Dual Stereoselection in the Addition of Diethylzinc to Benzaldehyde by Using Highly Structurally Close Ligands

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ABSTRACT The screening of the catalytic activity in the diethylzinc reaction of a series of easily accessible (1*S*)-ketopinic-acid derived hydroxyamides, designed by key structure modifications of a parent highly active related bis(hydroxyamide), has allowed to find the first case of dual stereoselection in highly structurally close ligands of such interesting chemically sustainable typology. The found striking dual stereoselection is explained on the basis of empiric models for the acting zinc catalysts and involved controlling transition states, which are supported by additional specific experimental structure-activity tests. *Chirality 24:255–261, 2012.*

KEY WORDS: asymmetric catalysis; diethylzinc reaction; dual stereoselection; ketopinic acid; hydroxyamides

INTRODUCTION

One of the most useful asymmetric reactions is the catalyzed enantioselective addition of organozinc reagents to aldehydes, which allows the straightforward preparation of valuable enantioenriched secondary-alcohol building blocks (Scheme 1).[1–11] Once the main grounds of its mechanism have been established (on the basis of the formation of a chiral metal-chelate catalyst)[1] and different series of active ligands, mainly β-(dialkylamino)alcohols such as Nuggent's MIB **1** (Fig. 1),[12] have been developed, the current research in this important reaction is focused in finding versatile ligands able to promote the highly enantioselective addition of a wide range of organozinc reagents to a wide range of aldehydes (e.g., Wang's ligand **2** in Fig. 1),[13] as well as designing sustainable reactions according to the principles and practices of the Green Chemistry.[14]

The main basis to achieve sustainable additions of organozinc reagents to aldehydes are related to the development of ligands which can promote the reaction without participation of other metals (e.g., titanium), are obtained straightforwardly from accessible starting materials (cheap ligands) and, if possible, can be reused several times. In this sense, we have recently demonstrated that certain isoborneol-based ketopinic-acid derived hydroxyamides [e.g., bis(hydroxyamide) **3** in Fig. 1] constitute a new class of ligands able to efficiently promote the enantioselective addition of organozinc reagents to aldehydes in absence of titaninum.[15] Moreover, these ligands are easily obtained from an enantiomerically pure renewable starting material coming from the Chiral Pool (available camphor-derived ketopinic acid), as well as inert enough to develop long-life reusable catalysts.[15]

The development of a useful chiral ligand requires the accessibility to both enantiomers of such ligand, to have access to both enantiomers of the reaction product. Unfortunately, the two enantiomers of the mentioned chiral hydroxyamides are not equally accessible, since both enantiomers of the starting ketopinic acid are not commercially available. This is a general situation for most of the chiral agents derived from chiral natural products, where normally only one enantiomer is easily accessible from nature, which makes the other enantiomer more expensive or even commercially unavailable.[16]

This important problem has been addressed in limited cases by switching the sense of the stereoselection exerted by the acting chiral catalyst (dual stereoselection, dual switch, or stereoselection switch), which is mainly achieved by modifying the structure of the parent chiral ligand. In this line, most of the effective stereoselection switches reported up to date for the enantioselective addition of organozinc reagents to aldehydes have been achieved by designing pseudo-enantiomeric (e.g., **4** vs. **5** in Fig. 2)[16] or epimeric ligands (e.g., **6** vs. **7** in Fig. 2),[17] as well as by introducing bulky groups in specific places of the parent structure (e.g., **8** vs. **9** in Fig. 2).[18] Unfortunately, in most of these cases, the important structural modifications introduced in the switching ligand make its preparation more complicated and, therefore more expensive. This problem could be solved by designing highly structurally close dual ligands, therefore with minimal differences in their synthesis.

According to all the above exposed, we became interested in checking a possible dual stereoselection in highly structurally close (1*S*)-ketopinic-acid derived hydroxyamide-based ligands, which would enhance the potential of these compounds as a new class of sustainable ligands for the enantioselective addition of organozinc reagents to aldehydes.

EXPERIMENTAL

Common solvents were dried and distilled by standard procedures. All starting materials and reagents were obtained commercially and used without further purifications. Flash chromatography purifications were performed on silica gel (230–400 mesh ASTM). Melting points are uncorrected. NMR spectra were recorded at 20°C in $CDCl_3$ and the

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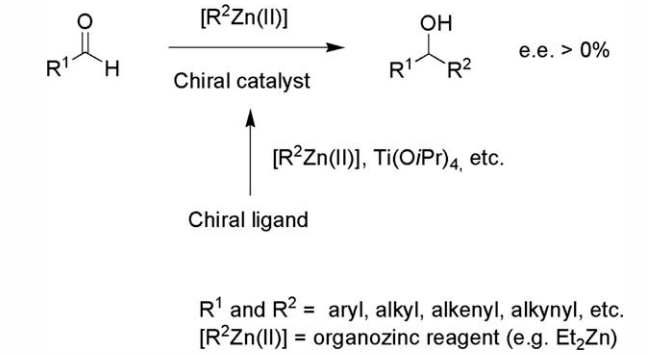


Scheme 1. Enantioselective addition of organozinc reagents to aldehydes.

residual solvent peak was used as internal standard. FTIR spectra were obtained using the thin-layer technique. GC analyses were realized at 120°C in a chromatograph equipped with a capillary silicon-gum (SGL-1) column and a FID, and using nitrogen as mobile phase. Chiral-HPLC analyses were realized at r.t. in a chromatograph equipped with a Chiralpak-IC column and a DAD, and using hexane/isopropanol (98:2) as mobile phase. MS were recorded using the ESI ionization technique. FT was used for the HRMS determinations.

Ligand Syntheses

Ligand 10:

(1S,4R)-1-[(4-Acetylpiperazin-1-yl)carbonyl]-7,7-dimethylnorbornan-2-one [18(acetyl)]. In a round-bottom flask, equipped with a magnetic stirrer, (1*S*)-ketopinic acid (**16**) (0.30 g, 1.6 mmol), EDC hydrochloride (0.35 g, 1.8 mmol), DMAP (0.23 g, 1.8 mmol) and 1-acetylpiperazine [**17(acetyl)**] (0.23 g, 1.8 mmol) were dissolved in CH_2Cl_2 (6 ml) and the mixture was stirred at room temperature for 24 h. Water (6 ml) was then added and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 ml). The combined organic layers were washed successively with 10% HCl (1 × 5 ml), water (1 × 5 ml), 10% NaOH (2 × 5 ml), water (1 × 5 ml), and brine (1 × 5 ml), and dried with anhydrous Na_2SO_4. After filtration and solvent evaporation under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate 2:1; 0.43 g, 93% yield). White solid. Mp: 115–117°C. $[a]_D^{20}$ −13.9 (*c* 0.85, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 3.53–3.24 (m, 8H), 2.57 (ddd, *J* = 18.5 Hz, *J* = 4.8 Hz, *J* = 2.8 Hz, 1H), 2.32–2.21 (m, 1H), 2.16–1.97 (m, 3H), 2.11 (s, 3H), 1.92 (d, *J* = 18.5 Hz, 1H), 1.50–1.41 (m, 1H), 1.21 (s, 3H), 1.20 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 212.5 (C=O), 169.0 (N−C=O), 167.9 (N−C=O), 67.4 (C), 50.6 (C), 46.4 (CH_2), 43.7 (CH_2), 43.1 (CH), 41.6 (CH_2), 27.3 (CH_2), 27.0 (CH_2), 21.3 (CH_3), 21.2 (CH_3), and 20.9 (CH_3) ppm. FTIR, ν: 1736 (str), 1634 (str) cm^{-1}. MS (ESI), *m/z* (%): 316 ($[M+1+23]^+$, 24), 315 ($[M+23]^+$, 100), 293 ($[M+1]^+$, 4). HRMS (ESI), *m/z*: 315.1687 (calcd for $C_{16}H_{24}N_2NaO_3$: 315.1679).

(1S,2R,4R)-1-[(4-Acetylpiperazin-1-yl)carbonyl]-7,7-dimethylnorbornan-2-ol (10). A two-necked round-bottom flask, equipped with a magnetic stirrer and a water condenser was charged with (1*S*,4*R*)-1-[(4-acetylpiperazin-1-yl)carbonyl]-7,7-dimethylnorbornan-2-one [**18(acetyl)**], (0.15 g, 0.5 mmol), methanol (10 ml) and $NaBH_4$ (0.08 g, 2.0 mmol). The mixture was refluxed for 24 h under argon. After cooling it down to room temperature, water (0.01 ml) was added and the resulting mixture was concentrated under reduced pressure to evaporate methanol. The obtained residue was diluted with chloroform (10 ml). Water (10 ml) was added and the resulting layers separated. The aqueous layer was extracted with chloroform (3 × 5 ml). The combined organic layers were washed with brine (1 × 10 ml) and dried with anhydrous Na_2SO_4. After filtration and solvent evaporation under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate 1:1; 0.14 g, 95% yield). White solid. Mp: 213–214°C. $[a]_D^{20}$ −15.8 (*c* 0.26, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4,18 (dd, *J* = 7.6 Hz, *J* = 4.2 Hz, 1H), 3.74–3.42 (m, 8H), 2.12 (s, 3H), 2.05–1.78 (m, 5H), 1.66 (dd, *J* = 4.2 Hz, *J* = 4.2 Hz, 1H), 1.55–1.47 (m, 1H), 1.39 (s, 3H), 1.29–1.11 (m, 1H), 1.15 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 172.0 (N−C=O), 169.2 (N−C=O), 78.0 (CH−OH), 60.6 (C), 50.6 (C), 46.2 (CH_2), 44.8 (CH), 44.4 (CH_2), 43.7 (CH_2), 41.8 (CH_2), 41.5 (CH_2), 30.0 (CH_2), 27.0 (CH_2), 22.1 (CH_3), 21.6 (CH_3), 21.3 (CH_3) ppm. FTIR, ν: 3322 (br, w), 1614 (str) cm^{-1}. MS (ESI), *m/z* (%): 318 ($[M+1+23]^+$, 24), 317 ($[M+23]^+$, 100), 295 ($[M+1]^+$, 3). HRMS (ESI), *m/z*: 317.1841 (calcd for $C_{16}H_{26}N_2NaO_3$: 317.1836).

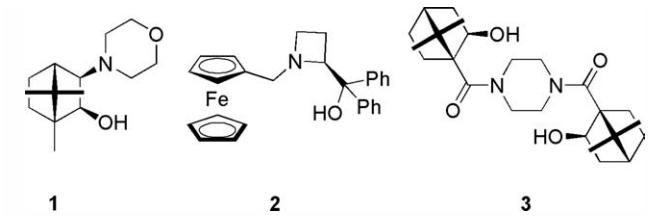


Fig. 1. Some efficient ligands for the addition of organozinc reagents to aldehydes.

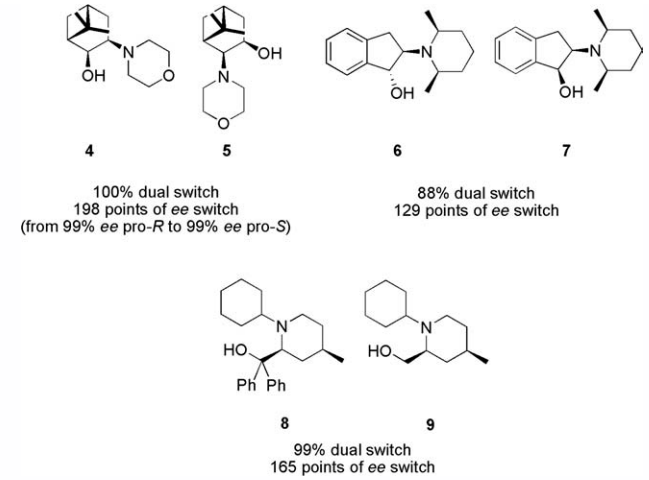


Fig. 2. Some examples of effective dual stereoselection in the enantioselective addition of diethylzinc to benzaldehyde.

Ligand 11:

(1S,4R)-1-{[4-(terc-Butoxycarbonyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [18(BOC)]. 1-(*terc*-Butoxycarbonyl)piperazine [**17(BOC)**] (0.34 g, 1.8 mmol) was reacted following the experimental procedure for the preparation of **18(acetyl)**. 0.55 g (98% yield). White solid. Mp. 148–150°C. $[a]_D^{20}$ −12.1 (*c* 0.87, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 3.58–3.23 (m, 8H), 2.49 (ddd, *J* = 18.5 Hz, *J* = 5.1 Hz, *J* = 2.7 Hz, 1H), 2.30–2.20 (m, 1H), 2.12–1.95 (m, 3H), 1.90 (d, *J* = 18.5 Hz, 1H), 1.48–1.41 (m, 1H), 1.44 (s, 9H), 1.20 (s, 3H), 1.18 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 212.5 (C=O), 167.9 (N−C=O), 154.6 (N− (C=O) −O), 80.1 (C−O), 67.4 (C), 50.7 (C), 46.4 (CH_2), 43.7 (CH_2), 43.1 (CH), 42.3 (CH_2), 28.4 (CH_3), 27.4 (CH_2), 27.1 (CH_2), 21.3 (CH_3), 21.0 (CH_3) ppm. FTIR, ν: 1740 (str), 1696 (str), 1633 (str) cm^{-1}. MS (ESI), *m/z* (%): 723 ($[2M+23]^+$, 38), 373 ($[M+23]^+$, 100), 351 ($[M+1]^+$, 1). HRMS (ESI), *m/z*: 351.2273 (calcd for $C_{19}H_{30}N_2O_4$: 351.2278).

(1S,2R,4R)-1-{[4-(terc-Butoxycarbonyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-ol (11). (1*S*,4*R*)-1-{[4-(*terc*-Butoxycarbonyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [**18(*t*-BOC)**] (0.15 g, 0.4 mmol) was reacted following the experimental procedure for the preparation of **10**. 0.13 g (92% yield). White solid. Mp: 207–209°C. $[a]_D^{20}$ −12.8 (*c* 0.80, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.17 (dd, *J* = 7.8 Hz, *J* = 3.8 Hz, 1H), 3.64–3.61 (m, 4H), 3.46–3.38 (m, 4H), 2.04–1.75 (m, 5H), 1.63 (dd, *J* = 4.2 Hz, *J* = 4.2 Hz, 1H), 1.54–1.46 (m, 1H),

1.46 (s, 9H), 1.37 (s, 3H), 1.18–1.09 (m, 1H), 1.14 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 172.3 (N−C=O), 155.0 (N− (C=O) −O), 80.6 (C−O), 78.4 (CH−OH), 61.1 (C), 51.0 (C), 45.2 (CH), 44.5 (CH_2), 44.2 (CH_2), 42.0 (CH_2), 30.4 (CH_2), 28,8 (CH_3), 27.5 (CH_2), 22.6 (CH_3), 22.0 (CH_3) ppm. FTIR, ν: 3425 (wide, w), 1688 (str), 1605 (str), 1236 (str) cm^{-1}. MS (ESI), *m/z* (%): 727 ($[2M+23]^+$, 100), 375 ($[M+1+23]^+$, 31), 353 ($[M+1]^+$, 2). HRMS (ESI), *m/z*: 353.2432 (calcd for $C_{25}H_{41}N_2O_4$, 353.2435).

Ligand 12:

(1S,4R)-1-{[4-(Ethylsulfonyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [18(ethylsulfonyl)]. 1-(Ethylsulfonyl)piperazine [**17(ethylsulfonyl)**] (0.32 g, 1.8 mmol) was reacted following the experimental procedure for the preparation of **18(acetyl)**. 0.47 g (86% yield). White solid. Mp. 163–165°C. $[a]_D^{20}$ −15.8 (*c* 1.22, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 3.77–3.04 (m, 8H), 2.95 (c, *J* = 7.4 Hz, 2H), 2.50 (ddd, *J* = 18.5 Hz, *J* = 4.7 Hz, *J* = 2.6 Hz, 1H), 2.30–2.17 (m, 1H), 2.15–1.95 (m, 3H), 1.91 (d, *J* = 18.5 Hz, 1H), 1.51–1.41 (m, 1H), 1.36 (t, *J* = 7.4 Hz, 3H), 1.19 (s, 3H), 1.18 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 212.7 (C=O), 167.8 (N−C=O), 67.4 (C), 50.7 (C), 46.1 (CH_2), 43.8 (CH_2), 43.6 (CH_2), 43.1 (CH), 27.2 (CH_2), 26.9 (CH_2), 21.2 (CH_3), 20.8 (CH_3), 7.7 (CH_3) ppm. FTIR, ν: 1735 (str), 1616 (str), 1382 (str), 1117 (str) cm^{-1}. MS (ESI), *m/z* (%): 367 ($[M+2+23]^+$, 3), 365 ($[M+23]^+$, 100). HRMS (ESI), *m/z*: 343.1698 (calcd for $C_{16}H_{27}N_2O_4S$: 343.1686).

(1S,2R,4R)-1-{[4-(Ethylsulfonyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-ol (12). (1*S*,4*R*)-1-{[4-(Ethylsulfonyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [**18(ethylsulfonyl)**] (0.40 g, 1.2 mmol) was reacted following the experimental procedure for the preparation of **10**. 0.38 g (92% yield). White solid. Mp: 140–141°C. $[a]_D^{20}$ −22.4 (*c* 1.40, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.14 (dd, *J* = 7.4 Hz, *J* = 4.2 Hz, 1H), 3.81–3.66 (m, 4H), 3.37–3.22 (m, 4H), 2.95 (c, *J*= 7.4 Hz, 2H), 2.04–1.75 (m, 5H), 1.65 (dd, *J* = 4.2 Hz, *J* = 4.2 Hz, 1H), 1.53–1.44 (m, 1H), 1.37 (s, 3H), 1.36 (t, *J* = 7.4 Hz, 3H), 1.19–1.10 (m, 1H), 1.13 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 171.8 (N−C=O), 78.2 (CH−OH), 60.6 (C), 50.6 (C), 45.9 (CH_2), 44.7 (CH), 44.2 (CH_2), 43.9 (CH_2), 41.8 (CH_2), 30.0 (CH_2), 26.9 (CH_2), 22.1 (CH_3), 21.6 (CH_3), 7.7 (CH_3) ppm. FTIR, ν: 3452 (wide, w), 1624 (str), 1282 (str), 1184 (str) cm^{-1}. MS (ESI), *m/z* (%): 369 ($[M+2+23]^+$, 3), 367 ($[M+23]^+$, 100). HRMS (ESI), *m/z*: 367.1661 (calcd for $C_{16}H_{28}N_2NaO_4S$, 367.1662).

Ligand 13:

(1S,4R)-1-{[4-(2-Hydroxyethyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [18(2-hydroxyethyl)]. In a round-bottom flask equipped with a magnetic stirrer, 4-(hydroxyethyl)piperazine [**17(2-hydroxyethyl)**] (0.23 g, 1.8 mmol) was dissolved in dry THF (4 ml) under argon. Then, triethylamine (0.35 g, 3.5 mmol) was added, followed by ketopinic acid chloride[19] (0.36 g, 1.8 mmol) in dry THF (1 ml). The reaction mixture was refluxed for 24 h. After cooling it down to room temperature, the mixture was filtrated in vacuo. The residue was dissolved in $CHCl_3$ (10 ml), water (10 ml) was added and the phases separated. The organic phase was washed with 10% NaOH (1 × 10 ml), water (1 × 10 ml), and brine (1 × 10 ml) and dried with anhydrous Na_2SO_4. After filtration and solvent evaporation under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate; 0.47 g, 89% yield). White solid. Mp: 93–94°C. $[a]_D^{20}$ −15.1 (*c* 0.77, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 3.79 (br. s, 1H), 3.62 (t, *J* = 5.4 Hz, 2H), 3.58–3.40 (m, 3H), 2.65–2.45 (m, 5H), 2.55 (t, *J* = 5.4 Hz, 2H), 2.31–2.21 (m, 1H), 2.16–1.90 (m, 3H), 1.89 (d, *J* = 18.4 Hz, 1H), 1.48–1.38 (m, 1H), 1.24–1.07 (m, 1H), 1.20 (s, 3H), 1.19 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 212.5 (C=O), 167.5 (N−C=O), 67.4 (C), 59.2 (CH_2), 57.7 (CH_2), 53.0 (CH_2), 50.6 (C), 43.7 (CH_2), 43.1 (CH), 27.4 (CH_2), 27.0 (CH_2), 21.3 (CH_3), 20.9 (CH_3) ppm. FTIR, ν: 3423 (br, w), 1739 (str), 1626 (str), 997 (str) cm^{-1}. MS (ESI-neg), *m/z* (%): 294 ($[M+1-1]^-$, 14), 293 ($[M-1]^-$, 100). HRMS (ESI-neg), *m/z*: 293.1897 (calcd for $C_{16}H_{28}N_2NaO_4S$, 293.1871).

(1S,2R,4R)-1-{[4-(2-Hydroxyethyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-ol (13). (1*S*,4*R*)-1-{[4-(2-Hydroxyethyl)-piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [**18(2-hydroxyethyl)**] (0.29 g, 1.0 mmol) was reacted following the experimental procedure for the preparation of **10**. 0.20 g (70% yield). White solid. Mp: 138–140°C. $[a]_D^{20}$ −7.7 (*c* 0.68, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.15 (dd, *J* = 7.8 Hz, *J* = 3.7 Hz, 1H), 3.72–3.52 (m, 4H), 3.64 (t, *J* = 5.5 Hz, 2H), 2.80–2.38 (m, 8H), 2.05–1.70 (m, 4H), 1.61 (t, *J* = 4.3 Hz, 1H), 1.52–1.42 (m, 1H), 1.35 (s, 3H), 1.24–1.06 (m, 1H), and 1.12 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 171.7 (N−C=O), 77.8 (CH−OH), 60.6 (C), 59.3 (CH_2), 57.7 (CH_2), 53.1 (CH_2), 50.5 (C), 44.8 (CH), 44.0 (CH_2), 41.4 (CH_2), 29.9 (CH_2), 27.0 (CH_2), 22.1 (CH_3), and 21.6 (CH_3) ppm. FTIR,ν: 3383 (br., w), 1610 (str) cm^{-1}. MS (ESI), *m/z* (%): 297 ($[M+1]^+$, 100). HRMS (ESI), *m/z*: 297.2169 (calcd for $C_{16}H_{29}N_2O_3$, 297.2173).

Ligand 14:

(1S,4R)-1-{[4-(2-Hydroxyphenyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [18(2-hydroxyphenyl)]. 1-(2-Hydroxyphenyl)piperazine [**17(2-hydroxyphenyl)**] (0.32 g, 1.8 mmol) was reacted following the experimental procedure for the preparation of **[18(2-hydroxyethyl)]**. 0.52 g (84% yield). White solid. Mp: 138–139°C. $[a]_D^{20}$ −8.7 (*c* 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.17 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 7.10 (td, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 6.96 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 6.87 (td, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 4.02 (br. s, 1H), 3.76–3.38 (m, 3H), 3.07–2.75 (m, 4H), 2.54 (ddd, *J* = 18.5 Hz, *J* = 4.9 Hz, *J* = 2.7 Hz, 1H), 2.38–2.28 (m, 1H), 2.17–2.00 (m, 3H), 1.94 (d, *J* = 18.5 Hz, 1H), 1.52–1.43 (m, 1H), 1.25 (s, 3H), and 1.24 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 212.6 (C=O), 167.8 (N−C=O), 151.3 (C), 138.3 (C), 126.7 (CH), 121.5 (CH), 120.1 (CH), 114.2 (CH), 67.4 (C), 52.8 (CH_2), 50.7 (C), 43.7 (CH_2), 43.1 (CH), 27.4 (CH_2), 27.0 (CH_2), 21.3 (CH_3), and 21.0 (CH_3) ppm. FTIR, ν: 3351 (br., w), 1737 (str), 1624 (str) cm^{-1}. MS (ESI-neg), *m/z* (%): 342 ($[M+1-1]^-$, 27), 341 ($[M-1]^-$, 100). HRMS (ESI-neg), *m/z*: 341.1874 (calcd for $C_{20}H_{25}N_2O_3$, 341.1871).

(1S,2R,4R)-1-{[4-(2-Hydroxyphenyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-ol (14). (1*S*,4*R*)-1-{[4-(2-Hydroxyphenyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [**18(2-hydroxyphenyl)**] (0.34 g, 1.0 mmol) was reacted following the experimental procedure for the preparation of **10**. 0.29 g (81% yield). White solid. Mp: 149–150°C. $[a]_D^{20}$ −9.8 (*c* 0.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.10 (td, *J* = 7.6 Hz, *J* = 1.4 Hz, 2H), 6.97 (dd, *J* = 7.6 Hz, *J* = 1.4 Hz, 1H), 6.87 (td, *J* = 7.6 Hz, *J* = 1.4 Hz, 1H), 4.21 (dd, *J* = 7.8 Hz, *J* = 3.7 Hz, 1H), 3.89–3.77 (m, 4H), 2.95–2.82 (m, 4H), 2.11–1.78 (m, 5H), 1.67 (t, *J* = 4.3 Hz, 1H), 1.59–1.51 (m, 1H), 1.42 (s, 3H), 1.34–1.24 (m, 1H), and 1.19 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 171.9 (N−C=O), 151.3 (C), 138.2 (C), 126.9 (CH), 121.4 (CH), 120.2 (CH), 114.4 (CH), 78.1 (CH−OH), 60.8 (C), 52.8 (CH_2), 50.7 (C), 44.9 (CH_2), 44.8 (CH), 41.6 (CH_2), 30.1 (CH_2), 27.1 (CH_2), 22.2 (CH_3), 21.7 (CH_3) ppm. FTIR,ν: 3383 (br., w), and 1592 (str) cm^{-1}. MS (ESI-neg), *m/z* (%): 344 ($[M+1-1]^-$, 18), 343 ($[M-1]^-$, 100). HRMS (ESI-neg), *m/z*: 343.2029 (calcd for $C_{20}H_{27}N_2O_3$, 343.2027).

Ligand 15:

(1S,4R)-1-{[4-(3-Hydroxyphenyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [18(3-hydroxyphenyl)]. 1-(3-Hydroxyphenyl)piperazine [**17(3-hydroxyphenyl)**] (0.32 g, 1.8 mmol) was reacted following the experimental procedure for the preparation of **[18(2-hydroxyethyl)]**. 0.52 g (84% yield). White solid. Mp: 64–65°C. $[a]_D^{20}$ −12.1 (*c* 0.40, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.12 (t, *J* = 8.1 Hz, 1H), 6.49 (dd, *J* = 8.1 Hz, *J* = 1.9 Hz, 1H), 6.40 (t, *J* = 1.9 Hz, 1H), 6.37 (dd, *J* = 8.1 Hz, *J* = 1.9 Hz, 1H), 5.60 (br. s, 1H), 3.66–3.55 (m, 4H), 3.28–3.11 (m, 4H), 2.54 (ddd, *J* = 18.4 Hz, *J* = 4.9 Hz, *J* = 2.8 Hz, 1H), 2.41–2.28 (m, 1H), 2.21–2.01 (m, 3H), 1.95 (d, *J* = 18.4 Hz, 1H), 1.52–1.43 (m, 1H), 1.25 (s, 3H), and 1.24 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 212.7 (C=O), 167.8 (N−C=O), 157.3 (C), 152.4 (C), 130.0 (CH), 108.4 (CH), 107.4 (CH), 103.5 (CH), 67.5 (C), 50.7 (C), 49.5 (CH_2), 43.7 (CH_2), 43.2 (CH), 27.5 (CH_2), 27.0 (CH_2), 21.3 (CH_3), 21.0 (CH_3) ppm. FTIR,ν: 3317 (br, w), 1738 (str), and 1607 (str) cm^{-1}. MS (ESI), *m/z* (%): 343 ($[M+1]^+$, 100). HRMS (ESI), *m/z*: 343.2018 (calcd for $C_{20}H_{27}N_2O_3$, 343.2016).

(1S,2R,4R)-1-{[4-(3-Hydroxyphenyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-ol (15). (1*S*,4*R*)-1-{[4-(3-hydroxyphenyl)-piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [**18(3-hydroxyphenyl)**] (0.34 g, 1.0 mmol) was reacted following the experimental procedure for the preparation of **10**. 0.27 g (79% yield). White solid. Mp:

205–206°C. $[a]_D^{20}$ −6.1 (*c* 0.59, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz), δ: 7.04 (t, *J* = 8.1 Hz, 1H), 6.46 (dd, *J* = 8.1 Hz, *J* = 2.0 Hz, 1H), 6.41 (t, *J* = 2,0 Hz, 1H), 6.32 (dd, *J* = 8.1 Hz, *J* = 2.0 Hz, 1H), 4.28 (dd, *J* = 7.7 Hz, *J* = 3.7 Hz, 1H), 3.89–3.65 (m, 4H), 3.22–2.99 (m, 4H), 2.00–1.75 (m, 4H), 1.70–1.62 (m, 1H), 1.55 (t, *J* = 4.2 Hz, 1H), 1.38 (s, 3H), 1.28–1.15 (m, 1H), and 1.13 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 173.8 (N−C=O), 159.2 (C), 153.9 (C), 130.8 (CH), 109.1 (CH), 108.4 (CH), 104.7 (CH), 78.2 (CH−OH), 61.7 (C), 51.5 (C), 50.7 (CH_2), 46.5 (CH), 45.1 (CH_2), 42.6 (CH_2), 31.0 (CH_2), 28.0 (CH_2), 22.7 (CH_3), and 22.2 (CH_3) ppm. FTIR, ν: 3310 (br., w), 1604 (str) cm^{-1}. MS (ESI), *m/z* (%): 345 ($[M+1]^+$, 100). HRMS (ESI), *m/z*: 345.2161 (calcd for $C_{20}H_{29}N_2O_3$, 345.2173).

Ligand 27:

(1S,4R)-1-{[4-(2-Methoxyethyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [18(2-methoxyethyl)]. 1-(2-Methoxyethyl)piperazine [**17(2-methoxyethyl)**] (0.26 g, 1.8 mmol) was reacted following the experimental procedure for the preparation of **[18(2-hydroxyethyl)]**. 0.53 g (95% yield). Pale brown oil. $[a]_D^{20}$ −18.8 (*c* 0.68, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz), δ: 6.00 (br. s, 1H)), 3.51 (t, *J* = 5.5 Hz, 4H), 3.34 (s, 3H), 2.70–2.44 (m, 5H), 2.59 (t, *J* = 5.5 Hz, 2H), 2.36–2.22 (m, 1H), 2.13–1.81 (m, 4H), 1.89 (d, *J* = 18.4 Hz, 1H), 1.47–1.38 (m, 1H), 1.20 (s, 3H), and 1.19 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 212.4 (C=O), 167.4 (N−C=O), 69.8 (CH_2), 67.3 (C), 58.8 (CH_3), 57.7 (CH_2), 53.7 (CH_2), 50.6 (C), 43.7 (CH_2), 43.1 (CH), 27.4 (CH_2), 27.1 (CH_2), 21.3 (CH_3), and 21.0 (CH_3) ppm. FTIR,ν: 3537 (br, w), 1739 (str), 1629 (str) cm^{-1}. MS (ESI), *m/z* (%): 309 ($[M+1]^+$, 100). HRMS (ESI), *m/z*: 309.2169 (calcd for $C_{17}H_{29}N_2O_3$, 309.2173).

(1S,2R,4R)-1-{[4-(2-Methoxyethyl)piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-ol (27). (1*S*,4*R*)-1-{[4-(2-Methoxyethyl)-piperazin-1-yl]carbonyl}-7,7-dimethylnorbornan-2-one [**18(2-methoxyethyl)**] (0.34 g, 1.1 mmol) was reacted following the experimental procedure for the preparation of **10**. 0.27 g (79% yield). White solid. Mp: 89–91°C. $[a]_D^{20}$ −45.7 (*c* 0.21, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz), δ: 4.16 (dd, *J* = 7.8 Hz, *J* = 3.8 Hz, 1H), 3.70 (t, *J* = 4.8 Hz, 4H), 3.53 (t, *J* = 5.4 Hz, 2H), 3.36 (s, 3H), 2.61 (t, *J* = 5.4 Hz, 2H), 2.55–2.44 (m, 4H), 2.05–1.74 (m, 5H), 1.63 (t, *J* = 4.4 Hz, 1H), 1.54–1.45 (m, 1H), 1.37 (s, 3H), 1.28–1.06 (m, 1H), 1.15 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 171.6 (N−C=O), 77.9 (CH−OH), 69.9 (CH_2−OH), 60.7 (C), 58.9 (CH_3), 57.7 (CH_2), 53.7 (CH_2), 50.5 (C), 44.8 (CH), 44.0 (CH_2), 41.2 (CH_2), 29.9 (CH_2), 27.1 (CH_2), 22.2 (CH_3), 21.5 (CH_3) ppm. FTIR, ν: 3427 (br., w), 1613 (str.), 1427 (str) cm^{-1}. MS (ESI), *m/z* (%): 311 ($[M+1]^+$, 100). HRMS (ESI), *m/z*: 311.2320 (calcd for $C_{17}H_{31}N_2O_3$, 311.2330).

Asymmetric Reaction

Typical procedure Into a 10-ml round-bottom flask, equipped with a magnetic stirrer under argon and containing the corresponding ligand (0.02 mmol), diethylzinc solution (1.10 mmol, 1.0 M in hexanes) was added at room temperature. The mixture was stirred at room temperature for 5 min. Benzaldehyde (1.0 mmol) was then added and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched by the addition of 10% HCl (3 ml). The resulting mixture was extracted with ether (3 × 3 ml). The combined organic layers were submitted to celite filtration and solvent evaporation. The obtained residue was dissolved in HPLC-grade hexanes and submitted to analysis by GC and chiral HPLC.

RESULTS AND DISCUSSION

In our previous studies on how structural variations could affect the catalytic activity of ketopinic-acid derived hydroxyamides in the enantioselective addition of diethylzinc to benzaldehyde, we demonstrated that bis(hydroxyamides) having diamine spacers based on piperazine are more efficient than related simple hydroxyamides or tris(hydroxyamides).[20,21] Moreover, the catalytic activity of 4-methylpiperazine- and piperidine-based ligands (aminohydroxyamide vs. hydroxyamide) is extremely close, which indicates that the nonprotic amino group of the 4-methylpiperazine moiety does not participate in the catalytic activity of the corresponding aminohydroxyamide.[21] In this context, we decided to check the catalytic activity of a set of piperazine-based ketopinic-acid derived hydroxy(diamides) (**10–12** in Fig. 3) and amino(dihydroxy)amides (**13–15** in Fig. 3), which are closely related to the highly efficient bis(hydroxyamide) **3** and also easily obtainable from both commercial (1*S*)-ketopinic acid and 1-substituted piperazines, to know if the new structural variations introduced in the parent ligand could produce some noticeably switch in the stereoselection sense.

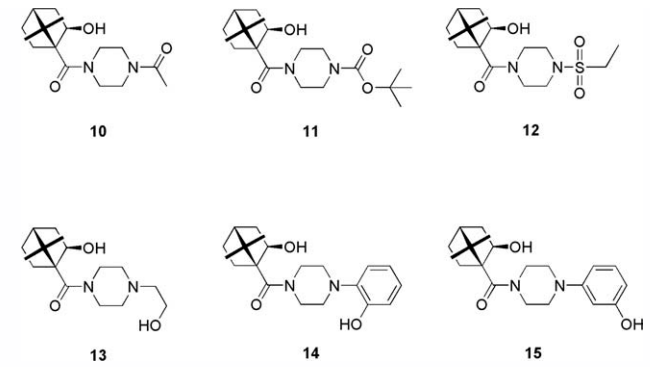


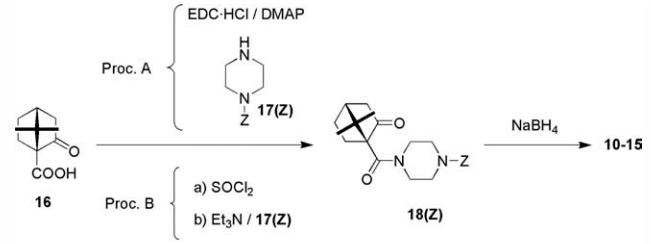
Fig. 3. Chosen ligands for the proposed screening.

The ligand set has been chosen as follows: on the one hand, ligand **10** is a structural simplification of **3**, where one chiral β-hydroxyacyl moiety of the latter has been substituted for a simple achiral acyl (acetyl) moiety in the former. Therefore, the new ligand **10** keeps the two amide groups of parent **3**, but lacks one hydroxyl function. In ligands **11** and **12**, analogous to **10**, the coordinative ability of the acyl group has been modified by substituting it by an (alkyloxy)-carbonyl in the case of **11** or by an alkylsulfonyl in the case of **12** (cf., ligands **3**, **10**, **11**, and **12** in Figs. 1 and 3).

On the other hand, ligands **13** and **14** are also simplifications of **3**, but now, one chiral β-hydroxyacyl moiety of the latter has been substituted for a simple β-hydroxyalkyl or β-hydroxyaryl moiety in the former ones. Therefore, new ligands **13** and **14** keep the two hydroxyl functions of parent **3**, but change one amide function for a nonprotic amine. Finally, ligand **15** is a positional isomer of **14**, where the new hydroxyl group has been distanced from the other functional groups (cf., ligands **3**, **13**, **14**, and **15** in Figs. 1 and 3).

All the chosen ligands were straightforwardly prepared (see yields in the experimental part) by amidation of (1*S*)-ketopinic acid (**16**) with the corresponding commercial 1-substituted piperazine **17(Z)**,* followed by a chemo- and highly stereoselective reduction of the obtained norbornanone-based amide **18(Z)** with sodium borohydride, as shown in Scheme 2. The catalytic activity of ligands **10–15** was tested in the addition of diethylzinc to benzaldehyde. Table 1 shows the obtained results.

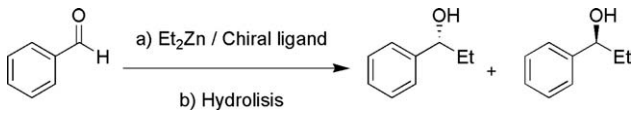
*For the acylation of aminoamides 17(Z) (Z being acetyl, t-BOC and ethylsulfonyl) with ketopinic acid, EDC was used as the acid activator (procedure A in Scheme 1). However the corresponding N-acylation of hydroxydiamines 17(Z) (Z being 2-hydroxyethyl, 2-hydroxyphenyl and 3-hydroxyphenyl) under the same conditions took place with very low yield. Nevertheless, the desired hydroxyaminoamides could be obtained by using ketopinoyl chloride as the acid activated specie (procedure B in Scheme 1).



Scheme 2. Preparation of the chosen ligands.

The *ee*s reached with the new ligands were lower to that reached with bis(hydroxyamide) **3** (Table 1). These results demonstrate the importance of the four functional groups of the latter (two carboxamides and two hydroxyls) in its catalytic activity, which is in agreement with the zinc-chelate catalyst proposed previously by us for bis(hydroxyamides) (acting as O/O/O/O tetradentated ligands).[15,20,21] Moreover, the catalytic activity exerted by the hydroxy(diamides) **10–12** (72–78% *ee* pro-*R*) was very similar to that exerted by simple piperidine-based hydroxyamides[20] or piperazine-based aminohydroxyamides[21] (e.g., 72% *ee* pro-*R* for **19** or 74% *ee* for **20** in Fig. 4). This fact indicates that the additional nonprotic amide group of piperazine-based hydroxy(diamides) **10–12** does not participate (simple O/O bidentated ligands), as previously demonstrated for the additional nonprotic amino group in piperazine-based aminohydroxyamides (Fig. 4).[21]

TABLE 1. Catalytic activity of ligands 10–15 in enantioselective addition of diethylzinc to benzaldehyde[a]



Ligand	1-Phenylpropan-1-ol		
	Yield (%)[b]	*ee* (%)[c]	Configuration[c]
3[d]	97	90	*R*
10	91	72	*R*
11	97	78	*R*
12	79	74	*R*
13	99	66	*S*
14	99	66	*R*
15	92	62	*R*
18(2-Hydroxyethyl)	99	4	*R*
18(2-Hydroxyphenyl)	99	8	*R*
27	93	78	*R*

Previous results for ligand **3** are included for comparison.
[a]2.0 mol equiv. of Et_2Zn (1.0 M in hexanes); 0.05 mol equiv. of ligand; t = 5 h; T = r.t.
[b]Determined by GC.
[c]Determined by chiral HPLC (Chiralpak IC). Both elution peaks were previously assigned from a known mixture of enantiomers, in which the configuration for the major isomer was also known on the basis of the sign of the mixture's optical rotation.
[d]Data previously reported in references 15, 19, and 20.

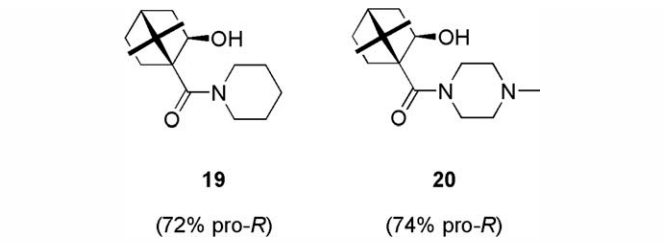


Fig. 4. Some previously reported ketopinic-acid derived hydroxyamide-based O/O ligands (in parentheses *ee* and sense of the stereoselection for benzaldehyde ethylation).

On the contrary, the high variation in the catalytic activity reached with the amino(dihydroxy)amides **13–15** (from 66% *ee* pro-*S* to 66% *ee* pro-*R*, see Table 1), shows a clear participation of the variable structural moiety, that is, the hydroxyalkyl or hydroxyaryl moiety, in such activity. Moreover, the pro-*S* stereoselection exerted by ligand **13**, instead of the common pro-*R* one exerted by all the previous reported (1*S*)-ketopinic-acid derived isoborneol-based hydroxyamides, constitutes the first example of dual stereoselection for this interesting type of ligands (73% dual switch, with 156 points of *ee* switch, for the ligand couple **3**/**13**; values calculated from the data in Table 1). Strikingly, the ligand couple **13**/**14**, which is formed by highly structurally close individuals, shows a noticeably strong dual stereoselection (100% dual switch, with 132 points of *ee*, values calculated from the data in Table 1).

We explain the behavior of the tested amino(dihydroxy)amides **13–14**, as well as the found striking dual stereoselection, by participation of both hydroxyl groups in the catalytic activity, through the formation of the catalytic zinc dialkoxide **21** (Fig. 5), like the zinc dialkoxides were proposed previously for bis(hydroxyamides) (**22** in Fig. 5).[15,20,21] We also propose for **21** a chelation of the zinc centre by the amide oxygen atom, but not by the amine nitrogen. This proposed chelation is based on the well-established participation of such oxygen in the catalytic activity of all the reported isoborneol-based ketopinic-acid derived hydroxyamides,[15,20,21]

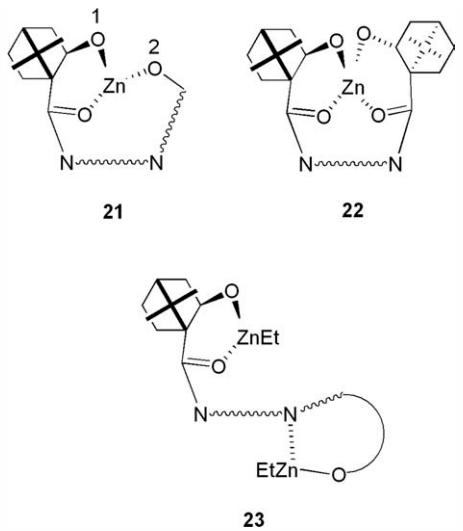


Fig. 5. Proposed catalyst models.

and also on the established nonexistent participation of the nonprotic amine piperazine in the catalytic activity of analogous ligands based on 1-substituted piperazine (e.g. **20** in Fig. 4).[21] Thus, whereas bis(hydroxyamides) act as tetradentated O/O/O/O ligands (see **22**), amino(dihydroxy)amides would act as tridentated O/O/O ones (see **21**).

For ligands **13** and **14** a bis(zinc-chelate) catalyst of the type of **23** (Fig. 5) would be possible, in which the amino(dihydroxy)amide ligand would act as the sum of two independent and competing hydroxyamide and amino-alcohol ligands. However, we have discarded this possibility because, if this was the case, the activity would be mainly controlled by the expected higher activity of the amino-alcohol-based chelate, giving place to a low *ee* due to its remoteness from the ligand stereocentres. To support this hypothesis, we have tested the catalytic activity of the norbornanone-based precursors of **13** and **14** (i.e., **18(Z)** with Z = 2-hydroxyethyl or 2-hydroxyphenyl, see Scheme 2), where the action of an active low-stereodifferentiating amino-alcohol-based chelate, analogue to that depicted in **23**, should be predominant. The results obtained from testing the mentioned ligands **18(Z)**, in the same conditions used for **13** and **14** (Table 1), show a high catalytic activity (high reaction yields), but with a low stereodifferentiation (4–8% *ee*), in agreement with our hypothesis.

Conversely, whereas in catalyst **22** both catalytic oxides are equal, leading to a favored "endo/anti/anti" pro-*R* transition state **24** (Fig. 6),[15,20] in **21** are not. Thus, for catalyst **21**, the coordination through the norbornane alkoxide (oxide 1 in Fig. 5) would lead to a favored endo/anti/anti pro-*R* transition state **25**, whereas the other competing oxide (oxide 2 in Fig. 5) would lead to a favored endo/anti/anti pro-*S* transition state **26** (Fig. 6).

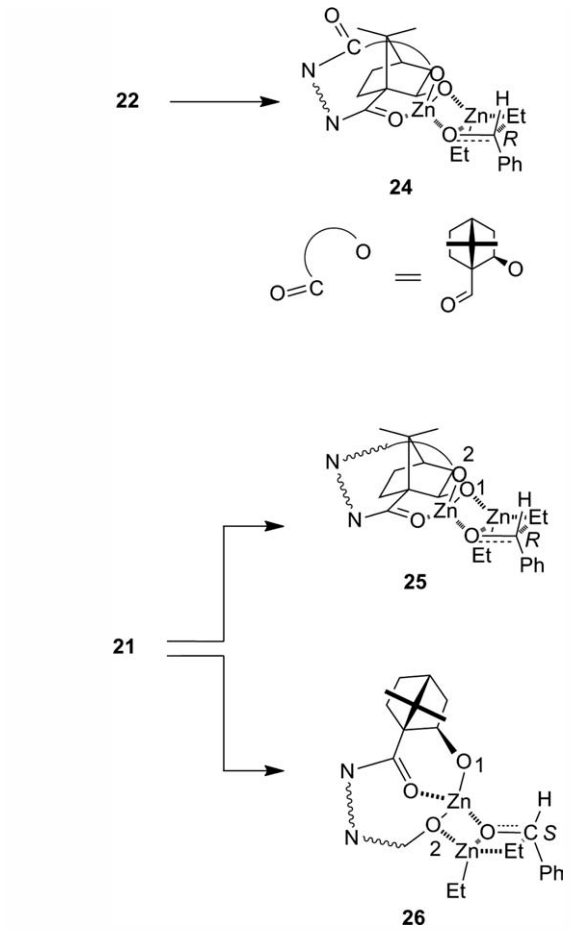
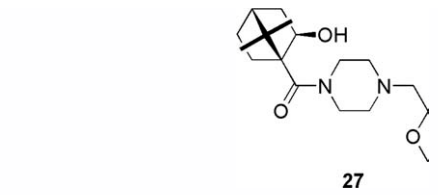


Fig. 6. Proposed favored transitions states from catalysts **22** and **21**.



27

Fig. 7. Analogue of ligand **13**, lacking the key pro-*S* hydroxyl group.

This pro-*R*/pro-*S* dual activity of catalyst **21** explains the lower pro-*R* activity of the amino(dihydroxy)amides **13–15** when compared to other ketopinic-acid derived hydroxyamides (Table 1). Moreover, the activity of catalyst **21** must be modulated by the relative activity of both competing catalyst oxides, which explains the dual stereoselection found for the couple **13**/**14**. Thus, for pro-*S* ligand **13**, both oxides of the corresponding catalyst **21** are alkoxides: a pro-*R* oxide 1 based on nobornanol and a pro-*S* oxide 2 based on ethanol (Figs. 3 and 5). The expected higher activity for oxide 2, due to its less sterical hindrance to the reactive-diethylzinc coordination (activation), explains the found experimental pro-*S* stereoselection of ligand **13**. On the contrary, for the corresponding catalyst **21** derived from pro-*R* ligand **14** (and also from ligand **15**), where the pro-*S* oxide 2 is a phenoxide (Figs. 3 and 5), the less coordinative ability of phenoxides when compared to alkoxides would explain the found experimental pro-*R* stereoselection.

Finally, we have synthesized and tested ligand **27** (Fig. 7) to support the solidness of our empiric models of catalysts and controlling transition states for the studied ketopinic-acid ligands. Ligand **27** is an analogue of ligand **13**, in which the key pro-*S* hydroxyl group of the latter has been changed for a nonprotic methoxyl. Therefore, for this new ligand the common pro-*R* behavior of the simple ketopinic-acid derived hydroxyamide-based O/O ligands (Fig. 4) must be expected.

The synthesis of **27** was straightforwardly realized (see experimental part) according to the standard route (procedure B) shown in Scheme 2, but starting from commercial 2-(methoxyethyl)piperazine instead (**17(Z)** with Z = 2-methoxyethyl). The catalytic test (ethylation of benzaldehyde) was also realized under the standard conditions (Table 1), the obtained result demonstrating (78% *ee* pro-*R*) the reliability of the proposed models.

CONCLUSIONS

Readily accessible (1*S*)-ketopinic-acid derived hydroxyamides based on hydroxyalkyl or hydroxyaryl piperazine [i.e., amino(dihydroxy)amides] are able to promote the enantioselective addition of diethylzinc to benzaldehyde as other ligands belonging to the same interesting hydroxyamide-based typology do. However, the sense of the stereoselection exerted by these new ligands can be easily switched by tuning the coordinative ability of the additional hydroxyl group of the piperazine moiety. An explanation to this fact is given on the basis of the formation of an acting zinc-dialkoxide catalyst with two different catalytic centres for the diethylzinc activation, a pro-*R* zinc-oxide centre versus a pro-*S* one. This

fact allows the establishment of an effective dual stereoselection in highly structurally close ligands obtained by similar synthetic routes with similar economic costs, which enhances the interest of the sustainable ketopinic-acid derived hydroxyamides.

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