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Hydroxyamide-catalyzed enantioselective addition of diethylzinc to benzaldehyde in the absence of titanium

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Abstract—Three camphor-based tertiary-amido isoborneols have been obtained from ketopinic acid and tested as ligands for the hydroxyamide-catalyzed enantioselective addition of diethylzinc to benzaldehyde in the absence of Ti(O-*i*-Pr)$_4$. The results obtained have been compared with previous results published by Oppolzer. The new chiral ligands showed effective asymmetric activity in the absence of titanium (up to 98% yield and 90% ee). It is demonstrated that non-bulky dialkylamino groups are necessary for obtaining high chemical yields, whereas the C_2 symmetry is necessary to reach a good enantioselection level.

1. Introduction

The hydroxyamide-catalyzed enantioselective addition of organozinc reagents to aldehydes is one of the most important synthetic methods for the preparation of enantioenriched secondary alcohols,[1] which are valuable intermediates in the preparation of interesting chiral molecules, including natural products, synthetic drugs, or new materials.[2] Additionally, most of the organozinc reagents can be easily prepared and stored, and are compatible with many functional groups.[3]

Since Noyori et al. demonstrated and explained the highly efficient DAIB **1** (Fig. 1) as a chiral ligand for the enantioselective addition of diethylzinc to benzaldehyde,[4] many other N/O ligands, mainly β-(dialkylamino)alcohols, have been prepared and tested in this reaction. The principal target of all these intensive efforts was to find versatile and efficient ligands, whose use could be extended to less reactive substrates.

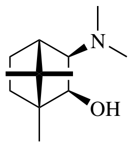

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Figure 1. DAIB.

Among the great number of ligands tested, only a small number of them are easily obtained by simple synthetic methods. In this sense, straightforwardly-obtained stable ligands are still desirable. Inside this last group, the amide-based ligands constitute a privileged series, due to the facility for the formation of the amide bond.[5]

Some amide-based ligands have already been reported. Thus, Yus et al. and Walsh et al. have described the use of C_2 secondary-sulfonamido alcohols (i.e., **2** in Fig. 2) for the efficient enantioselective addition of different organozinc reagents to prochiral ketones in the presence of titanium tetraisopropoxide;[6] Du et al. have reported the use of C_3 secondary-amido alcohols (i.e., **3** in Fig. 2) for the enantioselective addition of alkynylzincs to aldehydes in the presence of titanium tetraisopropoxide;[7] and Pedro et al. have described the use of both C_1 and C_2 secondary-amido alcohols (i.e., **4** in Fig. 2) for the enantioselective addition of diethylzinc and dimethylzinc to aldehydes, also in the presence of the same titanium complex.[8,9]

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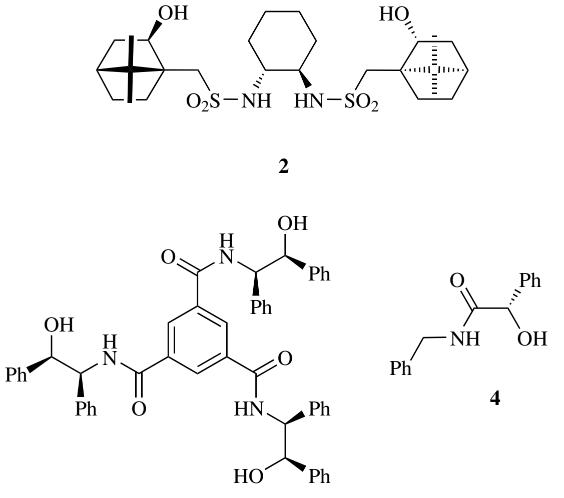

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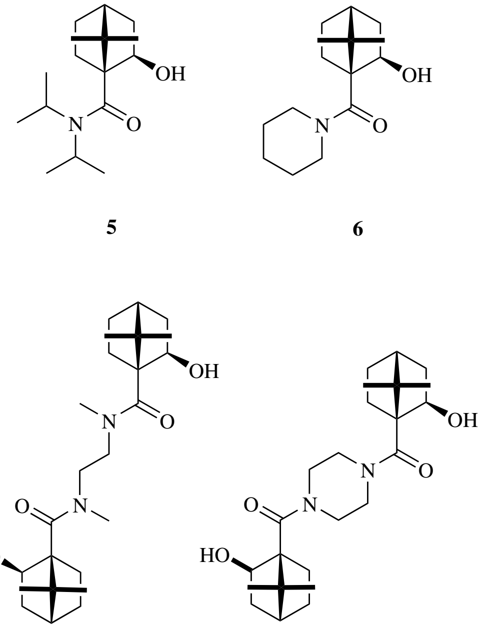
Figure 2. Some secondary-amido alcohols used as ligands for the enantioselective addition of organozinc reagents to carbonyl groups.

The development of amide-based ligands that are able to catalyze the addition of organozinc reagents to aldehydes in the absence of titanium is highly interesting, not only from the point of view of Green chemistry, but also to prevent possible incompatibilities between titanium and some functional groups which can be present in the reacting materials.[10]

In a previous work, Oppolzer et al. described the activity of the camphor-based tertiary-amido alcohol **5** (Fig. 3) as a chiral ligand for the addition of diethylzinc to benzaldehyde in the absence of titanium (68% yield, 91% ee).[11] Unfortunately, new tertiary-amido alcohols have not been tested further in this reaction, probably due to the low chemical yield obtained with **5**.



5

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7

8

Figure 3. Oppolzer's **5** and related new tertiary-amido alcohols.

2. Results and discussion

With all this information, we became interested in testing new tertiary-amido alcohols, related to the original Oppolzer's **5**, as these are easily prepared ligands for the enantioselective addition of diethylzinc to benzaldehyde in the absence of titanium, in order to find high chemical yields, while also keeping a high enantioselection level. For this purpose, we have chosen three simple tertiary-amido alcohols **6**–**8** (Fig. 3) to explore not only the influence of the nitrogen's alkyl substitution,[12] but also the influence of the ligand's symmetry[13] on the catalytic activity.

Tertiary-amido alcohols **6**,[14] **7**,[15] and **8**[16] were obtained from commercial (1*S*)-ketopinic acid in two steps (amidation[17] followed by selective reduction of the ketoamide obtained with sodium borohydride[18]) and tested as chiral ligands for the standard enantioselective addition of diethylzinc to benzaldehyde in the absence of titanium tetraisopropoxide.[19] The measured catalytic activity (yield and ee) is shown in Table 1 (the previously-reported activity of **5** is included for comparison).

As shown in Table 1, on replacement of **5** with **6**, the less hindered piperidino derivative increased the chemical yield to 96 %, but, unfortunately, the ee strongly decreased to 48%. Aoyama et al. found a similar behavior for the chemical-yield variation in relation to 10-(diisopropylamino)- and 10-(piperidin-1-yl)isoborneols, but, in this last case, the ee obtained was nearly the same for both amino alcohols.[12]

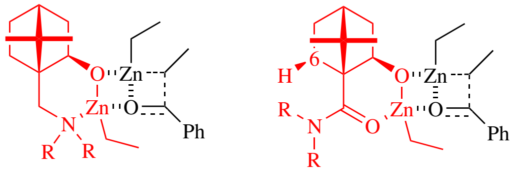
Table 1. Enantioselective addition of diethylzinc to benzaldehyde in the presence of ligands **5**–**7**[11,19]

Ligand	Yield (%)	ee (%)	Dominant config.
5[a]	68	91	(*R*)
6	96	48	(*R*)
7	98	78	(*R*)
8	97	90	(*R*)

[a] Experiment reported in the literature.[11]

On the basis of the proposed transition-state models for 10-(dialkylamino)isoborneols **9** (Fig. 4.)[11,12] and 10-(dialkylamino)-10-oxoisoborneols **10** (Fig. 4),[11] the found strong effect exerted by the nitrogen's alkyl substitution on the obtained ee for amido alcohols is noteworthy, since the key nitrogen's alkyl chains, R, are located far away from the coordination site in the amido alcohol-based model **10** (see Fig. 4).

This dialkylamino effect on the catalytic behavior of amido isoborneols, not only in the ee but also in the chemical yield (see reactivity differences for **5** and **6** in Table 1), can be explained by taking into consideration the possibility of key conformational changes in **10**, which could be

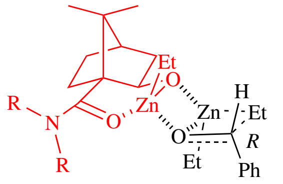


9 **10**

Figure 4. Transition-state models for the enantioselective addition of diethylzinc to benzaldehyde catalyzed by 10-(dialkylamino)isoborneols **9** and 10-(dialkylamino)-10-oxoisoborneols **10**. Eight diastereomers are possible for each model. Zinc-chelate catalyst in red.

modulated by the type of dialkylamino group present in the starting ligand. Thus, bulky enough R groups (i.e., the α-branched alkyl groups of **5**) must produce a conformational change in the flexible six-membered zinc-chelate of **10**, to relieve steric interaction between a bulky R group and the 6-*exo* hydrogen (see Fig. 4). This conformational change would cause a reactivity change in the sense of the observed differences found between **5** and **6** (see Table 1).[20]

Additionally, for both **5** and **6**, the diastereomeric transition state with minimal steric interactions is *Re-endo-anti*-**10**[21] (Fig. 5),[11,12] which agrees with the observed dominant configuration for the obtained 1-phenylpropan-1-ol (see Table 1).



Re-endo-anti-**10**

Figure 5. Most stable diastereomer for transition-state model **10**.

Replacement of the C_1 symmetry of **6** by the C_2 symmetry of **7** increased the ee from 48% to 78 % (Table 1). Moreover, ligand **7** produces a high chemical yield, as **6** does (note the low bulkiness of the dialkylamino groups for both ligands).

The strong enantioselective increase for the C_2 ligand **7** is in agreement with the formation of zinc-chelate catalyst **11** (Fig. 6), which keeps the privileged symmetry of the starting ligand.[22]

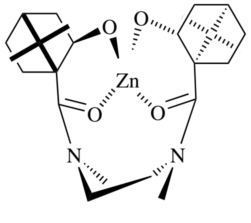


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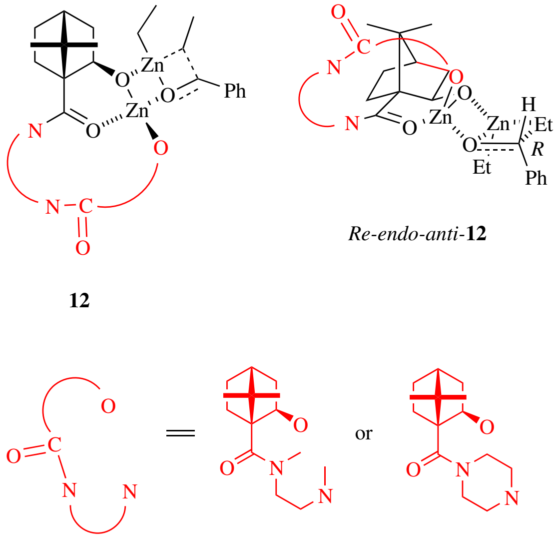
Figure 6. Proposed C_2 zinc-chelate catalysts for ligand **7**.

Thus, coordination of a reactive diethylzinc molecule to one of the two symmetric alcoxide oxygens of **11,** via the less hindered oxygen's *endo*-face, and replacement of the carbonyl ligand located at the same face by a reactive molecule of benzaldehyde would give rise to transition-state model **12** (Fig. 7). Starting from C_2 **11**, only four diastereomers are possible for **12** (note the fixed *exo* disposition of the red oxygen in **12**, Fig. 7), which explains the increase of the enantioselection obtained with C_2 **7**, in comparison with that obtained with C_1 **6**. Moreover, the transition state with the minimal steric interactions would be *Re-endo-anti*-**12** (Fig. 7), which would explain the dominant configuration found with the obtained 1-phenylpropan-1-ol (see Table 1).



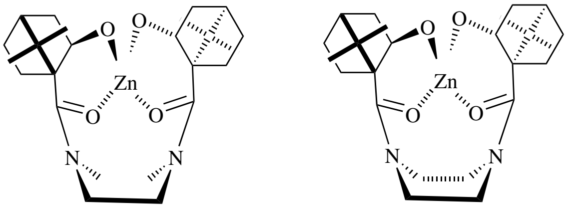
12

Re-endo-anti-**12**

Figure 7. Transition-state model for ligands **7** and **8** (**12**) and corresponding most stable transition state (*Re-endo-anti*-**12**).

Nevertheless, for ligand **7** the formation of the C_1 zinc-chelate catalyst **13** is also possible (Fig. 8). The possible competing actuation of this C_1 catalyst, together with C_2 **11**, causes a decrease in the enantioselection level, due to the participation of competing diastereomeric transition states with similar energies.

To test the last hypothesis, we obtained ligand **8** (Fig. 3). In this case, differently to **7**, only the corresponding C_2 zinc-chelate catalyst **14** (Fig. 8) is possible, which is in



13 **14**

Figure 8. Proposed C_1 zinc-chelate catalyst for ligand **7** (**13**) and C_2 zinc-chelate catalyst for ligand **8** (**14**).

agreement with the strong enantioselection increase reported in Table 1 (from 78% ee for **7** to 90% ee for **8**). This last ligand **8** is, therefore, able to produce the same high enantioselection level of the seminal Oppolzer's ligand **5**, but with an interesting higher chemical yield.

3. Conclusion

In conclusion, straightforwardly-obtained ketopinic acid-derived tertiary-amido isoborneols are able to act as effective ligands for the enantioselective addition of diethylzinc to benzaldehyde in the absence of titanium. Additionally, the structural bases for the rational design of such ligands have been established. Thus, the chemical yield for the enantiospecific reaction can be increased by using non-bulky dialkylamino-based amido alcohols, whereas the ee can be effectively increased by using C_2-symmetric amido alcohols. In the last case, an interesting new model to explain the catalytic activity, which is based on a C_2-symmetric zinc-chelate, has also been proposed.

Acknowledgments

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14. White solid. Mp: 131–133 °C. $[\alpha]_D^{20} = -0.7$ (c 1.34, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): 4.19 (dd, $J = 2.00$, 4.00, 1H), 3.68–3.49 (several br m, 4 H), 2.08–1.46 (several m, 13H), 1.37 (s, 3H), 1.18–0.93 (m, 1H), 1.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): 171.5, 77.9, 60.9, 50.6, 45.3, 44.8, 41.1, 29.9, 27.1, 26.3, 24.7, 22.3, 21.6 FTIR: 2925.7, 1593.0 (s), 1433.9. MS (%): 251 (12), 236 (27), 233 (27) 84 (100). HRMS: 251.1879 (calcd for $C_{16}H_{25}NO_2$: 251.1885).
15. White solid. Mp: 205–206 °C. $[\alpha]_D^{20} = -73.6$ (c 0.28, $CHCl_3$). ^1H NMR (MeOH-d_4, 300 MHz): 4.32 (dd, $J = 7.86$, 3.75, 2H), 3.74 (br s, 4H), 3.32 (br s, 6H), 1.95–1.70 (several m, 12H), 1.57 (m, 2H), 1.39 (s, 6H), 1.20 (m, 2H), 1.10 (s, 6H). ^{13}C NMR (MeOH-d_4, 75 MHz): 175.3, 77.4, 61.8, 51.4, 48.2, 46.2, 42.2, 36.9, 30.2, 27.9, 22.8, 22.3. FTIR: 3424,2 (m), 2954.2 (m), 1622,0 (s), 1592.9 (s). MS (%): 420 (1), 392 (4), 253 (21), 167 (100). HRMS: 420.2996 (calcd for $C_{24}H_{40}N_2O_4$: 420.2988).
16. White solid. Mp: 244–245 °C. $[\alpha]_D^{20} = -50.9$ (c 0.17, $CHCl_3$). ^1H NMR (MeOH-d_4, 300 MHz): 4.27 (dd, $J = 7.48$, 3.70, 2H), 3.67 (br s, 8H), 3.35 (br s, 2H), 1.98–1.79 (several m, 8H), 1.67 (m, 2H), 1.56 (m, 2H), 1.37 (s, 6H), 1.17 (m, 2H), 1.13 (s, 6H). ^{13}C NMR (MeOH-d_4, 75 MHz): 174.2, 78.3, 61.9, 51.7, 46.7, 45.5, 42.8, 31.0, 28.2, 22.9, 22.4. FTIR: 2965.9 (m), 1607,2 (s), 1411.0 (s), 1228,3 (s). MS (%): 418 (3), 390 (2), 251 (35), 167 (72), 149 (90), 95 (85), 69 (100). HRMS: 400.2723 (calcd for $C_{24}H_{36}N_2O_3[M^{+\cdot}-18]$: 420.2726).
17. (1*S*)-Ketopinic acid (5.0 mmol) and $SOCl_2$ (5.2 mmol) were refluxed in anhydrous THF for 15 min. The reaction mixture was then cooled down to 0 °C and, triethylamine (10.5 mmol) and piperidine (5.0 mmol), or *N*,*N*′-dimethylethane-1,2-diamine (2.5 mmol), or piperazine (2.5 mmol), slowly added. The reaction mixture was then stirred for 1 h at rt. Standard work-up (extraction and acid- and base-washing) yielded pure amide in ca. 85% yield for both the cases. Spectroscopic data agree with the corresponding structure. Piperazine-based ketoamide has been previously-reported by Aoyama (see Ref. 12) as a synthetic intermediate.

18. *Reduction*: Standard $NaBH_4$ reduction in refluxing THF (for example, see Ref. 11). Yield: 80% for the obtention of **6**, 63% for the obtention of **7**, and 91% for the obtention of **8**.
19. Under argon, 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) and the mixture stirred for 1 h at rt. Freshly distilled benzaldehyde (1.0 mmol) was then 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 (for example, see Ref. 12) yielded the resulting enantioenriched mixture of 1-phenylpropan-1-ol. The ee was determined by GC (cyclodex-B). The dominant configuration was determined by both the sign of the mixture's specific rotation and the elution time on chiral GC.
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21. *endo* versus *exo* Indicates the coordination face of the reacting species to the catalyst's Zn–O bond. *syn* versus *anti* Indicates the relative disposition of both the zinc ethyl groups. *Re* versus *Si* indicates the carbonyl face on which the ethyl transfer occurs.
22. Initial attempts to confirm the proposed C_2 structure for the controlling catalytic chelate by NMR experiments were unsuccessful (complicated spectra were recorded). On the other hand, it should be noted that the mixtures of several catalytic chelates, together with the proposed controlling C_2 chelate, can be possible.