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The role of the substitution pattern on the catalytic activity of chiral bridgehead norbornane-derived β-amino alcohols

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Abstract—The enantioselective addition of diethylzinc to benzaldehyde has been used as standard procedure to test a series of new chiral catalysts derived from norbornane framework. The new ligands are β-amino alcohols possessing both heteroatomic substituents attached to the C(1) and C(2)-*endo* positions (novel non-coplanar disposition) of a 3,3-dimethylsubstituted norbornane. The results obtained, compared with other previously reported on the related C(2)-*exo*-7,7-dimethyl series, demonstrate that the relative disposition of the amino, hydroxy and *gem*-dimethyl groups, as well as the *N*-alkyl substituents, play an important role on the catalytic activity. Interesting transition-state models have been also proposed in order to explain the observed experimental results.

The preparation of enantiopure or enantiomerically enriched secondary alcohols by enantioselective addition of diethylzinc to aldehydes, catalyzed by optically active bidentate ligands, is an important synthetic method which has been a subject of considerable interest over the last decade.[1–4] Since the Noyori group demonstrated the high effectiveness of (−)-3-*exo*-(*N*,*N*-dimethylamino)isoborneol (DAIB) as a catalytic ligand,[1a,5] a great number of chiral β-amino alcohols with diverse structural features have been prepared and applied as catalysts for such asymmetric reaction.[1,2,5–8]

The mechanism of the reaction has been discussed for *N*,*N*-disubstituted (tertiary-amino) β-amino alcohols[1,5b,c] and, in general, it has been shown that the stereochemical outcome is primarily determined by the configuration of the asymmetric carbon bearing the hydroxy group.[1,5b,8a] On the other hand, the enantioselectivity is dependent on certain structural factors such as: (a) the degree of alkyl substitution at the nitrogen atom as well as the bulkiness of these alkyl substituents, (b) the spatial orientation of the amino and hydroxy groups, and (c) the stereochemistry and nature of the substituents attached to both hydroxyl- and nitrogen-bearing stereocenters.[1,7c,8a]

The experimental evidence indicates that the reaction requires two equivalents of diethylzinc per equivalent of aldehyde, the catalytic intermediate for β-amino alcohols being a five-membered ethylzinc-chelated aminoalkoxide in equilibrium with a dimeric species.[1a,5a,9] The catalytic activity is only displayed by the monomeric aminoalkoxide complex, whose adjacent Zn and O atoms respectively coordinate with the aldehyde and a second molecule of diethylzinc, giving rise to a bimetallic complex where the enantioselective ethyl-group transfer occurs. On the basis of these findings and a computational study of this reaction, Noyori et al. have postulated tricyclic diastereomeric transition-state models, which explain the experimental observations.[1a,5c,d] Further theoretical calculations, using the Noyori model, have also been carried out by other authors in order to rationalize the origin for the enantioselectivity of this reaction.[10] In addition, alternative transition-state models have also been proposed.[1b,6b,6e,11]

We have recently reported on the structural factors influencing the chirality transfer displayed by some 1,2-disubstituted 7,7-dimethylnorbornane amino alcohols.[12] We have found that the relative position of both hydroxy and amino groups in such system, as well as

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the *N*-alkyl substituents, play a crucial role in the levels of enantioselection.

Herein, we present the results obtained using as catalysts a new series of conformationally rigid 1,2-disubstituted 3,3-dimethylnorbornane amino alcohols, which have been synthesized by us starting from (1*R*)-(+)-camphor (Fig. 1).

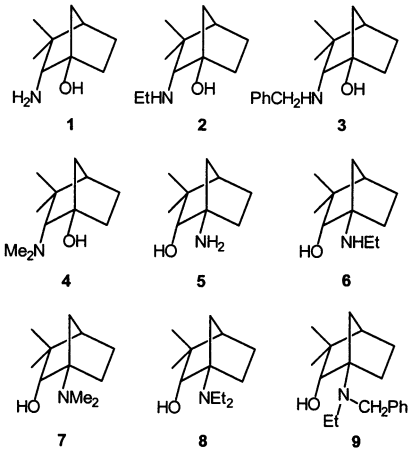

Figure 1. Studied bridgehead-norbornane-derived β-amino alcohols.

The (1*R*,2*R*)-absolute configuration of both stereocenters is now determined by the *endo* substitution at C(2). This fact, together with the position of the *gem*-dimethyl group at C(3), implies a different geometry to that of DAIB. This also means that the deviation from coplanarity presented by the amino and hydroxy groups (a spatial orientation close to *trans* configuration) is greater than that displayed by their 1,2-*exo*-disubstituted 7,7-dimethylated analogues, previously studied by us.[12] The variation of the relative position of both heteroatomic substituents with this new spatial orientation allows us to undertake a more complete study on the combined effects of the global substitution pattern on the chirality transfer in such bridgehead systems.

The synthesis of amino alcohols **1**, **5** and **6**, starting from (1*R*)-(+)-camphor, has been previously reported by us.[13,14] Amino alcohols **2** and **8** were obtained by controlled alkylation of **1** and **6**, respectively.[15] The preparation of **3** and **9** was carried out by *N*,*O*-dibenzoylation of **1** and **6**, respectively, and subsequent reduction with $LiAlH_4$.[16] The ligands **4** and **7** were synthesized by treatment of **1** and **5**, respectively, with aqueous formaldehyde followed by reduction with $NaBH_4$.[17]

The catalytic ability of amino alcohols **1**–**9** towards the enantioselective addition of diethylzinc to benzaldehyde was evaluated using these ligands in pure form. The results are summarized in Table 1.

As shown in Table 1, the absolute configuration of the main enantiomer of 1-phenylpropanol is the same for all the ligands examined with the exception of **5**. Therefore, for these new catalysts (3,3-dimethylated and 2-*endo*-substituted, instead of the previously cited 7,7-dimethylated and 2-*exo*-substituted), it is not possible to affirm that the stereochemical outcome is controlled by the C–O stereocenter.

Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by amino alcohols **1**–**9**[a]

Entry	Ligand	Yield (%)[b]	E.e.[c]	Config.[d]
1	**1**	74	4	*R*
2	**2**	94	13	*R*
3	**3**	83	19	*R*
4	**4**	90	21	*R*
5	**5**	93	25	*S*
6	**6**	99	47	*R*
7	**7**	98	67	*R*
8	**8**	97	34	*R*
9	**9**	50[e]	7	*R*

[a] Solvent: hexane; [PhCHO]/[ligand]/[Et_2Zn] = 1:0.05:2.
[b] Determined by integration of GLC 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 sign of the optical rotation and the elution order in GLC analysis.
[e] The reaction was carried out in refluxing hexane.

The effect of the relative position of hydroxy and amino groups on the chirality transfer can be studied by comparison of the results obtained with all the *N*,*N*-dimethyl derivatives, such as the ligands **4** and **7**, and their 7,7-dimethylated isomers **10** and **11** (see Fig. 2).[12] The degree of enantioselectivity reached with the new ligands, displaying different topological dispositions of amino and hydroxy groups is, in general, similar to that observed with their 7,7-dimethyl analogues.[12] It is noteworthy that the stereochemical outcome is now inverted, the highest enantioselection levels being reached when the amino and hydroxy groups are respectively attached to the C(1) and C(2) position. Therefore, it can be deduced that an increase in the steric hindrance around the C–O stereocenter favors better stereodiscrimination (similar trends have been observed for *N*-(9-phenylfluoren-9-yl)amino alcohols).[7c] Thus, the chirality transfer also seems to be dependent on the position of the *gem*-dimethyl group.[18]

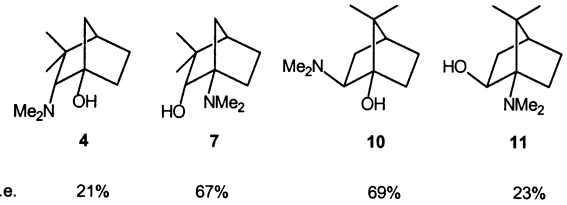

Figure 2. Relative disposition of amino, hydroxy and *gem*-dimethyl groups on bridgehead norbornane-derived β-amino alcohols: Effects on the chirality transfer.

The degree of alkyl substitution at the nitrogen atom also plays an important role in the performance of the

new ligands **5**–**9**, the tertiary-amino alcohol **7** being the most effective ligand with respect to chiral induction, as could be expected on the basis of previous observations.[1,7a,b,8,12] However, as can be seen by comparison of the e.e. achieved with the tertiary-amino alcohols **7**–**9**, an increase in the bulkiness of the *N*-alkyl substituents is detrimental, leading to a drastic decrease in enantioselectivity, and lower yields. This behavior is in opposition to other previously reported trends.[1b,12,19,20] In contrast, the effect of the alkyl substituent at the nitrogen atom is much less important in substrates **1**–**4**, where the amino group is attached to the C(2)-*endo* position.

In order to qualitatively explain the stereochemical course of the catalyzed additions studied, two pairs of diastereomeric *anti*-type transition-state models, based on those proposed by Noyori et al.,[1a,5c,5d] must be considered (Fig. 3). Only the more energetically favored, avoiding the steric repulsion between the phenyl and Zn_A–Et groups, have been depicted.

As shown in Fig. 3, the *anti*(*S*) transition-state model proposed for amino alcohols **6**–**9** is clearly sterically congested, being therefore of higher energy and is thus disfavored cf. the corresponding *anti*(*R*) transition state. This energy difference favors attack to the *Re* face, leading to (*R*)-1-phenylpropanol as the major enantiomer. An increase in the bulkiness of the substituents at the nitrogen atom causes a greater steric congestion in both transition-state models due to the unfavorable eclipsing *syn* alignments of the *N*-alkyl groups R relative to the Zn_A–Et group, the Zn_A–O atom, and the C(6) and C(7) carbons of the norbornane moiety. This probably results in destabilization of the chelate by weak complexation of the Zn_A atom, giving rise to a more flexible bimetallic intermediate complex, with a less stereo-differentiating geometry.

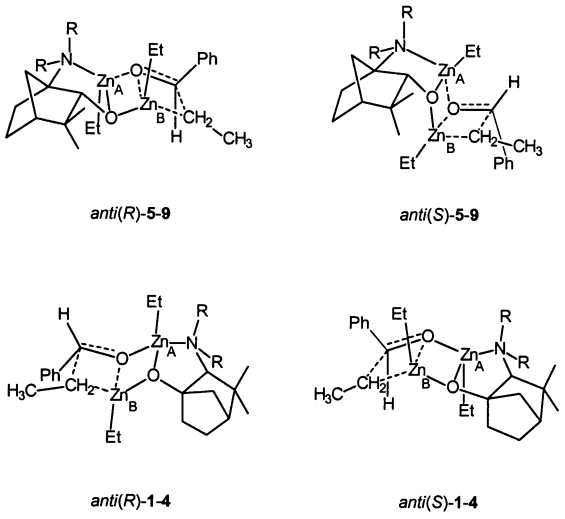

Figure 3. Proposed *anti*-type transition-state models.

Similar transition-state models can be applied to the catalysts **1**–**4**, where the amino group is attached to the C(2) position. In these cases, the lower enantioselectivities observed may be due to a minor energy difference between the *anti*(*R*) and *anti*(*S*) transition states.

In summary, nine new enantiopure norbornane-derived β-amino alcohols, in which the non-coplanar heteroatomic groups are alternatively attached to the C(1) and C(2)-*endo* positions of the norbornane skeleton, have been synthesized and tested as catalysts for the enantioselective addition of diethylzinc to benzaldehyde. Our studies on the catalytic activity of 7,7-dimethyl-1,2-*exo*- and 3,3-dimethyl-1,2-*endo*-substituted norbornane-derived amino alcohols have demonstrated that the relative position of hydroxy, amino and *gem*-dimethyl groups at the norbornane skeleton, as well as the *N*-alkyl substitution, play a crucial role in the chirality transfer. However, the combined effects of the substitution pattern in both series are opposite. Thus, in the 7,7-dimethylnorbornane-based β-amino alcohols, the best enantioselectivity is achieved when the hydroxy group is attached at the bridgehead position and the amino group at the C(2)-*exo* position.[12] The level of enantioselection can be tuned by altering the steric properties of the *N*-alkyl substituents. For the 3,3-dimethylated analogues the best enantioselectivities are reached when the amino group is attached to the bridgehead position. In contrast, in these ligands, an increase of the bulkiness of the *N*-alkyl substituents has a negative effect on the enantioselectivity. Further work in this type of bridgehead systems, as well as theoretical calculations on the proposed transition states, are now in progress.

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15. Controlled standard alkylation of amino alcohol **1** and **6** with EtI/K_2CO_3 in absolute ethanol was carried out. After usual work up *N*-monoethylated amino alcohol **2** (60% yield), or *N*,*N*-diethylated amino alcohol **8** (90% 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. Reaction of amino alcohols **1** and **6** with benzoyl chloride and pyridine leads to the corresponding *N*,*O*-dibenzoyl derivatives, which, after reduction with $LiAlH_4$ in refluxing Et_2O, give place to the desired *N*-benzyl amino alcohols **3** (53% overall yield) and **9** (34% overall yield). After usual work up, the final products were purified by recrystallization of the corresponding hydrochlorides from $MeOH/Et_2O$. IR, MS, ^1H and ^{13}C NMR agree with the proposed structures.
17. Amino alcohols **1** and **5** were 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 alcohols **4** (62% yield) and **7** (71% yield) were purified by recrystallization of the corresponding hydrochlorides from $MeOH/Et_2O$. IR, MS, ^1H and ^{13}C NMR agree with the structures.
18. The effect of a C3- or a C7-*gem*-dimethyl group over the chirality transfer in bridgehead norbornane-derived δ-amino alcohols has been studied by Fujita et al.: (a) Hanyu, N.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2000**, *41*, 4587–4590; (b) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 2971–2979. See also Ref. 1d.
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