)-**1a** gave a higher enantioselectivity than (*R*,*S*)-**1b**. Especially, (*S*)-**7b** was obtained as the major product in 97% ee using (*R*,*S*)-**1a** as a ligand. This product is a useful chiral building block for the syntheses of many kinds of natural products.[10] As in the case of dihydrofurans **4a** and **6a**, the hydroformylation of **4b** and **6b** afforded **7b** with an inverse configuration. The ee of **5b** (71% ee) from **6b** was much higher than that from **4b** (47% ee) using (*R*,*S*)-**1a**. By the use of (*R*,*S*)-**1b**, however, the ee of **5b** from **6b** (22% ee) was much lower than that from **4b** (73% ee).

The hydroformylation of *N*-acetyl-3-pyrroline (**4c**) afforded (−)-**5c** as the only product in 65% ee (Table 1, runs 10 and 11). From the reaction of this substrate, almost the same results were obtained using both ligands. The enantiomeric excess of **5c** was determined by ^{19}F NMR spectroscopy of the (*R*)-MTPA ester **8** derived by the reduction of the product **5c** and then the reaction with (*R*)-MTPA-Cl. The trifluoromethyl group of **8** derived from (±)-**5c** appeared as three singlets which consisted of the rotational isomers **8a** and **8b** (Figure 1). These signals coalesced at 90 °C in toluene-d_8. The highest field resonance was assigned as one isomer, and the remainder as a diastereomeric pair of another isomer. The ratio of **8a** and **8b** was always 1:1.

Hydroformylation of Seven-Membered Cyclic Unsaturated Acetals. The hydroformylation of *cis*-4,7-dihydro-1,3-dioxepin (**9a**) afforded (−)-1,3-dioxepane-5-carbaldehyde [(−)-**10a**] as the sole product (eq 4 and Table 3). The enantiomeric excess of (−)-**10a** was better with (*R*,*S*)-**1a** (73% ee at 40 °C, run 2) than with (*R*,*S*)-**1b** (56% ee, run 5). The reaction at 40 °C and at 100 atm was completed in 65 h using (*R*,*S*)-**1a** at the expense of enantioselectivity (66% ee, run 3). At 20 atm, the reaction proceeded much faster and was completed in 24 h. In addition, the ee of **10a** was higher than at 100 atm (76% ee, run 4). These results suggest the existence of racemization of the product under the reaction conditions.

(10) (a) Mori, S.; Ohno, T.; Harada, H.; Aoyama, T.; Shioiri, T. *Tetrahedron* **1991**, *47*, 5051. (b) Reed, P. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 2624. (c) Pettit, G. R.; Singh, S. B.; Herald, D. L.; Lloyd-Williams, P.; Kantoci, D.; Burkett, D. D.; Barkóczy, J.; Hogan, F.; Wardlaw, T. R. *J. Org. Chem.* **1994**, *59*, 6287.

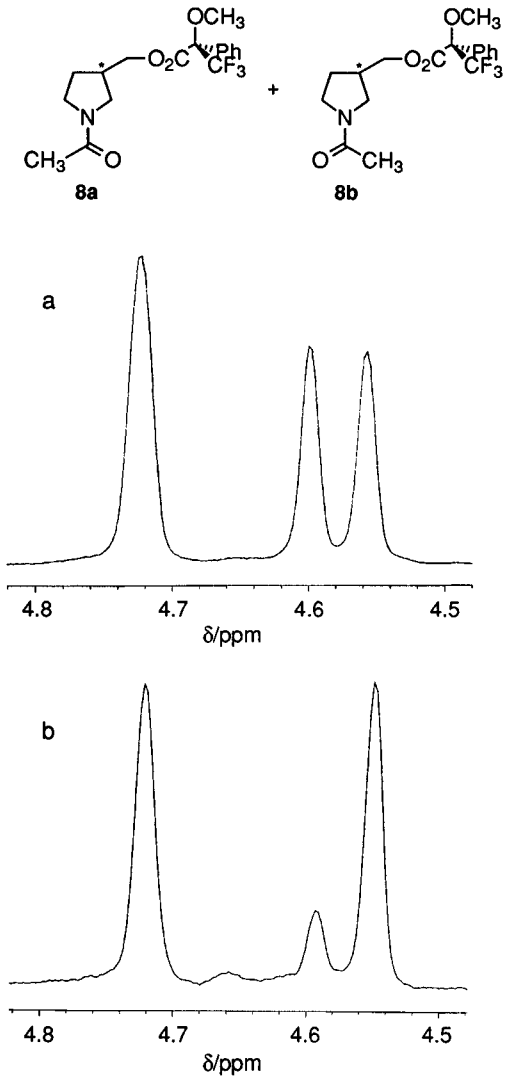
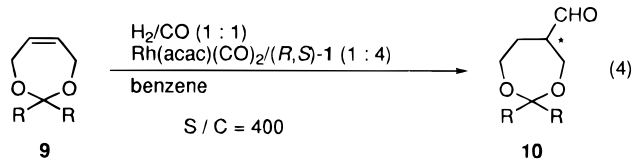


Figure 1. ^{19}F NMR spectrum of (*R*)-MTPA ester **8** derived from (a) racemic and (b) optically active (57% ee) **5c** in $CDCl_3$.

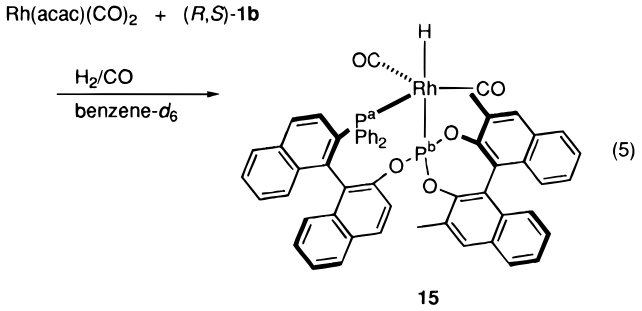
Indeed, the racemization of **10a** took place during the isolation procedure (see Experimental Section).



a : R = H
b : R = CH_3

The hydroformylation of *cis*-2,2-dimethyl-4,7-dihydro-1,3-dioxepin (**9b**) was much slower than the reaction of **9a** (Table 3, runs 6−9). On the other hand, the enantioselectivity was higher, particularly with (*R*,*S*)-**1b**. The absolute configuration of **10b** was confirmed by converting it into (*R*)-**14** (Scheme 2). Compound **14** is of interest as a building block in organic synthesis.[11] As in the case of **9a**, the reaction rate was much higher at 20 atm (runs 8 and 9). In this reaction, the ee of **10b** was not improved in spite of the shorter reaction time. This result is consistent with the fact that racemization of the product was not observed during the isolation procedure. In addition, cleavage of the dimethylacetal moiety became significant at 20 atm, especially with (*R*,*S*)-**1a** (run 8). By the use of (*R*,*S*)-**1b**, the deacetalization was greatly suppressed (run 9). These results suggest the weaker Lewis acidity of the (*R*,*S*)-**1b**−Rh(I) complex than that of the (*R*,*S*)-**1a**−Rh(I) complex.

Comparison between (*R*,*S*)-BINAPHOS and (*R*,*S*)-3,3′-Me_2-BINAPHOS. In order to compare the new phosphine−phosphite ligand (*R*,*S*)-**1b** with (*R*,*S*)-**1a**, the hydridorhodium complex of (*R*,*S*)-**1b** was prepared. The treatment of a solution of $Rh(acac)(CO)_2$ and (*R*,*S*)-**1b** in benzene-d_6 with a 1:1 mixture of hydrogen and carbon monoxide at atmospheric pressure afforded a single monohydride complex that has been assigned a trigonal bipyramidal structure $RhH(CO)_2$[(*R*,*S*)-**1b**] (**15**) (eq 5).[8a,g,12] From the NMR spectroscopic studies, the large $J\{P^b-H\}$ (139 Hz) and the small $J\{P^a-H\}$ (21 Hz) values suggest a hydride orientation cis to the phosphine moiety and trans to the phosphite, respectively,[13] similar to (*R*,*S*)-**1a**.[8a,g]



Comparison of the NMR spectral data of the complex **15** with those of the corresponding hydridorhodium complexes of (*R*,*S*)- and (*R*,*R*)-**1a** (**16** and **17**, respectively)[8g] revealed that the character of the phosphine moiety of **15** resembles that of **16** and that the character of the phosphite moiety of **15** resembles that of **17** (Table 4). Namely, (1) the $J\{P^a-H\}$ value of **15** is similar to that of **16** and is smaller than that of **17**, (2) the $J\{P^b-H\}$ value of **15** is similar to that of **17** and is smaller than that of **16**, (3) the $J\{P^b-Rh\}$ value of **15** is larger than that of **16**, which could be explained by a smaller trans influence of the hydride in **15** than in **16**, and (4) the $J\{P^a-P^b\}$ value of **15** is much smaller than those of **16** and **17**. These trends indicate a larger structural deviation from an ideal trigonal bipyramidal structure in the complex **15** compared to **16**. It may come from the steric hindrance of the methyl groups near the phosphorus atom of the phosphine moiety in (*R*,*S*)-**1b**. That is, a more sterically demanding chiral environment may be constructed around the metal center.

From the results obtained from the present hydroformylation, the more crowded chiral environment, provided by (*R*,*S*)-**1b**, is considered to be advantageous for the enantioface discrimination of sterically small compounds such as **4a**−**c**. On the other hand, this feature would be unfavorable for sterically more demanding substrates such as **6b** and **9a**−**b**. This trend is clearly

(11) (a) Sime, J. T.; Barnes, R. D.; Elson, S. W.; Jarvest, R. L.; O'Toole, K. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1653. (b) Larsen, D. S.; Schofield, A.; Stoodley, R. J.; Tiffin, P. D. *Tetrahedron Lett.* **1994**, *35*, 9285.

(12) Buisman, G. J. H.; Vos, E. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1995**, 409.

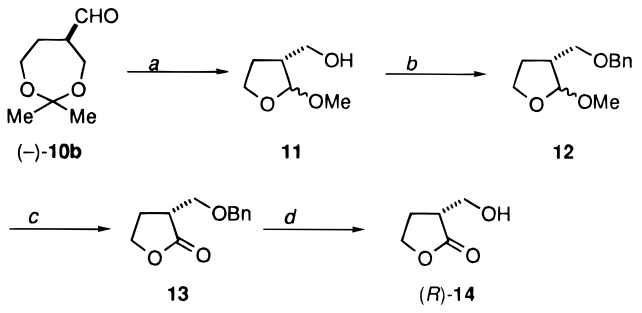
(13) Meakin, P.; Muetterties, E. L.; Jesson, J. P. *J. Am. Chem. Soc.* **1972**, *94*, 5271.

Table 3. Hydroformylation of 4,7-Dihydro-1,3-dioxepins 9[a]

run	substrate	ligand	temp, °C	press., atm	time, h	% conv[b]	% ee of **10** (config)[c]
1	**9a**	(*R*,*S*)-**1a**	60	100	24	96	68 (−)
2	**9a**	(*R*,*S*)-**1a**	40	100	48	95	73 (−)
3	**9a**	(*R*,*S*)-**1a**	40	100	65	>99	66 (−)
4	**9a**	(*R*,*S*)-**1a**	40	20	24	>99	76 (−)
5	**9a**	(*R*,*S*)-**1b**	40	100	48	99	56 (−)
6	**9b**	(*R*,*S*)-**1a**	60	100	48	77	73 (*R*)
7	**9b**	(*R*,*S*)-**1b**	60	100	48	98	69 (*R*)
8	**9b**	(*R*,*S*)-**1a**	60	20	24	*d*	70 (*R*)
9	**9b**	(*R*,*S*)-**1b**	60	20	24	>99[e]	68 (*R*)

[a] Reactions were carried out with **9** (5 mmol), $Rh(acac)(CO)_2$ (0.25 mol %), and (*R*,*S*)-**1** (4 equiv to Rh) in benzene (1.0 mL) under a 1:1 mixture of H_2 and CO. [b] Determined by ^1H NMR spectroscopy. [c] The sign of optical rotation is given, when the absolute configuration has not been determined. [d] Substantial amount of acetone was detected. NMR yields of **10b** and recovery of **9b** were 55% and 7%, respectively (triphenylmethane was used as an internal standard). [e] A small amount of acetone (ca. 2%) was detected.

Scheme 2



[a] Reaction conditions: (a) I_2, MeOH, reflux; (b) BnBr, NaH, Bu_4NI, DMF; (c) *m*-CPBA, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (d) H_2, Pd/C

demonstrated in the hydroformylation of **4b** and **6b** in which **5b** was obtained in much higher ee from **4b** than from **6b** using (*R*,*S*)-**1b** as a ligand. On the contrary, the enantiomeric excess of **5b** was higher from **6b** using (*R*,*S*)-**1a** (*vide supra*).

Another notable feature is that the (*R*,*S*)-**1b**−Rh(I) complex has a higher catalytic activity than the (*R*,*S*)-**1a**−Rh(I) complex for most of the substrates employed. This fact shows that the steric hindrance of (*R*,*S*)-**1b** does not retard the reaction.[14] Finally, undesirable side reactions such as a formation of oligomeric materials during the hydroformylation of **4a** and cleavage of the acetal moiety during hydroformylation of **9b** were suppressed using (*R*,*S*)-**1b** as a ligand. The latter result indicates a lower Lewis acidity of the (*R*,*S*)-**1a**−Rh(I) complex than that of the (*R*,*S*)-**1a**−Rh(I) complex.

Conclusion

Promising results were obtained from the asymmetric hydroformylation of heterocyclic olefins catalyzed by phosphine−phosphite−Rh(I) complexes. Especially, excellent enantioselectivity was achieved for *N*-(*tert*-butoxycarbonyl)-2-pyrroline. The enantioselectivity was improved using (*R*,*S*)-**1b** for the reaction of the sterically small substrates such as **4a**−**c**. This difference can be attributed to the more crowded chiral environment provided by (*R*,*S*)-**1b**. In addition, the catalytic activity was improved and the side reactions were suppressed using (*R*,*S*)-**1b** as a ligand. This feature of (*R*,*S*)-**1b** should be important for the effective hydroformylation of the compounds with sensitive functional groups, such as heterocyclic olefins employed in this study. The present hydroformylation provides a new approach toward the stereocontrolled synthesis of natural products possessing a heterocycle moiety.

Experimental Section

General Remarks. All manipulations of the oxygen- and moisture-sensitive materials were conducted under a purified argon atmosphere (deoxygenated by BASF-Catalyst R3−11 at 80 °C and dried by molecular sieves 3A) using standard Schlenk techniques.

Chemicals. Solvents were purified by distillation under argon after drying over suitable drying agents as follows: sodium benzophenone ketyl (benzene, toluene, ether, and THF); phosphorus pentoxide (hexane and CH_2Cl_2); magnesium alkoxides (methanol and ethanol); and calcium hydride (DMF). Chloroform-*d* and benzene-d_6 for the NMR spectroscopy of oxygen- and moisture-sensitive materials were distilled over P_2O_5 ($CDCl_3$) or Na−K alloy (C_6D_6) and were vacuum-transferred into an NMR tube prior to use. Triethylamine was distilled over CaH_2. Acetic anhydride was distilled over molecular sieves 3A. Commercial reagents such as 2,3-dihydrofuran (**6a**) and *cis*-4,7-dihydro-1,3-dioxepin (**9a**) were used without further purification. 2,5-Dihydrofuran (**4a**) was distilled over molecular sieves 3A. *N*-(*tert*-Butoxycarbonyl)-2-pyrroline (**6b**)[6a] and *cis*-2,2-dimethyl-4,7-dihydro-1,3-dioxepin (**9b**)[15] were prepared according to the literature methods. (*R*,*S*)-BINAPHOS [(*R*,*S*)-**1a**] was prepared by the known procedure.[8a,g] Commercial $Rh(acac)(CO)_2$ (Aldrich) was used as received.

(*S*)-3,3′-Dimethyl-1,1′-binaphthalene-2,2′-dioxychlorophosphine [(*S*)-3]. A mixture of (*S*)-2,2′-dihydroxy-3,3′-dimethyl-1,1′-binaphthyl[16] (3.0 g, 9.5 mmol) and phosphorus trichloride (25 g, 0.18 mol) was heated at reflux under argon overnight. The excess PCl_3 in the reaction mixture was removed under reduced pressure. The last trace of PCl_3 in the residue was removed by azeotropic distillation with toluene (25 mL) under reduced pressure, and this procedure was repeated three times. A white solid (3.55 g, 98%) was obtained after freeze drying of the benzene solution (25 mL) of the residue. The crude product (*S*)-**3** was used for the next reaction without further purification. ^{31}P NMR (benzene-d_6) δ 175.1 (s); ^1H NMR δ 2.04 (s, 3H), 2.27 (s, 3H), 6.9−7.1 (m, 2H), 7.2−7.4 (m, 2H), 7.4−7.8 (m, 6H).

Preparation of (*R*)-2-(Diphenylphosphino)-1,1′-binaphthalen-2′-yl (*S*)-3,3′-Dimethyl-1,1′-binaphthalene-2,2′-diyl Phosphite [(*R*,*S*)-1b, (*R*,*S*)-3,3′-Me$_2$-BINAPHOS]. To a solution of (*R*)-**2**[17] (2.1 g, 4.6 mmol) and (*S*)-**3** (2.7 g, 7.1 mmol) in ether (125 mL) was dropwise added a solution of triethylamine (1.0 mL, 7.2 mmol) in ether (25 mL) at 0 °C. The resulting mixture was stirred at this temperature for 1 h and

(14) van Leeuwen reported the rhodium-catalyzed hydroformylation of less reactive olefins under mild conditions using the bulky phosphite, tris(*o*-*tert*-butylphenyl) phosphite. van Leeuwen, P. W. N. M.; Roobeek, C. F. *J. Organomet. Chem.* **1983**, *258*, 343.

(15) Elliott, W. J.; Fried, J. *J. Org. Chem.* **1976**, *41*, 2469.

(16) Peacock, S. S.; Walba, D. M.; Gaeta, F. C. A.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 2043.

(17) (a) Kurz, L.; Lee, G.; Morgans, D., Jr.; Waldyke, M. J.; Ward, T. *Tetrahedron Lett.* **1990**, *31*, 6321. (b) Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945.

Table 4. ^{31}P and ^{1}H NMR Spectral Data of the Complexes $RhH(CO)_2$(phosphine−phosphite) 15−17[a]

complex	ligand	δ P^a	J{P^a−H}, Hz	J{P^a−Rh}, Hz	δ P^b	J{P^b−H}, Hz	J{P^b−Rh}, Hz	J{P^a−P^b}, Hz	δ H	J{H−Rh}, Hz
15	(*R,S*)-**1b**	27.96	21.1	119.1	179.75	139.4	190.7	21.4	−8.94	9.2
16	(*R,S*)-**1a**	26.92	23.2	119.0	184.86	159.9	181.6	39.7	−8.85	9.8
17	(*R,R*)-**1a**	30.26	33.6	119.8	179.52	134.3	193.0	32.8	−9.08	9.1

[a] NMR Spectra were taken in C_6D_6.

then at room temperature for 24 h. The reaction was quenched with cold water (150 mL). The phases were separated, and the aqueous layer was extracted with ether (100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/CH_2Cl_2 = 3/2 → 1/1) to give (*R,S*)-**1b** (3.59 g, 98%) as a white solid. Mp 163−165 °C dec; ^{31}P NMR ($CDCl_3$) δ −13.60 (d, J = 22.9 Hz), 141.83 (d); (C_6D_6) δ −13.32 (d, J = 24.4 Hz), 142.35 (d); ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 3H), 2.29 (s, 3H), 6.76 (d, J = 8.24 Hz, 1H), 6.85−7.5 (m, 23H), 7.65−8.0 (m, 7H), 8.00 (d, J = 8.90 Hz, 1H); (C_6D_6) δ 2.03 (s, 3H), 2.17 (s, 3H), 6.7−7.8 (m, 31H), 7.87 (d, J = 8.91 Hz, 1H); $[\alpha]^{22}_D$ = +410 (*c* 0.92, toluene). Anal. Calcd for $C_{54}H_{38}O_3P_2$: C, 81.40; H, 4.81. Found: C, 81.44; H, 4.63.

Preparation of *N*-(*tert*-Butoxycarbonyl)-3-pyrroline (4b). To a solution of 3-pyrroline[18] (5.0 g, 72 mmol) in CH_2Cl_2 (150 mL) was slowly added di-*tert*-butyl dicarbonate (17 g, 78 mmol) at 0 °C. The resulting solution was stirred overnight at room temperature. The solution was concentrated, and then the residue was distilled under reduced pressure to give **4b** as a colorless oil (8.5 g, 69%). ^{1}H NMR ($CDCl_3$)[6a] δ 1.48 (s, 9H), 4.0−4.2 (m, 4H), 5.7−5.9 (m, 2H); ^{13}C NMR δ 28.5, 52.8, 53.1, 79.2, 125.7, 125.8, 154.3.

Preparation of *N*-Acetyl-3-pyrroline (4c). Compound **4c** was prepared according to the literature method[19] with the slight modification as follows: A 100-mL two-necked flask was charged with 3-pyrroline[18] (2.94 g, 42.5 mmol), potassium carbonate (6.5 g, 47 mmol), and benzene (30 mL). To this was dropwise added a solution of acetic anhydride (4.1 mL, 43 mmol) in benzene (10 mL) and then the whole stirred at reflux temperature for 5.5 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated, and the residue was sublimed under reduced pressure to give **4c** (3.74 g, 79%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 4.24 (s, 4H), 5.7−5.8 (m, 1H), 5.8−5.9 (m, 1H); ^{13}C NMR δ 22.1, 52.7, 54.1, 124.9, 126.5, 168.9.

Hydroformylation of 2,5-Dihydrofuran (4a). A Typical Procedure for the Asymmetric Hydroformylation at High Pressure. In a 20-mL Schlenk tube were placed 2,5-dihydrofuran (**4a**) (328 mg, 4.68 mmol) and benzene (0.7 mL). The solution was degassed by three freeze-thaw cycles and transferred by a cannula into another 20-mL Schlenk tube containing $Rh(acac)(CO)_2$ (3.1 mg, 0.012 mmol) and (*R,S*)-3,3′-Me_2-BINAPHOS (39.6 mg, 0.0497 mmol). The resulting solution was degassed again by two freeze-thaw cycles and then transferred into a 50-mL stainless-steel autoclave. Carbon monoxide (50 atm) and hydrogen (50 atm) were charged, and the solution was stirred for 41 h at 40 °C. Conversion and selectivity of the reaction were determined by ^{1}H NMR analysis of the crude reaction mixture without evaporation of the solvent: ^{1}H NMR of **5a** ($CDCl_3$) δ 2.0−2.25 (m, 2H), 2.9−3.1 (m, 1H), 3.65−3.8 (m, 1H), 3.8−3.9 (m, 2H), 4.05 (dd, J = 9.24, 4.62 Hz, 1H), 9.61 (d, J = 2.64 Hz, 1H); ^{13}C NMR δ 26.5, 51.1, 67.3, 68.0, 201.0. Absence of tetrahydro-2-furancarbaldehyde (**7a**) was also confirmed by GLC analysis (PEG 20 M, 100 °C, He 1 kg cm^{-2}).

Hydroformylation of 2,5-Dihydrofuran (4a) at 1 atm. In a 20-mL Schlenk tube were placed 2,5-dihydrofuran (**4a**) (332 mg, 4.74 mmol) and benzene (0.7 mL). The solution was degassed by three freeze-thaw cycles and transferred by cannula into another 20-mL Schlenk tube containing $Rh(acac)(CO)_2$ (3.1 mg, 0.012 mmol) and (*R,S*)-3,3′-Me_2-BINAPHOS (39.0 mg, 0.0489 mmol). The resulting solution was degassed again by two freeze-thaw cycles, and finally the Schlenk tube was refilled with H_2/CO from a rubber balloon. The solution was stirred for 24 h at 40 °C. The reaction mixture was analyzed as described above.

Determination of Absolute Configuration and Enantiomeric Excess of 5a. The reaction mixture was diluted with acetone and cooled with an ice bath. To this was slowly added Jones reagent, and the mixture was stirred at room temperature overnight. The reaction mixture was treated with $NaHSO_3$. After the orange color disappeared, the insoluble material was filtered off. After the filtrate was concentrated, the residue was diluted with brine and extracted three times with ether. The combined organic layers were washed twice with brine, dried over $MgSO_4$, and then concentrated to give the corresponding carboxylic acid: ^{1}H NMR ($CDCl_3$) δ 2.1−2.3 (m, 2H), 3.0−3.2 (m, 1H), 3.8−4.0 (m, 2H), 4.00 (d, J = 6.93 Hz, 2H), 10.34 (br s, 1H). The crude acid was dissolved in ether and treated with ethereal diazomethane. Distillation in a Kugelrohr apparatus afforded the methyl ester: ^{1}H NMR ($CDCl_3$) δ 2.0−2.3 (m, 2H), 3.0−3.2 (m, 1H), 3.71 (s, 3H), 3.75−4.05 (m, 4H); $[\alpha]^{22}_D$ = +14.1 (*c* 1.12, MeOH) at 63% ee. Enantiomeric excess was determined by ^{1}H NMR spectroscopy using $Eu(hfc)_3$ as the chiral shift reagent ((*R*)-methyl tetrahydro-3-furoate δ 4.40, (*S*)-methyl tetrahydro-3-furoate δ 4.43). The absolute configuration of the major enantiomer of **5a** was determined to be *R* by comparing the optical rotation of the corresponding alcohol derived by $LiAlH_4$ reduction of the methyl ester: $[\alpha]^{22}_D$ = +18.9 (*c* 1.16, MeOH) (lit.[20] (*S*)-3-hydroxymethyltetrahydrofuran $[\alpha]^{23}_D$ = +24.8 (*c* 2.14, MeOH))

(*R*)-*N*-(*tert*-Butoxycarbonyl)pyrrolidine-3-carbaldehyde [(*R*)-5b]: bp 90 °C (bath temp, 0.1 mmHg). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.0−2.3 (m, 2H), 2.9−3.1 (m, 1H), 3,2−3.8 (m, 4H), 9.69 (d, J = 1.65 Hz, 1H); ^{13}C NMR[21] δ 25.2, 25.7, 28.4, 44.7, 45.0, 49.5, 50.4, 79.5 154.2, 200.5; $[\alpha]^{24}_D$ = −21.2 (*c* 1.61, THF) at 53% ee. Anal. Calcd for $C_{10}H_{17}O_3N$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.51; H, 8.56; N, 7.07.

Determination of Enantiomeric Excess of 5b and 7b. The reaction mixture (hydroformylation of **4b** or **6b**) was diluted with absolute THF (2.0 mL) and cooled with an ice bath. To this was carefully added two equivalents of borane−THF complex (1 M solution) under argon. The mixture was stirred at 0 °C for 2 h and at room temperature overnight. The reaction mixture was cooled to 0 °C, and then water and potassium carbonate were added. The aqueous mixture was extracted three times with ethyl acetate. The combined organic layers were washed three times with brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by bulb-to-bulb distillation to give the corresponding alcohols as a colorless oil. The isomers can be separated by silica-gel column chromatography (hexane/AcOEt = 1/1). *N*-(*tert*-Butoxycarbonyl)pyrrolidine-2-methanol:[10c] $[\alpha]^{22}_D$ = −52.7 (*c* 1.11, MeOH) at 97% ee (lit.[10a] (*S*)-*N*-(*tert*-butoxycarbonyl)-pyrrolidine-2-methanol $[\alpha]^{24.5}_D$ = −53.9 (*c* 1.04, MeOH)). *N*-(*tert*-Butoxycarbonyl)pyrrolidine-3-methanol: bp 130 °C (bath temp, 0.1 mmHg). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 1.6−1.8 (m, 1H), 1.9−2.1 (m, 1H), 2.05 (br s, 1H), 2.40 (sep, J = 7.26 Hz, 1H), 3.13 (dd, J = 10.89, 7.26 Hz, 1H), 3.2−3.7 (m, 5H); ^{13}C NMR[21] δ 27.4, 28.1, 28.5, 40.4, 41.3, 45.0, 45.4, 48.2, 48.7, 64.3, 79.2, 154.7; $[\alpha]^{23}_D$ = +9.6 (*c* 1.05, MeOH) for 44% ee of (*R*)-*N*-(*tert*-butoxycarbonyl)pyrrolidine-3-methanol. Anal.

(18) (a) Warmus, J. S.; Dilley, G. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 270. (b) Meyers, A. I.; Warmus, J. S.; Dilley, G. J. *Org. Synth.* **1995**, *73*, 246.

(19) Oida, S.; Kumano, H.; Ohashi, Y.; Ohki, E. *Chem. Pharm. Bull.* **1970**, *18*, 2478.

(20) Brown, H. C.; Gupta, A. K.; Rangaishenvi, M. V.; Vara Prasad, J. V. N. *Heterocycles* **1989**, *28*, 283.

(21) Two different sets of ^{13}C chemical shifts were observed for some carbon atoms of each rotameric pair.

Calcd for $C_{10}H_{19}O_3N$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.94; H, 9.80; N, 6.94. Enantiomeric excess was determined by HPLC analysis of the corresponding (*R*)-MTPA ester (Daicel Chiralcel OD, hexane/2-propanol = 99/1, 1.0 mL min^{-1} for *N*-(*tert*-butoxycarbonyl)pyrrolidine-2-methanol; hexane/2-propanol = 49/1, 0.5 mL min^{-1} for *N*-(*tert*-butoxycarbonyl)-pyrrolidine-3-methanol).

Determination of Absolute Configuration of (−)-5b. Hydroformylation of **4b** (675 mg, 3.99 mmol) was carried out as described above using (*R,S*)-**1b**. The reaction mixture was diluted with DMF (16 mL). To this was added PDC (4.5 g, 12 mmol), and the mixture was stirred for 20 h at room temperature. The reaction mixture was diluted with water (300 mL) and extracted with ether (2 × 150 mL). The aqueous phase was acidified with concd HCl to pH 4 and further extracted with ether (2 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL), concentrated to ca. 80 mL, and extracted with an aqueous solution of $Na_3PO_4 \cdot 12H_2O$ (4.5 g/100 mL). The extract was acidified to pH 4 with concd HCl at 0 °C and then stirred at this temperature for 3 h. The precipitates were collected and dried over P_2O_5: yield 318 mg (47% from **4b**). $[\alpha]^{21}_D = -12.1$ (*c* 2.33, EtOH) (lit.[22] (*R*)-*N*-(*tert*-butoxycarbonyl)pyrrolidine-3-carboxylic acid $[\alpha]^{25}_D = -16.0$ (*c* 2.4, EtOH)).

(−)-*N*-Acetylpyrrolidine-3-carbaldehyde [(−)-5c]: bp 105 °C (bath temp, 0.1 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 1.5H), 2.04 (s, 1.5H), 2.0−2.15 (m, 1.5H), 2.2−2.45 (m, 0.5H), 2.9−3.1 (m, 1.0H), 3.3−3.6 (m, 3.0H), 3.7−3.9 (m, 1.0H), 9.62 (d, J = 0.99 Hz, 1.0H); ^{13}C NMR[21] δ 22.3, 22.4, 24.8, 25.9, 44.4, 44.8, 45.8, 46.2, 49.0, 50.7, 169.1, 169.3, 199.6, 200.1; $[\alpha]^{22}_D = -27.2$ (*c* 3.40, THF) at 56% ee. Anal. Calcd for $C_7H_{11}O_2N$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.58; H, 7.98; N, 9.80.

Determination of Enantiomeric Excess of 5c. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethanol (3 mL). To this was added 1.0 equiv of $NaBH_4$ at −78 °C, and the mixture was stirred overnight with gradually warming to room temperature to preclude the racemization of **5c**. The reaction mixture was cooled to 0 °C and carefully treated with 1 N HCl. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was distilled under reduced pressure to give *N*-acetylpyrrolidine-3-methanol: bp 160 °C (bath temp, 0.1 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.6−1.9 (m, 1H), 1.9−2.2 (m, 1H), 2.04 (s, 1.5H), 2.05 (s, 1.5H), 2.3 (br s, 1H), 2.35−2.6 (m, 1H), 3.25−3.35 (m, 1H), 3.35−3.8 (m, 5H); ^{13}C NMR[21] δ 22.3, 22.4, 26.8, 28.4, 39.9, 41.6, 44.9, 46.8, 48.1, 50.1, 64.0, 64.1, 169.4; $[\alpha]^{22}_D = +17.1$ (*c* 0.65, MeOH) at 65% ee. Anal. Calcd for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.29; H, 9.00; N, 9.71. Enantiomeric excess was determined by ^{19}F NMR spectroscopy of the corresponding (*R*)-MTPA ester **8** in $CDCl_3$ (δ 4.54 and 4.58; another rotamer δ 4.71, see text and Figure 1). The chemical shift of ^{19}F NMR is referred to CF_3COOH as δ 0.00. When the reduction was carried out at higher temperature, racemization of **5c** took place to some extent.

(−)-1,3-Dioxepane-5-carbaldehyde [(−)-10a]: bp 60 °C (bath temp, 1.5 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.87 (dddd, J = 14.51, 8.91, 5.94, 3.63 Hz, 1H), 2.14−2.25 (m, 1H), 2.62 (qd, J = 5.28, 2.64 Hz, 1H), 3.73 (ddd, J = 12.20, 8.91, 2.64 Hz, 1H), 3.85 (ddd, J = 12.20, 5.28, 3.62 Hz, 1H), 4.04 (dd, J = 12.20, 2.64 Hz, 1H), 4.27 (dd, J = 12.20, 4.62 Hz, 1H), 4.74 and 4.71 (ABq, J = 4.62 Hz, 2H), 9.78 (s, 1H); ^{13}C NMR δ 28.3, 51.4, 64.7, 64.8, 94.5, 201.9; $[\alpha]^{22}_D = -41.4$ (*c* 1.91, THF) at 51% ee. Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.11; H, 7.95. The enantiomeric excess of **10a** was determined by ^{1}H NMR of the crude reaction mixture in $CDCl_3$ in the presence of Eu(hfc)$_3$ (δ 10.77 and 10.81). Distillation of the product (66% ee) (at 60 °C, 1.5 mmHg) caused a decrease in the enantiomeric excess (to 51% ee).

(*R*)-2,2-Dimethyl-1,3-dioxepane-5-carbaldehyde [(*R*)-10b]: bp 50 °C (bath temp, 1 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.33 (s, 3H), 1.6−1.8 (m, 1H), 2.0−2.2 (m, 1H), 2.4−2.6 (m, 1H), 3.6−3.8 (m, 2H), 4.00 (dd, J = 12.54, 2.31 Hz, 1H), 4.11 (dd, J = 12.54, 4.62 Hz, 1H), 9.77 (s, 1H); ^{13}C NMR δ 24.5, 24.7, 28.5, 51.4, 59.9, 60.5, 101.4, 202.5; $[\alpha]^{22}_D = -38.0$ (*c* 1.54, THF) at 67% ee. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.74; H, 8.91.

Determination of Absolute Configuration and Enantiomeric Excess of 10b. To a suspension of $NaBH_4$ (1.5 eq to **10b**) in absolute EtOH (5 mL) was added the hydroformylation reaction mixture at −10 °C. The resulting mixture was stirred for 2 h. The reaction mixture was concentrated and excess $NaBH_4$ was destroyed with water. The product was extracted three times with ether. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by bulb-to-bulb distillation to afford the corresponding alcohol as a colorless oil: bp 75 °C (bath temp, 0.1 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.34 (s, 3H), 1.4−1.6 (m, 2H), 1.6−1.9 (m, 2H), 3.58 (d, J = 6.26 Hz, 2H), 3.6−3.8 (m, 4H); ^{13}C NMR δ 24.8, 32.1, 41.4, 60.2, 63.4, 63.8, 101.2; $[\alpha]^{21}_D = +2.3$ (*c* 1.47, MeOH) at 63% ee. Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.86; H, 10.17. The enantiomeric excess was determined by HPLC analysis of the corresponding (*R*)-MTPA ester (Daicel Chiralcel OJ, UV = 230 nm, hexane/2-propanol = 97/3, 1 mL·min^{-1}). Absolute configuration of **10b** was confirmed by converting it into (*R*)-**14** (*vide infra*).

(3*R*)-3-(Hydroxymethyl)-2-methoxytetrahydrofuran (11). To a 1% (w/v) solution of iodine in methanol (60 mL) was added **10b** (2.5 g, 16 mmol). The resulting solution was heated at reflux for 4 h. The reaction mixture was treated with $Na_2S_2O_3$ and concentrated. Chloroform (60 mL) was added to the residue, and the insoluble solid was removed by filtration. The filtrate was concentrated and distilled in a Kugelrohr apparatus to give **11** (1.9 g, 94%) as a cis/trans mixture: bp 70 °C (bath temp, 1 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.5−1.7 (m, 1H), 1.9−2.2 (m, 2H), 2.3−2.5 (m, 1H), 3.35 (s, 2.25H), 3.37 (s, 0.75 H), 3.4−3.6 (m, 1H), 3.8−4.1 (m, 2H), 4.88 (d, J = 1.32 Hz, 0.75H), 4.98 (d, J = 4.95 Hz, 0.25H); ^{13}C NMR major: δ 26.6, 47.9, 54.63, 63.7, 66.3, 107.2; minor: δ 24.9, 45.2, 54.59, 60.6, 66.9, 105.8. HRMS Calcd for $C_6H_{12}O_3$: 132.0786. Found: 132.0747 (M).

(3*R*)-3-[(Benzyloxy)methyl]-2-methoxytetrahydrofuran (12). Sodium hydride (60% in mineral oil, 0.7 g, 0.02 mol) was washed with dry hexane and dried in vacuo. To this were added DMF (80 mL), **11** (1.8 g, 14 mmol), and benzyl bromide (3.4 mL, 29 mmol). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water (300 mL) and extracted three times with ether. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by silica-gel column chromatography (hexane/AcOEt = 2/1) to give **12** (2.7 g, 88%) as a cis/trans mixture. ^{1}H NMR ($CDCl_3$) δ 1.5−1.7 (m, 0.8H), 1.7−1.9 (m, 0.2H), 2.0−2.2 (m, 1H), 2.4−2.6 (m, 1H), 3.31 (s, 0.6H), 3.33 (s, 2.4 H), 3.2−3.4 (m, 1.6H), 3.4−3.5 (m, 0.2H), 3.6−3.7 (m, 0.2H), 3.8−4.0 (m, 2H), 4.51 (br s, 2H), 4.86 (d, J = 0.99 Hz, 0.8H), 4.90 (d, J = 4.62 Hz, 0.2H), 7.2−7.4 (m, 5H); ^{13}C NMR major: δ 26.8, 45.6, 54.5, 66.1, 70.9, 72.9, 107.1, 127.51, 128.3, 138.1; minor: δ 26.8, 44.4, 54.4, 66.4, 69.1, 73.0, 104.0, 127.46, 128.2, 138.4. HRMS Calcd for $C_{13}H_{18}O_3$: 222.1255. Found: 222.1389 (M), 191.1087 (M − CH_3O), 191.1019 (M − CH_3OH).

(*R*)-3-[(Benzyloxy)methyl]-tetrahydro-2-furanone [(*R*)-13]. To a solution of **12** (2.7 g, 12 mmol) in CH_2Cl_2 (45 mL) were added $BF_3 \cdot OEt_2$ (900 μL) and *m*-CPBA (80% purity, 2.9g, 13 mmol). The resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with ether (300 mL) and washed successively with 10% $Na_2S_2O_3$(aq), saturated $NaHCO_3$(aq), and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (ether) and then distilled under reduced pressure to give (*R*)-**13** (1.8 g, 72%).[11a]

(*R*)-3-(Hydroxymethyl)-tetrahydro-2-furanone [(*R*)-14]. The benzyl ether (*R*)-**13** (1.8 g, 8.7 mmol) was dissolved in ethanol (40 mL) and hydrogenated for 8 h over 10% palladium on carbon (40 mg). The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was purified by bulb-to-bulb distillation to give (*R*)-**14** (1.0 g, 99%):[11a] bp 120 °C (bath temp, 0.1 mmHg). $[\alpha]^{23}_D =$

(22) Yuki, H.; Okamoto, Y.; Kobayashi, Y. *J. Polym. Sci., Polym. Chem. Ed.* **1979**, *17*, 3867.

−11.8 (*c* 3.2, $CHCl_3$) (lit.[11a] (*R*)-3-Hydroxymethyl-tetrahydro-2-furanone $[\alpha]_D = -21.1$ (*c* 4.2, $CHCl_3$)).

Preparation of the Hydride Complex $RhH(CO)_2$[(*R,S*)-1b] (15). A solution of $Rh(acac)(CO)_2$ (5.9 mg, 0.023 mmol) and (*R,S*)-**1b** (18.2 mg, 0.0228 mmol) in benzene-d_6 (*ca.* 1 mL) was stirred under a mixture of hydrogen and carbon monoxide (1:1, 1 atm) at room temperature overnight. The resulting solution was transferred into an NMR tube under CO atmosphere (1 atm) to record the ^{31}P and ^1H NMR spectra. ^{31}P NMR (benzene-d_6) δ 27.96 (dd, $J_{Rh-P} = 119.1$ Hz, $J_{P-P} = 21.4$ Hz), 179.75 (dd, $J_{Rh-P} = 190.7$ Hz); ^1H NMR δ −8.94 (ddd, $J_{P(phosphite)-H} = 139.38$ Hz, $J_{P(phosphine)-H} = 21.14$ Hz, $J_{Rh-H} = 9.25$ Hz, 1H), 1.33 (s, 3H), 3.00 (s, 3H). The assignment of J_{P-H} values was confirmed by partially proton-decoupled ^{31}P NMR spectroscopy.

JO9624051