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Chirality Recognition of 1,1'-Bi-2-naphthol with Optically Active Bis(oxazolinyl)pyridines

Hisao Nishiyama,* Tomonori Tajima, Masahiro Takayama, and Kenji Itoh

School of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi 441, Japan

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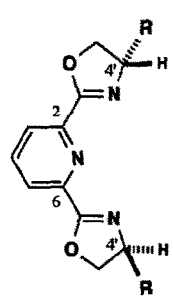
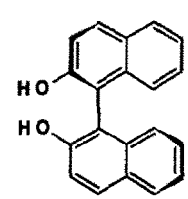
Abstract: Optically active 2,6-bis[(*S*)-4'-benzyloxazolin-2'-yl]pyridine, pybox-(*S,S*)-*bz* (**1**), proved to make a well-matched base-acid pair with the (*S*)-enantiomer of 1,1'-bi-2-naphthol on the basis of ^{1}H-NMR study.

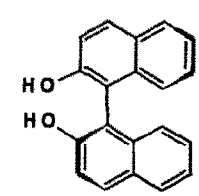
Recognition of molecular chirality is of importance in the wide range of bio-organic and organic chemistry. Especially, some model studies in chirality recognition of organic molecules have been reported for determination of enantiomeric excess by spectroscopic or chromatographic methods.[1] Among them, a new concept "*complementary twist*" was proposed for the complexation through dual hydrogen bond association with a C_2-symmetrical diimine-diol pair.[2] We have been interested in the chirality recognition with an optically active bis(oxazolinyl)pyridine, *pybox*, which was developed by us as a chiral nitrogen auxiliary for transition-metal catalyzed asymmetric reactions.[3]

We reasoned that the C_2-symmetrical pybox derivatives (**1**, R = CH_2Ph[4]; **2**, R = i-Pr[3]) can make a reasonable chiral basic cavity having their three nitrogen atoms and the two bulky substituents to accept appropriate chiral acids or alcohols. We report here the chirality recognition of 1,1'-bi-2-naphthol (**3**) with the pybox derivatives as basic receptors on the basis of ^{1}H NMR study.





(*S*)-(-)-**3**



(*R*)-(+)-**3**

Pybox-(*S,S*)-*bz* **1** R = benzyl

Pybox-(*S,S*)-*ip* **2** R = iso-propyl

Addition of one equivalent of pybox-(*S,S*)-*bz* (**1**) to a solution of racemic 1,1'-bi-2-naphthol (**3**) in $CDCl_3$ solution showed a downfield shift of the original phenolic proton signal (O*H*, δ 5.03 ppm) separated to the two broad signals at δ 6.48 and δ 5.58 ppm (Fig. 1, **a**~**e**). The downfield signal proved to be the O*H* proton derived from (*S*)-**3** strongly associated with pybox **1** through hydrogen bonds in an equilibrium. The O*H*-signals of each pure enantiomer of **3** with **1** appeared at δ 6.50 ppm for (*S*)-**3** and at δ 5.82 ppm for (*R*)-**3**, respectively (Fig. 1, **d** and **e**). Significantly, the resonance of the C_4-*H* on the oxazoline ring, originally appearing at δ 4.64 ppm, was shifted upfield by 0.53 δ to 4.11 ppm in the presence of (*S*)-**3**. In contrast, such a remarkable shift could not be observed for (*R*)-**3** moving, only by 0.13 δ to 4.51 ppm (Fig.1, **e**). The greater upfield shift of the C_4-*H* of **1** with (*S*)-**3** could be accounted for an anisotropic effect of the naphthalenic ring by the intense complexation of **1** and (*S*)-**3** rather than (*R*)-**3**, as illustrated in Fig.2, **a**. Small intermolecular NOE difference effects were observed between the benzylic protons of **1** and the phenolic protons of (*S*)-**3**.

Titration of each (*S*)- and (*R*)-binaphthol **3** with **1** in a NMR tube gave the association constants and the limiting chemical shifts in the associates (Table 1). We obtained a large magnitude of enantioselectivity, Δ(ΔG) = -5.1 kJ mol^{-1} (-1.2 kcal mol^{-1}), derived from the K_S/K_R value.

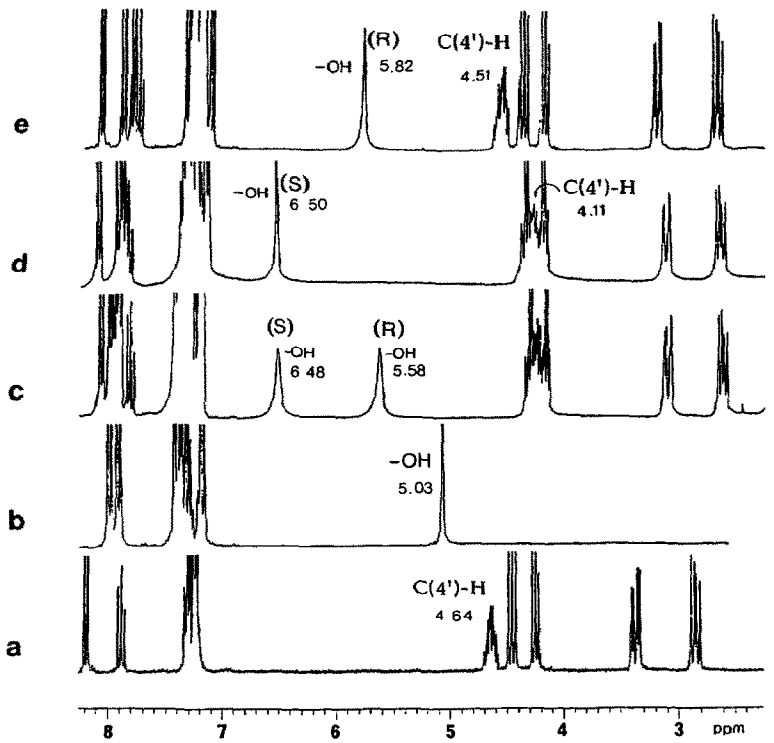
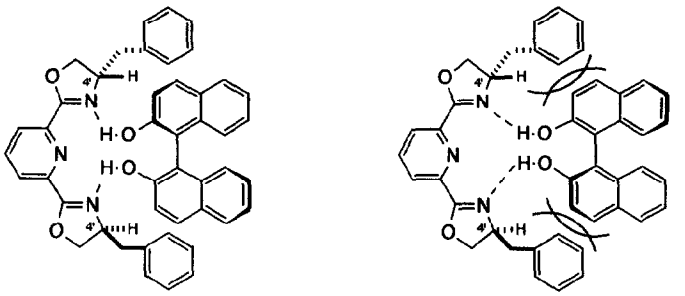


Fig. 1 ^1H NMR spectra (270 MHz, CDCl3) of pybox-(*S,S*)-*bz* **1** and 1,1'-bi-2-naphthol, (*S*)-**3** and (*R*)-**3**: (**a**) **1**; (**b**) racemic **3**; (**c**) **1** + racemic **3**; (**d**) **1** + (*S*)-**3** (1:1); (**e**) **1** + (*R*)-**3** (1:1).



1 + (*S*)-**3** **1** + (*R*)-**3**

Fig. 2 Hypothetical association of **1** + (*S*)-**3** (left) and **1** + (*R*)-**3** (right).

Thus pybox-(*S,S*)-*bz* (**1**) has been shown to make a well-matched base-acid pair with the (*S*)-1,1'-bi-2-naphthol. We think that the benzyl groups of **1** could serve to assist their association by the face-face stacking between each aromatic rings. The stacking works intensively for the well matched pair of **1** and (*S*)-**3** rather than **1** and (*R*)-**3** (Fig. 2). We assume that the two nitrogen atoms of the oxazoline rings on pybox could play a major role for the association through the dual hydrogen bonds. Pybox-(*S,S*)-*ip* (**2**) showed the same properties for the chirality recognition of the binaphthol (Table 1, run 3 and 4).

We also found the chirality differentiative recognition of binaphthyl-2,2'-diyl hydrogen phosphate (**4**) with **1** through mono hydrogen bond association. Pybox **1** binds strongly the (*S*)-enantiomer of **4**: the chemical shift of the O*H* protons occurring at 9.30 ppm for (*S*)-**4** and 8.95 ppm for (*R*)-**4** with one equivalent of **1** (0.02 mol dm^{-3} in $CDCl_3$), respectively.

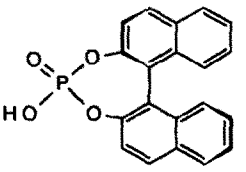
Table 1 Association constants of 1,1'-bi-2-naphthol and bis-oxazoline derivatives.[a]

run	bis-oxazoline	binaphthol	association constant *K* (dm^3 mol^{-1})	K_S/K_R	Δ(ΔG) kJ mol^{-1} (kcal mol^{-1})
1	**1**	(S)-**3**	42	} 8.0	-5.1 (-1.2)
2	**1**	(R)-**3**	5.3		
3	**2**	(S)-**3**	14	} 4.0	-3.5 (0.83)
4	**2**	(R)-**3**	3.4		

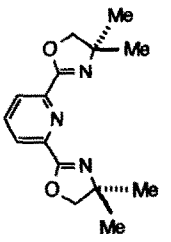
[a] Concentration for the titration, 1.75 x 10^{-2} mol dm^{-3} of **3** ($CDCl_3$); addition of the bis-oxazoline, 0.5~2.0 equivalent to **3**. The simple 1:1 association in the equilibrium was hypothetically adopted for the calculation. The limiting chemical shifts of O*H* signals for the associates, δ 6.9 for [**1**:(S)-**3**], δ 6.2 for [**1**:(R)-**3**], δ 6.6 for [**2**:(S)-**3**], δ 6.0 for [**2**:(R)-**3**].

Non chiral receptors, 2,6-bis(4',4'-dimethyloxazolin-2'-yl)pyridine [pybox-*dm* (**5**)] and 2,2':6',2"-terpyridine (**6**), gave smaller downfield shifts of the O*H* protons of binaphthol **3** by 0.32 δ to 5.35 ppm and by 0.40 to 5.43 ppm ($CDCl_3$), respectively. These facts indicate that the steric matching in the chiral environment by the two bulky groups, benzyl or iso-propyl, of the chiral pybox **1** and **2** is also of importance for their strong associations.

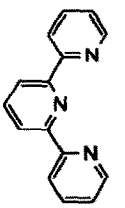
We are now applying the pybox derivatives as the NMR shift-reagents for the determination method of enantiomeric purity for common chiral acids and alcohols.[5]



(*S*)-**4**



Pybox-*dm* **5**



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References and Notes

1 For examples, (a) W. H. Pirkle and T. C. Pochapsky, *Chem. Rev.*, **1989**, *89*, 347. (b) R. Kellogg, *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 782. (c) F. Vögtle, H.-G. Löhr, J. Franke, and D. Worsch, *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 727. (d) J. Canceil, L. Lacombe, and A. Collett, *J. Am. Chem. Soc.*, **1985**, *107*, 6993. (e) J. Rebek, Jr., B. Askew, P. Ballester, and M. Doa, *J. Am. Chem. Soc.*, **1987**, *109*, 4119. (f) W. H. Pirkle and D. S. Reno, *J. Am. Chem. Soc.*, **1987**, *109*, 7189. (g) P. P. Castro, T. M. Georgiadis, and F. N. Diederich, *J. Org. Chem.*, **1990**, *55*, 5184. (h) K. S. Jeong, A. V. Muehldorf, and J. Rebeck, Jr., *J. Am. Chem. Soc.*, **1990**, *112*, 7393. (i) F. Garcia-Tellado, J. Albert, and A. D. Hamilton, *J. Chem. Soc., Chem. Commun.*, **1991**, 1761.

2 Y. Dobashi, A. Dobashi, H. Ochiai, and S. Hara, *J. Am. Chem. Soc.*, **1990**, *112*, 6121; the references for the recognition of molecular chirality are also sited therein.

3 (a) H. Nishiyama, M. Kondo, T. Nakamura, and K. Itoh, *Organometallics*, **1991**, *10*, 500. (b) H. Nishiyama, S. Yamaguchi, M. Kondo, K. Itoh, *J. Org. Chem.*, **1992**, *57*, 4306. (c) H. Nishiyama, S.-B. Park, K. Itoh, *Tetrahedron: Asymmetry*, **1992**, *3* , 1029. (d) H. Nagashima, T. Ueda, H. Nishiyama, K. Itoh, *Chem. Lett.*, **1993**, 347.

4 The preparation of **1** was performed with (*S*)-phenylalaninol by the method previously reported; see ref 3. **1**: white solids; m.p. 147~148 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 2.75 (dd, *J* = 8.8, 13.7 Hz, 2 H), 3.27 (dd, *J* = 4.9, 13.7 Hz, 2 H), 4.26 (t, *J* = 8.8, 8.8 Hz, 2 H), 4.46 (t, *J* = 8.8, 8.8 Hz, 2 H), 4.64 (m, 2 H), 7.2~7.4 (m, 10 H), 7.89 (t, *J* = 8.3, 8.3 Hz, 1 H), 8.20 (d, *J* = 8.3 Hz, 2 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) 41.63, 68.06, 72.54, 125.7, 126.5, 128.5, 129.1, 137.2, 137.7, 146.8, 162.7 ppm. Anal. for $C_{25}H_{23}N_3O_2$:Found (Calcd); C, 75.55 (75.55); H, 5.82 (5.83); N, 10.51 (10.57). $[\alpha]^{22}_D$ = -71.7 (CH_2Cl_2, c = 1.02) .

5 For example: with Pirkle's alcohol [2,2,2-trifluoro-1-(9-anthryl)ethanol (**7**), see ref 1a]; ^1H NMR (270 MHz, $CDCl_3$) for the O*H* of **7** (a doublet at δ 2.90 ppm); **1** + (*R*)-**7** (2:1), a doublet at δ 5.40; **1** + (*S*)-**7** (2:1), a doublet at δ 5.30; **2** + (*R*)-**7** (2:1), a doublet at δ 5.40; **2** + (*S*)-**7** (2:1), a doublet at δ 5.30 ppm.