Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1–4

TETRAHEDRON: *ASYMMETRY*

Bridgehead-norbornane-derived β-amino alcohol catalysts: structural factors influencing the chirality transfer

Antonio García Martínez,[a] Enrique Teso Vilar,[b,*] Amelia García Fraile,[b] Santiago de la Moya Cerero,[a,*] Paloma Martínez-Ruiz[a] and Paloma Chicharro Villas[a]

[a]*Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Ciudad Universitaria s/n, E-28040 Madrid, Spain*

[b]*Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, c/ Senda del Rey 9, 28040 Madrid, Spain*

Received 10 December 2001; accepted 8 January 2002

Abstract—Five new optically active bridgehead-norbornane-derived β-amino alcohols with different substitution patterns have been obtained using a straightforward procedure from commercial (+)-camphor or (−)-fenchone, and tested as chiral catalysts in the enantioselective diethylzinc-addition to benzaldehyde. The obtained results show that chirality transfer is mainly governed by the hydroxyl group and, therefore, by the surroundings of the C–O stereocenter. On the other hand, the *N*-alkyl substitution play an important role by modulating the degree of enantioselectivity. © 2002 Published by Elsevier Science Ltd.

The enantioselective addition of organometallic reagents to prochiral carbonyl compounds in the presence of catalytic amounts of a chiral ligand constitutes one of the most important and fundamental asymmetric reactions.[1] The obtained chiral non-racemic alcohols are present in many natural products and can also serve as starting materials and intermediates for the preparation of a great number of interesting organic molecules with various other functionalities.[2]

Among organometallic compounds, dialkylzinc reagents are ideal alkyl nucleophiles due to their low reactivity towards aldehydes in absence of ligands containing Lewis-acidic functionalities. Thus, dialkylzinc is activated to react with aldehydes by the addition of chiral ligands such as β-, γ-, and δ-diols,[1,3] amino alcohols[1,4] and diamines.[1,5] In this sense, a plethora of chiral ligands have been synthesized and their asymmetric induction properties evaluated, β-amino alcohols being the most widely used.[1,3,6] Tertiary-amino alcohols generally lead to the best results,[7,8] although it has been found that some secondary ones have also given high degrees of stereoselectivity.[9] In order to rationalize the obtained results, some empirical and theoretical calculations on this asymmetric reaction (mechanisms, intermediates, diastereomeric transition states, etc.) have been carried out.[10]

Bicyclic terpenes, such as camphor and fenchone, play an important role in this field, and constitute valuable sources for the preparation of chiral ligands and catalysts,[1,10d,f,11] 3-*exo*-(dimethylamino)isoborneol (DAIB) is known to be one of the most useful ones.[1a] Noyori et al. have reported an extensive experimental and computational study of the highly enantioselective (e.e. >98%) DAIB-catalyzed dialkylzinc-addition to benzaldehyde.[1a,10a,e] These authors have established that the enantioselective step proceeds through *anti*- and *syn*-tricyclic 5/4/4 transition states (*anti*-TS and *syn*-TS in Fig. 1), pointing out the preference for the *anti*-type TS over the *syn*-type ones. From this, the stereochemical outcome is primarily determined by the configuration of the asymmetric carbon bearing the hydroxy group (C-O) (Empirical Noyori's rule).

In further studies, other camphor- or fenchone-based 1,2- and 1,4-amino alcohols have been tested showing a good degree of enantioselectivity.[10d,f,11d,12] Therefore, the preparation and study of new enantiopure amino alcohols with norbornane framework is the subject of increasing interest. Moreover, the search for a definitive model for the prediction of chirality-transfer, essential for the rational design of new catalysts, is still an important challenge.

* Corresponding authors. Tel.: +34 913944236; fax: +34 91 3944103 (S.de la M.C.); tel.: +34 913987332; fax: +34 91 3986697 (E.T.V.); e-mail: eteso@ccia.uned.es; santmoya@quim.ucm.es

0957-4166/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0957-4166(02)00011-3

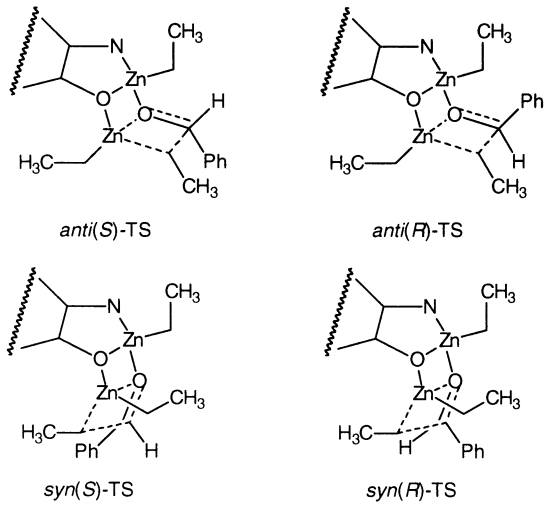

Figure 1. Noyori's transition states for the DAIB-catalyzed diethylzinc-addition to benzaldehyde.

With these aims in mind, and following our research on the chemistry of enantiopure bridgehead norbornane derivatives, we have now synthesized a new set of sterically congested and conformationally rigid β-amino alcohols bearing a different substitution pattern (Fig. 2). To the best of our knowledge, such bridgehead norbornane-derived β-amino alcohols have not been used before as catalysts for the enantioselective addition of diethylzinc to benzaldehyde.

The geometry of our ligands resembles that of the well-known DAIB; however, two significant differences must be considered: (a) the amino and hydroxyl groups deviate slightly from coplanarity and, (b) either the amino or hydroxyl group are linked to the C(1) quaternary center. The *exo*-substitution at the norbornane C(2) position determinates the absolute configuration of both stereocenters to be (1*R*,2*S*). This allows a study of the stereochemical outcome of the reaction as a function of the relative position (and hence, the spatial orientation) of both heteroatomic substituents, as well as on the effect of the substituents at the nitrogen atom. Qualitative analysis of the obtained results can provide some insight about the combined effects of the global

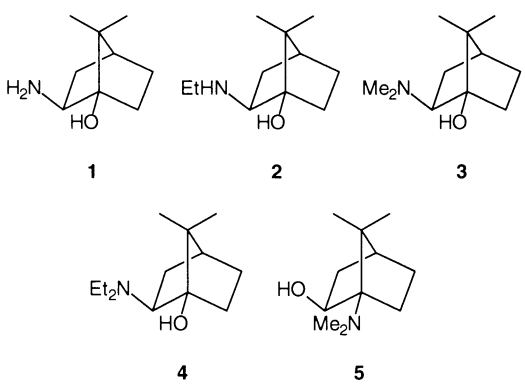

Figure 2. Studied bridgehead-norbornane-derived β-amino alcohols.

substitution pattern influencing chirality transfer (i.e. obtained major enantiomer and product e.e.).

The synthesis of amino alcohol **1** has been reported by us starting from (1*R*)-fenchone in previous papers.[13,14] Amino alcohols **2** and **4** were prepared by controlled alkylation of **1** with C_2H_5I/K_2CO_3 in refluxing ethanol.[15] Synthesis of **3** was carried out by methylation of **1** with HCHO/HCOOH, following the Eschweiler–Clarke procedure.[16] The preparation of **5** was accomplished by treatment of the corresponding primary precursor, previously synthesised by us,[13,14] with 40% aqueous formaldehyde followed by reduction with $NaBH_4$/MeOH.[17]

Amino alcohols **1**–**5** were tested in pure form (5 mol%) as promoters in the enantioselective addition of diethylzinc to benzaldehyde. The results are summarized in Table 1.

The results obtained (Table 1) show that the degree of enantioselectivity is strongly dependent, not only on the alkyl substitution at the nitrogen atom, but also on the relative position of the amino and hydroxyl groups in the norbornane framework. With the exception of **1**, and in agreement with previous observations,[1a] the absolute configuration of the major enantiomer correlates with the configuration of the hydroxyl-bearing stereocenter (C–O). Therefore, the stereochemical outcome is mainly controlled by the hydroxyl group with regard to its relative position on the norbornane skeleton.

Concerning the degree of enantioselectivity, a comparison of the results obtained in the cases of **3** and **5** (see Table 1) clearly shows that the directing effect of the hydroxy group on chirality transfer is much more important when it is attached at C(1) (a quaternary center) than when it is attached to the tertiary C(2) centre. Taking into account that the alkyl substitution at the nitrogen atom is the same for both substrates (excluding the norbornane skeleton), the enantioselec-

Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by amino alcohols **1**–**5**[a]

Entry	Catalyst	Yield (%)[b]	E.e.[c]	Config.[d]
1	**1**	99	9	*S*
2	**2**	83	2	*R*
3	**3**	90	69	*R*
4	**4**	98	93	*R*
5	**5**	97	23	*S*

[a] Solvent:hexane; [PhCHO]/[catalyst]/[Et_2Zn] = 1:0.05:2; standard reaction time = 48 h was used for comparsion of all catalysts; $T = 25°C$.

[b] Determined by integration of GCl peaks using an achiral stationary phase (TRB-1).

[c] Determined by integration of GLC peaks using a chiral stationary phase (cyclodex-B).

[d] Absolute configuration of the obtained major enantiomer determined by the optical rotation sign and the relative retention times in chiral-phase GLC.

tivity is clearly dependent on the topological disposition of both hydroxyl and dimethylamino groups.

The reversal of the stereochemical outcome observed in the case of **1** with respect to **3** and **4** (for the amino alcohol **2** it is not significant) reveals a change in the asymmetric-reaction mechanism, which is not surprising since the behavior of amino alcohols bearing primary-amino groups is more erratic. Thus, according to the literature,[1a] the acidic proton on the nitrogen may cause some complications (different chiral intermediates and parallel reaction pathways can be involved, making the sense of induction unpredictable).

A qualitative explanation of the results obtained for the tertiary β-amino alcohols **3**–**5**, can be given by the corresponding diastereomeric *anti*-type transition-state models (*anti*-(*R*)-**3**–**5** and *anti*-(*S*)-**3**–**5** in Fig. 3), whose geometry resembles those proposed by Noyori for DAIB (see Fig. 2).

For amino alcohols **3** and **4**, the steric interaction between the phenyl and the ethyl (Et-Zn_A) groups in the corresponding *anti*-(*S*)-**3** or *anti*-(*S*)-**4**, transition state makes such states more energetic, and therefore less favored than the corresponding *anti*-(*R*)-**3** or *anti*-(*R*)-**4** (see Fig. 3). This energy difference favors attack to the *Re* face leading to (*R*)-phenylpropanol as the major enantiomer. On the other hand, the degree of enantioselection can be tuned by means of combined steric interactions between the phenyl and the Zn_A-Et groups and the *N*-alkyl substituents. Thus, in order to enhance the stereoselectivity of the reaction, we replaced the *N*-methyl substituents of **3** with more bulky Et-groups in **4**. This causes an increase in the energy difference between the two diastereomeric transition states and, hence, produces a higher e.e. (see Table 1). In the same way, the change of one ethyl group by hydrogen in **4** results in a total lack of stereoselectivity (cf. **4** and **2** in Table 1). Therefore, the degree of steric hindrance around the nitrogen atom plays a crucial role for optimal chirality transfer.

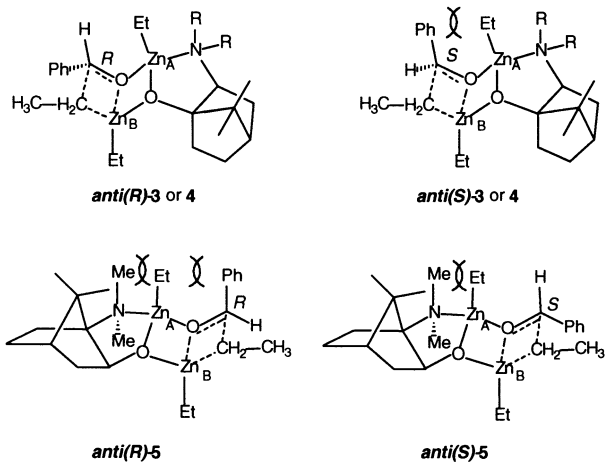

Figure 3. Proposed transition states.

The same qualitative explanation can be applied to catalyst **5**, where the dimethylamino group is attached to the bridgehead position. In this case, the observed low enantioselectivity may be due to the unfavorable steric interaction between the two *N*-methyl groups and carbons C(6) and C(7) of the norbornane moiety. This should result in a destabilization of both proposed *anti*-(*R*)-**5** and *anti*-(*S*)-**5** transition states, which favors a competitive reaction pathway involving a more flexible bimetallic intermediate where the nitrogen atom would complex weakly with the Zn_A atom.

In summary, five new optically active norbornane-derived β-amino alcohols, in which one of the non-coplanar heteroatomic groups is attached to a bridgehead carbon, have been prepared and tested as catalysts for the enantioselective addition of diethylzinc to benzaldehyde, showing a wide range of enantioselectivities. Our studies have demonstrated that the relative position of both the hydroxyl and amino groups on the norbornane skeleton, as well as the *N*-alkyl substituent, play crucial roles in governing the achieved e.e. On the other hand, amino alcohol **4**, which has been readily obtained from commercially available natural (1*R*)-fenchone, has proved to be a good catalyst for the mentioned reaction (the displayed e.e. is comparable to that obtained from DAIB). These results will contribute to the design of optimal norbornane-derived catalysts for the asymmetric addition of organometallic compounds to carbonyl derivatives. Further theoretical calculations on the proposed transition states (see Fig. 3) are now in progress.

Acknowledgements

We wish to thank the DGCYT (Spain) for financial supports of this work (Grant PB 97-0264).

References

1. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (c) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons: New York, 1992; (d) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757–824.
2. (a) Nógrádi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1995; (b) *Houben-Weyl, Methods of Organic Chemistry-Vol E21*; Helmchen, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1996.
3. (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99–101; (b) Dreisbach, C.; Kragl, U.; Wandrey, C. *Synthesis* **1994**, 911–912; (c) Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 1957–1960; (d) P. You, J.-S.; Shao, M.-Y.; Gau, H.-M. *Organometallics* **2000**, *19*, 3368–3373.
4. (a) Soai, K.; Shimada, C.; Takeuchi, M.; Itabashi, M. *J. Chem. Soc., Chem. Commun.* **1994**, 567–568; (b) Yang, X.; Shen, J.; Da, C.; Wang, R.; Choi, M. C. K.; Yang, L.; Wong, K.-Y. *Tetrahedron: Asymmetry* **1999**, *10*, 133–138;

(c) Wassmann, S.; Wilken, J.; Martens, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4437–4445.
5. (a) Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4165–4173; (b) Eriksson, J.; Arvidsson, P. I.; Davidsson, O. *Chem. Eur. J.* **1999**, *5*, 2356–2361.
6. (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072; (b) Solá, L.; Vidal-Ferrán, A.; Moyano, A.; Pericás, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1559–1568; (c) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530–2535; (d) Chao, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1998**, *9*, 1489–1492; (e) Kang, J.; Kim, H. Y.; Kim, J. H. *Tetrahedron: Asymmetry* **1999**, *10*, 2523–2533; (f) Rasmusen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 2464–2465.
7. (a) Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *J. Org. Chem.* **1991**, *56*, 2218–2224; (b) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264–4268; (d) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108–2113.
8. (a) Vidal-Ferrán, A.; Moyano, A.; Pericás, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970–4982; (b) Wilken, J.; Gröger, H.; Kossenjans, M.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2761–2771; (c) Solá, L.; Reddy, K. S.; Vidal-Ferrán, A.; Moyano, A.; Pericás, M. A.; Riera, A.; Álvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078–7082; (d) Reddy, K. S.; Solá, L.; Vidal-Ferrán, A.; Moyano, A.; Pericás, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 3969–3974; (e) Sibi, M. P.; Chen, J.; Cook, G. R. *Tetrahedron Lett.* **1999**, *40*, 3301–3304.
9. (a) Tanaka, K.; Ushio, H.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1700–1701; (c) Corey, E. J.; Yuen, P. W.; Hannon, F. J.; Wierda, D. A. *J. Org. Chem.* **1990**, *55*, 784–786.
10. (a) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335; (b) Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1391–1401; (c) Vidal-Ferrán, A.; Moyano, A.; Pericás, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773–8776; (d) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998–9006; (e) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128–133; (f) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77–82; (g) Vázquez, J.; Pericás, M. A.; Masseras, F.; Lledós, A. *J. Org. Chem.* **2000**, *65*, 7303–7309.
11. (a) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935–952; (b) Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron: Asymmetry* **1997**, *8*, 1869–1876; (c) Suzuki, Y.; Ogata, Y.; Hiroi, K. *Tetrahedron: Asymmetry* **1999**, *10*, 1219–1222; (d) Goldfuss, B.; Steigelmann, M.; Rominger, F. *Eur. J. Org. Chem.* **2000**, 1785–1792.
12. (a) Kwong, H. L.; Lee, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3791–3801; (b) Knollmüller, M.; Ferencic, M.; Gärtner, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3969–3975; (c) Rosner, T.; Sears, P. J.; Nuggent, W. A.; Blackmond, D. G. *Org. Lett.* **2000**, *2*, 2511–2513; (d) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4127–4136.
13. García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1996**, *7*, 1257–1260.
14. García Martínez, A.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1737–1745.
15. Controlled standard alkylation of amino alcohol **1** with EtI/K_2CO_3 in absolute ethanol was carried out. After usual work up *N*-monoethylated amino alcohol **2** (69% yield), or *N*,*N*-diethylated amino alcohol **4** (72% yield), were purified by recrystallization of the corresponding hydrochlorides from $MeOH/Et_2O$. IR, MS, ^1H and ^{13}C NMR agree with the corresponding structures.
16. Amino alcohol **1** was submitted to standard reductive formylation with $HCHO/HCO_2H$ according to: Pine, S. H.; Sanchez, B. L. *J. Org. Chem.* **1971**, *36*, 829–832. After usual work up, amino alcohol **3** was purified by recrystallization of corresponding hydrochloride from $MeOH/Et_2O$ (76% yield). IR, MS, ^1H and ^{13}C NMR agree with the structure.
17. (1*R*,2*S*)-1-Amino-7,7-dimethyl-1-aminonorbornan-2-ol (see lit.[13,14]) was submitted to standard reductive formylation with $HCHO/NaBH_4$ according to: Sondengam, B. L.; Hémo, J. H.; Charles, G. *Tetrahedron Lett.* **1973**, *3*, 261–263. After usual work up, amino alcohol **5** was purified by recrystallization of corresponding hydrochloride from $MeOH/Et_2O$ (81% yield), IR, MS, ^1H and ^{13}C NMR agree with the structure.