

# N/N/O versus N/O/O and N/O amino isoborneols in the enantioselective ethylation of benzaldehyde

Tomás de las Casas Engel, Beatriz Lora Maroto, Antonio García Martínez and Santiago de la Moya Cerero\*

*Departamento de Química Orgánica I de la Universidad Complutense de Madrid, Facultad de Ciencias Químicas, Ciudad Universitaria s/n, 28040 Madrid, Spain*

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**Abstract**—Enantiopure 10-(4-methylpiperazin-1-yl)isoborneol, a N/N/O-tridentate chiral diamino isoborneol, has been obtained from enantiopure ketopinic acid and its catalytic activity (as chiral ligand in the enantioselective addition of diethylzinc to benzaldehyde) measured and compared with the previously reported data for related N/N/O, N/O/O, and N/O isoborneols. It is demonstrated that the pentacoordinated-zinc Oppolzer's model for transition states is useful for explaining the catalytic behavior of N/N/O-tridentate ligands. In such cases, stable *syn*- or *anti*-type transition states can be proposed depending on the catalyst's conformational flexibility. © 2008 Elsevier Ltd. All rights reserved.

## 1. Introduction

The enantioselective addition of organozinc reagents to aldehydes catalyzed by chiral ligands<sup>1</sup> is one of the most important asymmetric processes of synthetic utility, since the optically active secondary alcohols obtained are the key intermediates for the preparation of important biologically active compounds (including several synthetic drugs) and new materials with interesting optical properties.<sup>2</sup>

Since Noyori et al. demonstrated the high efficiency of 3-*exo*-(dimethylamino)isoborneol (DAIB) **1** (Fig. 1), an N/O-bidentate  $\beta$ -amino alcohol, as a chiral ligand for the enantioselective addition of diethylzinc to benzaldehyde,<sup>3</sup> explaining such activity in terms of activated bimetallic species formed from a reactive zinc-chelate catalyst,<sup>4</sup> many

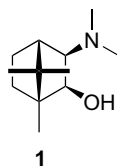


Figure 1. DAIB, a N/O-bidentate chiral amino alcohol.

other chiral N/O-bidentate ligands, specially  $\beta$ -amino alcohols,<sup>5</sup> have been prepared and tested in this reaction. On the other hand, chiral ligands with three coordination sites have been far less studied.<sup>6,7</sup>

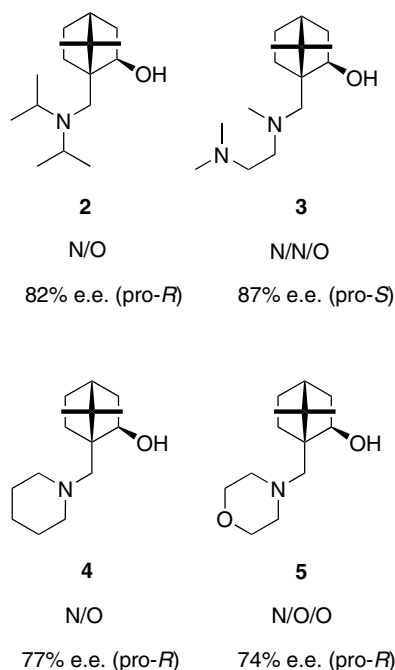
It is expected that a tridentate chiral ligand should confer more rigidity to the reactive zinc-chelate catalyst than a bidentate one, and thus may enhance the enantioselectivity of the addition reaction.<sup>7d</sup> Nevertheless, the role played by the third coordination site is more complicated and unknown. Thus, the very few reported comparison studies between bidentate and tridentate ligands<sup>7</sup> show different tendencies, from unchanged enantioselectivities<sup>7b,d</sup> to enantioselectivity reversal.<sup>7a</sup>

Herein we report the factors controlling the catalytic activity of tridentate amino alcohols as chiral ligands for the enantioselective addition of diethylzinc to benzaldehyde, by a comparison of the catalytic behavior of a series of N/O, N/N/O, and N/O/O 10-aminoisoborneols described previously by Oppolzer and Aoyama, with a new related N/N/O ligand obtained and tested by us.

## 2. Results and discussion

In 1988, Oppolzer described that both N/O amino isoborneol **2** and N/N/O diamino isoborneol **3** (Fig. 2) are able to

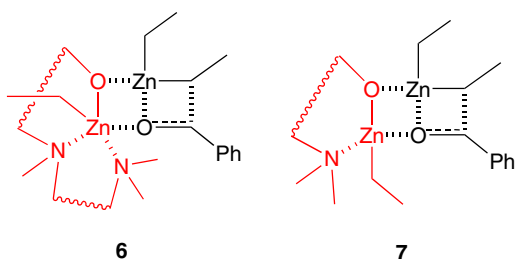
\* Corresponding author. Tel.: +34 91 394 5090; fax: +34 91 394 4103; e-mail: [santmoya@quim.ucm.es](mailto:santmoya@quim.ucm.es)



**Figure 2.** Previously described catalytic activities for related isoborneol-based N/O, N/N/O, and N/O/O ligands.

catalyze the enantioselective addition of diethylzinc to benzaldehyde with high and similar enantioselectivities (82% and 87% ee), but with a reversal of the sense of enantioselection.<sup>7a</sup> Fifteen years later, Aoyama described the same enantioselection grade (near 75% ee) and sense of enantioselection (pro-*R*) for both N/O amino isoborneol **4** and N/O/O oxoamino isoborneol **5** (Fig. 2).<sup>8</sup>

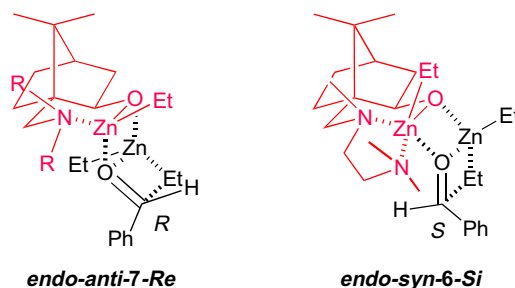
In the seminal work of Oppolzer, the enantioselection reversal exhibited by **3** was explained on the basis of its tridentate character, which makes possible the formation of bimetallic transition states with a pentacoordinated catalytic zinc atom.<sup>7a</sup> This pentacoordinated-zinc transition-state model of Oppolzer **6** is different to the tetracoordinated-zinc model **7**, initially proposed by Noyori for bidentate DAIB<sup>4</sup> (Fig. 3).



**Figure 3.** Pentacoordinated-zinc Oppolzer's transition-state model **6** and tetracoordinated-zinc Noyori's one **7**. Zinc-chelate catalyst in red.

Application of Noyori's model to bidentate amino isoborneols **2** or **4** predicts the (pro-*R*) TS (transition state) *endo-anti-7-Re*<sup>9</sup> (Fig. 4) to be the most stable,<sup>10</sup> which is in agreement with the sense of enantioselection found

(Fig. 2) whereas application of the Oppolzer's model to tridentate diamino isoborneol **3** predicts the (pro-*S*) *endo-syn-6-Si* (Fig. 4),<sup>7a,11</sup> also in agreement with the experimental data shown in Figure 2.



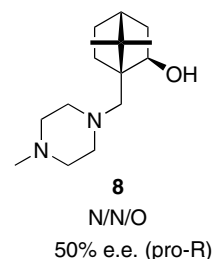
**Figure 4.** Proposed most stable TS for bidentate **2**, **4** or **5** (*endo-anti-7-Re*, by the application of Noyori's transition-state model) and for tridentate **3** (*endo-syn-6-Si*, by the application of Oppolzer's transition-state model). Zinc-chelate catalyst in red.

On the other hand, N/O/O Aoyama's ligand **5** (pro-*R*) must act as a simple N/O-bidentate ligand, similar to analogous pro-*R* ligands **2** and **4** (see Fig. 2). This fact can be easily explained due to the low coordinative character of the second oxygen of **5** (ether oxygen), when compared with the second nitrogen of **3** (amine nitrogen).

For testing such hypotheses, we were interested in studying the catalytic behavior of a new N/N/O ligand of the type of **3**, that is, a 10-[(2-aminoethyl)amino]isoborneol. This new analogue should act as a tridentate ligand and its catalytic activity should be explained on the basis of a stable Oppolzer's pro-*S* TS of the type of *endo-syn-6-Si* (see Fig. 4).

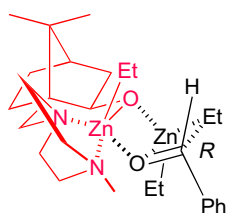
Following this line, we obtained (1*R*)-10-(4-methylpiperazin-1-yl)isoborneol **8**<sup>12</sup> from commercial (1*S*)-ketopinic acid in two steps (amidation with piperazine<sup>13</sup> followed by reduction with LAH,<sup>14</sup> overall yield: 82%) and studied its catalytic activity in the enantioselective addition of diethylzinc to benzaldehyde<sup>15</sup> (Fig. 5).

Surprisingly, instead of the expected (pro-*S*) catalytic activity for **8**, a moderate (pro-*R*) enantioselection was observed (Fig. 5, 50% ee). In principle, this experimental fact seemed to indicate that **8** is acting in the reaction in a similar manner as (pro-*R*) amino isoborneols **2**, **4**, or **5**; that is, as a simple N/O bidentate ligand. On the other hand, a comparison between the use of bidentate ligands **2**, **4**, or **5**, and new ligand **8** shows a considerable enantioselection-degree



**Figure 5.** Catalytic activity of N/N/O ligand **8**.

diminution (Fig. 2). However, we believe that the extraordinary similarity between the structures of **3** and **8** (see Figs. 2 and 5) makes it not possible to discard a tridentate behavior for **8**. In this sense, ligand **8** must be able to generate Oppolzer-type pentacoordinated-zinc transition states (type **6** in Fig. 6), as tridentate ligand **3** does. Nevertheless, the mentioned similarity is not enough to maintain the structure (absolute configuration) for the most stable TS (controller of the enantioselection sense). Thus, while *endo-syn-6-Si* was proposed by Oppolzer as the most stable TS for N/N/O-tridentate ligand **3** (see Fig. 4),<sup>7a</sup> we now propose *endo-anti-6'-Re* as the most stable one for N/N/O-tridentate ligand **8** (Fig. 6).<sup>16</sup>



*endo-anti-6'-Re*

**Figure 6.** Proposed most stable TS for ligand **8** (*endo-anti-6'-Re*, by application of Oppolzer's transition-state model). Zinc-chelate catalyst in red.

This difference between **3** and **8** can be explained on the basis of the catalyst's conformational flexibility (with a flexible six-membered zinc-chelate ring), and its modulation by the type of geometry imposed by the second-nitrogen coordination. Thus, the simple ethylene bridge joining the two nitrogens in ligand **3** gives place to a set of relatively flexible pentacoordinated-zinc transition states of type **6**. This TS flexibility, joined to the fact that the catalyst's zinc-ethyl group (red ethyl) is folded over the catalyst in such pentacoordinated-zinc transition states (note the different disposition of such ethyl group in both tetracoordinated-zinc *endo-anti-7-Re* and pentacoordinated-zinc *endo-syn-6-Si*, Fig. 4), makes favorable a *syn* assembly of the reacting species to the catalyst, which agrees with Oppolzer's suggestion of *endo-syn-6-Si* as the most stable TS for **3**. Nevertheless, the introduction of a second ethylene bridge between the nitrogens in ligand **8** makes the corresponding set of pentacoordinated-zinc transition states more rigid. This increase in rigidity would disfavor the *syn* assemblies for the transition states, to the advantage of the *anti* ones. This return to favored *anti*-type transition states, initially proposed by Noyori for N/O-bidentate ligands<sup>4</sup> (i.e., *endo-anti-7-Re*), agrees with the suggestion of *endo-syn-6'-Si* as the most stable TS for **8** (note the minimal steric interaction between the close benzaldehyde's hydrogen and catalyst's zinc ethyl).

### 3. Conclusion

In conclusion, it has been demonstrated that: (1) Oppolzer's transition-state model (pentacoordinated zinc) is a useful model for explaining the catalytic behavior of N/N/O-tridentate 10-amino isoborneols, (2) a high conforma-

tional flexibility for the catalyst energetically favors the formation of *syn*-type transition states, whereas low catalyst flexibility favors the formation of *anti* ones, and (3) the catalyst's flexibility can be modulated by the structure of the nitrogen–nitrogen link.

### Acknowledgments

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- Endo* versus *exo* indicates the coordination face of the reacting species to the catalyst's Zn–O bond. *syn* versus *anti* indicates the relative disposition of both zinc-ethyl groups. *Re* versus *Si* indicates the carbonyl face on which the ethyl transference occurs.
- Note*: (1) the most favored coordination of the reacting species by the less hindered catalyst's *endo* face, (2) the most favored less-hindered *anti* disposition for both zinc-ethyl

- groups, and (3) the minimal steric interaction for benzaldehyde's phenyl group.
- In this case, the geometry imposed by the pentacoordinated zinc allows the *syn* disposition of both zinc-ethyl groups (both *syn* groups are now more separated).
  - White solid. Mp: 65–66 °C.  $[\alpha]_D^{20} = -66.2$  (*c* 0.38, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz): 3.93 (dd, *J* = 7.87, 3.86, 1H), 2.77 (d, *J* = 13.22, 1H), 2.44 (br s, 8H), 2.27 (d, *J* = 13.22, 1H), 2.26 (s, 3H), 1.89–1.19 (several m, 7H), 1.13 (s, 3H), 1.08–0.84 (m, 1H), 0.79 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz): 78.2, 58.7, 55.3, 54.7, 50.8, 45.9, 44.7, 39.0, 34.0, 27.6, 20.4, 20.4. FTIR: 3207.5 (str.). MS (%): 252 (7), 234 (6), 219 (11), 113 (26), 100 (61), 71 (100), 57 (99). HRMS: 252.2203 (calcd for C<sub>15</sub>H<sub>28</sub>N<sub>2</sub>O: 252.2202).
  - (1*S*)-Ketopinic acid (5.0 mmol) and SOCl<sub>2</sub> (5.2 mmol) were refluxed in anhydrous THF for 15 min. The reaction mixture was then cooled down to 0 °C and 4-methylpiperazine (10.5 mmol) slowly added. After that, the reaction mixture was stirred for 1 h at rt. Standard work-up (extraction and acid- and base-washing) yield pure amide in 98% yield. Excess of the amine can be recovered from the aqueous acid extract.
  - Standard LAH reduction in refluxing THF (for example, see Ref. 8). Yield: 84%.
  - Under argon, diethylzinc (1.0 M in hexane, 2 mL, 2.0 mmol) was added to ligand **8** (0.050 mmol) in anhydrous hexane (1 mL) and the mixture stirred for 1 h at rt. After that, freshly distilled benzaldehyde (1.0 mmol) was slowly added and the resulting mixture stirred for 5 h at rt. Final treatment with 1 N HCl at 0 °C and standard work up (see Ref. 8) yielded the resulting scalemic mixture of 1-phenylpropan-1-ol. Yield: 99%. The ee (50%) was determined GC (cyclodex-B). The dominant configuration was determined by both the sign of the mixture's specific rotation and the elution time in chiral GC.
  - Piperazine ring shows a preference for the boat conformation in the coordination with different metals including Zn(II). For example, see: (a) Bharati, K. S.; Sreedaran, S.; Rahiman, A. K.; Rajesh, K.; Narayanan, V. *Polyhedron* **2007**, *26*, 3993; (b) Valks, G. C.; McRobbie, G.; Lewis, E. A.; Hubin, T. J.; Hunter, T. M.; Sadler, P. J.; Pannecouque, C.; De Clercq, E.; Archibald, S. J. *J. Med. Chem.* **2006**, *49*, 6162; (c) Nuutinen, J. M. J.; Ratilainen, J.; Rissanen, K.; Vaniootalo, P. *J. Mass Spectrom.* **2001**, *36*, 902.