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Hydroxyamides versus amino alcohols in the enantioselective addition of diethylzinc to benzaldehyde

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ABSTRACT

Two series of structurally related enantiopure isoborneols (10-amino- and 10-amino-10-oxoisoborneols) have been obtained from ketopinic acid and compared as chiral ligands for the enantioselective addition of diethylzinc to benzaldehyde in the absence of Ti(O-*i*-Pr)$_4$. The results obtained (chemical yields and enantiomeric excesses) show that identical structural factors (functionalization grade and symmetry group) exert very different effects on both series. The observed differences have been rationalized on the basis of the coordination ability of each ligand type to form the corresponding reactive zinc-chelate catalyst.

1. Introduction

Chiral amino alcohols, especially *N*,*N*-dialkyl-substituted β-amino alcohols, are privileged ligands for the enantioselective addition of organozinc reagents to carbonyl groups.[1,2] This asymmetric reaction allows the easy preparation of enantioenriched carbinols, which are interesting key intermediates in the preparation of biologically active compounds and new materials with peculiar chiroptic properties.[3]

From the establishment of the first efficient ligands (e.g., Noyori's DAIB **1** or Nugent's amino isoborneol **2** shown in Fig. 1), many new structures, mainly amino alcohols, have been obtained and proven in this important asymmetric process.[1] In most of these cases, the ligands obtained were only able to promote the addition to reactive carbonyls (i.e., aromatic aldehydes); the main objective of this synthetic effort was to find a versatile ligand able to promote the enantioselective addition to a broad variety of carbonyl substrates, including less reactive ketones.[4]

In addition to amino alcohols, certain chiral hydroxyamides have recently been proved to be efficient promoters for this valuable asymmetric addition.[5] In these cases, the additional presence of Ti(IV), generally titanium tetraisopropoxide, is usually required.[6]

On the other hand, we have described ligand **3a** as the first isoborneol-based amide, which is able to promote the enantioselective addition of diethylzinc to benzaldehyde in the absence of titanium at a similar level of effectiveness (chemical yield and enantioselectiviy) to the well-established isoborneol-based amino alcohols **1** and **2** do (Fig. 1).[5g]

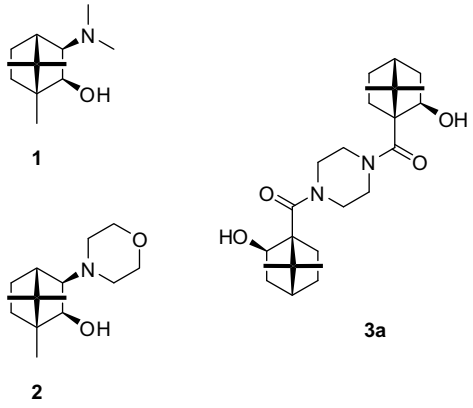

Figure 1. Some efficient isoborneol-based ligands for the enantioselective addition of diethylzinc to benzaldehyde in the absence of titanium.

The advantage of hydroxyamides versus amino alcohols lies in the easy preparation of hydroxyamides by simple amidation of a great variety of enantiopure materials coming from the chiral pool (e.g., amidation between natural hydroxy acids and amines, or between acids and natural amino alcohols).[5g] In this sense, the straightforward preparation of enantiopure hydroxyamides must allow the easy generation of structurally diverse ligands, making the search for the versatile ligand easier. Unfortunately, the catalytic behaviour of hydroxyamides has been less studied, and the key structural factors controlling the catalytic activity are still unknown. This fact makes the rational design of efficient hydroxyamide-based ligands impossible.

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With this in mind and continuing with our initial work on this ligand type,[5g] we became interested in comparing the catalytic behaviour of a series of hydroxyamides with the catalytic behaviour of a series of structurally related amino alcohols. Since the catalytic behaviour of amino alcohols is better known,[7] the establishment of analogies or differences in the catalytic behaviour of both series should be a good tool to gain knowledge about the catalytic behaviour of hydroxyamides, and therefore, to establish useful empiric roles correlating structure versus activity in this interesting new type of ligands.[8]

2. Results and discussion

For our objective, we have chosen four simple *N*,*N*-dialkyl-substituted hydroxyamides **3a**–**6a** (Fig. 2) and the corresponding *N*,*N*-dialkyl-substituted amino alcohols **3b**–**6b** (Fig. 2) in order to compare the influence of both the ligand's symmetry[9] and the ligand's conformational flexibility[10] on the catalytic activity of both series. We have chosen the enantioselective diethylzinc addition to benzaldehyde as the test reaction.[11]

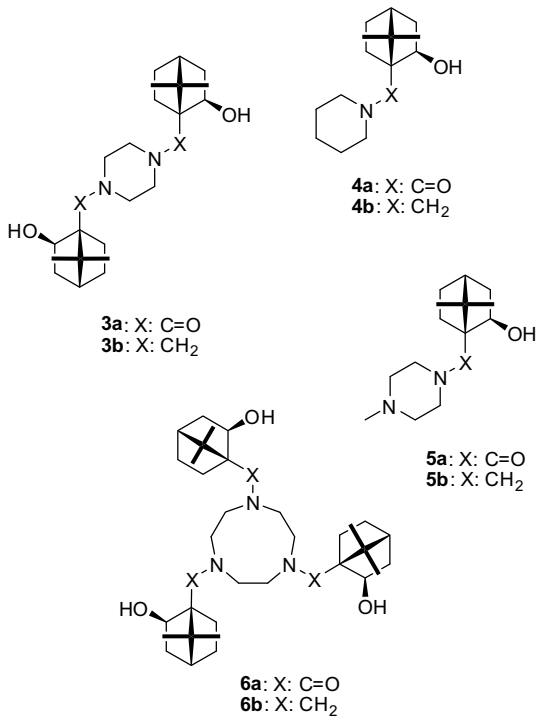

Figure 2. Isoborneol-based hydroxyamides and amino alcohols studied.

The catalytic activity of hydroxyamides **3a** and **4a**,[5g] and amino alcohol **5b**[12] have recently been reported by us. The catalytic activity of amino alcohol **4b** was measured by Aoyama et al. in 2005 (ee 77%);[13] nevertheless, we have also obtained **4b** and measured its catalytic activity (ee 72%, see Table 1) in order to work with a normalized catalytic-activity report, with all data obtained in the same test-reaction and analysis conditions.

Ligands **5a**,[14] **6a**,[15] **3b**,[16] **4b**[17] and **6b**[18] were obtained from commercial (1*S*)-ketopinic acid in two steps: amidation,[19] followed by a selective reduction with an appropriate hydride transfer reagent ($NaBH_4$ for hydroxyamides vs. LAH for amino alcohols) according to the corresponding procedures described previously by us[5g,12] (overall yield: 72–82%). The new ligands were proven in the test reaction in the absence of titanium tetraisopropoxide.[11] Table 1 shows the measured catalytic activity for each ligand (yield and ee). Previously reported data for the catalytic activity of **3a**, **4a** and **5b** in the same test reaction have also been included in Table 1.

Table 1
Enantioselective addition of diethylzinc to benzaldehyde in the presence of ligands **3a**–**6a** and **3b**–**6b**[15]

Ligand symmetry	Hydroxyamides				Amino alcohols			
	Ligand	Yield (%)	ee (%)	Dominant config.	Ligand	Yield (%)	ee (%)	Dominant config.
C_1	**4a**[a]	96	48	(*R*)	**4b**	96	72	(*R*)
	5a	93	50	(*R*)	**5b**[a]	99	50	(*R*)
C_2	**3a**[a]	97	90	(*R*)	**3b**	94	56	(*R*)
C_3	**6a**	70	39	(*R*)	**6b**	72	12	(*R*)

[a] Data reported previously (see main text).

The data in Table 1 show that all the ligands studied are able to promote the enantioselective addition in the same sense (pro-*R*). All the C_1 and C_2 ligands promote the reaction with high yields (93–97%) and moderate-to-high enantioselectivities (48–90% ee). On the other hand, C_3 ligands promote the reaction poorly (moderate yields and low enantioselectivities). The most efficient hydroxyamide was C_2-symmetric **3a** (97% yield and 90% ee), whereas the most efficient amino alcohol was C_1-symmetric **4b** (96% yield and 72% ee).

The high enantioselectivity exerted by C_2-symmetric hydroxyamide **3a**, in comparison to related C_1-symmetric **4a** (90% vs 48% ee), was explained previously by us on the basis of the formation of the reactive C_2-symmetric zinc-chelate catalyst **7** instead of the C_1-symmetric **8** (Fig. 3).[5g]

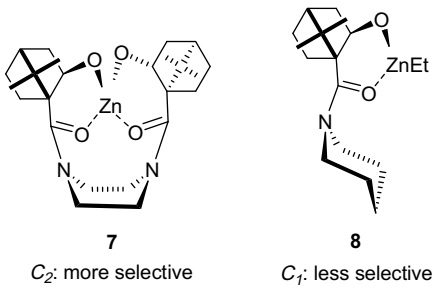

Figure 3. Previously proposed catalyst for ligands **3a** (**7**) and **4a** (**8**).

On the other hand, the low enantioselectivity exerted by tridentate amino alcohol **5b**, in comparison to the related bidentate amino alcohol **4b** (50% vs 72% ee), was also explained by us on the basis of the formation of catalyst **9**, with an extra-coordinated zinc atom (by the methylamino group), instead of catalyst **10** (Fig. 4).[12]

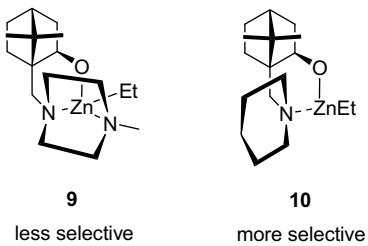

Figure 4. Previously proposed catalyst for ligands **5b** (**9**) and **4b** (**10**).

We have now discovered that (1) the catalytic behaviour of the polyfunctionalized C_2-symmetric amino alcohol **3b** is very similar to that exhibited by the established tridentate[12] C_1-symmetric

amino alcohol **5b**, and (2) the catalytic behaviour of polyfunctionalized C_1-symmetric hydroxyamide **5a** is very similar to that exhibited by the established bidentate[5g] C_1-symmetric hydroxyamide **4a** (see Table 1).

The catalytic behaviour found for the C_2-symmetric ligand **3b** can be explained by the formation of reactive catalyst **11** (Fig. 5), which does not have the advantageous C_2-symmetry[9] of the starting ligand. In this bimetallic catalyst, the most reactive metallic centre should be the most coordinated one, that is, the alcoxidic zinc intramolecularly coordinated with the bidentated piperazine moiety. Therefore, the activity of catalyst **11** should be very similar to the activity of catalyst **9**, due to the structural similitude of both catalysts (note the similar reactive-centre surroundings of catalysts **9** and **11** in Figs. 4 and 5).

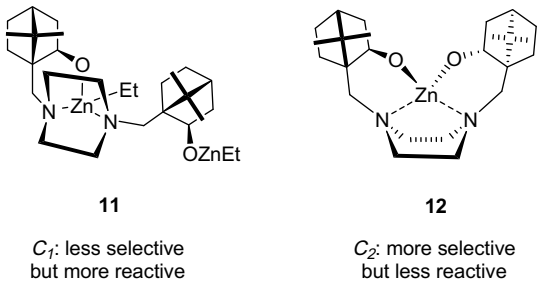

Figure 5. Proposed catalysts for ligand **3b.**

Ligand **3b** could also form a more-selective C_2-symmetric catalyst **12** (Fig. 5) similar to **7** (Fig. 3). Therefore, catalyst **12** could compete with **11** for reaction activation, making the process more enantioselective due its C_2 symmetry.[9] However, these diamine-coordinated zinc alcoxides have been demonstrated to activate the aldehyde by simple coordination to the zinc centre (without interchange of any coordinative group), increasing the zinc coordination-number from 4 to 5,[12,20] probably due to the strong coordinative character of the amine groups). This must make catalyst **12** less reactive than catalyst **11,** due to the higher steric hindrance around the reactive zinc in **12** (cf. both structures in Fig. 5). Therefore, **11** must be the working catalyst, as mentioned above on the basis of the observed low enantioselectivity reached with ligand **3b** (see Table 1). This situation is totally different for C_2-symmetric hydroxyamide-based catalyst **7**, which can activate the aldehyde with an amide-group—aldehyde interchange (increase of the zinc coordination number is not necessary).[5g]

The different coordination ability of the identical methylamino groups of ligands **5b** and **5a** in the respective catalytic complexes **9** (Fig. 4) and **13** (Fig. 6) is explained on the basis of the less-flexible amide group of **5a**, which places the piperazinic methylamino group far away from the metallic centre avoiding the extra coordination (Fig. 6). Nevertheless, the substitution of the methylamino group of **5a** by the carbonylamino group (amide) in **3a** must be enough to allow the extra coordination (by the closer carbonyl oxygen, Fig. 6), giving rise to the efficient C_2 catalyst **7**.

The low enantioselectivity reached with the C_3-symmetric ligands **3a** and **3b** (see Table 1) can be explained by the possibility of the coexistence of different active catalyst (thermodynamic equilibrium) in the reaction media (note the multiple coordination possibilities for these ligands), whereas the lower chemical yields reached with these ligands (70–12% vs 93–96%) must be related to the higher steric hindrance (produced by the bulkier organic ligand) around the reactive metallic centre.

Finally, the observed same enantioselectivity sense (pro-*R*) for all the ligands studied (Table 1) can be easily explained on the basis of favoured pro-*R* transition states analogous to those proposed previously by Oppolzer,[20] Aoyama[13] and us[5g,12] for related ligands.

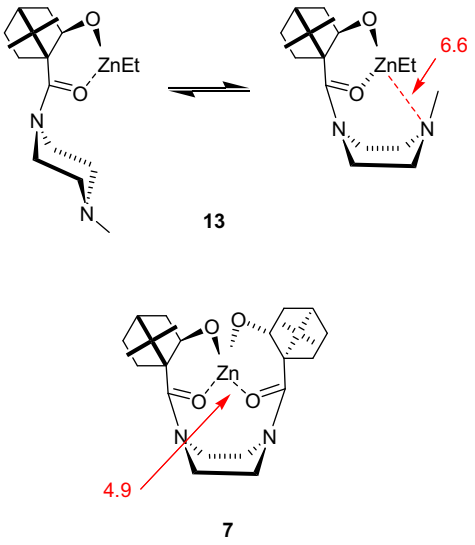

Figure 6. Different coordination ability of ligands **5a** and **3a** in their respective zinc complexes **13** and **7**. PM3-calculated selected distances in red (in Å).[21]

3. Conclusion

In conclusion, structurally related 10-amino- and 10-amino-10-oxoisoborneols have different structural requirements to act as effective catalysts for the enantioselective addition of diethylzinc to benzaldehyde. It is demonstrated that the structure of a C_2-symmetric bis(hydroxyamide) based on a symmetric secondary diamine, such as piperazine, seems to be the best one for 10-amino-10-oxoisoborneols. Conversely, the privileged structure for 10-aminoisoborneols is the simple C_1-symmetric one. It is also demonstrated that certain hydroxyamides can be better ligands than the corresponding structurally related amino alcohols. The catalytic behaviour of the ligands studied has been rationalized on the basis of a comparison of the measured enantioselectivities and the proposal of compatible catalytic structures based on others previously reported. Unfortunately, initial attempts to confirm the proposed structures for the controlling catalytic chelates by NMR experiments were unsuccessful.

The reported study constitutes the first attempt to rationalize the catalytic activity of a promising new type of ligands, bis(hydroxyamides), for the enantioselective addition of organozinc reagents to carbonyl substrates.

Acknowledgements

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11. Diethylzinc (1.0 M in hexane, 2 mL, 2.0 mmol) was added to the corresponding ligand (0.050 mmol) in anhydrous hexane (1 mL) under argon, and the mixture was stirred for 1 h at rt. After that, freshly distilled benzaldehyde (1.0 mmol) was slowly added and the resulting mixture stirred for 5 h at rt. Final treatment with 1 M HCl at 0 °C and standard work-up (e.g., see Ref. [12]) yielded the resulting enantioenriched mixture of 1-phenylpropan-1-ol. The ee was determined by chiral GC (cyclodex-B). The dominant configuration was determined by both the sign of the mixture's specific rotation and the elution time in chiral GC.
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14. *Compound* **5a:** White solid. Mp: 170–171 °C. $[\alpha]_D^{20} = -7.6$ (*c* 0.34, CH_2Cl_2). ^1H NMR (MeOH-d_4, 200 MHz): 4.28 (dd, *J* = 7.6, 7.3, 1H), 3.85–3.50 (several m, 4H), 2.47 (m, 4H), 2.33 (s, 3H), 2.00–1.50 (several m, 6H), 1.39 (s, 3H), 1.20–1.00 (m, 1H), 1.15 (s, 3H). ^{13}C NMR (MeOH-d_4, 50 MHz): 174.6, 79.0, 62.6, 58.8, 52.3, 47.4, 46.8, 45.6, 43.5, 31.8, 28.8, 23.6, 23.1. FTIR: 2920.6 (s), 1614.9 (m), 993.0 (m). MS (EI): 266 (9), 209 (8), 99 (75), 83 (100), 70 (99), 58 (75). HRMS: 266.1998 (calcd for $C_{15}H_{26}N_2O_2$: 266.1994).
15. *Compound* **6a:** White solid. Mp: 223–224 °C. $[\alpha]_D^{20} = -137.2$ (*c* 0.50, CH_2Cl_2). ^1H NMR (MeOH-d_4, 200 MHz): 4.27 (br m, 3 H), 4.50–3.10 (several br m, 12H), 2.00–1.50 (several br m, 18H), 1.39 (s, 9H), 1.30–1.10 (m, 3H), 1.15 (s, 9H). ^{13}C NMR (MeOH-d_4, 50 MHz): 177.2, 79.0, 62.8, 62.4, 52.6, 47.4, 43.6, 31.8, 28.9, 23.8, 23.2. FTIR: 2937.7 (s), 1612.2 (m). MS (EI): 627 (1), 239 (32), 167 (40), 149 (52), 95 (100). HRMS: 627.4243 (calcd for $C_{36}H_{57}N_3O_6$: 627.4247).
16. *Compound* **3b:** White solid. Mp: 176–179 °C. $[\alpha]_D^{20} = -69.3$ (*c* 0.31, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 5.02 (br s, 2H), 3.92 (dd, *J* = 7.8, 4.1, 2H), 2.7 (d, *J* = 13.1, 2H), 2.90–2.10 (br m, 8H), 2.25 (d, *J* = 13.1, 2H), 1.85–0.80 (several m, 14H), 1.12 (s, 6H), 0.78 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz): 78.2, 58.6, 54.8, 50.8, 47.9, 44.7, 39.0, 34.0, 27.6, 20.4, 20.3. FTIR: 3421.5 (br s), 2950.9 (m). MS (EI): 390 (33), 372 (32), 357 (31), 251 (67), 196 (89), 86 (100). HRMS: 390.3254 (calcd for $C_{24}H_{42}N_2O_2$: 390.3246).
17. Characterization data agree with those previously reported by Aoyama (Ref. 13).
18. *Compound* **6b:** White solid. Mp: 143 °C (decomposition). $[\alpha]_D^{20} = -22.1$ (*c* 0.095, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): 5.90–5.00 (br s, 3H) 3.87 (br m, 3H), 3.80–2.40 (several br m, 12H), 3.13 (d, *J* = 13.3, 3H), 2.86 (d, *J* = 13.3, 3H), 1.85–0.80 (several m, 21H), 1.06 (s, 9H), 0.80 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 76.0, 58.4, 56.9, 52.3, 47.6, 45.0, 40.8, 31.2, 29.7, 27.4, 20.7, 20.4. FTIR: 3373.9 (br s), 2951.5 (m). MS (FAB using *m*-NBA): 586 (100). HRMS: 586.4988 (calcd for $C_{36}H_{64}N_3O_3^+$: 586.1712).
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