Synthesis of Novel Chiral Diazole Ligands for Enantioselective Addition of Diethylzinc to Benzaldehyde[#]

**Hiyoshizo Kotsuki,* Hiroyuki Hayakawa, Masahiro Wakao,
Tomoyasu Shimanouchi, and Masamitsu Ochi**

Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780, Japan

Abstract: A variety of chiral pyrazole and imidazole derivatived ligands have been prepared under high pressure conditions and their catalytic efficiency in the enantioselective addition of diethylzinc to benzaldehyde has been examined.

The molecular design of enantiomerically pure chiral ligands for use in catalytic asymmetric reactions is one of the most challenging issues in modern organic chemistry.[1] In our extensive efforts in this area, we recently reported an efficient procedure to prepare chiral pyridine[2] and diamine derivatives[3] with C_2-symmetry. Although the former ligands showed an interesting behavior in forming a novel helical network through metal coordination,[2a] their catalytic activity in the enantioselective addition of diethylzinc to benzaldehyde gave only modest results.[2b, 4]
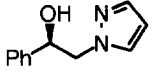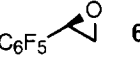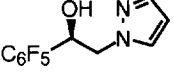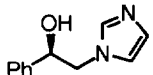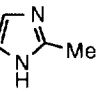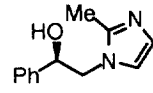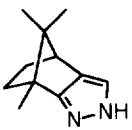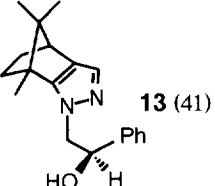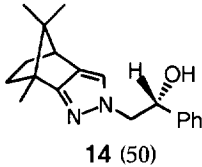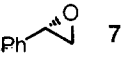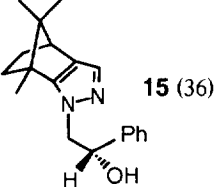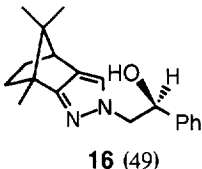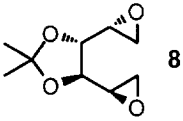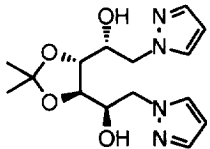
In our separate work on the use of high pressure in organic synthesis,[5] we found that epoxide opening reactions with several nitrogen heterocycles proceeded cleanly at high pressure without the use of any acid or base catalysts.[6] These results prompted us to extend the method for the synthesis of optically active homologues having a pyrazole or an imidazole functionality as novel chiral ligands, since their coordinating ability is well-established in inorganic chemistry.[7] Unfortunately, however, there are only a few reports on the use of these heterocycles in asymmetric transformations.[8] Herein we wish to report an efficient construction of optically active pyrazole and imidazole derivatives and their use in catalytic asymmetric reaction of diethylzinc to benzaldehyde.[9]

The desired chiral diazole derivative ligands were easily prepared by *N*-alkylation of pyrazoles or imidazoles with optically active epoxides (eq 1 and Table 1).[10]

$$(eq\ 1)$$

40-91%
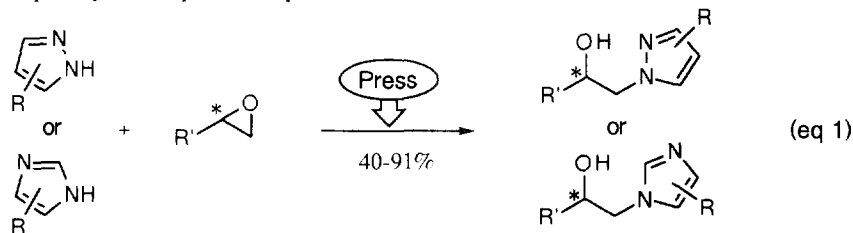
[#]Dedicated to Prof. T. Tokoroyama upon his retirement from Osaka City University.

Table 1. Preparation of diazole derivative ligands under high pressure conditions[a]

Run	Substrate	Epoxide	Product(s) (yield, %)[b]
1	**1**	**5**	**9** (50)
2	**1**	**6**	**10** (76)
3	**2**	**5**	**11** (60)
4	**3**	**5**	**12** (40)
5[c]	**4**	**5**	**13** (41) **14** (50)
6[c]	**4**	**7**	**15** (36) **16** (49)
7	**1**	**8**	**17** (40)

[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 eq of n-Bu$_4$NF.

Thus, treatment of pyrazole **1** and (R)-(+)-styrene oxide **5** in acetonitrile at 10 kbar and 65 °C for 3 days produced the desired adduct **9**, mp 153-154 °C (from MeOH); $[\alpha]^{27}_D$ -10.0 (c 1.00, MeOH), in 50% yield (Run 1). Similarly, the reaction of (+)-camphorpyrazole **4**[8] with **5** at 10 kbar in the presence of 1.0 eq of tetra-n-butylammonium fluoride[11] gave **13**, mp 150.5-152 °C (from hexane-Et$_2$O); $[\alpha]^{25}_D$ +65.7 (c 0.35, EtOH), and **14**, $[\alpha]^{25}_D$ +47.8 (c 1.38, EtOH), in 41 and 50% yield, respectively (Run 5).[12] The corresponding diastereomers **15** and **16** were also prepared from **4** and (S)-(-)-styrene oxide **7**. In addition, imidazole derivatives **11** and **12**, and the C$_2$-symmetric bispyrazole **17** were obtained in moderate yields.

With these ligands in hand, the catalytic activities of **9-17** for the enantioselective addition of diethylzinc to benzaldehyde was then examined (Scheme 1 and Table 2).

Scheme 1
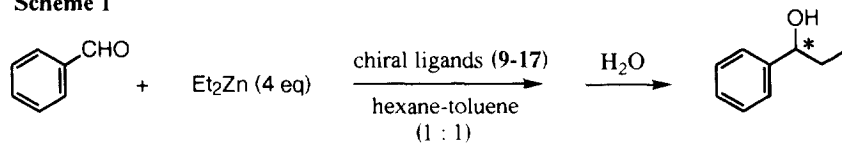
Table 2. Enantioselective addition of diethylzinc to benzaldehyde in the presence of chiral ligands **9-17**[a]

Entry	Ligand (eq)	Time (day)	Yield (%)[b]	Ee (%)[c]	Abs. Config.[d]
1	**9** (0.2)	5	95	83	*R*
2[e]	**9** (0.2)	3	88	68	*R*
3[f]	**9** (0.2)	1	70	18	*R*
4[g]	**9** (0.2)	1	84	17	*R*
5	**10** (0.2)	2	70	57	*R*
6	**11** (0.2)	6	80	5	*S*
7	**12** (0.2)	4	95	7	*S*
8	**13** (0.2)	2	90	93	*R*
9	**14** (0.2)	1	73	69	*R*
10	**15** (0.2)	1	95	87	*S*
11	**16** (0.2)	1	77	53	*S*
12	**17** (0.1)	1	66	2	*S*
13	**17** (0.2)	1	74	3	*S*

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

As expected, the relatively high enantioselectivity (83% ee) was realized when the pyrazolyl ligand **9** was employed as a chiral catalyst (Entry 1), whereas the corresponding imidazole homologues were all fruitless (Entries 6 and 7). These results can be understood by considering the favorable coordination structure of **9** to form a 6-membered organozinc intermediate. In contrast to our previous results,[2b] the addition of titanium salts to the present catalytic system significantly prevented the desired asymmetric induction (Entries 3 and 4). After numerous attempts to improve the enantioselectivity, we finally found that the sterically congested ligand **13** gave the best result: 93% ee was achieved in favor of an *R*-enantiomer (Entry 8). Interestingly, simply by using the diastereomer **15**, in which the stereogenic carbon center bearing a hydroxyl function has an S-configuration, the completely reversed enantioselectivity was effected in 87% ee (Entry 10). Although the actual active species in these reactions are unclear, it is conceivable that the stereochemical environment around **13** during the reaction is completely different from that of **15**. Unfortunately, the C_2-symmetric bispyrazole ligand **17** showed no reactivity irrespective of catalytic ratio (Entries 12 and 13).

In conclusion, we were successful in developing a convenient method to synthesize a variety of diazole chiral ligands using high pressure-promoted epoxide opening reactions, and in clarifying the novel catalytic

activity of these ligands in enantioselective addition of diethylzinc to benzaldehyde. The best results for the chiral catalysts **13** and **15** were 93 and 87% ee, respectively, wherein the reversed asymmetric induction was achieved. In view of the ready accessibility of these chiral ligands, the present method offers potential utility for the design of other types of chiral ligands.

Further studies to elucidate the mechanistic pathway of the above reactions and also applications to different kinds of asymmetric transformations are now in progress.

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10.   Satisfactory analytical and spectral data were obtained for all new compounds. Selected data for specific rotations are as follows: **10**: $[\alpha]^{25}_D$ +34.3 (*c* 1.02, EtOH); **11**: $[\alpha]^{25}_D$ -47.6 (*c* 1.00, EtOH); **12**: $[\alpha]^{27}_D$ -24.8 (*c* 1.00, MeOH); **15**: $[\alpha]^{25}_D$ -34.5 (*c* 0.81, EtOH); **16**: $[\alpha]^{25}_D$ -31.1 (*c* 0.90, EtOH); **17**: $[\alpha]^{25}_D$ +45.3 (*c* 0.50, EtOH).

11.   In this case the use of tetra-*n*-butylammonium fluoride as a base was essential. In the absence of this reagent **13** was obtained only in 12% yield.

12.   The structure of **13** was confirmed unambiguously by X-ray diffraction analysis. The results will be reported in a full paper.