Synthesis of Novel Chiral Diazole Derivative Ligands for the Enantioselective Addition of Diethylzinc to Benzaldehyde

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The high-pressure-promoted reaction of epoxides with pyrazoles and imidazoles provided access to a variety of chiral diazole derivative ligands such as **11**−**23**. Furthermore, chiral pyrazoles **26** and **27**, which have a primary alcohol side chain, were also prepared from (+)-camphopyrazole **4**. Each of these chiral diazole ligands was used for the catalytic enantioselective addition of diethylzinc to benzaldehyde. The best results were obtained for **16** and **18**: 93% ee was achieved in both cases, and reversed asymmetric induction was observed. A plausible mechanism for this efficient asymmetric induction is offered on the basis of X-ray crystallographic data.

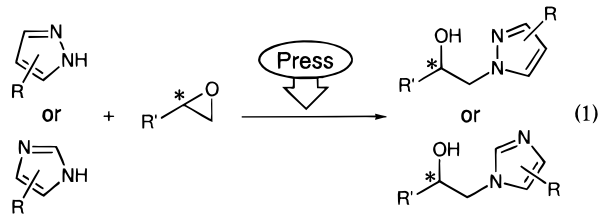
Introduction

The molecular design of enantiomerically pure chiral auxiliaries and ligands for use in asymmetric reactions is arguably one of the most important issues in modern organic chemistry.[1,2] Chiral ligands with nitrogen functionalities, such as β-amino alcohols, are one of the most attractive classes of compounds for achieving a high degree of asymmetric induction.[1−3] However, mainly due to the instability of aliphatic amino functionalities, considerable attention has recently been focused on the use of nitrogen heterocycles as their congeners. For example, chiral pyridine derivatives are frequently used in asymmetric transformations.[4] In addition, it is generally accepted that nitrogen heterocycles can coordinate to both inorganic and organometallic reagents.[5]

We considered that the incorporation of a pyrazole or imidazole heterocyclic unit into certain chiral molecules might provide new chiral ligands, since the potential utility of pyrazoles and imidazoles as efficient coordinating ligands is well-established in inorganic chemistry.[6] However, a survey of the literature revealed only the limited use of chiral diazole derivatives for asymmetric synthesis.[7] We report here the efficient construction of optically active pyrazole and imidazole derivatives and their use in the catalytic asymmetric reaction of diethylzinc to benzaldehyde.[8]

Results and Discussion

In our previous paper on the use of high pressure in organic synthesis,[9] we reported that epoxide-opening reactions with several nitrogen heterocycles proceeded cleanly at high pressure without the use of any acid or base catalysts.[10] On the basis of this general strategy, an efficient synthetic route can easily be designed to obtain chiral diazole derivatives by applying the high-pressure-promoted *N*-alkylation of pyrazoles or imidazoles to optically active epoxides (eq 1).[11] The results



are summarized in Table 1.[12]

Treatment of pyrazole **1** with (*R*)-(+)-styrene oxide (**5**) or (*R*)-(+)-2,3,4,5,6-pentafluorostyrene oxide (**6**) in acetonitrile at 10 kbar and 65 °C for 3 days produced the

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(6) (a) Trofimenko, S. *Chem. Rev.* **1972**, *72*, 497. (b) Sundberg, R. J.; Martin, R. B. *Chem. Rev.* **1974**, *74*, 471. (c) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Potts, K. T., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, Chapter 4.04. (d) Reedijk, J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1986; Vol. 2, Chapter 13.2. (e) Trofimenko, S. *Prog. Inorg. Chem.* **1986**, *34*, 115.
(7) Brunner, H.; Singh, U. P.; Boeck, T.; Altmann, S.; Scheck, T.; Wrackmeyer, B. *J. Organomet. Chem.* **1993**, *443*, C16. Bovens, M.; Togni, A.; Venanzi, L. M. *J. Organomet. Chem.* **1993**, *451*, C28. Kashima, C.; Fukuchi, I.; Takahashi, K.; Hosomi, A. *Heterocycles* **1994**, *38*, 1407. Kashima, C.; Fukuchi, I.; Hosomi, A. *J. Org. Chem.* **1994**, *59*, 7821. Popov, S. A.; Tkachev, A. V. *Tetrahedron: Asymmetry* **1995**, *6*, 1013. Schnyder, A.; Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 931. Christenson, D. L.; Tokar, C. J.; Tolman, W. B. *Organometallics* **1995**, *14*, 2148. Kashima, C.; Takahashi, K.; Hosomi, A. *Heterocycles* **1996**, *42*, 241. Kashima, C.; Fukuchi, I.; Takahashi, K.; Hosomi, A. *Tetrahedron* **1996**, *52*, 10335.
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(11) Epoxides are now readily available in optically pure form via chemical or biological transformations: Pfenninger, A. *Synthesis* **1986**, 89. Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437. Schurig, V.; Betschinger, F. *Chem. Rev.* **1992**, *92*, 873. Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885. Pedragosa-Moreau, S.; Archelas, A.; Furstoss, R. *Bull. Soc. Chim. Fr.* **1995**, *132*, 769.
(12) Commercially available optically active epoxides were used throughout this work, and all high-pressure reactions were conducted with a Hikari-Koatsu HR-15-B3 apparatus. Bis-epoxide **7** was prepared from D-mannitol according to the literature procedure: Wiggins, L. F. *J. Chem. Soc.* **1946**, 384. Le Merrer, Y.; Dureault, A.; Gravier, C.; Languin, D.; Depezay, J. C. *Tetrahedron Lett.* **1985**, *26*, 319.

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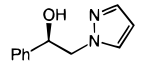
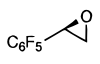
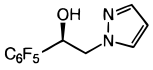
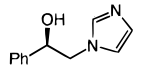
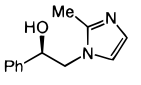
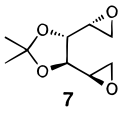
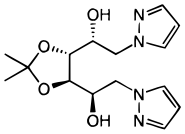
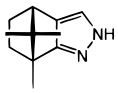
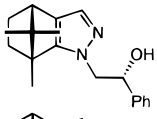
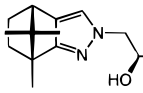
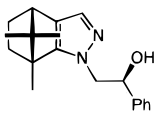
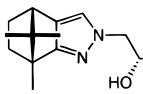
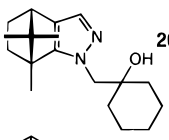
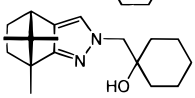
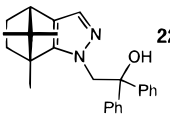
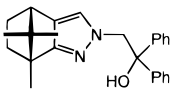
Table 1. Preparation of Diazole Derivative Ligands under High-Pressure Conditions[a]

entry	substrate	epoxide	product(s) (yield, %)[b]
1	 **1**	 **5**	 **11** (50)
2	**1**	 **6**	 **12** (76)
3	 **2**	**5**	 **13** (60)
4	 **3**	**5**	 **14** (40)
5	**1**	 **7**	 **15** (40)
6[c]	 **4**	**5**	 **16** (41)  **17** (50)
7[c]	**4**	 **8**	 **18** (36)  **19** (49)
8[c]	**4**	 **9**	 **20** (26)  **21** (43)
9[c]	**4**	 **10**	 **22** (12)  **23** (45)

[a] Unless otherwise noted, all reactions were performed in MeCN at 10 kbar and 65 °C for 3 days. [b] Isolated yield. [c] In THF in the presence of 1 equiv of *n*-Bu_4NF.

desired adducts **11**[10b] (mp 153−154 °C (from MeOH); $[\alpha]^{27}_D$ −10.0° (*c* 1.0, MeOH)) and **12** (mp 132−133.5 °C (from Et_2O−hexane); $[\alpha]^{25}_D$ +34.3° (*c* 1.0, EtOH)) in yields of 50 and 76%, respectively (Table 1, entries 1 and 2).[13]

Similarly, imidazole homologs **13**[10b] and **14**[10b] as well as bis-pyrazole ligand **15** with C_2-symmetry were prepared in moderate yields (Table 1, entries 3−5).

We further extended the above technique to (+)-camphopyrazole (**4**)[14] as a chiral pyrazole component. In this case, the addition of tetra-*n*-butylammonium fluoride as a mild base was needed to facilitate the desired epoxide-opening reaction. Thus, a stoichiometric mixture of **4** and **5** in the presence of 1.0 equiv of tetra-*n*-butylammonium fluoride in THF was pressurized as above to give a regioisomeric mixture of **16** (mp 150.5−152 °C (from Et_2O−hexane); $[\alpha]^{25}_D$ +65.7° (*c* 0.35, EtOH)) and **17** ($[\alpha]^{25}_D$ +47.8° (*c* 1.38, EtOH)). These products were separable by silica gel column chromatography, and the yields were determined to be 41 and 50%, respectively (Table 1, entry 6).[15] The structures of these compounds were determined by ^1H and ^{13}C NMR spectroscopy.[16] For compound **16**, the proton on the pyrazole ring appeared at 7.16 (s) ppm and the carbons appeared at 128.5 (C-3a), 131.5 (C-3), and 154.3 (C-7a) ppm, indicative of a 1-substituted pyrazole derivative. On the other hand, the 2-substituted isomer **17** showed the proton on the pyrazole ring at 6.73 (s) ppm and the carbons at 122.6 (C-3), 126.2 (C-3a), and 166.8 (C-7a) ppm. Similarly, the reaction of (*S*)-(−)-styrene oxide (**8**) produced another set of regioisomers **18** and **19** in good combined yields (Table 1, entry 7).

To confirm unambiguously the structures of these products, particularly **16** and **18**, and also to predict their coordinating behavior around the pyrazole ring, X-ray crystallographic structure analyses were performed.[17] The ORTEP depiction of the two molecules is shown in Figure 1. Evidently, **16** and **18** reflect a completely different asymmetric environment in which the stereogenic carbon center bearing a hydroxyl function plays the central role. Thus, **16** has a pseudoaxial hydroxyl group at the benzylic carbon and might be able to coordinate with guest molecules under the plane of a camphor framework, whereas in **18** the hydroxyl group spreads out to the upper side, which produces the steric constraint that the reagent approaches from the top.[18] The inherent difference in these molecules will become apparent after an investigation of asymmetric synthesis (*vide infra*). Interestingly, in the solid state, each molecule was self-assembled through hydrogen bonding to form an infinite "helical" network with left-handed helicity for **16** and right-handed helicity for **18** (Figure 2).[19] The intermolecular hydrogen bond distance between N(1) and O(1) is 2.80 Å for **16** and 2.79 Å for **18**.

(13) For a related work at normal pressure, see: Elguero, J.; Fruchier, A.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1969**, 2064.

(14) Jacquier, R.; Maury, G. *Bull. Soc. Chim. Fr.* **1967**, 295. Nagai, S.-I.; Oda, N.; Ito, I.; Kudo, Y. *Chem. Pharm. Bull.* **1979**, *27*, 1771. Brunner, H.; Scheck, T. *Chem. Ber.* **1992**, *125*, 701. LeCloux, D. D.; Tokar, C. J.; Osawa, M.; Houser, R. P.; Keyes, M. C.; Tolman, W. B. *Organometallics* **1994**, *13*, 2855.

(15) It has been known that **4** exists as a mixture of two tautomers in which the N2−H tautomer is the major component.[6c] All efforts to improve the regioselectivity in this reaction failed.

(16) House, D. A.; Steel, P. J.; Watson, A. A. *Aust. J. Chem.* **1986**, *39*, 1525. Watson, A. A.; House, D. A.; Steel, P. J. *Polyhedron* **1989**, *8*, 1345. Llamas-Saiz, A. L.; Foces-Foces, C.; Sobrados, I.; Elguero, J.; Meutermans, W. *Acta Crystallogr.* **1993**, *C49*, 724.

(17) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinate can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(18) It should be emphasized, however, that this argument is only based on solid-state conformational preferences, which may be quite different in solution.

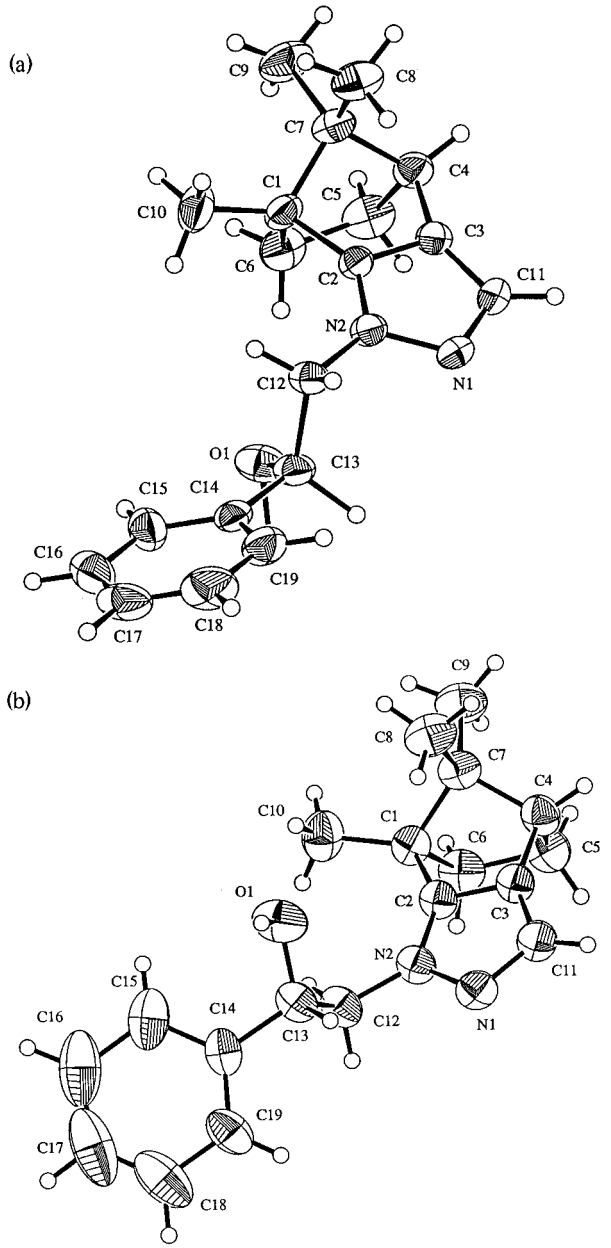


Figure 1. ORTEP depiction of the chiral pyrazole ligands **16** (a) and **18** (b).

The usefulness of this method was also demonstrated in the synthesis of chiral pyrazoles **20**−**23**, which have a tertiary alcohol side chain, by the action of nonchiral 1,1-disubstituted epoxides **9**[20] and **10**[20] (Table 1, entries 8 and 9). Furthermore, to confirm the steric effect around the hydroxyl group, the primary alcohol derivatives **26** and **27** were also prepared straightforwardly from **4** in a two-step sequence: *N*-alkylation with ethyl bromoacetate followed by reduction with lithium aluminum hydride (Scheme 1). The assignments of these products were mainly based on a comparison of their ^{13}C NMR data to those of **16** and **17**.

(19) For a similar finding, see: Barz, M.; Herdtweck, E.; Thiel, W. R. *Tetrahedron: Asymmetry* **1996**, *7*, 1717. See also: MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383. Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229. Bernstein, J.; Davis, R. E.; Shimoni, L.; Chang, N.-L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1555.

(20) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353; *Organic Syntheses;* Wiley: New York, 1973; Collect. Vol. V, p 755.

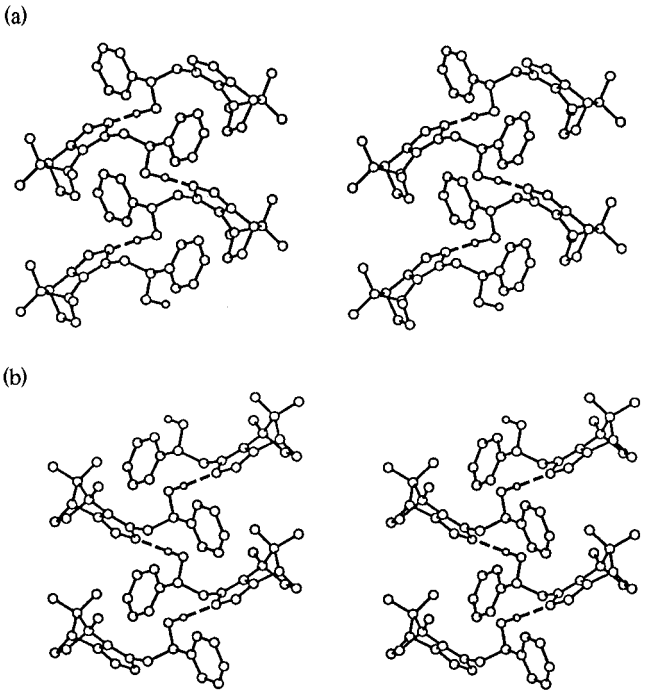


Figure 2. ORTEP stereodrawing of the chiral pyrazole ligands **16** (a) and **18** (b) showing the intermolecular hydrogen bond between N(1) and O(1).

With a variety of chiral diazole derivative ligands in hand, we then proceeded to evaluate their feasibility for use in catalytic asymmetric transformations. As a convenient tool for this purpose, the enantioselective addition of diethylzinc to benzaldehyde was examined.[21] On the basis of the analogy to the use of chiral pyridine catalysts,[22] we expected that almost comparable activity should be achieved. In general, the reaction was carried out in toluene at room temperature using 4 equiv of diethylzinc in the presence of 0.2 equiv of the chiral ligand, and the results are summarized in Table 2.

As expected, relatively high enantioselectivity (83% ee) was obtained when the chiral pyrazole ligand **11**, a common skeleton in our molecular design, was used as a catalyst (Table 2, entry 1), while the corresponding imidazole homologues **13** and **14** were all ineffective (Table 2, entries 6 and 7). These results can be explained by considering the favorable coordination structure of **11** for forming a rigid 6-membered organozinc intermediate. In contrast to our previous results,[23] the addition of titanium(IV) salts to the present catalytic system significantly retarded the desired asymmetric reactions (Table 2, entries 3 and 4). The unexpectedly lower

(21) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. Soai, K.; Niwa S. *Chem. Rev.* **1992**, *92*, 833. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

(22) For some recent examples, see: Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982. Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205. Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron: Asymmetry* **1990** *1*, 843. Chelucci, G.; Soccolini, F. *Tetrahedron: Asymmetry* **1992** *3*, 1235. Conti, S.; Falorni, M.; Giacomelli, G.; Soccolini, F. *Tetrahedron* **1992**, *48*, 8993. Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169. Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191. Ishizaki, M.; Hoshino, O. *Chem. Lett.* **1994**, 1337. Baker, R. W.; Rea, S. O.; Sargent, M. V.; Schenkelaars, E. M. C.; Skelton, B. W.; White, A. H. *Tetrahedron: Asymmetry* **1994**, *5*, 45. Ishizaki, M.; Fujita, K.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 411. Ishizaki, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1901. Macedo, E.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 549. Shibata, T.; Choji, K.; Morioka, H.; Hayase, T.; Soai, K. *J. Chem. Soc., Chem. Commun.* **1996**, 751.

Scheme 1

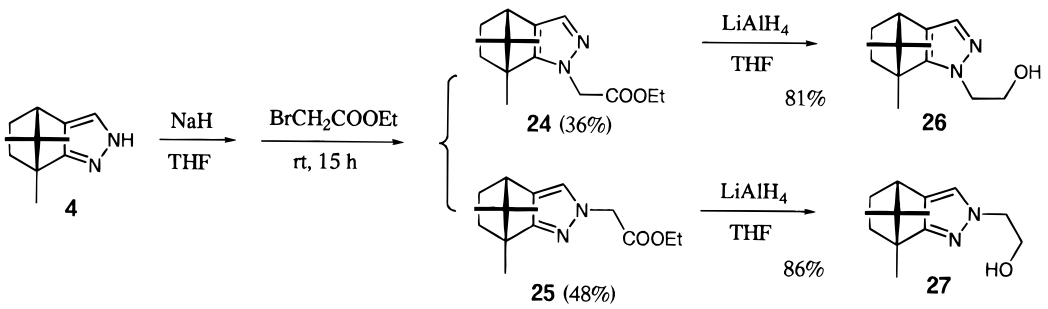
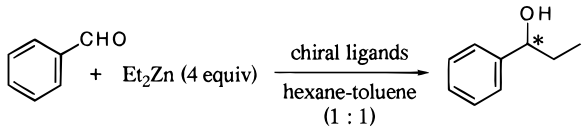


Table 2. Enantioselective Addition of Diethylzinc to Benzaldehyde in the Presence of Chiral Ligands[a]



entry	ligand (equiv)	time (day)	yield[b] (%)	ee[c] (%)	abs confign[d]
1	**11** (0.2)	5	95	83	R
2[e]	**11** (0.2)	3	88	68	R
3[f]	**11** (0.2)	1	70	18	R
4[g]	**11** (0.2)	1	84	17	R
5	**12** (0.2)	2	70	57	R
6	**13** (0.2)	6	80	5	S
7	**14** (0.2)	4	95	7	S
8	**15** (0.1)	1	66	2	S
9	**15** (0.2)	1	74	3	S
10	**16** (0.2)	2	90	93	R
11	**16** (0.1)	2	95	91	R
12	**16** (0.05)	6	93	87	R
13	**17** (0.2)	1	73	69	R
14	**18** (0.2)	2	99	93	S
15	**18** (0.1)	2	97	91	S
16	**18** (0.05)	6	82	88	S
17	**19** (0.2)	1	77	53	S
18	**20** (0.2)	2	95	9	S
19	**21** (0.2)	2	96	17	S
20	**22** (0.2)	4	77	19	S
21	**23** (0.2)	2	95	1	R
22	**26** (0.2)	2	90	21	S
23	**27** (0.2)	2	90	2	R

[a] Unless otherwise noted, all reactions were conducted at rt using 4 equiv of diethylzinc. [b] Isolated yields. [c] Determined by HPLC (DAICEL Chiralcel OB). [d] Determined from the sign of the specific rotation. [e] 2 equiv of diethylzinc was used. [f] 1.2 equiv of $Ti(OBu^t)_4$ was added. [g] 1.2 equiv of $Ti(OPr^i)_4$ was added.

efficiency of **12** might be due to the decreased stability of the transient organozinc intermediate through the electronic effect of a pentafluorophenyl ring. Remarkably, the C_2-symmetric bispyrazole ligand **15** showed no reactivity regardless of the catalytic ratio (Table 2, entries 8 and 9).

Interestingly, we found that the sterically congested ligands **16** and **18** gave the best results: 93% ee was achieved in both cases with completely opposite signs of specific rotation (Table 2, entries 10 and 14). Although the actual active species in these reactions are unclear, X-ray crystallographic analyses suggest a plausible mechanism (*vide supra*). Thus, assuming the mechanism proposed by Noyori,[21,24] the reaction in the presence of **16** derived from (*R*)-styrene oxide can proceed through the six-centered transition state **A**, in which benzaldehyde is attacked on its *re*-face to form (*R*)-1-phenyl-1-propanol, as illustrated in Figure 3.[25] On the other hand, the high *S*-enantioselectivity for **18** can be explained by the preferential attack from the *si*-face of benzaldehyde through transition state **B**. It should be noted that in either case sufficient catalytic activity of these chiral ligands was present even at a very low concentration (0.05 equiv; Table 2, entries 12 and 16), implying that there is a strongly favorable interaction between the chiral ligand and diethylzinc.

These results, together with those obtained using **11** and **12**, suggest that there is a good correlation between the absolute configuration of the chiral ligand and that of the product alcohol; *i.e.*, a ligand with an (*R*)-configuration on the hydroxyl side chain produces (*R*)-1-phenyl-1-propanol and *vice versa*. However, in view of the greater efficacy of **16** and **18** compared with **17** and **19**, we cannot discount the possibility that the double ligand effect of the camphopyrazole ring might also be crucial. Hence, it can be concluded that the transition state structures **A** and **B** have a rather rigid chairlike form due to the presence of significant steric repulsion between the bridgehead methyl group and the hydroxyphenyl side chain on nitrogen. On the other hand, the reduced catalytic activity of regioisomers **17** and **19** can be explained by assuming that they are flexible during complexation with diethylzinc (Table 2, entries 13 and 17). Ligands **20**−**23**, which have a tertiary alcohol substituent, gave even worse results (Table 2, entries 18−21): it is likely that indistinct mixing of transition state structures, such as **A** and **B**, might be involved in these systems. This is also true for the reactions using primary alcohols **26** and **27** (Table 2, entries 22 and 23).

Conclusions

In conclusion, we developed a convenient method for synthesizing a variety of chiral diazole ligands using high-pressure-promoted epoxide-opening reactions. In view of the ready accessibility and fairly mild conditions of high-pressure technology, the present method may be useful in the synthesis of other types of chiral ligands for which the usual techniques are not easily applicable. Furthermore, the novel catalytic activity of these ligands in the enantioselective addition of diethylzinc to benzaldehyde was investigated. The best results achieved with

(23) Kotsuki, H.; Nakagawa, Y.; Moriya, N.; Tateishi, H.; Ochi, M.; Suzuki, T.; Isobe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1165. See also: Nowotny, S.; Vettel, S.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 4539. Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363 and references cited therein.

(24) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832.

(25) PM3-optimized structures of the lowest energy conformations are shown. Calculations were performed by MOPAC '93 implemented in ANCHOR II, a molecular design system for SUN computers, developed by FUJITSU, Ltd., and Kureha Chemical Industry Co., Ltd., 1992. MOPAC 93: Stewart, J. J. P. Fujitsu, Ltd., Tokyo, Japan, 1993.

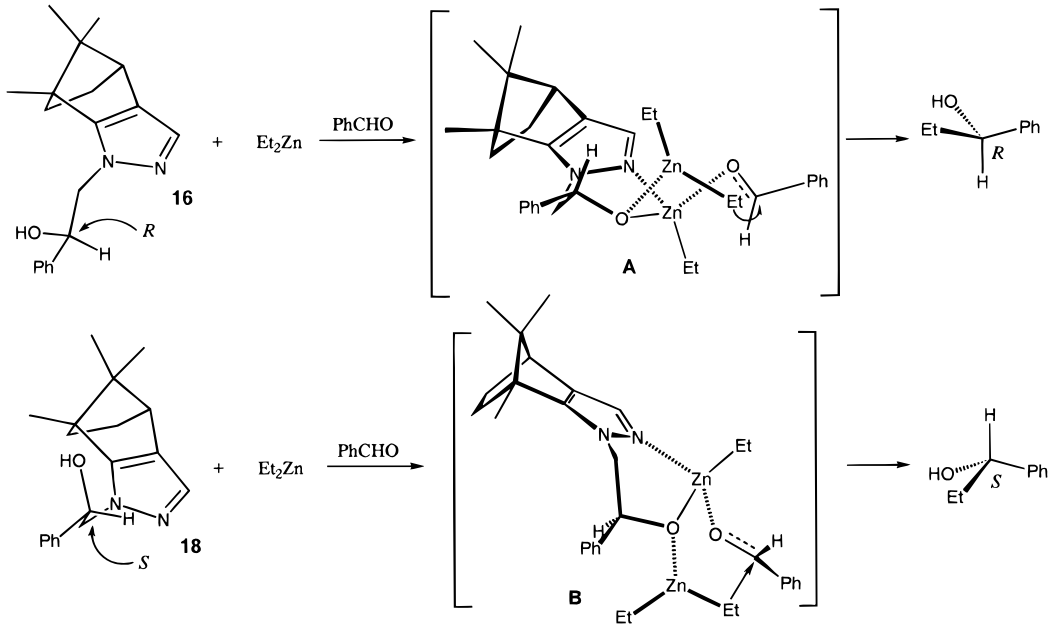


Figure 3. Plausible mechanism for enantioselective alkylation of benzaldehyde with diethylzinc using chiral ligand **16** or **18**.

the chiral catalysts **16** and **18** were 93% ee in both cases, and the reversed asymmetric induction was realized.

Experimental Section[26]

Typical Procedure for the Reaction of Epoxide with Diazole under High-Pressure Conditions.[12] A mixture of epoxide (1.5 mmol) and diazole (1.5 mmol) in MeCN (1.5 mL) was placed in a Teflon reaction vessel and allowed to react at 10 kbar under the conditions indicated in Table 1. When **4** was used as a diazole component, the reactions were conducted in THF in the presence of 1 equiv of *n*-Bu_4NF. After evaporation of the solvent, the residue was purified by preparative TLC or by flash column chromatography.

(*R*)-2-(1-Pyrazolyl)-1-phenylethanol (11): R_f 0.43 (hexane/AcOEt = 1:2); mp 153.0−154.0 °C (from MeOH) (lit.[10b] mp 125.5−127.0 °C); $[\alpha]^{27}_D$ −10.0° (*c* 1.0, MeOH); IR (KBr) *ν* 3206, 1514, 1495 cm^{-1}; ^1H NMR *δ* 4.07 (1H, m), 4.23 (1H, dd, *J* = 14.1, 7.5 Hz), 4.33 (1H, dd, *J* = 14.1, 4.0 Hz), 5.1 (1H, br), 6.23 (1H, t, *J* = 2.0 Hz), 7.33 (6H, s), 7.54 (1H, d, *J* = 2.0 Hz).

(*R*)-2-(1-Pyrazolyl)-1-(pentafluorophenyl)ethanol (12): R_f 0.52 (hexane/AcOEt = 2:1); mp 132.0−133.5 °C (from Et_2O−hexane); $[\alpha]^{25}_D$ +34.3° (*c* 1.0, EtOH); IR (KBr) *ν* 3162, 1503 cm^{-1}; ^1H NMR *δ* 3.75 (1H, br), 4.40 (1H, dd, *J* = 13.6, 4.1 Hz), 4.60 (1H, dd, *J* = 13.6, 7.6 Hz), 5.49 (1H, dd, *J* = 7.6, 4.1 Hz), 6.26 (1H, dd, *J* = 2.2, 1.5 Hz), 7.37 (1H, d, *J* = 2.2 Hz), 7.53 (1H, d, *J* = 1.5 Hz); ^{13}C NMR[27] *δ* 55.6, 65.7, 106.0, 130.3, 140.3. Anal. Calcd for $C_{11}H_7N_2OF_5$: C, 47.47; H, 2.54; N, 10.07. Found: C, 47.55; H, 2.91; N, 10.14.

(*R*)-2-(1-Imidazolyl)-1-phenylethanol (13): R_f 0.38 ($CHCl_3$/MeOH = 9:1); mp 153.5−154.5 °C (from acetone) (lit.[10b] mp 145.0−145.5 °C); $[\alpha]^{25}_D$ −47.6° (*c* 1.0, EtOH); IR (KBr) *ν* 3119, 1595, 1512 cm^{-1}; ^1H NMR *δ* 4.05 (2H, d, *J* = 6.3 Hz), 4.88 (1H, t, *J* = 6.3 Hz), 4.9−5.4 (1H, br), 6.82 (2H, d, *J* = 1.1 Hz), 7.24 (1H, br s), 7.31 (5H, s).

(*R*)-2-(2-Methyl-1-imidazolyl)-1-phenylethanol (14): R_f 0.37 ($CHCl_3$/MeOH = 9:1); mp 149.0−150.0 °C (from CH_2Cl_2) (lit.[10b] mp 117.0−118.0 °C); $[\alpha]^{27}_D$ −24.8° (*c* 1.0, MeOH); IR (KBr) *ν* 3111, 1534, 1505 cm^{-1}; ^1H NMR *δ* 2.07 (3H, s), 3.97 (2H, d, *J* = 6.2 Hz), 4.3−5.2 (1H, br), 4.87 (1H, t, *J* = 6.2 Hz), 6.66 (1H, d, *J* = 1.0 Hz), 6.76 (1H, d, *J* = 1.0 Hz), 7.29 (5H, s).

1,6-Dideoxy-1,6-bis(1-pyrazolyl)-3,4-*O*-isopropylidene-D-mannitol (15): colorless oil; R_f 0.37 (AcOEt); $[\alpha]^{25}_D$ +45.3° (c 0.5, EtOH); IR (neat) *ν* 3333, 1516 cm^{-1}; ^1H NMR *δ* 1.39 (6H, s), 3.5−4.5 (6H, m), 4.20 (2H, dd, *J* = 13.5, 6.4 Hz), 4.48 (2H, dd, *J* = 13.5, 2.4 Hz), 6.25 (2H, t, *J* = 2.1 Hz), 7.49 (4H, d, *J* = 2.1 Hz); ^{13}C NMR *δ* 26.9 (× 2), 54.3 (× 2), 72.1 (× 2), 80.4 (× 2), 105.3 (× 2), 109.6, 130.7 (× 2),139.5 (× 2); MS *m*/*z* (rel intensity) 323 (M^+ + 1, 2), 307 (23), 241 (100), 183 (82), 154 (40), 111 (49), 82 (60); HRMS calcd for $C_{15}H_{22}N_4O_4$ + H 323.1719, found 323.1709.

(*R*)-2-[(4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-1-indazolyl]-1-phenylethanol (16): R_f 0.29 (hexane/AcOEt = 1:1); mp 150.5−152.0 °C (from Et_2O−hexane); $[\alpha]^{25}_D$ +65.7° (*c* 0.35, EtOH); IR (KBr) *ν* 3191, 1537 cm^{-1}; ^1H NMR *δ* 0.68 (3H, s), 0.85 (3H, s), 1.21 (3H, s), 0.9−2.2 (4H, m), 2.70 (1H, d, *J* = 3.7 Hz), 4.15 (1H, dd, *J* = 13.8, 6.6 Hz), 4.34 (1H, dd, *J* = 13.8, 3.3 Hz), 4.8−5.2 (2H, m), 7.16 (1H, s), 7.29 (5H, s); ^{13}C NMR *δ* 11.3, 19.5, 20.4, 27.9, 33.1, 47.5, 52.3, 56.5, 63.0, 73.9, 125.8 (× 2), 127.7, 128.3 (× 2), 128.5, 131.5, 141.3, 154.3. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.29; H, 7.95; N, 9.42.

(*R*)-2-[(4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl]-1-phenylethanol (17): colorless oil; R_f 0.30 (hexane/AcOEt = 1:1); $[\alpha]^{25}_D$ +47.8° (*c* 1.38, EtOH); IR (neat) *ν* 3266, 1582 cm^{-1}; ^1H NMR *δ* 0.65 (3H, s), 0.93 (3H, s), 1.29 (3H, s), 1.0−2.2 (4H, m), 2.70 (1H, d, *J* = 3.5 Hz), 4.10 (1H, dd, *J* = 14.1, 7.0 Hz), 4.25 (1H, dd, *J* = 14.1, 3.5 Hz), 4.1−4.5 (1H, br), 5.05 (1H, dd, *J* = 7.0, 3.5 Hz), 6.73 (1H, s), 7.28 (5H, s); ^{13}C NMR *δ* 10.7, 19.2, 20.5, 27.8, 33.8, 47.2, 50.3, 58.2, 60.6, 73.7, 122.6, 125.8 (× 2), 126.2, 127.5, 128.2 (× 2), 141.2, 166.8; MS *m*/*z* (rel intensity) 296 (M^+, 59), 281 (27), 253 (100), 235 (77), 189 (73), 133 (60), 77 (27); HRMS calcd for $C_{19}H_{24}N_2O$ 296.1889, found 296.1887.

(*S*)-2-[(4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-1-indazolyl]-1-phenylethanol (18): R_f 0.27 (hexane/AcOEt = 2:1); mp 115.5−116.5 °C (from Et_2O−hexane); $[\alpha]^{25}_D$ −34.5° (*c* 0.8, EtOH); IR (KBr) *ν* 3179, 1537 cm^{-1}; ^1H NMR *δ* 0.51 (3H, s), 0.83 (3H, s), 1.13 (3H, s), 0.9−2.2 (4H, m), 2.70 (1H, d, *J* = 3.7 Hz), 2.8−3.3 (1H, br), 4.20 (1H, dd, *J* = 13.5, 6.6 Hz), 4.31 (1H, dd, *J* = 13.5, 3.5 Hz), 5.06 (1H, dd, *J* = 6.6, 3.5 Hz), 7.16 (1H, s), 7.29 (5H, s); ^{13}C NMR *δ* 11.3, 19.5, 20.2, 27.8, 33.6, 47.4, 52.2, 56.3, 62.8, 73.4, 125.8 (× 2), 127.6, 128.1, 128.3 (× 2), 131.5, 141.2, 154.2. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.78; H, 8.42; N, 9.47.

(*S*)-2-[(4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl]-1-phenylethanol (19): colorless oil;

(26) For general experimental information, see our previous paper: Kotsuki, H.; Nishikawa, H.; Mori, Y.; Ochi, M. *J. Org. Chem.* **1992**, *57*, 5036. Unless otherwise noted $CDCl_3$ was used as the solvent for the NMR experiments.

(27) Unfortunately, the ^{13}C NMR signals of the pentafluorophenyl ring were too weak to observe.

R_f 0.31 (hexane/AcOEt = 2:1); $[\alpha]^{25}_D$ −31.1° (*c* 0.9, EtOH); IR (neat) ν 3250, 1580 cm^{-1}; ^1H NMR δ 0.66 (3H, s), 0.94 (3H, s), 1.29 (3H, s), 0.9−2.2 (4H, m), 2.70 (1H, d, J = 3.5 Hz), 4.12 (1H, dd J = 14.5, 6.8 Hz), 4.22 (1H, dd, J =14.5, 4.0 Hz), 4.48 (1H, br), 5.03 (1H, m), 6.75 (1H, s), 7.28 (5H, s); ^{13}C NMR δ 10.8, 19.3, 20.6, 27.9, 33.9, 47.3, 50.4, 58.5, 60.7, 74.0, 122.6, 125.8 (× 2), 126.4, 127.6, 128.3 (× 2), 141.2, 167.0; MS *m*/*z* (rel intensity) 296 (M^+, 65), 281 (30), 253 (100), 235 (88), 189 (91), 133 (79), 77 (57); HRMS calcd for $C_{19}H_{24}N_2O$ 296.1889, found 296.1892.

(1-Hydroxycyclohexyl)-[(4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-1-indazolyl]methane (20): R_f 0.37 (hexane/AcOEt = 4:1); mp 65.5−66.5 °C (from hexane); $[\alpha]^{22}_D$ −14.8° (c 0.94, $CHCl_3$); IR (KBr) ν 3329, 1528 cm^{-1}; ^1H NMR δ 0.73 (3H, s), 0.90 (3H, s), 1.33 (3H, s), 1.0−2.2 (14H, m), 2.74 (1H, d, J = 3.3 Hz), 3.97 (2H, s), 4.94 (1H, br), 7.11 (1H, s); ^{13}C NMR[28] δ 11.6, 19.5, 20.3, 21.8 (× 2), 25.9, 27.7, 33.8, 35.2, 35.5, 47.3, 52.3, 58.3, 62.8, 70.9, 127.6, 131.1, 154.3. Anal. Calcd for $C_{18}H_{28}N_2O$: C, 74.96; H, 9.78; N, 9.71. Found: C, 74.86; H, 9.82; N, 9.72.

(1-Hydroxycyclohexyl)-[(4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl]methane (21): R_f 0.30 (hexane/AcOEt = 4:1); mp 70.0−72.0 °C (from hexane); $[\alpha]^{25}_D$ −4.1° (c 0.98, $CHCl_3$); IR (KBr) ν 3324, 1580 cm^{-1}; ^1H NMR δ 0.65 (3H, s), 0.93 (3H, s), 1.25 (3H, s), 1.0−2.3 (14H, m), 2.73 (1H, d, J = 3.7 Hz), 3.95 (2H, s), 4.21 (1H, br s), 6.90 (1H, s); ^{13}C NMR[28] δ 10.6, 19.2, 20.5, 22.1 (× 2), 25.9, 27.8, 33.7, 35.1, 35.2, 47.2, 50.2, 59.9, 60.6, 71.3, 123.0, 125.9, 166.6. Anal. Calcd for $C_{18}H_{28}N_2O$: C, 74.96; H, 9.78; N, 9.71. Found: C, 74.90; H, 9.79; N, 9.73.

2-[(4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-1-indazolyl]-1,1-diphenylethanol (22): R_f 0.45 (hexane/AcOEt = 4:1); mp 97.5−98.5 °C (from Et_2O−hexane); $[\alpha]^{24}_D$ −25.1° (*c* 1.0, $CHCl_3$); IR (KBr) ν 3223, 1528, 1491 cm^{-1}; ^1H NMR δ 0.42 (3H, s), 0.79 (3H, s), 1.23 (3H, s), 0.8−2.1 (4H, m), 2.60 (1H, d, J = 3.5 Hz), 4.71 (1H, d, J_{AB} = 12.0 Hz), 4.77 (1H, d, J_{AB} = 12.0 Hz), 7.06 (1H, s), 7.1−7.5 (11H, m); ^{13}C NMR δ 11.4, 19.4, 20.1, 27.7, 33.2, 47.2, 52.3, 57.5, 62.8, 78.1, 126.2 (× 4), 126.9, 127.0, 127.6, 127.9 (× 2), 128.0 (× 2), 131.0, 144.6, 144.8, 154.3. Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.58; N, 7.52. Found: C, 80.59; H, 7.68; N, 7.20.

2-[(4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl]-1,1-diphenylethanol (23): R_f 0.42 (hexane/AcOEt = 4:1); mp 73.0−74.5 °C (from Et_2O−hexane); $[\alpha]^{24}_D$ −13.9° (*c* 1.0, $CHCl_3$); IR (KBr) ν 3248, 1584 cm^{-1}; ^1H NMR δ 0.42 (3H, s), 0.84 (3H, s), 1.20 (3H, s), 0.8−2.1 (4H, m), 2.53 (1H, d, J = 3.5 Hz), 4.64 (2H, s), 6.39 (1H, s), 6.52 (1H, s), 7.0−7.5 (10H, m); ^{13}C NMR δ 10.5, 19.1, 20.1, 27.6, 33.5, 46.9, 50.1, 59.9, 60.4, 78.4, 123.4, 125.7, 126.0 (× 2), 126.1 (× 2), 126.6, 126.7, 127.6 (× 3), 127.8, 144.0, 144.2, 166.6. Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.58; N, 7.52. Found: C, 80.71; H, 7.65; N, 7.19.

Preparation of Ethyl (4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-1-indazolylacetate and Ethyl (4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolylacetate (24 and 25). A solution of camphopyrazole **4** (1.7 g, 9.6 mmol) in THF (30 mL) was added slowly to a suspension of NaH (460 mg, 11.5 mmol, 60% oil dispersion) in THF (20 mL). The mixture was stirred at rt for 30 min, $BrCH_2CO_2Et$ (2.40 g, 14.4 mmol) was then introduced at 0 °C, and the mixture was stirred at rt overnight. After being quenched with water, the mixture was extracted with AcOEt. The extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 4:1 to 1:1) to give **24** (0.9 g, 36%) and **25** (1.2 g, 48%).

For **24:** yellow oil; R_f 0.38 (hexane/AcOEt = 1:1); $[\alpha]^{27}_D$ +11.6° (*c* 1.03, $CHCl_3$); IR (neat) ν 1755, 1528 cm^{-1}; ^1H NMR δ 0.78 (3H, s), 0.90 (3H, s), 1.26 (3H, s), 1.26 (3H, t, J = 7.3 Hz), 1.0−2.2 (4H, m), 2.75 (1H, d, J = 3.5 Hz), 4.21 (2H, q, J = 7.3 Hz), 4.84 (2H, s), 7.14 (1H, s); ^{13}C NMR δ 10.4, 13.7, 19.2, 19.9, 27.3, 32.7, 47.2, 51.0, 51.8, 60.9, 62.5, 128.3, 131.1, 153.5, 167.5; MS *m*/*z* (rel intensity) 262 (M^+, 52), 247 (48), 219 (38), 189 (30), 173 (46), 145 (100); HRMS calcd for $C_{15}H_{22}N_2O_2$ 262.1681, found 262.1680.

For **25:** yellow oil; R_f 0.48 (hexane/AcOEt = 1:1); $[\alpha]^{26}_D$ +15.3° (*c* 1.11, $CHCl_3$); IR (neat) ν 1755, 1586 cm^{-1}; ^1H NMR δ 0.69 (3H, s), 0.95 (3H, s), 1.23 (3H, t, J = 7.0 Hz), 1.28 (3H, s), 1.0−2.2 (4H, m), 2.75 (1H, d, J = 3.3 Hz), 4.18 (2H, q, J = 7.0 Hz), 4.80 (2H, s), 6.95 (1H, s); ^{13}C NMR δ 10.3, 13.7, 18.7, 20.1, 27.3, 33.3, 46.8, 49.7, 52.1, 60.0, 60.7, 122.2, 127.0, 166.3, 168.0; MS *m*/*z* (rel intensity) 262 (M^+, 24), 247 (32), 219 (100), 191 (34), 173 (20), 145 (44); HRMS calcd for $C_{15}H_{22}N_2O_2$ 262.1681, found 262.1681.

2-[(4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-1-indazolyl]ethanol (26). To a stirred suspension of $LiAlH_4$ (60 mg, 1.5 mmol) in THF (5 mL) at 0 °C was added dropwise a solution of **24** (400 mg, 1.5 mmol) in THF (1 mL), and the mixture was stirred at rt overnight. After being quenched with water, the mixture was extracted with AcOEt. The extracts were washed with brine, dried (Na_2SO_4), and concentrated. The almost pure compound was recrystallized from AcOEt to give **26** (280 mg, 81%) as colorless crystals: R_f 0.17 (AcOEt); mp 123.5−124.5 °C (from AcOEt); $[\alpha]^{24}_D$ +4.7° (*c* 1.1, $CHCl_3$); IR (KBr) ν 3250, 1537 cm^{-1}; ^1H NMR δ 0.72 (3H, s), 0.89 (3H, s), 1.33 (3H, s), 1.0−1.4 (2H, m), 1.6−2.2 (2H, m), 2.73 (1H, d, J = 3.5 Hz), 3.8−4.0 (2H, m), 4.0−4.3 (2H, m), 4.38 (1H, br), 7.07 (1H, s); ^{13}C NMR δ 11.4, 19.5, 20.3, 27.7, 33.6, 47.4, 51.5, 52.2, 61.8, 62.7, 128.0, 131.0, 153.8. Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.97; H, 9.32; N, 12.66.

2-[(4*S*,7*R*)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-2-indazolyl]ethanol (27). As described above, **25** (400 mg, 1.5 mmol) was converted to **27** (295 mg, 86%): R_f 0.26 (AcOEt); mp 100.5−101.5 °C (from Et_2O-hexane); $[\alpha]^{24}_D$ +22.6° (*c* 1.1, $CHCl_3$); IR (KBr) ν 3254, 1580 cm^{-1}; ^1H NMR δ 0.65 (3H, s), 0.93 (3H, s), 1.26 (3H, s), 1.1−1.4 (2H, m), 1.6−2.2 (2H, m), 2.73 (1H, d, J = 3.5 Hz), 3.60 (1H, br), 3.8−4.0 (2H, m), 4.0−4.3 (2H, m), 6.93 (1H, s); ^{13}C NMR δ 10.7, 19.2, 20.5, 27.8, 33.8, 47.3, 50.3, 53.1, 60.7, 62.3, 122.0, 126.4, 166.5. Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 71.15; H, 9.21; N, 12.88.

General Procedure for Enantioselective Addition of Diethylzinc to Benzaldehyde. To a solution of the chiral ligand (0.19 mmol) in toluene (4 mL) at −15 °C was added a solution of 1.0 M Et_2Zn in hexane (3.8 mL, 3.8 mmol), and the resulting yellow solution was stirred at this temperature for 15 min before addition of benzaldehyde (96 μL, 0.94 mmol). The mixture was gradually warmed to rt and stirred for 1−6 days. After being quenched with 2 M HCl, the insoluble substance was removed by filtration through Celite. The filtrate was extracted with AcOEt, dried (Na_2SO_4), and concentrated. The crude product was purified by preparative TLC (petroleum ether/AcOEt = 5:1) to give 1-phenyl-1-propanol as a colorless oil. The ee was determined by HPLC analysis (λ = 254 nm) using a DAICEL Chiralcel OB column with 1% *i*-PrOH in hexane as an eluent at a flow rate of 0.5 mL/min.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **11**−**27** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(28) Interestingly, the cyclohexane carbons were detected to be nonequivalent. Clearly, this may be indicative of an internal hydrogen bonding between hydroxyl and pyrazole nitrogen groups.