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Tetrahedron: *Asymmetry* 14 (2003) 1959–1963

TETRAHEDRON: *ASYMMETRY*

Synthesis and catalytic activity of 10-(aminomethyl)isoborneol-based catalysts: the role of the C(2)-group on 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*

Received 1 April 2003; accepted 20 May 2003

Abstract—Five enantiopure C(2)-substituted 10-[(dimethylamino)methyl]isoborneols has been prepared by a novel straightforward camphor-based route, and probed as δ-amino-alcohol ligands for the enantioselective addition of diethylzinc to benzaldehyde. The established route constitutes a divergent model procedure for this class of δ-amino-isoborneol ligands, allowing different substitutions, not only at the nitrogen atom, but also at the more interesting hydroxyl-bearing C(2)–norbornane position. This last synthetic possibility has made possible a study of the role played by the group located at the C(2)–norbornane position on the catalytic activity. New catalyst models and transition-state models for explaining such a role are also proposed and discussed.

The great importance that catalytic asymmetric carbon–carbon bond generation has in synthetic organic chemistry is well known.[1] In this sense, the catalyzed enantioselective addition of dialkylzinc to aldehydes must be highlighted, since it produces valuable enantiomerically pure or enriched alcohols, which are key synthetic starting materials and intermediates for the preparation of a large number of interesting organic molecules (i.e. valuable natural products).[2] Since Noyori et al. demonstrated the high efficiency of (−)-3-*exo*-(dimethylamino)isoborneol (DAIB) as a chiral catalyst for the addition of diethylzinc to benzaldehyde,[3] and suggested a mechanistic model for the catalytic cycle based on the formation of a five-membered Zn-chelate,[4] many other chiral β-amino alcohols have been synthesized and employed as chiral catalysts for such asymmetric reactions.[5]

Although the catalytic role of β-amino alcohols has been extensively outlined and understood on the basis of a stable five-membered Zn-chelate,[4,5] the utility of γ- and δ-amino alcohols as chiral catalysts for the enantioselective diethylzinc-addition to aldehydes has been less studied.[6] In these last cases, the Zn-atom would be potentially part of a more flexible six- or seven-membered ring and, therefore, the rigidity of the chiral amino alcohol would play an important role in order to limit the conformational freedom of the Zn-chelate, especially around of the oxygen and nitrogen atoms.[6l] In this sense, some rigid camphor- and fenchone-derived δ-amino isoborneols (e.g. **1**, **2**, **3** and **4** in Fig. 1)

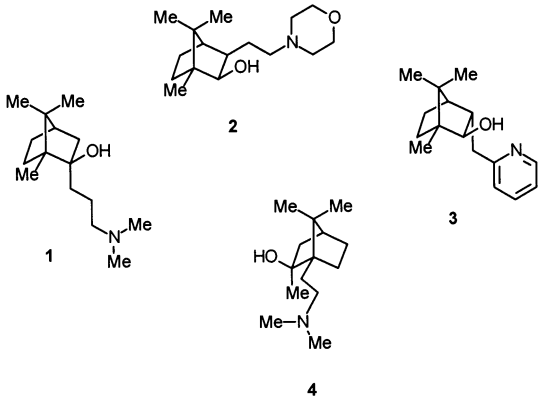

Figure 1. Some interesting reported δ-amino-isoborneol catalysts.

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

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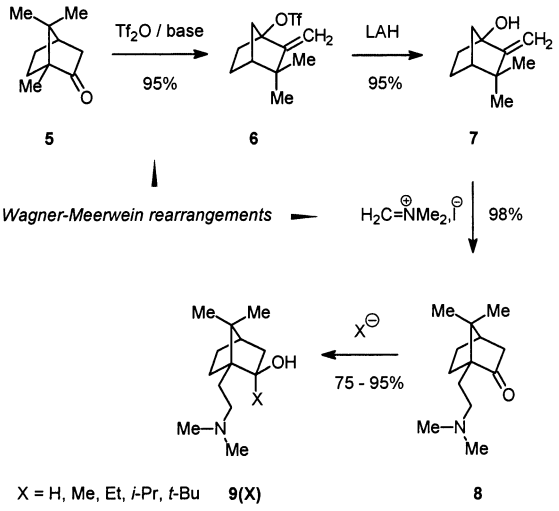
doi:10.1016/S0957-4166(03)00411-7

have been recently described as interesting chiral catalysts for the enantioselective diethylzinc-addition to benzaldehyde.[6c,g,h,j,l] Nevertheless, in order to do a systematic study on the influence that the substitution pattern of the δ-amino isoborneol has in its catalytic activity, more information about such activity (new catalysts and corresponding obtained e.e.s) is necessary.

In this sense, and continuing with our ongoing research on the straightforward preparation of enantiopure C(10)-substituted camphor- and fenchone-derived chiral sources,[7] we now report a new highly efficient synthetic route to enantiopure C(2)-substituted 10-[(dimethylamino)methyl]isoborneols **9(X)**, starting from inexpensive and readily available natural (+)-(1*R*)-camphor **5**, as described in Scheme 1.



Scheme 1. New enantiospecific route to C(2)-substituted 10-[(dimethylamino)methyl]isoborneols based on camphor.

The key intermediate of this route is amino ketone **8**, whose synthesis has been previously reported by us by means of: (a) a first enantiospecific Wagner–Meerwein rearrangement of (+)-camphor **5** by triflic anhydride treatment, to generate the bridgehead 1-norbornyl triflate **6**, and (b) a second enantiospecific Wagner–Meerwein rearrangement of the 2-methylenenorbornan-1-ol **7**, by reaction with *N*,*N*-dimethylmethaniminium iodide (Eschenmoser's salt).[7g] Finally, the highly stereocontrolled addition of different nucleophiles X^- (H^-, Me^-, Et^-, *i*-Pr^- and *t*-Bu^-) to the carbonyl group of **8** yields the corresponding C(2)-substituted δ-amino isoborneols **9(X)** in high yield (75–95%).[8]

Our route has made possible the highly efficient preparation of Fujita's ligand *ent*-**4** [**9(Me)**] in four individual steps, as in Fujita's route to **4**,[6h–j] but with a higher overall yield (66% instead of 40%) and starting from (+)-camphor instead of the more expensive and less enantiopure (−)-fenchone].[7g] On the other hand, the established synthetic route constitutes a valuable model procedure for the preparation of other interesting 10-(aminomethyl)isoborneols, allowing also variation of the substitution at the N-atom by simple substitution of Eschenmoser's salt by other *N*,*N*-disubstituted methaniminium salts (see Scheme 1).

In addition to the synthetic work, we have also tested the obtained C(2)-substituted δ-amino isoborneols **9(X)** (see Scheme 1) as chiral catalysts for the enantioselective addition of diethylzinc to benzaldehyde, under the same conditions used by Fujita et al. for testing **4**.[6i] The results are summarized in Table 1.

As shown in Table 1, the e.e. reached by the use of ligand *ent*-**4** is slightly higher than that achieved with the use of **4** (61% versus 56%). This fact can be explained as due to the different enantiomeric excess of both catalysts, which must be due to a different enantiomeric excess of the starting materials to generate such catalysts: (−)-fenchone for Fujita's ligand **4** and (+)-camphor for our ligand *ent*-**4**. Nevertheless, there is not a linear relationship between the observed stereoselectivities and the enantiomeric excesses of the used catalysts (a slight positive non-linear effect could be invoked).[9]

On the other hand, an interesting steric influence of the group located at the C(2)-*endo*-norbornane position (X) on the asymmetric induction (observed e.e. and configuration of major enantiomer) has been detected (see Table 1). Thus, when the methyl group of **9(Me)** is substituted by an ethyl group in **9(Et)**, there is no substantial change in the catalytic activity: yields, e.e.s and configurations for the major enantiomer are almost the same (see Table 1). Nevertheless, the introduction of an isopropyl group at such position [see **9(*i*-Pr)** in Table 1] produces a strong change in the catalytic behavior: the e.e. decreases considerably (from 61–62 to 6%) and the configuration of the major product changes from *R* to *S*. Finally, the substitution of isopropyl by *tert*-butyl, as the substitution methyl by ethyl, [cf. couples **9(Me)**/**9(Et)** and **9(*i*-Pr)**/**9(*t*-Bu)** on Table 1] does not produce any substantial change in the catalytic activity.

Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by amino isoborneols **4** and **9(X)**[a]

Ligand	1-Phenyl-1-propanol			
	$[\alpha]_D^{25}$[b]	Yield (%)[c]	E.e.[d]	Config.[e]
4	+16[f]	99[f]	56[f,g]	*R*[f]
9(Me) (*ent*-**4**)	−18[h]	98	61	*S*
9(Et)	−13	97	62	*S*
9(*i*-Pr)	−14	98	6	*R*
9(*t*-Bu)	−19	95	8	*R*
9(H)	+7	98	66	*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 Chiral GC using a Cyclodex-B column.
[e] Determined by the sign of the specific rotation.
[f] Previous reported results (see Ref. 6i).
[g] Determined by chiral HPLC with a OD-H column.
[h] Measured at the same concentration as **4**.

Finally, the substitution of the methyl group in **9(Me)** by hydrogen in **9(H)** produces a complete inversion in the stereochemical outcome of the catalytic addition [cf. corresponding reached e.e.s and major-enantiomer configurations in Table 1].

The above results can be easily explained according to the empirical catalyst models **A**, **B** and **C**, and the transition-state models **TS-1**, **TS-2** and **TS-3** as shown in Scheme 2.

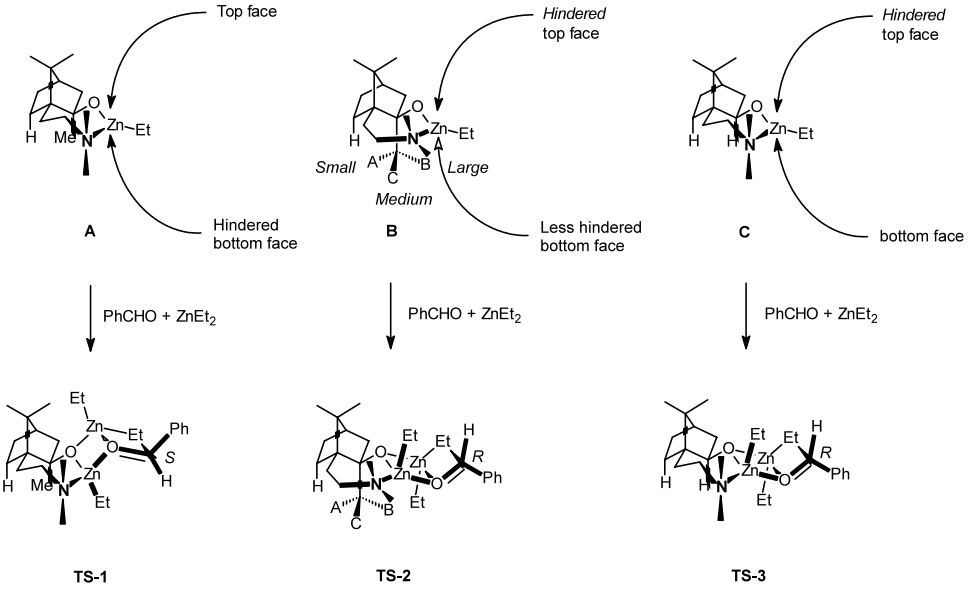
Catalyst model **A** and transition-state model **TS-1** were proposed by Fujita for explaining the catalytic activity of δ-amino isoborneol **4**.[6i] Thus, reaction of *ent*-**4** with Et_2Zn generates chiral catalyst **A**, in which the conformation of the seven-membered metallacycle disposes the dimethylamino group in an '*endo*' disposition, avoiding steric interaction between the N- and C(7)-*syn*-methyl groups. Benzaldehyde's oxygen must then coordinate the Zn atom of catalyst **A** by the top face (steric hindrance at the bottom face is exerted by the C(2)-*endo*-methyl group),[6i] giving place to the formation of the *anti*-7/4/4 tricyclic transition-state **TS-1** (Noyori's *anti*-type transition-state).[4] In this transition state, the Zn-ethyl group attacks the benzaldehyde *Si*-face, explaining the formation of an enriched (*S*)-product.

Accordingly to model **A**, the substitution of the C(2)-methyl group by a new group with a higher steric volume must produce a higher stereoselection in the asymmetric addition (higher observed e.e.), favoring the top-face attack at generating the corresponding tricyclic transition state. On the other side, substitution of such methyl group by a minor group must produce a smaller stereoselection (smaller observed e.e.).

In contrast to the above, the situation in δ-amino isoborneols **9(*i*-Pr)** and **9 (*t*-Bu)** is quite different [cf. corresponding e.e. in Table 1], which makes a new catalyst model different to **A** necessary. Thus, for explaining the catalytic activity of such chiral ligands, we have proposed the catalyst model **B**, in which, due to the higher steric interaction exerted by the bulky C(2)-isopropyl [or C(2)-*tert*-butyl] group, the conformation adopted by the seven-membered metallacycle disposes the dimethylamino group in an '*exo*' disposition.

For **9(*i*-Pr)**, the conformation adopted by the C(2)-isopropyl group in catalyst-model **B** must be A = H, C = B = Me, in order to minimize steric interactions [*C*(6)-*endo*-hydrogen with rest A (higher interaction), and *N*-methyl with rest C]. Therefore, it is the steric interaction exerted by the methyl C-group the main responsible for the different conformation adopted by the seven-membered metallacyclo in catalyst-model **B**, respect to that adopted in catalyst-model **A**.

Now, in model **B** when compared with model **A**, both diastereotopic faces are less distinguished: the top face is hindered by the C(7)-*syn*-methyl group, whereas the bottom face is hindered (less) by the C(2)-group (mainly by rest C). Therefore, benzaldehyde's oxygen must attack the zinc atom of **B** by its slightly less-hindered bottom face, giving place to the *anti*-7/4/4 transition state **TS-2** with a low stereoselection, which explains the formation of a slightly enriched (*R*)-product (see Table 1). Model **B** predicts also the same catalytic behavior for **9(*i*-Pr)** and **9(*t*-Bu)** (see corresponding reached e.e.s in Table 1), since in both cases the main-stereodistinguishing C-group is a methyl one.



Scheme 2. Proposed empirical catalyst and transition-state models.

From all the above, for δ-amino isoborneol **9(Et)**, the conformation of the C(2)-ethyl group in the catalyst would be A = C = H B = Me, (see model **B** in Scheme 2). Therefore, the steric effect exerted by such ethyl group must be similar to that exerted by a methyl group (in both cases the stereodistinguishing C-group is hydrogen), and, therefore, the seven-membered metallacycle will adopt the conformation shown in model **A**. By the same reason, the stereoselection at forming the tricyclic transition state will be the same as in the case of **9(Me)**, which explains the same stereochemical behavior for both chiral ligands (see corresponding reached e.e.s in Table 1).

Finally, the stereochemical behavior of ligand **9(H)** can be explained starting from catalyst-model **C**. Due to the low steric hindrance exerted by the C(2)-hydrogen group, catalyst-model **C** is similar to catalyst-model **A** [*N*-*gem*-dimethyl group as far as possible from the C(7)-*gem*-dimethyl group, see Scheme 2]. Nevertheless, in this last case the attack of benzaldehyde's oxygen to the Zn atom of the catalyst must preferentially occur by the less hindered bottom face, forming the transition state **TS-3**, and, therefore, explaining the formation of a (*R*)-enriched product (see Table 1).

In summary, the establishment of a new straightforward route to enantiopure 10-(aminomethyl)isoborneols has allowed the synthesis of a set of such δ-amino isoborneols with different substitution at the C(2)-norbornane position (the hydroxyl-bearing position). This has made possible the comparative study of the behavior of those δ-amino alcohols as chiral ligands for the catalytic enantioselective addition of diethylzinc to benzaldehyde, allowing the establishment of an empirical rule (empirical catalyst and transition-state models) to explain the role played by such C(2)-group on the asymmetric induction. Further experimental and theoretical support studies (based on the consideration of different reaction conditions, chiral ligands, aldehydes and transition-state models) are in progress.

Acknowledgements

We would like to thank the Ministerio de Ciencia y Tecnología of Spain (plan nacional I+D, research project BQU2001-1347-C02) and UNED (research project 2001V/PROYT/18) for the financial support of this work. B.L.M. wish to thank Ministerio de Educación Cultura y Deportes of Spain for a post-graduate grant.

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8. The used nucleophile reagents are: LAH (1.0 M in ether, methylmagnesium iodide (3.0 M in ether), ethylmagnesium bromide (1.0 M in THF), isopropylmagnesium chloride (2.0 M in THF) and *tert*-butyllithium (1.7 M in pentane). Standard procedure: Over a dispersion of amino ketone **8** (0.5 mmol) in dry ether (10 mL), at 0°C and under argon atmosphere, was added corresponding nucleophile reagent (1.0 mmol). The reaction mixture was allowed to warm up to room temperature and stirred overnight. After standard hydrolysis, work-up and purification by elution chromatography (neutral aluminum oxide, CH_2Cl_2/MeOH 9:1), corresponding pure C(2)-substituted 10-[(dimethylamino)methyl]isoborneol was obtained as a colorless oil. Spectroscopic data for *ent*-**4** agree with the previously reported data for **4** (see Ref. 6i). For **9(H)**, **9(Et)**, **9(*i*-Pr)** and **9(*t*-Bu)**, spectroscopic data agree with corresponding structures.
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