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2-*exo*- versus 2-*endo*-Hydroxyl in δ-amino norbornan-2-ol-based catalysts: investigating the role of the C(2) configuration in the asymmetric induction

Antonio García Martínez,[a,*] Enrique Teso Vilar,[b] Amelia García Fraile,[b] Santiago de la Moya Cerero[a,*] and Beatriz Lora Maroto[b]

[a]*Departamento de Química Orgánica I, Fac. de Químicas, Universidad Complutense de Madrid (UCM), 28040 Madrid, Spain*
[b]*Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, Senda del Rey 9, 28040 Madrid, Spain*

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Abstract—Enantiopure 1-[2-(dimethylamino)ethy]-2,3,3-trimethylnorbornan-2-*endo*-ol, a new norbornane-based δ-amino alcohol, has been straightforwardly prepared from fenchone. The described route constitutes a model procedure for the preparation of other related C(2)-substituted δ-amino 2-*endo*-norbornanol ligands. The catalytic activity of the obtained δ-amino 2-*endo*-norbornanol (for the enantioselective addition of diethylzinc to benzaldehyde) has been compared with that previously described for the corresponding C(2)-epimer, which allows us to study about the role played by the configuration of the hydroxyl-bearing C(2) atom on the catalytic activity. Catalyst models and transition-state models for explaining such a role are proposed and discussed.

1. Introduction

Since Noyori et al. demonstrated the high efficiency of (−)-3-*exo*-(dimethylamino)isoborneol (DAIB) as a chiral ligand for the catalyzed enantioselective addition of dialkylzinc to benzaldehyde,[1] many other chiral amino alcohols (mainly β-amino alcohols) have been synthesized, probed, and studied as chiral ligands for important asymmetric C–C bond-formation reactions.[2]

The catalytic role of β-amino alcohols in the enantioselective addition of dialkylzinc to aldehydes has been extensively outlined and understood on the basis of a stable five-membered Zn-chelate.[1,2] Nevertheless, the utility of γ- and δ-amino alcohols as chiral ligands for such asymmetric processes has been less studied and, therefore, their catalytic role remains not totally understood.[3] In these cases, the Zn-atom is part of a more flexible six- or seven-membered ring in the catalytic chelate (Fig. 1), and, therefore, the rigidity of the chiral amino alcohol plays an important role in order to limit the conformational freedom of such catalytic species, particularly around the oxygen and nitrogen atoms.[3]

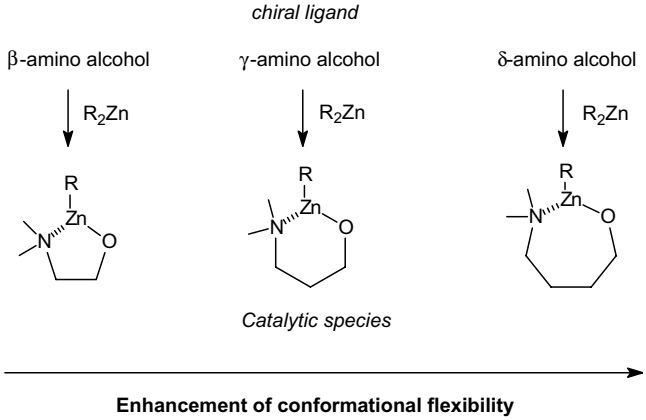

Figure 1.

Among the broad group of δ-amino alcohols, δ-amino norbornanols are favored candidates to act as chiral ligands, due to the rigidity imposed by the bicyclic framework. In this sense, some δ-amino norbornanols have recently been described as good chiral ligands for

* Corresponding authors. Tel.: +34-91-394-42-36; fax: +34-91-394-41-03; e-mail: santmoya@quim.ucm.es

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the catalyzed enantioselective addition of dialkylzinc to benzaldehyde.[3a–e,g]

Therefore the potential accessibility to enantiopure 1-(2-aminoethyl)norbornan-2-ols (**1**–**4** in Fig. 2) by synthetic routes based on camphor or fenchone,[3a–c,g] makes such semi-rigid (note highlighted conformationally restricted torsion angles in Fig. 2) δ-amino 2-norbornanols to be interesting models for studying the catalytic role of other related δ-amino alcohols.

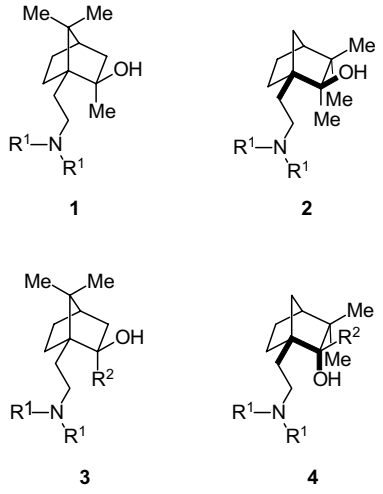


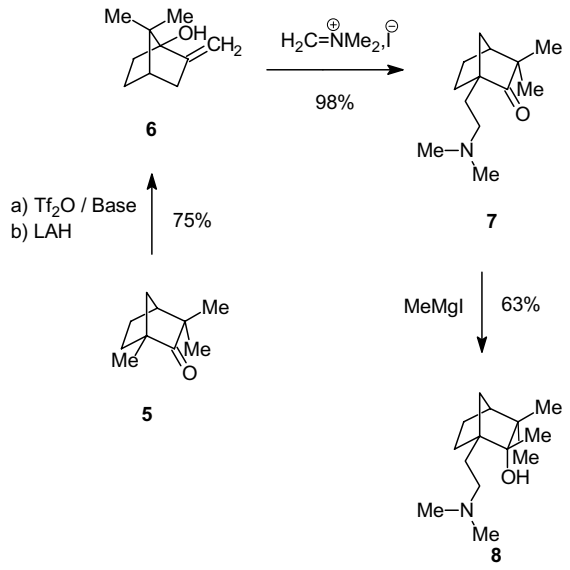
Figure 2. Semi-rigid camphor- and fenchone-based δ-amino alcohols used as models by Fujita et al. (**1** and **2**) and García Martínez et al. (**3** and **4**) for the study on the catalytic activity of related chiral ligands.

Fujita et al. have recently developed an elegant synthetic method for 1-(2-aminoethyl)-2-methylnorbornan-2-*exo*-ols **1** and **2**, which has allowed the study on the role played by the substitution on the nitrogen atom (R^1), as well as the methyl substitution on the norbornane framework (7,7-dimethyl substitution in **1** vs 3,3-dimethyl one in **2**), on the catalytic activity.[3a–c] We have recently proposed an alternative synthetic route for the preparation of 1-(2-aminoethyl)norbornan-2-*exo*-ols with a different substitution at the hydroxyl-bearing C(2) norbornane position (see **3** in Fig. 2).[3g] This has allowed the study of the catalytic role played by the C(2) group,[3g] completing the work initialized by Fujita.

Continuing our ongoing research in this field, we herein report a new route for the preparation of fenchone-based C(2)-substituted 1-(2-aminoethyl)norbornan-2-*endo*-ols **4**, starting from fenchone, which additionally allows the study on the role played by the C(2) configuration on the catalytic activity (note the epimeric relation between **2** and **4** in Fig. 2).

2. Results and discussion

The new synthetic route was exemplified by the synthesis of (1*R*)-1-[2-(dimethylamino)ethyl]-2,3,3-trimethylnorbornan-2-*endo*-ol **8** [**4**($\mathbf{R^1 = R^2 = Me}$)] from commercial (1*R*)-fenchone **5**, as shown in Scheme 1, in order to compare its catalytic activity with the previously reported one by Fujita for the corresponding C(2)-epimer ***epi*-8** [**2**($\mathbf{R^1 = Me}$)].



Scheme 1. Preparation of fenchone-based δ-amino 2-*endo*-norbornanol **8** from fenchone **5**.

The key intermediate amino ketone **7** was previously obtained by reaction of 2-methylenenorbornan-1-ol **6** with *N*,*N*-dimethylmethaniminium iodide (Eschenmoser's salt), (tandem electrophilic addition—Wagner–Meerwein rearrangement).[4] Bridgehead alcohol **6** was easily obtained by starting from (1*R*)-fenchone **5** by means of an initial treatment with triflic anhydride (Wagner–Meerwein rearrangement) and the subsequent reaction of the obtained bridgehead triflate with lithium and aluminum hydride (Scheme 1).[5] Finally, a highly stereocontrolled addition of methylmagnesium iodide to the carbonyl group of **7** yielded the desired δ-amino norbornan-2-*endo*-ol **8** in good overall yield (46%).[6]

For the comparison, the activity of δ-amino norbornanol **8**, as chiral catalyst for the enantioselective addition of diethylzinc to benzaldehyde, was tested in the same conditions used by Fujita et al. for ***epi*-8**.[3b,7] The results are summarized in Table 1.

As shown in Table 1, simply changing the configuration of the hydroxyl-bearing C(2), from ***epi*-8** to **8**, gave cause to a drastic fall in the ee (91–13%). On the other hand, the sense of the stereodifferentiation has also changed (see enantiomer configurations in Table 1).

These results can be explained according to the empirical catalyst models **A** and **B**, and transition-state models **TS-1** and **TS-2**, as shown in Scheme 2.

Catalyst model **A** and transition-state model **TS-1** were proposed by Fujita for explaining the catalytic activity of 2-*endo*-norbornanol ***epi*-8**.[3b] Thus, the initial reaction

Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by δ-amino norbornanols **8** and ***epi*-8**[a]

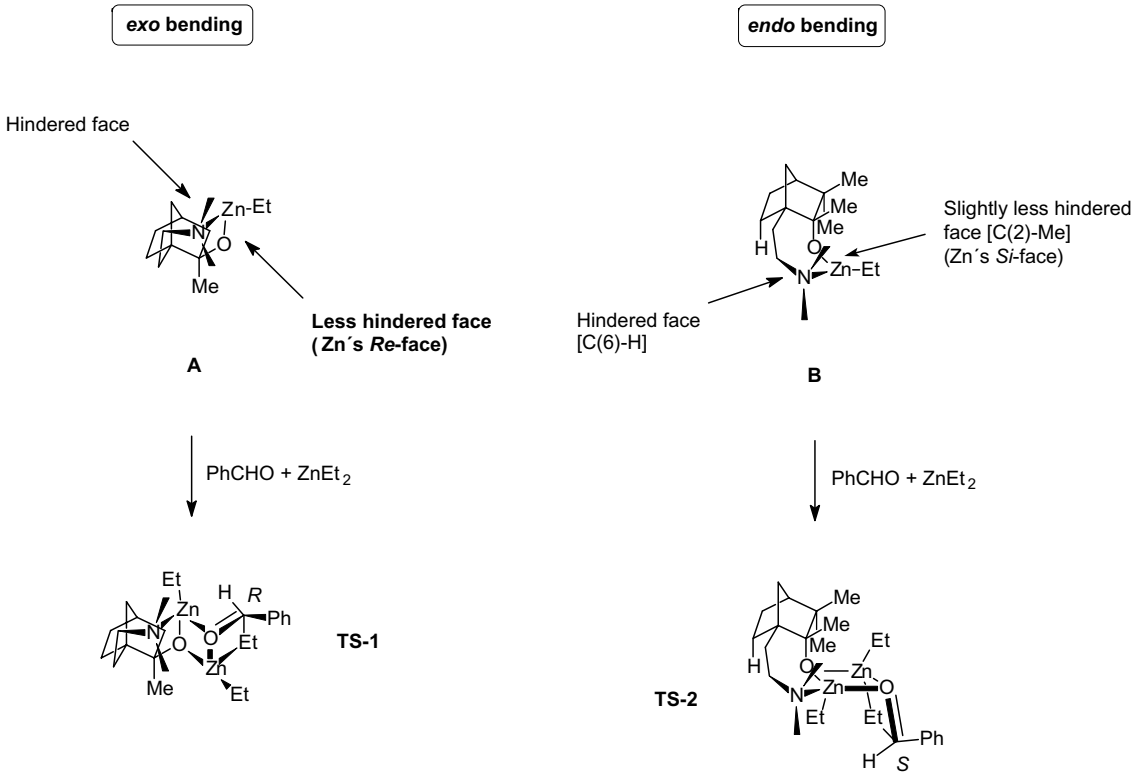
Ligand	$[\alpha]_D^{25}$ [b]	1-Phenyl-1-propanol		
		Yield (%)[c]	Ee	Configuration[d]
8	+15.4	97	13[e]	*S*
***epi*-8**[f]	+19.4	98	91[g]	*R*

[a] Solvent: toluene; [PhCHO]/[ligand]/[Et_2Zn] = 1:0.05:2; at rt.
[b] Measured in $CHCl_3$.
[c] Determined by GC.
[d] Determined by the sign of the specific rotation.
[e] Determined by Chiral GC using a Cyclodex-B column.
[f] Previous reported results (Ref. 3b).
[g] Determined by chiral HPLC with an OD-H column.

of ***epi*-8** with diethylzinc generates the catalytic species **A**, in which the flexible seven-membered Zn-chelate adopts an *exo* disposition (*exo* bending). This *exo* bending is imposed by the *exo* disposition of the C(2)–O bond. Additionally, the adopted conformation avoids steric interaction between the dimethylamino and C(2)-*endo*-methyl groups. In the second step, benzaldehyde's oxygen coordinates the Zn atom of catalyst **A** by its less hindered right face (Zn's *Re*-face) [steric hindrance at the left face is exerted by the methylene bridge (C(7) norbornane position)], giving place, together with a second molecule of diethylzinc, to Noyori's-type *anti*-7/4/4 tricyclic transition-state **TS-1**.[1] In **TS-1** the reactive ethyl group attacks the benzaldehyde moiety on its *Re*-face, thus explaining the formation of an enriched (*R*)-product (Scheme 2).

Analogously, 2-*endo*-norbornanol **8** would generate catalyst **B**, after the initial reaction with diethylzinc. Nevertheless, in this case, the *endo* disposition of the C(2)–O bond makes the flexible metallacycle adopt an *endo* bending (cf. **A** and **B** in Scheme 2). Moreover, the adopted conformation for such a metallacycle avoids steric interaction between the dimethylamino and the C(6)-*endo*-H groups.

In catalyst **B**, when compared to **A**, both reactive diastereotopic faces are less distinguishable. Thus, while the left face is hindered by the C(6)-*endo*-H, the right face is slightly less hindered by the C(2)-*exo*-methyl group. Therefore, in the subsequent step, benzaldehyde's oxygen must attack the zinc atom of **B** by its slightly less hindered right face (Zn's *Si*-face), giving rise to



Scheme 2. Proposed empirical catalyst and transition-state models [*gem*-dimethyl groups at C(3) have not been included in **A** and **TS-1** for making the view of such structures easier].

Noyori's-type *anti*-7/4/4 transition state **TS-2** with a low stereoselection, which explains the formation of a slightly enriched (*S*)-product (see Table 1).

3. Conclusion

In conclusion, the configuration of the hydroxyl-bearing C(2) atom plays a crucial role in defining the catalytic activity of 1-(2-aminoethyl)norbornan-2-ol-based ligands. Thus, while an *exo* C(2)–O configuration favors a high stereodifferentiation, while enhancing the catalytic activity, an *endo* one disfavors such differentiation. This high difference in behavior is due to the high flexibility of the catalytic Zn-chelate for δ-amino alcohols. Therefore, the C(2)-configuration results are an important structural factor to be accounted for when designing new, good δ-amino norbornan-2-ol-based ligands. Also, a straightforward synthetic method for 1-(2-aminoethyl)norbornan-2-ols with an *endo* C(2)–O configuration has been established for the first time.

Acknowledgements

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6. Over cooled (0 °C) dispersion of amino ketone **7** (0.5 mmol) in dry ether (10 mL) was added 1.0 mmol of MeMgI (3 M in ether). The reaction mixture was then stirred at refluxing temperature for 3 h. After standard hydrolysis, extraction, and purification by elution chromatography (neutral aluminium oxide, CH_2Cl_2/MeOH 9:1), the corresponding pure **8** was obtained as a colorless oil (63% yield). Spectroscopic data are in agreement with the structure. $[\alpha]_D^{20} = +15.4$ ($c = 2.20$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 5.00 (br s, 1H), 2.52 (td, $J = 12.5$, 3.6 Hz, 1H), 2.30–2.15 (m, 2H), 2.26 (s, 6H), 2.00 (m, 1H), 1.78 (m, 1H), 1.65 (m, 2H), 1.41–1.22 (m, 3H), 1.15 (s, 3H), 1.06 (m, 1H), 0.95 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 77.9, 57.5, 55.9, 42.9, 49.3, 45.7 (two signals), 41.8, 29.7, 26.2, 25.5, 27.6, 23.8, 22.3 ppm. MS *m*/*z* 182 ($M^+ - 43$, 1). 140 (2), 58 (100).
7. The enantiomer described by Fujita in Ref. 3b is not (+)-***epi*-8**, but the (−) one. We have used the (+) one for making easier the comparison study with **8**.