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The role of conformational flexibility on the catalytic activity of norbornane-derived β-, γ- and δ-amino alcohols

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Abstract—Enantiopure norbornane-based γ-amino alcohols **1**–**4** have been obtained from (+)-camphor and their catalytic behaviour as chiral ligands for the enantioselective addition of diethylzinc to benzaldehyde compared to these described for homologous β- and δ-amino alcohols. This has allowed the first study on the influence of the size of the catalytic zinc-chelate ring on the catalytic activity, which results in the unexpected observance of a non-linear correlation between enantioselectivity and chelate ring size (conformational flexibility). An empirical rationalisation of the observed phenomenon was realised on the basis of consideration of the energetically-favoured Noyori-type transition states.

1. Introduction

The enantioselective addition of dialkylzinc reagents to prochiral aldehydes catalysed by chiral ligands constitutes a fundamental tool for the synthesis of enantiopure or enantiomerically enriched secondary alcohols.[1,2] In this sense, a plethora of chiral diols, amino alcohols, diamines or amino thiols have been tested as catalysts in this important asymmetric process.[1] Among these, β-amino alcohols have been the most studied,[3] mainly due to Noyori's work on the use of (−)-3-*exo*-(dimethylamino)isoborneol (DAIB) as the first highly-efficient chiral ligand for the enantioselective addition of diethylzinc to benzaldehyde.[4] The catalytic role of DAIB was rationalised by the same author (Noyori's model) on the basis of: (1) the formation of a stable five-membered alkylzinc-chelated aminoalkoxide complex as the acting bifunctional chiral catalyst and, (2) the generation of a diastereomeric couple of tricyclic (5/4/4) *anti*-type transition states (*anti*-TS), that control the stereoselection of the process (*anti*-TS pro-*S* vs *anti*-TS pro-*R*).[1a,2a,4]

The Noyori model has been used by several authors to carry out further empirical and theoretical studies in order to rationalise the enantioselectivities displayed by many other chiral β-amino alcohols.[3] Nevertheless, in sharp contrast with the extensive studies devoted to β-amino alcohols, there is currently limited and sparse information concerning the mechanism, stereodifferentiation and scope of the reaction catalysed by γ- and δ-amino alcohols, where the Zn atom is part of a more conformationally flexible six- or seven-member catalytic chelate.[5,6] In these last cases, the rigidity of the chiral amino alcohol, among another structural features, plays an important role in order to limit the conformational freedom of such catalytic species, particularly around the oxygen and nitrogen atoms.[6i,j]

Until recently only a few examples of the application of γ-amino alcohols have been reported,[5] some of which with high stereoselectivity.[7] Although their catalytic role remains not totally understood and the reaction mechanism has been less studied, there has been increased interest in the synthesis and applications of new γ-amino alcohols.

2. Results and discussion

In recent years, we have developed in our laboratory diverse strategies for the synthesis of enantiopure bridgehead-substituted β- and δ-amino alcohols based on the norbornane framework and evaluated their catalytic

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activity in the enantioselective addition of diethylzinc to benzaldehyde.[3g,h,6k–m] The main structural characteristic of these amino alcohols is to possess one of the key heteroatomic functional groups (amino or hydroxyl) attached to the norbornane bridgehead position (directly or through a carbon unit), whereas the second key functional group is joined directly to the norbornane C2 position. Following our research work in this field, we have now synthesised a new set of γ-amino norbornan-2-ols derived from (1*R*)-(+)-camphor (Fig. 1) and evaluated their catalytic activity for the enantioselective addition of diethylzinc to benzaldehyde. Additionally, the catalytic behaviour of amino alcohols **1**–**4** has been rationalised empirically and compared to those previously described by us for β- and δ-amino 3,3-dimethylnorbornan-2-*endo*-ols.[3g,h,6m] The obtained results, in conjunction with the previous studies reported by us, will allows us to undertake a comparative study on the role played by the combined effects of both an increase in ring size of the catalytic zinc-chelate (with the consequent enhancement of conformational flexibility) and the alkyl substitution at the nitrogen atom.

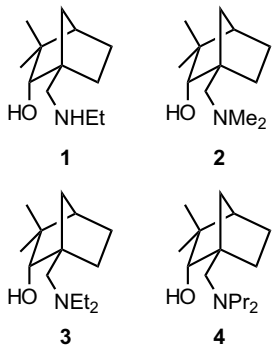


Figure 1. Bridgehead-norbornane-derived γ-amino alcohols studied.

Amino alcohol **1** was prepared by the controlled acylation of (1*S*,2*R*)-1-aminomethylnorbornan-2-ol **5**, previously reported by us,[8] with $MeCOCl/CH_2Cl_2$ followed by reduction of the corresponding *N*,*O*-diacetyl derivative **6** with $LiAlH_4/Et_2O$. Amino alcohols **2**–**4** were prepared by the controlled alkylation of **5** using the appropriate alkylating agent [HCHO/HCOOH for **2** (Eschweiler-Clarke procedure)[9] or RI/K_2CO_3 in refluxing ethanol for **3** and **4**] (Scheme 1).

The catalytic ability of ligands **1**–**4** towards the enantioselective addition of diethylzinc to benzaldehyde was evaluated using the free amino alcohols under the same conditions we employed in the previous reports;[3g,h,6k–m] the results are summarised in Table 1.

Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalysed by amino alcohols **1**–**4**[a]

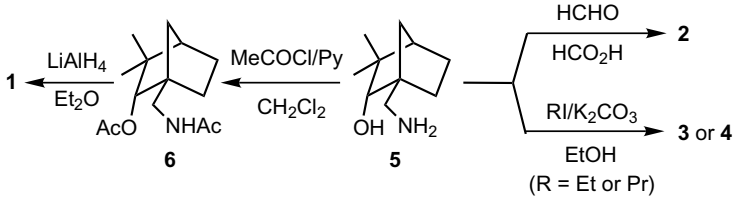
Chiral ligand	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	94	32	(*R*)
2	97	47	(*R*)
3	99	66	(*R*)
4	80	11	(*R*)

[a] Solvent: hexane; [PhCHO]/[ligand]/[Et_2Zn] = 1:0.05:2 at rt.
[b] Determined by GC using an achiral SGL-1 column.
[c] Determined by chiral GC using a Cyclodex-B column.
[d] Determined by the sign of the specific rotation and the elution order on chiral GC.

As shown in Table 1, the enantioselective addition promoted by our ligands gives 1-phenylpropan-1-ol in high yields with a stereoselectivity ranging from low to moderate. The absolute configuration of the main enantiomer of the obtained 1-phenylpropan-1-ol is (*R*) in all cases, thus indicating that the stereochemical outcome is controlled by the carbinolic stereocentre, as expected on the basis of the previous observations (empirical Noyori's rule).[1a,4b,10] On the other hand, alkyl substitution at the nitrogen atom has a very significant effect on the achieved enantioselectivity. Thus, the enantioselectivity increases with the *N*-alkyl substitution degree when going from *N*-ethyl amino alcohol **1** to *N*,*N*-diethyl amino alcohol **3**, the most efficient of the series (66% ee), but drops dramatically to the lowest value (11% ee) in the case of *N*,*N*-dipropylated ligand **4**.

A comparative study of the results for γ-amino norbornan-2-ol **2**, together with the preliminary ones reported by us on the catalytic behaviour of their homologue β-[3h] and δ-amino norbornan-2-ols[6m] **7** and **8**, respectively, may provide an empirical insight into the effect exerted on the enantioselectivity by the catalytic zinc-chelate ring size. As far as we know, this constitutes as the first comparative study on the catalytic activity between a series of β-, γ- and δ-amino alcohols bearing the same framework. Figure 2 shows the enantioselectivities displayed by the β-, γ- and δ-amino norbornan-2-ols synthesised by us.

A qualitative empirical explanation of the observed sense of enantioselection for ligands **7** and **8** has been previously proposed on the basis of five- and six-membered zinc-chelate catalysts **9** and *ent*-**11** (Scheme 2) and the corresponding controlling tricyclic 5/4/4 and 7/4/4 TS models.[3h,6m] Analogously, for our γ-aminonorbornan-2-ols **1**–**4** we



Scheme 1. Synthesis of ligands **1**–**4**.

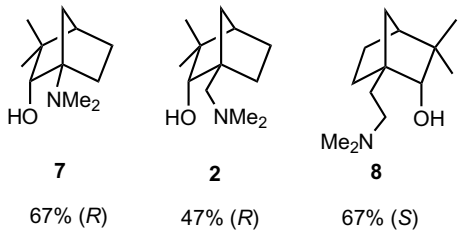
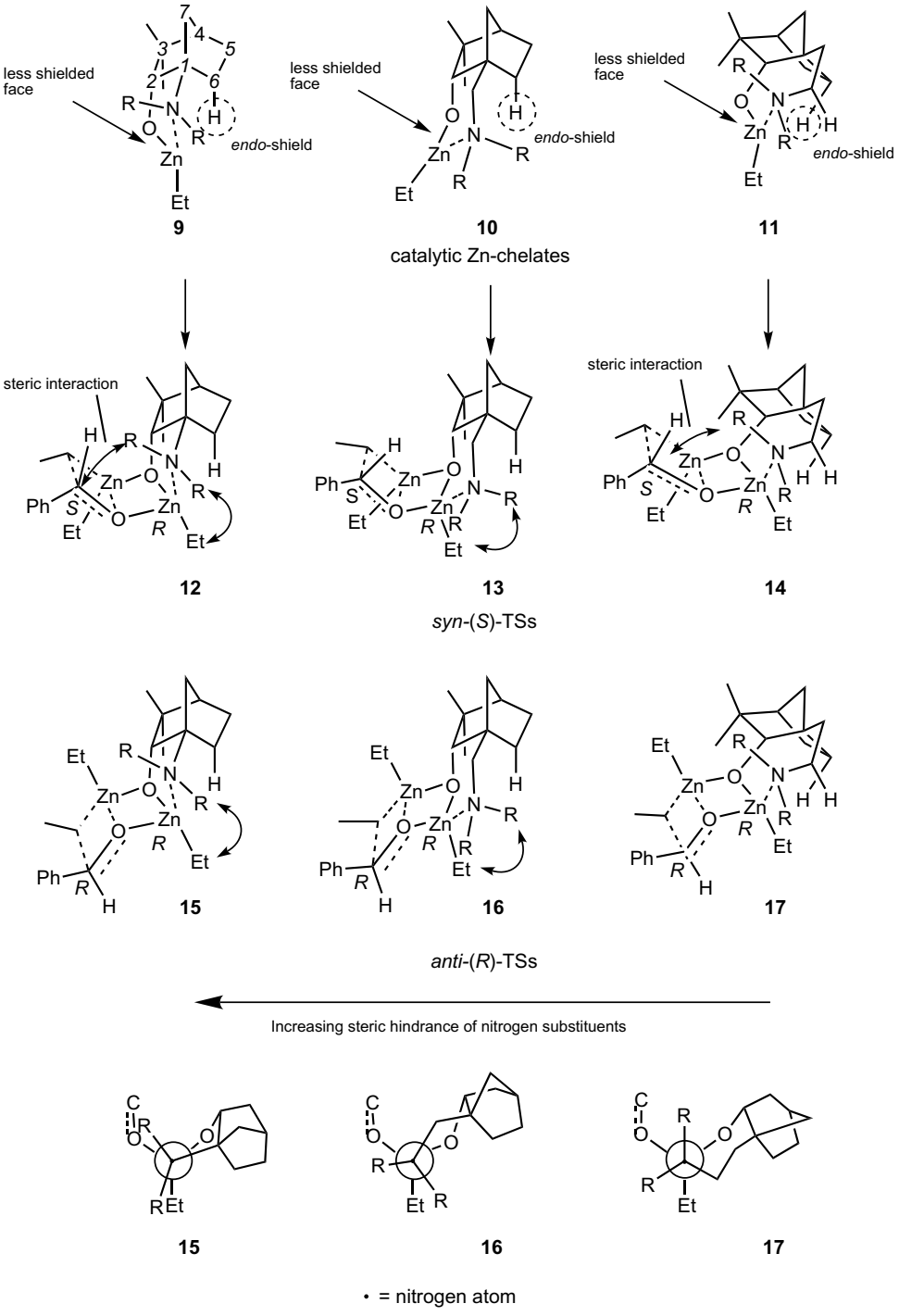


Figure 2. Enantioselectivities displayed by β-, γ- and δ-amino alcohols.

now propose the formation of the six-membered zinc-chelate catalyst **10** (distorted chair) and the corresponding tricyclic 6/4/4 TS models. 6/4/4 Models have been also proposed by Kozlowski for flexible *cis*-decalin-based γ-amino alcohols[5i] and by Costa for norbornane-based ones.[5k,o] Additionally, Kozlowski et al. have carried out theoretical calculations in order to rationalise the low to moderate enantioselectivities observed for their ligands and found that the experimental results can be best ex-



Scheme 2. Enantioselectivity controlling TSs and relative stability (arrows indicate steric interaction).

plained by means of tricyclic 6/4/4 TSs, rather than bicyclic 6/6 ones.[5i]

Thus, the coordination of $ZnEt_2$ and benzaldehyde to the O and Zn atoms of catalysts **9**, **10** and **11** takes place preferentially at the *Re* face of the Zn atom in all the cases (note the steric hindrance exerted by the *endo*-C6–H of the norbornane moiety that shields the *Si* face of Zn), giving place to two diastereomeric couples of tricyclic diastereomeric TSs (*syn*- and *anti*-TSs), that is, in all the cases studied, only the more energetically-favoured partners within each couple, *syn*-(*S*)-TS **12**–**14** and *anti*-(*R*)-TS **15**–**17** (avoiding *syn*-eclipsing between the phenyl group and the nitrogen-chelated Zn–Et one) are shown in Scheme 2. In such favoured TSs, the ethyl group transfer occurs by the *Si*- and the *Re*-face of the benzaldehyde carbonyl group, leading to (*S*)- or (*R*)-1-phenylpropan-1-ol respectively.

It has been recognised by several authors, on the basis of theoretical calculations, that the *anti*-type TSs are generally more stable than their diastereomeric *syn*-type ones,[1a,3b,j,4e,f,5i] particularly in supramolecular structures involving conformationally rigid ligands. According to these facts, the energy difference between the two lowest-energy *anti*-type TSs mainly determines the enantioselectivity of the reaction, as indicated for DAIB,[1a,4e,f] and other β-amino alcohols.[3b,j] However, in the cases of more conformationally flexible ligands, the preference for a given geometry (*anti* or *syn*) for the TS is greatly dependent on their structure.[3c–e] Thus, the stereoselectivity may decrease if other competitive reaction pathways involving less energetically-differentiated diastereomeric TS structures take place. This seems to be the most likely reason for the low to moderate enantioselectivity displayed by our ligands. The energy difference between the *syn*-(*S*)-TS and the *anti*-(*R*)-TS, each leading to opposite enantiomers, would explain the stereochemical outcome of the reaction with the formation of the enriched (*R*)-enantiomer of 1-phenylpropan-1-ol, but this energy difference would be not enough to provide a good stereoselection.

Once qualitatively explained, the sense of the stereoselection for all the ligands studied on the basis of the formation of the corresponding chelate catalysts **9**–**11** and diastereomeric TSs **12**–**17**, the establishment of an empirical rule for the degree of stereoselection appears not to be easy. Thus, from the comparison of Figure 2 data (on the catalytic behaviour of ligands **2**, **7** and **8**, keeping the same *N*-alkyl substitution pattern), it can be seen that both β- and δ-amino alcohols **7** and **8**, respectively, provide the same level of enantioselection (67% ee). However, a decrease of enantioselectivity to 47% ee is found for γ-amino alcohol **2**. It could be expected that the more flexible seven-membered catalyst **11** (from ligand **8)** should give a lower degree of stereoselection than the less flexible five- and six-membered catalysts **9** and **10** (from ligands **7** and **2** respectively), due to the participation of a higher number of competitive controlling TSs with similar energetic stabilities, which is in contradiction with the experimental results shown in Figure 2. An intriguing non-linear correlation between enantioselectivity and chelate ring's size (i.e., conformational flexibility) is therefore observed.

On the other hand, a comparison of the enantioselectivities displayed by the norbornane-based β- and γ-ethylamino-alcohol homologues **18** (47% ee)[3h] and **1** (32% ee), as well as by the menthane-based γ- and δ-dimethylamino-alcohol homologues **19** (77% ee)[5g] and **20** (95% ee)[6a] (see Fig. 3) shows the same trend: the γ-amino alcohol is the less stereodifferentiating one, when compared with the corresponding β- or δ-homologue within each couple. However, due to the absence of any data about the catalytic behaviour of the δ-homologue of **1** and **18**, as well as the β-homologue of **19** and **20**, it is not possible to verify such non-linear correlation for these structural patterns.

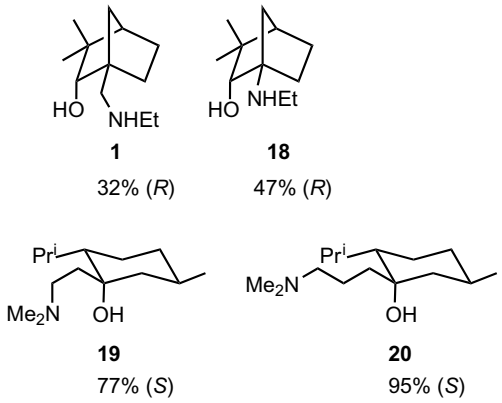


Figure 3. Enantioselectivities observed in secondary β- and γ- and tertiary γ- and δ-amino alcohols keeping the same structural pattern.

The observed striking non-linear correlation between enantioselectivity and chelate size (i.e., conformational flexibility) shown in Figure 2 can also be explained empirically taking in consideration that the controlling diastereomeric TSs are not only the couple pro-*R*/pro-*S* *anti*-TSs (*anti*(*R*)-/*anti*(*S*)-TS), but also the more stable *syn*-TS [i.e., the pro-*S* one: *syn*(*S*)-TS in Scheme 2]. In this line, Goldfuss has previously demonstrated that the energy difference between *syn*- and *anti*-TSs can decrease, or even reverse, for some conformationally flexible ligands.[3c] In such cases, stereoselectivity may decrease due to the competitive participation of less energetically-differentiated *syn*- and *anti*-TSs. According to the moderate stereoselection degrees displayed by **2**, **7** and **8** (see Fig. 2), this last case could probably occur in some of our ligands.

As a consequence, we have studied the possible additional participation of such *syn*-(*S*)-TSs (Scheme 2). In all the cases studied, the observed stereoselection sense indicates that the more stable TS is the pro-(*R*) one [*anti*(*R*)-TS], but a possible higher participation of the corresponding competitive *syn*-(*S*)-TS should be reflected in a lower degree of stereoselection. We have noticed that the *syn*-(*S*)-TSs **12** and **14** are strongly destabilised by a steric repulsion between *N*-alkyl substituent (R) and benzaldehyde methine group (note the corresponding arrows in Scheme 2). In contrast, this steric interaction is avoided (at least partially) in the *syn*-(*S*)-TS **13**. As a consequence, the energy difference between the *anti*(*R*)-TS **16** and the *syn*(*S*)-TS **13** (ligand **2**) is lower than the corresponding difference between **15** and **12** or **17** and **14** (ligands **7** and **8**,

respectively). This relative stabilisation of the diasteromeric pathway involving the pro-*S* TS *syn*-(*S*)-**13** for ligand **2**, which makes such TS more competitive, accounts for the decrease of enantioselectivity observed for ligand **2** with regards to **7** and **8**. This hypothesis could also explain the worst enantioselection displayed by the γ-amino alcohols **1** and **19** (Fig. 3) when compared respectively with their β- or δ-homologues **18** and **20**.

Based on our previous studies regarding the catalytic activity of bridgehead norbornane-based β-amino alcohols, on the influence of the nitrogen substituents on catalytic behaviour,[3g,h] we have also studied such an effect for related γ-amino alcohols, on the basis of the data now obtained for ligands **1**–**4**. As shown in Table 1, the secondary amino alcohol **1** is less selective than the tertiary ones **2** and **3**, as expected according to the general trends reported in the literature.[1a] The change of the *N*,*N*-dimethyl substitution in **2** by the more bulky *N*,*N*-diethyl one in **3** improves the stereoselectivity from 47 up to 66% ee. A similar effect was observed by Costa et al. in their studies on γ-amino alcohols based on 2,7-disubstituted norbornane.[5k,o] In our case, the enantioselectivity enhancement could be attributed to a lesser participation of a competitive diasteromeric pathway via *syn*-(*S*)-**13** TS, caused by an increase in steric hindrance exerted by the ethyl group with respect to the methyl one in such TS. However, a new increase in the bulkiness of the *N*-alkyl substituent by incorporation of the *N*,*N*-dipropyl substitution in **4**, in place of the *N*,*N*-diethyl one of **3**, causes a drastic decrease in stereoselectivity, which falls down to 11% ee. Probably, in this last case, the sterical hindrance exerted by the propyl group is too high, giving place either to a conformational change or to a destabilisation of chelate **10**, favouring competitive diastereomeric pathways involving less stereodifferentiating TS geometries. Similar trends, concerning the effect of the *N*-alkyl substituents, have been reported by Soai et al. for *N*,*N*-di-*n*-alkylnorephedrines,[1b] although with our ligands this effect is more critical and the highest enantioselection level reached is only moderated.

It is also noteworthy that the effect on the enantioselectivity caused by the replacement of a *N*,*N*-dimethyl substitution by an *N*,*N*-diethyl one in the β-[3h] and γ-amino norbornanols studied by us is reversed, as can be seen from comparison of the data shown in Figure 4.

This different behaviour can be attributed to the increase of conformational flexibility in both six-membered catalytic chelate **10** and tricyclic 6/4/4 TSs **13** and **16** with respect to the five-membered chelate **9** and the corresponding tricyclic 5/4/4 TSs **12** and **15**. In these last cases, the bulkiness increase of the *N*-alkyl substituents in **21**[3h] with respect to **7** has a critical effect either in chelate **9** or in all the resulting TSs (see Scheme 2), owing to unfavourable eclipsing of *syn*-alignments between the *N*- and Zn-substituents as well as between the R-groups and the norbornane C6 and C7 carbons, which would favour diastereomeric reaction pathways with low stereodifferentiating geometries as commented above for ligand **4**. On the other hand, TSs **13** and **16** (ligand **2** or **3**) are sterically less congested than TSs **12** and **15** (ligand **7** or **21**), due to the minor eclipsement degree between the *N*- and Zn-substituents (see Scheme 2). This fact could explain the modest tuning of the enantioselectivity from **2** (NMe_2 group, 47% ee) to **3** (NEt_2, 66% ee). Unfortunately, it was not possible to extend this comparative study to δ-amino alcohols, due to the synthetic restrictions imposed by the key use of Eschenmosser's salt reacting with bridgehead 2-methylenenorbornane alcohols,[6m] which determines that only *N*,*N*-dimethyl-substituted compounds can be achieved.

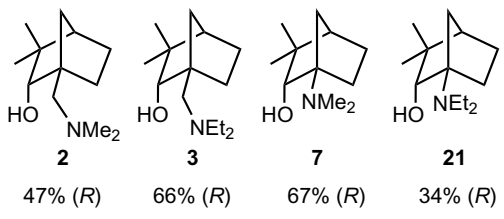


Figure 4. Effect of alkyl substitution at the nitrogen atom on the enantioselectivities displayed by tertiary β- and γ-amino alcohols.

3. Conclusions

In conclusion, the conformational flexibility of the γ-amino norbornanols synthesised here makes them able to adapt their geometries to both *anti*- and *syn*-type TSs when used as ligands for the enantioselective addition of diethylzinc to benzaldehyde. In the case of small *N*,*N*-dialkyl substituents (i.e., NMe_2 group), the lower energy difference between both types of TSs provide less stereodifferentiation when compared to their β- or δ-homologues keeping the same structural pattern. Better results are obtained by increasing the steric hindrance around the nitrogen atom up to a critical steric congestion point, determined by both nitrogen substituent bulkiness and chelate ring size. As a consequence, the enantioselectivity was found to vary in a non-systematic manner upon increasing both the catalyst chelate ring size, from five to seven-membered, and the bulkiness of the nitrogen substituents. This fact is due to a higher importance of the catalyst conformational flexibility factor, which influences not only on the participation of a higher number of energetically close controlling diastereomeric TSs, but also on a non-linear relative participation of them.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker-AC 200 (200 MHz for ^1H and 50 MHz for ^{13}C) with TMS as the internal standard; *J* values are given in hertz. IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. Melting points were measured using a Gallenkamp instrument. Elemental analysis were carried out using a Perkin–Elmer 2400-CHN instrument. Mass spectra were recorded on a GC–MS Shimadzu QP5000 (70 eV) spectrometer. For gas chromatography, a Shimadzu 17 AAF chromatograph equipped with a capillary SGL-1 column (30 m) was used.

Enantiomeric excesses were determined by chiral GC using a Hewlett-Packard 5890 instrument (chiral capillary column: Cyclodex-B, 30 m). Solvents were used after appropriate distillation. Optical rotation data were recorded on a Perkin–Elmer 241 polarimeter; concentrations are given as g/100 mL of solvent.

4.2. (1*S*,2*R*)-1-[(*N*-Acetyl)aminomethyl]-3,3-dimethylnorbornan-2-yl acetate 6

To a stirred solution of 2.96 mmol of (1*S*,2*R*)-1-aminomethyl-3,3-dimethylnorbornan-2-ol **5** and 7.00 mmol of pyridine in dry CH_2Cl_2 (10 mL) at room temperature was added dropwise 6.5 mmol of MeCOCl. The reaction mixture was stirred at room temperature for 24 h (the reaction progress was monitored by GC). The reaction was carefully quenched with 10 mL of 10% aqueous solution of NaOH and extracted with CH_2Cl_2 (5×10 mL). The organic extract was washed with 10% HCl (2×25 mL), saturated aqueous solution of $NaHCO_3$ (1×25 mL), brine (1×25 mL) and then dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the reaction crude was chromatographed (silica gel, CH_2Cl_2/Et_2O 9:1) to give **6** as a white solid which was submitted to subsequent reduction without further purification. Yield 69%; mp > 200 °C (decomp.). $[\alpha]_D^{20} = -42.3$ (*c* 0.51, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.04 (br s, 1H), 4,50 (s, 1H), 3.55 (dd, $J = 14.1$, 7.8 Hz, 1H), 2.95 (dd, $J = 14.1$, 4.9 Hz, 1H), 2.10 (s, 3H), 2.00 (s, 3H), 1.80–1.40 (m, 5H), 1.30–1.10 (m, 2H), 1.07 (s, 3H), 0.84 (s, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8, 170.0, 82.0, 53.0, 47.6, 41.4, 38.9, 37.6, 29.9, 25.3, 23.4, 23.3, 21.0, 20.3 ppm. FTIR (CCl_4) ν 3460, 3350, 1750, 1690, 1530, 1475, 1390, 1260, 1060, 920 cm^{-1}. MS *m*/*z* (%) 253 ($M^{+\cdot}$, 2), 210 (23), 194 (2), 193 (5), 150 (6), 134 (12), 81 (23), 80 (15), 60 (100), 43 (88), 41 (22).

4.3. (1*S*,2*R*)-1-[(Ethylamino)methyl]-3,3-dimethylnorbornan-2-ol 1

Over a stirred dispersion, cooled to 0 °C, of $LiAlH_4$ (0.50 mmol) in dry Et_2O (10 mL) was slowly added a solution of 0.25 mmol of **6** in 5 mL of dry Et_2O. The reaction mixture was refluxed for 6 h (the reaction progress was monitored by GC). After this time, the reaction was carefully quenched with H_2O (15 mL) and extracted with Et_2O (5×20 mL). The organic layer was extracted with 10% HCl (4×25 mL) and washed with CH_2Cl_2. The aqueous extract was treated with 10% aqueous NaOH until basic pH, and extracted with CH_2Cl_2 (4×25 mL). The organic extract was washed with brine and dried over KOH. After evaporation of solvent, amino alcohol **1** was purified by crystallisation of the corresponding hydrochloride in $MeOH/Et_2O$. Yield 74%; mp (hydrochloride) >200 °C (decomp.). $[\alpha]_D^{20} = -4.5$ (*c* 0.62, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.52 (d, $J = 1.8$ Hz, 1H), 2.93 (d, $J = 11.4$ Hz, 1H), 2.74 (d, $J = 11.4$ Hz, 1H), 2.70–2.52 (m, 4H), 2.00–1.80 (m, 1H), 1.75–1.70 (m, 3H), 1.44–1.34 (m, 2H), 1.26 (s, 1H), 1.09 (t, $J = 7.0$ Hz, 3H), 1.01 (s, 3H), 0.89 (s, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 85.5, 56.4, 52.2, 48.1, 44.9, 39.1, 38.0, 30.9, 25.9, 22.6, 19.9, 15.3 ppm FTIR (CCl_4) ν 3570, 3350, 1465, 1440, 1270, 1130, 1110, 1085 cm^{-1}. MS *m*/*z* (%) 196 ($M^{+\cdot}-1$, 9), 123 (11), 109 (5), 72 (100), 60 (54), 59 (40), 58 (18), 44 (85). Anal. Calcd for $C_{12}H_{24}ClNO$: C, 61.65; H, 10.35; N, 5.99. Found: C, 61.75; H, 10.48; N, 6.03.

4.4. (1*S*,2*R*)-1-[(Dimethylamino)methyl]-3,3-dimethylnorbornan-2-ol 2

To a stirred 40% aqueous solution of formaldehyde (0.54 mL, 6.48 mmol), cooled at 0 °C, were added 0.80 mL (16.30 mmol) of 85% formic acid and 2.00 mmol of **5**. The mixture was stirred for 10 m at 0 °C and then heated at 100 °C for 2 h (the reaction progress was monitored by GC). After the reaction had gone to completion, the excess of formaldehyde was removed in vacuo and the reaction was quenched with 15 mL of 10% aqueous solution of NaOH. The reaction mixture was extracted with CH_2Cl_2 (4×15 mL), the organic extract washed with brine (2×15 mL) and dried over anhydrous Na_2CO_3. After filtration and evaporation of solvent, amino alcohol **2** was purified by crystallisation of the corresponding hydrochloride in $MeOH/Et_2O$. Yield 88%; mp (hydrochloride) >200 °C (decomp.). $[\alpha]_D^{20} = -9.3$ (*c* 0.50, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.54 (d, $J = 3.9$ Hz, 1H), 2.72 (d, $J = 12.9$ Hz, 1H), 2.42 (d, $J = 12.9$ Hz, 1H), 2.26 (s, 6H), 2.23–1.99 (m, 1H), 1.79–1.26 (m, 5H), 1.12–1.08 (m, 2H), 1.01 (s, 3H), 0.90 (s, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 85.5, 67.0, 52.2, 47.9, 47.5, 39.0, 38.9, 31.0, 26.7, 24.1, 19.9 ppm. FTIR (CCl_4) ν 3350, 1465, 1090 cm^{-1}. MS *m*/*z* (%) 197 ($M^{+\cdot}$, 2), 58 (100), 46 (51), 45 (44), 44 (25). Anal. Calcd for $C_{12}H_{24}ClNO$: C, 61.65; H, 10.35; N, 5.99. Found: C, 61.78; H, 10.46; N, 6.06.

4.5. Typical procedure for the preparation of amino alcohols 3 and 4

To a stirred solution, at room temperature, of **5** (1.5 mmol) in dry EtOH (10 mL) were added 8.8 mmol of anhydrous K_2CO_3 and 8.8 mmol of EtI or PrI. The reaction mixture was refluxed for 24 h (the reaction progress was monitored by GC). After completion, the reaction was quenched with 15 mL of H_2O, then extracted with CH_2Cl_2 (3×20 mL) and dried over anhydrous K_2CO_3. After filtration and evaporation of solvent, the amino alcohol was purified by crystallisation of the corresponding hydrochloride in $MeOH/Et_2O$.

4.5.1. (1*S*,2*R*)-1-[(Diethylamino)methyl]-3,3-dimethylnorbornan-2-ol 3. Yield 80%; mp (hydrochloride) 183–185 °C $[\alpha]_D^{20}$ (hydrochloride) = −14.5 (*c* 1.17, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.47 (d, $J = 1.9$ Hz, 1H), 2.75 (d, $J = 13.4$ Hz, 1H), 2.71–2.53 (m, 2H), 2.51 (d, $J = 13.4$ Hz, 1H), 2.45–2.25 (m, 2H), 2.11–1.94 (m, 1H), 1.82–1.62 (m, 2H), 1.49–1.24 (m, 3H), 1.16–1.05 (dm, $J = 9.8$ Hz, 2H), 1.01 (t, $J = 7.3$ Hz, 6H), 1.00 (s, 3H), 0.89 (s, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 85.1, 60.8, 51.9, 48.3, 47.5, 38.8, 30.9, 29.7, 26.5, 24.3, 19.8, 11.9 ppm. FTIR (CCl_4) ν 3339, 1458, 1389, 1367, 1080 cm^{-1}. MS *m*/*z* (%) 210 ($M^{+\cdot}-15$, 8), 86 (100), 74 (25), 58 (57), 43 (11). Anal. Calcd for $C_{14}H_{28}ClNO$: C, 64.22; H, 10.78; N, 5.35. Found: C, 64.54; H, 10.76; N, 5.41.

4.5.2. (1*S*,2*R*)-1-[(Dipropylamino)methyl]-3,3-dimethylnorbornan-2-ol 4. Yield 60%; mp (hydrochloride) 110–112 °C $[\alpha]_D^{20}$ (hydrochloride) = −2.7 (*c* 0.70, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.48 (d, $J = 1.8$ Hz, 1H), 2.77 (d, $J = 13.2$ Hz, 1H), 2.52 (d, $J = 13.2$ Hz, 1H), 2.57–2.43 (m, 2H), 2.30–2.18 (m, 2H), 2.09–1.97 (m, 1H), 1.80–1.18 (m, 10H), 1.15–1.05 (m, 1H), 1.02 (s, 3H), 0.91 (s, 3H), 0.88 (t, $J = 7.4$ Hz, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 85.1, 62.2, 57.7, 52.1, 47.5, 38.8, 31.7, 30.9, 26.6, 24.3, 20.4, 19.9, 11.8 ppm. FTIR (CCl_4) ν 3339, 1458, 1417, 1364 cm^{-1}. MS *m*/*z* (%) 253 (M^+,2), 225 (14), 224 (100), 123 (24), 114 (42), 102 (7), 81 (28) 72 (15), 43 (49), 41 (41). Anal. Calcd for $C_{16}H_{32}ClNO$: C, 66.29; H, 11.13; N, 4.83. Found: C, 66.12; H, 10.87; N, 4.79.

4.6. Enantioselective addition of diethylzinc to benzaldhyde catalysed by ligands 1–4

To a dispersion of ligands **1**–**4** (0.05 mmol) in dry hexane (2.0 mL) under an argon atmosphere, at room temperature, was slowly added Et_2Zn (1.0 M in hexane, 0.9 mL, 2.0 mmol). The resulting solution was stirred at room temperature for 1 h and then freshly distilled benzaldehyde was added. The reaction mixture was stirred for the appropriate time to complete the reaction (GC monitoring) and quenched with 5 mL of aqueous saturated solution of NH_4Cl. After extraction, (Et_2O, 3×5 mL), the organic layer was dried over anhydrous $MgSO_4$ and analysed by GC for determining the conversion degree and by chiral GC for determining asymmetric induction reached (ee and major enantiomer).

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