## (S)-(-)- and (R)-(+)-4-Methyl-2-hydroxymethyl[2]paracyclo-[2](5,8)quinolinophane: Novel N,O-Planar Chiral Catalysts for the Enantioselective Addition of Diethylzinc to Aldehydes

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**Abstract:** Novel planar chiral N,O-ligands derived from (R)-(+)and (S)-(-)-2,4-dimethyl[2]paracyclo[2](5,8)quinolinophane were synthesized and employed as catalyst in the enantioselective addition of diethylzinc to aromatic aldehydes. On the basis of the ee values, ranging from 30% to 75%, and the configuration of the obtained 1-phenyl-1-propanols a plausible structure of the transition state for the alkylation process of the aldehydes is discussed.

**Key words:** amino-alcohols, cyclophanes, ligands, planar chirality, stereoselective additions, zinc

Stereoselective addition of dialkylzinc reagents to aldehydes catalysed by N,O-type chiral ligands is the most common and effective method to prepare chiral secondary alcohols.<sup>1</sup> Since the pioneer work of Oguni and Omi,<sup>2</sup> many researchers have attempted this reaction, developing at the same time an impressive number of chiral ligands, mostly  $\beta$ -aminoalcohols, by obtaining very high standard of asymmetric induction. Chiral systems belonging to different chirality classes have been investigated: central, C2-symmetric and planar chiral ligands, among which ferrocene-derived  $\beta$ - and  $\gamma$ -aminoalcohols have been the most studied systems.<sup>3</sup> In some cases the planar chirality is associated with that of a side-chain chiral carbon atom, so that it is very difficult to assess the contribution of each chirality class.<sup>4</sup> Among the reported planar chiral catalysts for stereoselective dialkylzinc addition to carbonyl compounds, those derived from [2.2]paracyclophane have received little attention, in spite of their higher resistance to oxidation and their stability at relatively high temperatures compared with arene and cyclopentadienederived transition metal complexes. In this respect, good stereoselectivities have been observed with a C2-symmetric bis[5-(4-hydroxy[2.2]paracyclophanyl]methane-Ti(i- $PrO_{4}$  complex.<sup>5</sup> More recently, the synthesis of N,O-type chiral [2.2]paracyclophane ligands and their application as catalyst in the dialkylzinc addition to aromatic aldehydes have been reported. However, once again, the presence of a chiral centre in the side-chain oxazoline N-tooth make difficult the effective role of the planar chirality to be assessed in determining the observed enantiomeric excess.<sup>6</sup> Our experience in the synthesis of chiral [2.2]paracyclophane derivatives<sup>7</sup> prompted us to study the role of the planar chirality in inducing stereoselectivity by using a new N,O-type [2.2]paracyclophane-derived chiral catalyst for the diethylzinc addition to aromatic aldehydes. The basic idea originated from the observation that the proximity of the reaction centre to the ethylene bridge of the [2.2]paracyclophane moiety in the transition state of a transition metal-catalysed reaction is crucial for the enantioselection. In this respect, we found that N-acetyl- and N-propionyl derivative of (R)-(+)-[2.2]paracyclophano[4,5-d]-oxazol-2(3H)-one used as chiral auxiliary gave good enantioselectivity results in the Bu<sub>2</sub>BOTf/Et<sub>3</sub>N-promoted aldol condensation with benzaldehyde. The results were explained by the steric interaction of the phenyl ring with the ethylene bridge of the [2.2]paracyclophane moiety which preclude the attack on one face of the aldehydic carbonyl group.8

In this paper we describe a simple procedure for the synthesis of (S)-(-)- and (R)-(+)-2-hydroxymethyl-4-methyl[2]paracyclo[2](5,8)quinolinophane [(S)-(-)-1 and (R)-(+)-1, respectively] and their use as a catalyst in the diethylzinc addition to aromatic aldehydes. An 87% overall yield of (S)-(+)-4-amino[2.2]paracycophane [(S)-(+)-5] was obtained from the corresponding (S)-(+)-4-carboxy[2.2]paracycophane [(S)-(+)-2] by Curtius rearrangement of the intermediate acylazide (S)-3 in anhydrous toluene followed by the hydrolysis of the resulting isocyanate (S)-4 with 40% aqueous tetrabutylammonium hydroxide in tetrahydrofuran at room temperature (Scheme).

The reaction of (S)-(+)-**5** with 2,4-pentanedione at room temperature, followed by cyclisation of the resulting ketoimine (S)-**6** in polyphosphoric acid at 75 °C, afforded the (S)-(-)-2,4-dimethyl[2]paracyclo[2](5,8)quinolinophane [(S)-(-)-**7**] in 65% yield (57% overall yield from (S)-(+)-**2**). Finally, the regioselective metalation of [(S)-(-)-**7**] with butyllithium in diethyl ether, at 20 °C,<sup>9</sup> and successive reaction with bis(trimethylsilyl)peroxide,<sup>10</sup> at -75 °C, afforded (S)-(-)-**1** in 79% yield (45% overall yield from (S)-(+)-**2**).<sup>11</sup> Starting from the enantiomeric acid (R)-(-)-**2**, the corresponding quinolinophane (R)-(+)-**1** was also prepared.<sup>12</sup>

(S)-(-)-1 was employed as a catalyst for the stereoselective addition of diethylzinc to the aromatic aldehydes performed in the classical way.<sup>13</sup>

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Scheme a) SOCl<sub>2</sub>, NaN<sub>3</sub>, acetone/H<sub>2</sub>O, r.t.; b) Toluene reflux, 97% from (*S*)-(+)-2; c) 50% aq Bu<sub>4</sub>NOH, THF, r.t., 90%; d) acetylacetone, r. t. 2 h; e) (H<sub>3</sub>PO<sub>4</sub>)<sub>n</sub>, 75 °C, 48 h, 65% from (*S*)-(+)-5; f) BuLi, Et<sub>2</sub>O, -40 °C, (Me<sub>3</sub>SiO)<sub>2</sub>, H<sub>3</sub>O<sup>+</sup>, 79% from (*S*)-(-)-7, 45% from (*S*)-(+)-2.

Reaction of diethylzinc with the aldehydes **8a–h** in the presence of (S)-(-)-**1** (0.1 equiv) in toluene at 20 °C afforded (+)-(R)-1-aryl-1-propanols **9a–h** in good yields with the *ee* ranging from 30 to 75%. Results are reported in the Table.

An increase of enantioselectivity was observed when the  $Et_2Zn/aldehyde$  molar ratio was increased, the optimal one being 5:1. This in accord with the finding of Noyori regarding the presence of different catalytic species in equilibrium in solution, the most effective one predominating at the highest concentration of diethylzinc.<sup>14</sup> The low temperatures bias both the yield and the enantioselectivity, while the reaction time increases considerably favouring the competing reduction of the aldehyde to benzylic alcohol (**10**). The absolute *R* configuration of the main enantiomer observed for all the 1-aryl-1-propanols and similar values of the optical rotation suggest a transition state structure for the transfer of the ethyl from zinc to the formyl group as depicted below (Figure).

Coordination of the carbonyl oxygen on the zinc atom of the catalytic species formed by reaction of (S)-(-)-**1** with diethyl zinc occurs at the less hindered side of the N-Zn-O heterocyclic ring (Figure). The steric interaction between the aldehydic hydrogen and the ethyl group on the



Figure

zinc atom is probably responsible for the enantioselectivity of the process. Semi-empiric calculations show that transition state **11a** is about 0.9 kcal/mol more stable than **11b**, which is compatible with the observed *ee* values. According to the most reliable pattern now accepted for this kind of processes,<sup>1c</sup> the ethyl group of a second molecule of diethylzinc in **11a** attacks the *re* face of the carbonyl group to give the (*R*)-(+)-1-aryl-1-propanol as the main enantiomer.

Although the enantioselectivities observed with this ligand are far from the standard achieved with other chiral  $\beta$ -aminoalcohols, the present work is one of the few examples of an N,O-type catalyst for the enantioselective alkylation of aromatic aldehydes exhibiting pure planar chirality.

A planar-chiral heterocyclic ligand that is structurally similar to (S)-(-)-1, but belonging to the ferrocene series, was used by Fu in the diethylzinc addition to benzaldehyde.<sup>15</sup> With this catalyst too, modest enantioselectivities were observed (ee 51%). No mechanistic hypothesis was advanced to account for the (S)-configuration of the main enantiomer obtained with (R)-(-)-ligand, although the same mechanism suggested for the reaction with (S)-(-)-1 could be invoked. Other homocyclic ferrocene-derived yamino-alcohols exhibiting pure planar chirality gave unsatisfactory ee values. The poor enantioselectivity found with this class of catalyst can most probably be imputed to the small differences between the conformational stabilities of the transition states like **11a** and **11b**.<sup>16</sup> Pure planar chirality, at least in this type of ligand, does not seem to allow a high standard of enantioselectivity, unless substantial modification are made in the OH-bringing sidechain.15

Work aimed at increasing the performance of this catalyst by structural changes in the side-chain hydroxymethyl, as well as in the dialkylzinc reagent, is currently in progress.

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Table Reaction of Diethylzinc with Aldehydes 8a–h catalysed by (S)-(–)-1 and (R)-(+)-1 (0.1 equiv) in toluene at 20 °C

Q	Ç	ЭН	ŎН		
$Y_{U}^{fr}$ + Zn(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> (S)-(-)-1 (0.1 Toluene, 20	eq.) °C Y <sup>∥</sup>	~ <sub>+</sub>	Y		
8a-h	9a-h		10a-h		
Aldehyde	Catalyst, (10%)	t (h)	Yield <b>9a–h</b> (%)	10a-h (%)	ee <sup>a</sup> (Config.)
2-Naphthaldehyde ( <b>8a</b> )	[( <i>S</i> )-(-)- <b>1</b> ]	14	93	7	66 ( <i>R</i> ) <sup>b</sup>
	[(S)-(-)-1]	110	33	50	$61 (R)^{c}$
	[( <i>R</i> )-(+)- <b>1</b> ]	21	74	10	$46 (S)^{d}$
	[( <i>S</i> )-(-)- <b>1</b> ]	14	97	3	75 ( <i>R</i> )
Benzaldehyde (8b)	[( <i>S</i> )-(-)- <b>1</b> ]	5	99	1	64 ( <i>R</i> )
4-(Trifluoromethyl)benzaldehyde (8c)	[( <i>S</i> )-(-)- <b>1</b> ]	5	93	1	70 ( <i>R</i> ) <sup>e</sup>
3,5-Bis(trifluoromethyl)benzaldehyde (8d)	[( <i>S</i> )-(-)- <b>1</b> ]	3	95	1	62 ( <i>R</i> )
3-Anisaldehyde (8e)	[( <i>S</i> )-(-)- <b>1</b> ]	8	85	6	66 ( <i>R</i> )
4-Anisaldehyde ( <b>8f</b> )	[( <i>S</i> )-(-)- <b>1</b> ]	17	86	5	61 ( <i>R</i> )
3-Pyridinecarboxaldehyde (8g)	[( <i>R</i> )-(+)- <b>1</b> ]	3	100	-	30 ( <i>S</i> )
Cinnamaldehyde (8h)	[( <i>S</i> )-(-)- <b>1</b> ]	3	98	2	42 ( <i>R</i> )

<sup>a</sup> Determined by HPLC analysis of the crude reaction mixture on a DAICEL OD-H column using mixtures of hexane/isopropanol as the eluent.

<sup>b</sup> A 2:1 Et<sub>2</sub>Zn/aldehyde molar ratio was used.

<sup>c</sup> Reaction performed at 0 °C.

<sup>d</sup> 0.02 Equiv of catalyst was employed.

<sup>e</sup> Determined by HPLC analysis of the corresponding acetate on a DAICEL OJ column using hexane as the eluent.

## References

- (a) Pu, L.; Yu, H.-B. Chem. Rev. 2001, 101, 757. (b) Soai, K.; Niwa, S. Chem. Rev. 1992, 92, 833. (c) Noyori, R.; Kitamura, M. Angew. Chem., Int. Ed. Engl. 1991, 30, 49.
- (2) (a) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823.
  (b) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841.
- (3) Dosa, P. I.; Ruble, J. C.; Fu, G. C. J. Org. Chem. **1997**, 62, 444.
- (4) (a) Watanabe, M.; Araki, S.; Butsugan, Y. J. Org. Chem.
  1991, 56, 2218. (b) Uemura, M.; Miyake, R.; Nakayama, K.; Shiro, M.; Hayashi, Y. J. Org. Chem. 1993, 58, 1238.
  (c) Malfait, S.; Pélinski, L.; Brocard, J. Tetrahedron: Asymmetry 1998, 9, 2595. (d) Malézieux, B.; Andrés, R.; Gruselle, M.; Rager, M.-N.; Thorimbert, S. Tetrahedron: Asymmetry 1999, 10, 3253. (e) Bolm, C.; Muñiz-Fernández, K.; Seger, A.; Raabe, G.; Günther, K. J. Org. Chem. 1998, 63, 7860.
- (5) Rozenberg, V. I.; Antonov, D. Y.; Zhuravsky, R. P.; Vorontsov, E. V.; Khrustalev, V. N.; Ikonnikov, N. S.; Belokon, Y. N. *Tetrahedron: Asymmetry* **2000**, *11*, 2683.
- (6) (a) Dahmen, S.; Bräse, S. Chem. Commun. 2002, 26.
  (b) Wu, X.-W.; Hou, X.-L.; Dai, L.-X.; Tao, J.; Cao, B.-X.; Sun, J. Tetrahedron: Asymmetry 2001, 12, 529.
- (7) (a) Cipiciani, A.; Fringuelli, F.; Mancini, V.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. J. Org. Chem. 1997, 62, 3744.
  (b) Cipiciani, A.; Fringuelli, F.; Mancini Piermatti, O. F.; Scappini, A. M.; Ruzziconi, R. Tetrahedron 1997, 53, 11853. (c) Rosini, C.; Ruzziconi, R.; Superchi, S.; Fringuelli, F.; Piermatti, O. Tetrahedron: Asymmetry 1998, 9, 55.

- (8) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *Chem. Lett.* **2000**, 38.
- (9) Kaiser, E. M.; Bartling, G. J.; Thomas, W. R.; Nochols, S. B.; Nash, D. R. J. Org. Chem. 1973, 38, 71.
- (10) Ricci, A.; Taddei, M. Synthesis 1986, 633.
- (11) (*S*)-(-)-**1** [45% from (*S*)-(+)-**2**]. Mp 116–118 °C (from diethyl ether).  $[\alpha]_{\rm D}^{20}$ –16.0 (*c* 0.50, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 6.93 (s, 1 H), 6.90 (d, *J* = 7.3 Hz, 1 H), 6.80 (d, *J* = 7.3 Hz, 1 H), 6.46 (s, 2 H), 5.72 (d, *J* = 7.8 Hz, 1 H), 5.46 (d, *J* = 7.8 Hz, 1 H), 4.93–4.80 (four peaks, AB system, *J* = 15.0 Hz, 2 H), 4.88 (br s, 1 H), 4.28–4.25 (m, 1 H), 3.84 (dd, *J* = 14.0 and 9.2 Hz, 1 H), 3.19–2.92 (m, 5 H), 2.68 (s, 3 H), 2.61–2.50 (m, 1 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  = 155.0, 148.4, 144.3, 139.4, 138.8, 137.8, 137.3, 133.7, 132.8, 132.5, 131.3, 129.6, 128.2, 127.8, 119.8, 63.4, 37.6, 35.2, 34.4, 31.9, 22.8. IR: (CHCl<sub>3</sub>) 3417 cm<sup>-1</sup>(broad, OH). Anal. Calcd for C<sub>21</sub>H<sub>21</sub>NO: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.20; H, 6.99; N, 4.54.
- (12) Chiral [2]paracyclo[2](5,8)quinolinophane and some derivatives were first isolated from semi-preparative chiral HPLC of the racemic mixture in turn obtained in poor overall yield by condensation of 5,8-bis(bromomethyl)quinolines with 1,4-bis(mercaptomethyl)benzene followed by sulphur extrusion. CD spectra of the resolved enantiomers were reported without configuration assignement: Wörsdörfer, U.; Vögtle, F.; Glorius, F.; Pfaltz, A. *J. Prakt. Chem.* **1999**, *341*, 445.
- (13) Typical Procedure. Diethylzinc (3.3 mL, 0.1 M in toluene, 3.3 mmol) was added by a syringe to a solution of [(*S*)-(-)-1] (20 mg, 0.066 mmol) in dry toluene (3 mL) under nitrogen at 20 °C and the mixture was allowed to react for 20 min. The aldehyde (0.66 mmol) was added and the mixture was

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made to react at 20 °C until it completely disappeared (monitored by GLC). Sat. aq NH<sub>4</sub>Cl was added (10 mL) and the mixture was extracted with diethyl ether ( $3 \times 20$  mL). The collected organic phases were washed with water, dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated. Preparative TLC on silica gel (eluent, petroleum ether/diethyl ether mixtures) allowed the corresponding 1-aryl-1-propanols to be isolated. The *ee* was determined by HPLC of the alcohols

or their derivatives on different chiral columns depending on the structure of the alcohol by using hexane/isopropanol mixtures as the eluent.

- (14) Kitamura, M.; Okada, S.; Surga, S.; Noyori, R. J. Am. Chem. Soc. **1989**, *111*, 4028.
- (15) Dosa, P. I.; Ruble, J. G.; Fu, G. J. Org. Chem. 1997, 62, 444.
- (16) Nicolosi, G.; Patti, A.; Morrone, R.; Piattelli, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1642.