Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2865–2869

TETRAHEDRON: *ASYMMETRY*

Single-chiral bis(oxazolinyl)pyridine (pybox). Efficiency in asymmetric catalytic cyclopropanation

Hisao Nishiyama,* Norikazu Soeda, Tomonari Naito and Yukihiro Motoyama

School of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi 441-8580, Japan

Received 24 June 1998; accepted 29 July 1998

Abstract

Single-chiral bis(oxazolinyl)pyridine ligands were examined as ligands for ruthenium-catalyzed asymmetric catalytic cyclopropanation of olefins: enantioselectivities up to 94% for the *trans*-cyclopropane were observed.

1. Introduction

Two-fold axial (C_2) symmetry in the shape of chiral ligands has been utilized in preference to obtain excellent results in asymmetric catalysis.[1,2] We have also perceived efficiency of C_2-symmetry in ligand design through our investigation of optically active bis(oxazolinyl)pyridine (pybox), whose potential has been revealed in the asymmetric cyclopropanation (ACP) of olefins and diazoacetates with ruthenium catalysts.[3–5] Whilst reviewing the features of our ACP, we arrived at the following interesting reasoning: in order to obtain high ees and *trans*:*cis* ratio of the products, single-chirality in pybox is presumably sufficient in place of the C_2-symmetry in pybox. The illustrative detail of our rationalization is described in Fig. 1. If the single-chiral pybox with only one substituent R is adopted, the resultant intermediate **A** may be selectively attacked by olefins from the third quadrant at the *re*-face of the carbene moiety. Even though the rotational isomer **B** might be formed as a possible minor intermediate, it may rotate back to **A** in an equilibrium. Therefore, we reasoned that the single-chirality in pybox is sufficient to a large extent for the high stereoselectivities in the ruthenium-catalyzed ACP.

* Corresponding author. E-mail: hnishi@tutms.ac.jp

0957-4166/98/$ - see front matter
PII: S0957-4166(98)00303-6

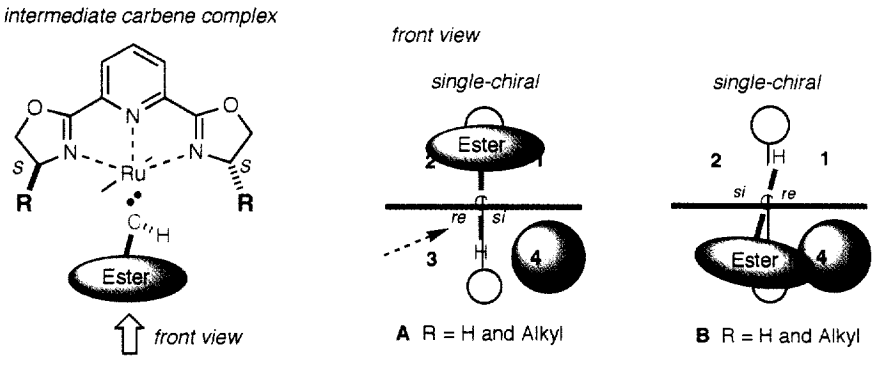
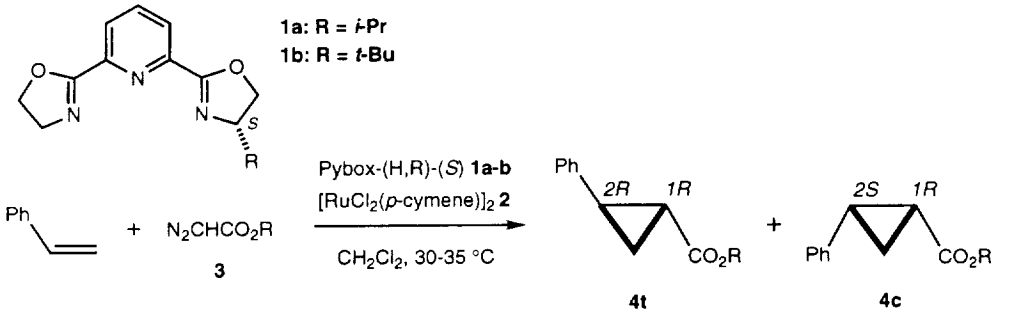


Fig. 1.

2. Results and discussion

The single-chiral pybox-(H,R)-(*S*) **1a** and **1b** [R=*i*-Pr (*ip*) for **a**, R=*t*-Bu (*tb*) for **b**] were synthesized by stepwise introduction of different amino alcohols into dimethyl pyridine-2,6-dicarboxylate. The asymmetric cyclopropanation of styrene (10 mmol) and diazoacetate **3a–g** (2 mmol) [ester group: **a**=Me, **b**=Et, **c**=*i*-Pr, **d**=*t*-Bu, **e**=*d*-menthyl, **f**=*l*-menthyl, **g**=2,6-di-*i*-propyl-phenyl] was carried out using the *in situ* catalyst of pybox-*ip* **1a** (7 mol%) and [Ru(*p*-cymene)Cl_2]$_2$ (**2**) (5 mol% of Ru to diazoacetate) as a standard condition (Scheme 1, Table 1). A reaction of pybox-*ip* **1a** with methyl diazoacetate **3a** resulted in 71% and 48% ees for the *trans*-cyclopropane **4t** and the *cis*-cyclopropane **4c**, respectively, in a ratio of 89:11 (entry 1). Pybox-*tb* **1b** increased the ees up to 86% for **4t** and 63% for **4c** (entry 2). All the products in entries 1 and 2 have a 1*R*-absolute configuration, the same as those previously reported by us with pybox-(*i*-Pr,*i*-Pr)-(*S*,*S*) **5a**.[3] This fact, giving the same absolute configuration with high ees for the *trans*-product, is consistent with the reaction course of styrene in both the C_2-symmetric ligand and the single-chiral one being similar; styrene attacks at the β-carbon atom to the *re*-face of the carbene moiety followed by cyclopropane formation.



Scheme 1. Asymmetric cyclopropanation of styrene

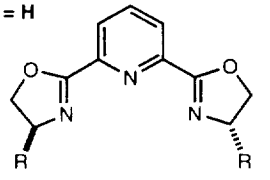
Under the same reaction conditions using pybox-*tb* **1b**, changing the ester groups of diazoacetate increased the *trans*:*cis* ratio from 89:11 to 99:1 due to the bulkiness of the *d*- and *l*-menthyl group (entries 3–7). The highest ee of 94% for the *trans*-product **4t** was eventually obtained with *l*-methyl diazoacetate **3f** (entry 7), but the ees of the *cis*-product **4c** settled in the middle range, 69% ee being the highest with *d*-menthyl ester (entry 6). 2,6-Di-*i*-propylphenyl diazoacetate **3g** in benzene at 60°C exclusively gave the *trans*-product with 90% ee (entry 8). The unexpected decrease of the ees for the *trans*-product with *t*-butyl ester and *d*-menthyl ester in entries 5 and 6 (68% and 55%, respectively) may be explained by a mismatching of the stereotopic situation. As a comparison, the reaction of methyl diazoacetate with

Table 1
Asymmetric cyclopropanation of styrene and diazoacetates with chiral pybox **1** and **5** and $[RuCl_2(p\text{-cymene})]_2$ (**2**)[a]

Entry	Pybox	N_2CHCO_2R' R' =	**4t+4c**[b] yield (%)	ratio	%ee **4t**	%ee **4c**
1	**1a**	Me	79	89:11	71	48
2	**1b**	Me	88	83:17	86	63
3	**1b**	Et	93	89:11	90	66
4	**1b**	*i*-Pr	80	92:8	90	68
5	**1b**	*t*-Bu	82	93:7	68	42
6	**1b**	*d*-Menthyl	81	96:4	55	69
7	**1b**	*l*-Menthyl	84	99:1	94	64
8	**1b**	2,6-(*i*-Pr)$_2$Ph[c]	91	100:0	90	-
9	**5a**	Me	82	89:11	92	97
10	**5b**	Me	57	89:11	-	-

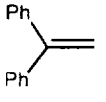
[a]Styrene (10 mmol), diazoacetate (2.0 mmol), Pybox (0.14 mmol, 7 mol%), $[RuCl_2(p\text{-cymene})]_2$ (0.05 mmol, 5 mol% of Ru), CH_2Cl_2 (ca. 3.0 ml), 30-35 °C, 20 h. A solution of diazoacetate in CH_2Cl_2 (ca. 1 *N*) was slowly added to the solution of styrene and the catalyst in CH_2Cl_2 (ca. 1 ml). [b]Isolated yield. The ratios by ^1H NMR. The %ees were determined by the reported method, see ref 3. [c]1.0 mmol.

5a: R = *i*-Pr
5b: R = H

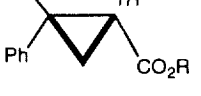


pybox-(*i*-Pr,*i*-Pr)-(*S*,*S*) **5a** and non-chiral pybox-(H,H) **5b** was reexamined by using 5 mol% of ruthenium under the same reaction conditions applied above to show similar *trans*:*cis* ratios (89:11), 92% ee for the *trans*-product **4t** and 97% ee for the *cis*-product **4c** (entries 9 and 10).

1,1-Diphenylethylene **6** was also cyclopropanated to give (1*R*)-product **7** in 68% ee with *d*-menthyl ester. However, 1,2-disubstituted olefins such as *trans*-PhCH=CHPh, *trans*-EtCH=CHEt and dihydronaphthalene gave no cyclopropane derivatives, similar to our previous results with pybox **5a**.



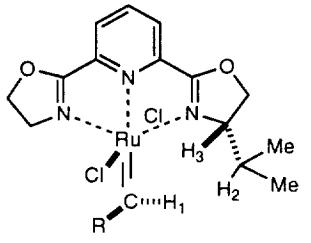
6

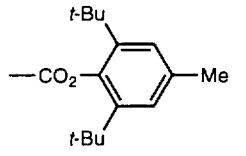


7

R = *d*-Menthyl 58% yield, 62% ee
R = *l*-Menthyl 52% yield, 21% ee

In order to confirm an intermediate complex, 2,6-di-*t*-butyltolyl diazoacetate **3h** was subjected to a reaction with $[Ru(p\text{-cymene})Cl_2]_2$ **2** and the single-chiral pybox-*ip* in dichloromethane at 20°C.[6] After stirring for 2 h, addition of hexane to the mixture produced a dark red product, which was defined as a single isomer of the corresponding carbene complex **8** on the basis of an NMR study; in CD_2Cl_2 (TMS), δ 21.68 (s, 1H) ppm for the carbene's proton and δ 304.8 for the carbene's carbon. In particular, 5% of the NOE between the carbene proton H_1 and the isopropyl proton H_2 was observed, whilst only a 1% NOE was observed for H_1 and the oxazoline proton H_3. We can conclude that the intermediate type **A** predominately forms in the reaction solution rather than intermediate type **B**, presumably in equilibrium due to free rotation at higher temperatures.[7]



8 R = 

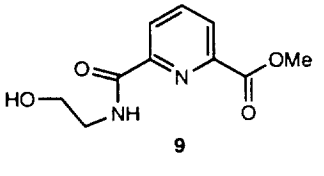
3. Experimental section

3.1. General

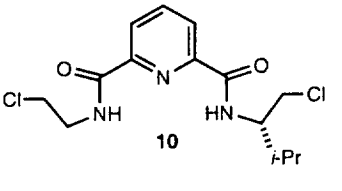
All reactions were carried out under nitrogen. Dichloromethane was distilled under nitrogen from phosphorus pentoxide. ^{1}H and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz, respectively, on a JEOL JNM-GX 270 spectrometer using tetramethylsilane as the internal reference in $CDCl_3$. Infrared spectra were recorded on a JASCO A-3 spectrometer. Column chromatography was performed with silica gel (Merck, Art 7734). Analytical TLC was performed on Merck (Art 5715) precoated silica gel plates (0.25 mm). Optical purity was determined on a Shimadzu capillary gas chromatograph 14A with a chiral capillary column (Astec Chiraldex B-DA, 30 m). Optical rotation was measured on a JASCO DIP-140 polarimeter.

3.2. Preparation of *1a* and *1b*

A solution of pyridine-2,6-dicarboxylic acid dimethyl ester (1.95 g, 10 mmol) and 2-aminoethanol (0.6 ml, 10 mmol) in toluene (30 ml) was heated at 100°C for 30 min. The corresponding monoamide methyl ester **9** (1.24 g, 55%) was obtained after silica gel chromatography. Then, the monoamide **9** (1.8 g, 8.0 mmol) and (*S*)-valinol (1 g, 10 mmol) in xylene (15 ml) was heated at 120°C for ca. 1 day. At 65°C, $SOCl_2$ (3.4 ml) was added to the mixture, which was stirred for a further 16 h. Hydrolysis and chromatography gave the bis-amide chloride **10** (2.46 g) in ca. 93%. Finally, the bis-amide **10** (1.83 g, 5.5 mmol) was treated with NaH (ca. 16 mmol) in THF (40 ml) at 35°C for 30 min to produce the desired pybox **1a** (1.33 g, 5.1 mmol, 93%). Compound **1b** was prepared by the same procedure with (*S*)-2-*t*-butyl-2-aminoethanol. **1a**: m.p. 149–150°C; $[\alpha]_D^{22}=-65.1$ (c=1.01, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ=0.94 (d, *J*=6.8 Hz, 3H), 1.05 (d, *J*=6.8 Hz, 3H), 1.88 (m, 1H), 4.09–4.26 (m, 4H), 4.50–4.57 (m, 3H), 7.84 (t, *J*=7.8 Hz, 1H), 8.15 (dd, *J*=7.8 Hz and 1.0 Hz, 1H), 8.21 (dd, *J*=7.8 Hz and 1.0 Hz, 1H). **1b**: m.p. 173–174°C; $[\alpha]_D^{22}=-58.0$ (c=1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ=0.97 (s, 9H), 4.08–4.16 (m, 3H), 4.33 (t, *J*=8.9 Hz, 1H), 4.44–4.58 (m, 3H), 7.86 (t, *J*=7.8 Hz, 1H), 8.16 (dd, *J*=7.8 Hz, and 1.6 Hz, 1H), 8.26 (dd, *J*=7.8 Hz and 1.6 Hz, 1H).



9



10

3.3. Isolation of 8

A solution of 2,6-di-*t*-butyltolyl diazoacetate **3h** (52 mg, 0.2 mmol) in CH_2Cl_2 (1 ml) was added to the solution of the pybox **1a** and $[RuCl_2(p\text{-cymene})]_2$ (61 mg, 0.1 mmol) in CH_2Cl_2 (4 ml) under *cis*-2-butene atmosphere. The mixture was stirred at 20°C for 2 h. After concentration, the residue was charged onto a silica gel column at 0°C with CH_2Cl_2:acetone (10:1–5:1) as eluent. The dark brown band was collected and the eluent was concentrated to give brown solids of **8** (92 mg, 0.13 mmol) in 67% yield: m.p. 119–120°C (dec): ^{1}H NMR (CD_2Cl_2): δ=0.69 (d, *J*=7.3 Hz, 3H), 0.78 (d, *J*=7.3 Hz, 3H), 1.43 (s, 9H), 1.47 (s, 9H), 1.94 (m, 1H), 2.36 (s, 3H), 3.83 (dd, *J*=10.8 Hz, 2H), 4.05 (m, 2H), 4.77 (m, 1H), 4.86–5.00 (m, 3H), 7.20 (s, 2H), 8.02 (d, *J*=7.7 Hz, 1H), 8.04 (d, *J*=7.7 Hz, 1H), 8.23 (t, *J*=7.7 Hz, 1H), 21.68 (s, 1H); ^{13}C NMR (CD_2Cl_2): δ=15.0, 19.3, 21.6, 28.8, 31.1, 32.2, 32.4, 36.1, 36.2, 57.2, 71.4, 73.0, 73.5, 123.7, 123.9, 127.5, 134.8, 140.0, 141.6, 142.0, 143.7, 146.1, 163.4, 182.8, 304.8; IR (KBr disk): 1717 cm^{-1}.

3.4. Cyclopropanation of styrene and diazoacetate with 1 and 3

To a solution of **1** (0.14 mmol), **2** (0.05 mmol), and styrene (10 mmol) in dichloromethane (1 ml) was added a dichloromethane solution of diazoacetate **3** (2.0 mmol, ca. 1 N) through a microsyringe controlled by mechanical feeder (ca. 4 ml/drop, ca. 0.4 ml/h) for 5 h at 30–35°C under an argon atmosphere. After stirring for an additional 5 h, the mixture was concentrated under reduced pressure. The residual oil was subjected to silica gel column chromatography with hexane–ether as eluent to give an oily mixture of *trans*-2-phenylcyclopropane-1-carboxylate **4t** and the *cis*-isomer **4c**. After the products were converted to the corresponding methyl ester, their enantiomeric purities were measured by GLPC (Astec, Chiraldex B-DA, 30 m×0.25 mm). See the detail in the literature.[3b]

References

1. (a) I. Ojima, *Catalytic Asymmetric Synthesis*, VCH, New York, 1993. (b) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Sons, Inc., New York, 1994, p. 199. (c) L. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, John Wiley & Sons, Inc., New York, 1995. (d) M. P. Doyle, *Advances in Catalytic Processes, Vol. 2*, JAI Press, London, 1997. (e) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry*, **1998**, *9*, 1.
2. (a) J. K. Whitesell, *Chem. Rev.*, **1989**, *89*, 1581. (b) S. L. Blystone, *Chem. Rev.*, **1989**, *89*, 1663.
3. (a) H. Nishiyama, Y. Itoh, H. Matsumoto, S.-B. Park, K. Itoh, *J. Am. Chem. Soc.*, **1994**, *116*, 2223. (b) H. Nishiyama, Y. Itoh, Y. Sugawara, H. Matsumoto, K. Aoki, K. Itoh, *Bull. Chem. Soc. Jpn*, **1995**, *68*, 1247 and references cited therein.
4. (a) S.-B. Park, N. Sakata, H. Nishiyama, *Chem. Eur. J.*, **1996**, *2*, 303. (b) H. Nishiyama, K. Aoki, H. Itoh, T. Iwamura, N. Sakata, O. Kurihara, Y. Motoyama, *Chem. Lett.*, **1996**, 1071.
5. In Ref. 1d (p. 180), we described the molecular orbital calculation of $RuCl_2$(pybox)(CH_2); the conformational isomer, having a 0° dihedral angle between the plane of Cl–Ru–Cl and CH_2, is a more stable isomer than the other isomer having a 90° angle on the basis of extended Hückel calculation.
6. The cyclopropanation with the diazoacetate **3h** and styrene did not proceed under the same condition at 60°C for entry 8.
7. We also confirmed that complex **8** acts as a catalyst of the cyclopropanation described above.