Pergamon

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Tetrahedron: *Asymmetry* 14 (2003) 2013–2019

TETRAHEDRON: *ASYMMETRY*

Novel chiral tridentate Schiff base ligands of the [2.2]paracyclophane series: synthesis and application

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Received 1 April 2003; accepted 10 April 2003

Abstract—The first example of the efficient application of chiral tridentate *N,O*-[2.2]paracyclophane ligands of the imino type for enantioselective diethylzinc addition to aliphatic and aromatic aldehydes is presented. The enantiomeric excess of the resulted secondary alcohols is up to 93% e.e.

1. Introduction

For a long while, chiral Schiff bases have traditionally been used as effective ligands for specific asymmetric reactions such as cyclopropanation and epoxidation of alkenes as well as the oxidation of sulfides.[1–3] Recently, the scope of this highly effective ligand system has been extended for its application to other stereoselective processes. For example, the synthesis of the chiral cyanhydrins,[4] the stereoselective pinacol coupling of aldehydes[5,6] and diorganozinc addition reactions to aldehydes[7,8] have been found to be effectively catalyzed by chiral Schiff bases.

The overwhelming majority of the Schiff base ligands employed for asymmetric catalysis have been constructed from chiral diamines or aminoalcohols and achiral salicylaldehyde derivatives.[1–3,5–7] Axially or planar chiral salicylaldehyde analogues have been used for the design of such ligands to a lesser extent.[8–10] Among them planar chiral *ortho*-formyl-**1**[11] (FHPC) as well *ortho*-acetyl-**2**, (AHPC) and *ortho*-benzoylhydroxy-[2.2]paracyclophanes-**3**[12] (BHPC) have become parent compounds for a family of different Schiff base ligands **4**–**7** (Fig. 1). Thus, chiral diastereomeric bidentate imines of type **4** and **5**[12] were found to catalyze efficiently the asymmetric diorganozinc addition to aldehydes and imines.[13–16] Tetradentate salen derivatives of FHPC **6** ($R^1=R^2=H$) were successfully used in the stereoselective trimethylsilylcyanation of benzalde-

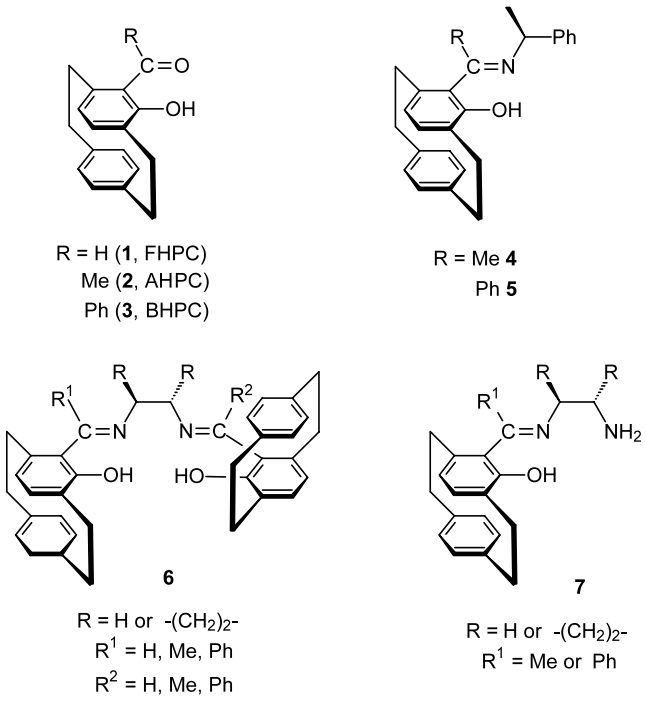

Figure 1.

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0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00326-4

hyde.[17] The symmetric as well as unsymmetric salens of type **6** together with tridentate hemisalen type ligands **7**[18] have also recently been shown to exhibit good efficiency in stereoselective diethylzinc additions to aldehydes.[19]

We present here the preparation and application in asymmetric synthesis of a new series of chiral Schiff base tridentate ligands derived from aldehyde FHPC **1** and ketone AHPC[20] **2** with different achiral or chiral aminoalcohols.

2. Results and discussion

The first key building block, **1** (FHPC), was obtained in accordance with an improved procedure which includes Friedel–Crafts oxaloylation of the 4-hydroxy-[2.2]paracyclophane followed by the reduction of the α-ketoester obtained and oxidation of the intermediate triol.[21] The resolution into enantiomers was carried out following the reported procedure.[22]

The other key intermediate of our strategy, **2** (AHPC), was prepared by *ortho*-regioselective direct acylation of *rac*-4-hydroxy[2.2]paracyclophane.[12] The result of the X-ray diffractional study of *rac*-**2** is shown in Figure 2.

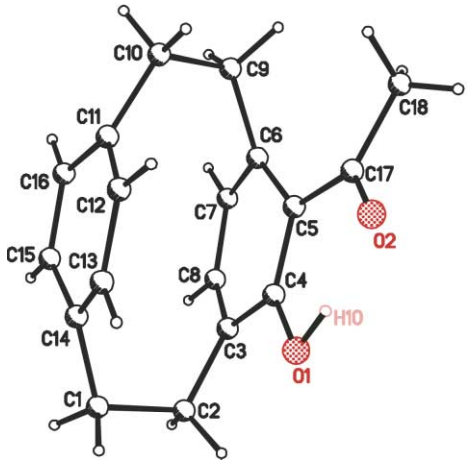


Figure 2. X-Ray structure of *rac*-**2**.

Our recent elaborated resolution technique[12] based on the separation of the diastereomeric ketimines **4** of AHPC with (*S*)-α-phenylethylamine by combination of fractional crystallization and preparative chromatography was improved in this study. We were fortunate to find an appropriate eluent (benzene/ethyl acetate/hexane 10/1/11) allowing almost complete separation of the diastereomeric **4** on silica gel without additional labor-consuming crystallizations. Thus, starting from a 1:1 mixture of diastereomers, individual diastereomers (*Rp*,*S*)-**4** and (*Sp*,*S*)-**4** were isolated in chemical yields of 48 and 47%, respectively, with diastereomeric purities >99% (by ^{1}H NMR). Individual enantiomers of **2** were obtained by subsequent quantitative hydrolysis of the corresponding diastereomerically pure ketimines **4.** Thus, AHPC can now be regarded as a readily available homochiral starting material for a wide range of useful *N*,*O*-ligands[12,18,23,24] because of it's quite high overall chemical yield (up to 65% of the resolved material) starting from parent commercial [2.2]paracyclophane.

Enantio- and diastereomerically pure iminoalcohols **8**–**12** were synthesized by refluxing the corresponding enantiomers of **1**[25] and **2** with several 2-aminoalcohols (achiral ethanolamine or centrally chiral (*R*)-, (*S*)-valinol and (*S*)-leucinol) in toluene in the presence of Et_2SnCl_2[12] as catalyst (Fig. 3). Although the condensation of this type sometimes leads to 1,3-oxazolidines besides imines,[26] no such side products were formed in this case. The crude products were purified by simply passing the reaction mixture through a pad of silica and the desired **8**–**12** were obtained in high chemical yields.

For (*Rp*)-**10** (Fig. 4, left) and (*Sp*,*S*)-**11** (Fig. 4, right) single crystals suitable for an X-ray diffraction study were obtained.

Thus, we prepared a number of novel planar chiral iminophenol ligands bearing additional carbinol moiety which in most cases were also modified by the presence of a stereogenic center. To the best of our knowledge, this type of tridentate *N*,*O*-ligand has never been used in the stereoselective Et_2Zn addition to aldehydes. We believe that such ligands, having an additional *O*-atom able to coordination, can provide more rigid monozinc dialkoxide structures and thus more differentiated diastereomeric transition states during the reaction proceeding as proposed for pyridine derived tridentate ligands.[27,28]

The efficiency of the iminophenols **8**–**12** in the Et_2Zn addition to aldehydes was therefore tested. The standard experiment includes the successive addition of 2 equiv. of Et_2Zn and 1 equiv. of benzaldehyde to a solution of the iminophenol catalyst (10 mol%) in toluene at 0°C and subsequent stirring at room temperature for 15 h. The excess of Et_2Zn was then destroyed by addition of 1N HCl and after standard work up, the conversion and enantiomeric excess of the resulted secondary alcohol were determined by GC and chiral GC analysis. The results obtained are collected in Table 1.

All reactions proceeded smoothly with high conversions of the starting aldehydes to give the corresponding secondary alcohols **13** and **14**. In the reaction with (*Rp*,*R*)-**9** as the ligand (Table 1, entry 2) the formation of the traces of benzyl alcohol (2–5%) due to reduction of the benzaldehyde by Et_2Zn was observed. In the case of aldimine ligand (*Rp*)-**8** with an achiral ethanolamine moiety (Table 1, entry 1) essentially no enantioselection was observed. The introduction of an additional stereogenic center in the carbinol moiety does not enhance the enantioselectivity significantly (Table 1, entry 2). At the same time the changing of hydrogen (FHPC type) to methyl (AHPC type) in the carbonyl moiety of the ligand has an impressive influence and the stereoselective formation of 1-phenylpropanol [(*R*)-**13**, 74% e.e.] was observed when the iminophenol (*Rp*)-**10** was used

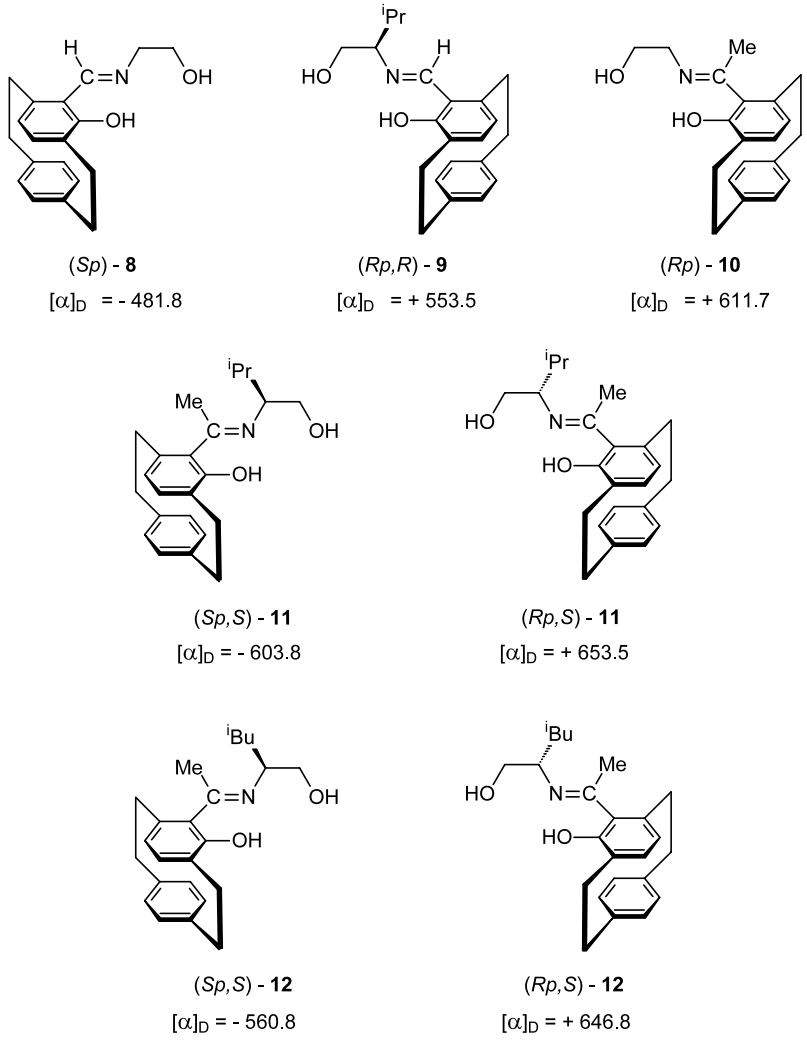


Figure 3.

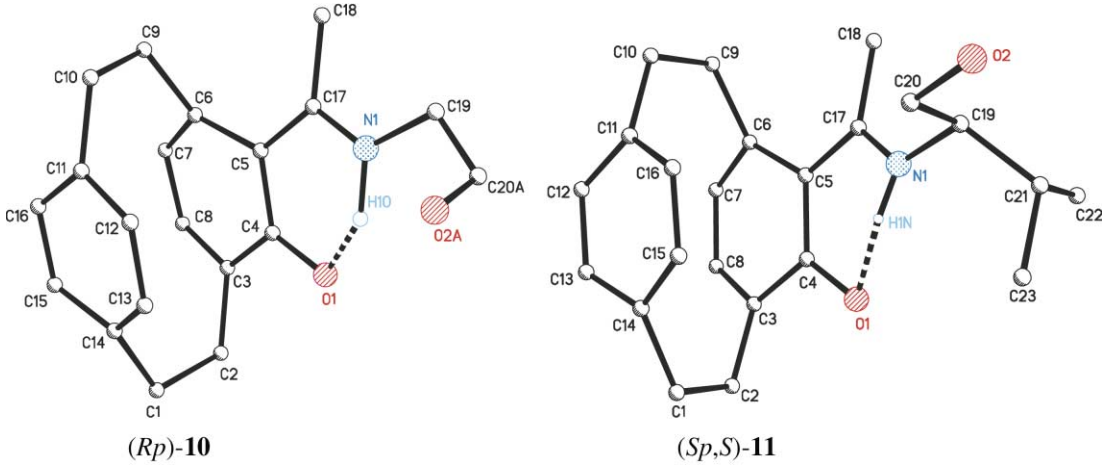
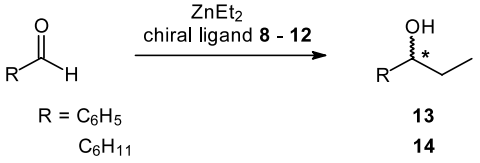


Figure 4. X-Ray crystal structure of (*Rp*)-**10** and (*Sp*,*S*)-**11**.

(Table 1, entry 3). Thus, the AHPC type ligand is beneficial for the highly selective generation of the new stereocenter in the product as demonstrated earlier.[14]

The combination of the planar chirality of the ketimine with the central chirality of the aminoalcohol allows the investigation of the cooperative effect of two chiral elements. The combination of the (*Sp*)-ketimine moiety

Table 1. Enantioselective addition of diethylzinc to aldehydes catalyzed by in situ formed zinc-complexes of ligands **8**–**12** (toluene, 25°C, 10 mol% of chiral ligand)



Entry	Chiral ligand	Aldehyde	Conversion (%)[a]	E.e.%[b]
1	(*Sp*)-**8**	PhCHO	Quant.	6 (*R*)
2	(*Rp*,*R*)-**9**	PhCHO	Quant.	10 (*R*)
3	(*Rp*)-**10**	PhCHO	Quant.	74 (*R*)
4	(*Sp*,*S*)-**11**	PhCHO	Quant.	93 (*S*)
5	(*Rp*,*S*)-**11**	PhCHO	89	67 (*S*)
6	(*Sp*,*S*)-**12**	PhCHO	Quant.	93 (*S*)
7	(*Rp*,*S*)-**12**	PhCHO	68	62 (*S*)
8	(*Rp*)-**10**	$C_6H_{11}CHO$	Quant.	92 (*S*)
9	(*Sp*,*S*)-**11**	$C_6H_{11}CHO$	Quant.	93 (*R*)

[a] The conversion was determined by GC of the reaction mixtures after standard work up.

[b] The absolute configurations of alcohols **13** and **14** were determined by the elution order on chiral GC analysis in comparison with standard samples.[14]

with a stereogenic center with the (*S*)-configuration gives rise to the ligand (*Sp*,*S*)-**11**, which yields (*S*)-**13** with an enantioselection of 93% e.e. (Table 1, entry 4). At the same time the application of the ligand (*Rp*,*S*)-**11** strongly affects the stereochemical course of the reaction and results in the formation of the alcohol **13** with the opposite configuration with moderate enantioselectivity (Table 1, entry 5). Similar results were observed for the pair of diastereomers (*Rp*,*S*)-**12** and (*Sp*,*S*)-**12** constructed from enantiomers AHPC and (*S*)-leucinol, which promoted the addition with almost the same levels of selectivity (Table 1, entries 6 and 7, correspondingly). The positive cooperative effect of the (*Sp*,*S*)-ligand over the (*Rp*,*S*)-ligand has been already observed in a similar reaction, promoted by paracyclophane ketimine ligands having no additional hydroxy group.[13] The configuration of the resulting alcohol was in this case determined by the planar chiral moiety of the ligand. It is interesting to note, that in the case of the tridentate ligands **11** and **12** the configuration of the stereogenic center in the 1-phenylpropanol was specified by central chirality of the alkylcarbinol fragment of the imine.

The results obtained reveal that the enantioselectivity of the addition reaction was dependent both on the presence of the methyl substituent α- to the carbonyl moiety (C=N group) and the stereogenic center of the appropriate configuration in the β-position of the carbinol moiety of the ligand. Therefore, the iminoalcohols (*Rp*)-**10** and (*Sp*,*S*)-**11** which demonstrated the best results in the benzaldehyde series, were also tested as chiral ligands for the Et_2Zn addition to the sterically more hindered cyclohexanecarbaldehyde. In both cases the reaction proceeded with the same high level of enantioselectivity (Table 1, entries 8 and 9), but inversion of the configuration of the product **14** was observed.

The high stability of the iminoalcohols **8**–**12** to acidic hydrolysis under work up conditions allows them to be recovered by preparative chromatography in high chemical yields and unchanged enantiomeric excess and reuse for the same reaction.

In summary, a series of novel chiral tridentate Schiff base *N*,*O*-[2.2]paracyclophanyl ligands starting from easily available FHPC and AHPC and different aminoalcohols were synthesized. Among them, ketimines revealed very high levels of enantioselectivity in diethylzinc addition to aldehydes. Further investigations of these ligands and their analogues are in progress in our laboratories.

3. Experimental

Toluene was distilled over Na before use. Benzene, heptane, hexane and ethyl acetate were distilled and used without further purification. Ethanolamine was distilled over Na before use. (*R*)- and (*S*)-valinol, (*S*)-leucinol and Et_2Zn (1 M solution on hexane) were purchased from Fluka and used without purification. Benzaldehyde and cyclohexanecarbaldehyde were purchased from Aldrich, stored and used under argon atmosphere without further purification. TLC analyses were performed on silica gel precoated plates DC-Alufolien Kieselgel 60 F_{254} (Merck). Column chromatography was performed on Kieselgel 60 (Merck). NMR: Bruker AMX-400 (400.13 MHz for ^1H), $CDCl_3$ as solvent, δ_H ($CHCl_3$) = 7.27. MS: KRATOS MS890A (70 eV). Optical rotations: EPO-1 in thermostated cell at 22°C. Enantiomerically pure 4-formyl-5-hydroxy-[2.2]paracyclophane **1**[22] and 4-acetyl-5-hydroxy-[2.2]paracyclophane **2**[12] were obtained according to a literature procedures. All reactions of asymmetric addition of diethylzinc to aldehydes were carried out with dry glassware under the argon atmosphere. Yields of iminoalcohols **8**–**12** are given after column chromatography.

3.1. Preparation of iminophenols 8–12

General methodology: The solution of 0.400 mmol of enantiomerically pure **1** or **2**, 0.400 mmol of aminoalcohol and catalytic quantity of Et_2SnCl_2 in 7 ml of toluene was refluxed in an apparatus equipped with a Dean–Stark trap filled with anhydrous $MgSO_4$ for 24 h. After solvent removal the orange crude product was purified by column chromatography on SiO_2 (eluent hexane/ethylacetate 5/1 to 1/1) from the small quantities of unreacted starting material to provide the corresponding Schiff base. Analytically pure samples were obtained by additional crystallization from toluene/heptane (1/3) or from pure heptane.

(*Sp*)-8: Yield 85%; mp (orange plates) 215–217°C; $[\alpha]_D^{22} = -481.8$ (*c* 0.230, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.60 (br. s, 1H, -O*H*), 2.52–2.62 (m, 1H, -CH_2-C*H*-),

2.72–2.88 (m, 2H, -C*H*H-CH_2-), 2.96–3.05 (m, 1H, -C*H*H-CH_2-), 3.08–3.22 (m, 2H, -C*H*H-CH_2-), 3.37–3.48 (m, 2H, -C*H*H-CH_2-), 3.70–3.84 (m, 2H, =NCH_2-), 3.93–4.00 (t, 2H, -CH_2OH), 6.15 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.28 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 6.40 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.49 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.59 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.85 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 8.29 (s, 1H, -C*H*N=) 14.00 (br. s, 1H, O*H*); MS (70 eV): *m*/*z* (%)=295 (22, M^+), 191 (78), 160 (87), 118 (27), 104 (100). Anal. calcd for $C_{19}H_{21}NO_2$: C, 77.30; H, 7.11; N, 4.74. Found: C, 77.25; H, 7.28; N, 4.67.

(*Rp*,*R*)-9: Yield 72%; mp (orange needles) 162.5–164°C; $[\alpha]_D^{22}$=+553.5 (*c* 0.360, MeOH); ^{1}H NMR ($CDCl_3$): δ 0.90 (d, 6H, ^3J=6.5 Hz, CH(CH_3)$_2$), 1.60 (br. s, 1H, -O*H*), 1.88–2.01 (m, 1H, -C*H*(CH_3)$_2$), 2.52–2.62 (m, 1H, -C*H*H-CH_2-), 2.72–2.89 (m, 2H, -C*H*H-CH_2-), 2.95–3.21 (m, 4H, -C*H*H-CH_2-), 3.39–3.52 (m, 1H, =NC*H*, 1H, -C*H*H-CH_2-), 3.82–3.92 (t, 1H, -CH_2OH), 3.93–4.02 (m, 1H, -CH_2OH), 6.19 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.41 (d, 1H, H-15 or H-16, 1H, H-12 or H-13), 6.48 (dd, ^3J=7.8 Hz, H-7 or H-8), 6.58 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.85 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 8.29 (s, 1H, C*H*N=) 14.0 (br. s, 1H, O*H*); MS (70 eV): *m*/*z* (%)=337 (10, M^+), 233 (30), 147 (20), 117 (16), 104 (100). Anal. calcd for $C_{22}H_{27}NO_2$: C, 78.35; H, 8.01; N, 4.15. Found: C, 78.25; H, 8.23; N, 3.93.

(*Rp*)-10: Yield 89%; mp (orange plates) 155–155.5°C; $[\alpha]_D^{22}$=+611.7 (*c* 0.210, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.10 (br. s, 1H, -O*H*), 2.23 (s, 3H, CH_3), 2.47–2.59 (m, 1H, -CH_2-CH*H*-), 2.60–2.72 (m, 1H, -C*H*H-CH_2-), 2.87–3.23 (m, 4H, -C*H*H-CH_2-), 3.32–3.47 (m, 2H, -C*H*H-CH_2-), 3.62–3.79 (m, 2H, =NCH_2-), 4.03–4.14 (t, 2H, -CH_2OH), 6.20 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.34 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 6.42 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.49 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.62 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.96 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 15.3 (br. s, 1H, O*H*); MS (70 eV): *m*/*z* (%)=309 (38, M^+), 205 (67), 188 (34), 174 (100), 162 (26), 161 (93), 160 (88), 146 (24), 131 (24), 104 (100). Anal. calcd for $C_{20}H_{23}NO_2$: C, 77.68; H, 7.44; N, 4.53. Found: C, 77.87; H, 7.58; N, 4.40.

(*Sp*,*S*)-11: Yield 73%; mp (orange needles) 141–142°C; $[\alpha]_D^{22}$=−603.8 (*c* 0.270, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.98 (d, 3H, ^3J=6.5 Hz, CHCH_3), 1.02 (d, 3H, ^3J=6.5 Hz, CHCH_3), 1.60 (br. s, 1H, -O*H*), 1.92–2.10 (m, 1H, -C*H*(CH_3)$_2$), 2.32 (s, 3H, CH_3), 2.44–2.56 (m, 1H, -C*H*H-CH_2-), 2.57–2.71 (m, 1H, -C*H*H-CH_2-), 2.80–3.20 (m, 4H, -C*H*H-CH_2-), 3.30–3.46 (m, 2H, -CH_2-CH*H*-), 3.62–3.72 (m, 1H, =NC*H*-), 3.80–3.89 (t, 1H, -CH*H*OH), 3.95–4.06 (m, 1H, -CH*H*OH), 6.19 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.38 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 6.40 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.45 (dd, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.60 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.95 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 15.45 (br. s, 1H, O*H*); MS (70 eV): *m*/*z* (%)=351 (37, M^+), 247 (73), 217 (15), 216 (88), 204 (30), 160 (60), 104 (100). Anal. calcd for $C_{23}H_{29}NO_2$: C, 78.65; H, 8.26; N, 3.99. Found: C, 78.78; H, 8.40; N, 3.87.

(*Rp*,*S*)-11: Yield 66%; mp (yellow needles) 149.5–150°C; $[\alpha]_D^{22}$=+653.5 (*c* 0.250, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.10 (d, 3H, ^3J=6.5 Hz, CHCH_3), 1.15 (d, 3H, ^3J=6.5 Hz, CHCH_3), 1.60 (br. s, 1H, -O*H*), 2.00–2.18 (m, 1H, -C*H*(CH_3)$_2$), 2.35 (s, 3H, CH_3), 2.44–2.56 (m, 1H, -C*H*H-CH_2-), 2.62–2.73 (m, 1H, -C*H*H-CH_2-), 2.88–3.20 (m, 4H, -C*H*H-CH_2-), 3.25–3.43 (m, 2H, -C*H*H-CH_2-), 3.69–3.87 (m, 1H, =NC*H*-, 2H, -CH_2OH), 6.17 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.35 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 6.40 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.48 (dd, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.62 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.94 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 15.9 (br. s, 1H, O*H*); MS (70 eV): *m*/*z* (%)=351 (47, M^+), 247 (78), 216 (100), 204 (31), 162 (62), 161 (55), 160 (60), 104 (97). Anal. calcd for $C_{23}H_{29}NO_2$: C, 78.65; H, 8.26; N, 3.99. Found: C, 78.49; H, 8.39; N, 3.82.

(*Sp*,*S*)-12: Yield 72%; mp (yellow floss) 101–102°C; $[\alpha]_D^{22}$=−560.8 (*c* 0.220, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.05 (d, 3H, ^3J=6.5 Hz, -CHCH_3), 1.07 (d, 3H, ^3J=6.5 Hz, -CHCH_3), 1.45–1.57 (m, 1H, -CH*H*-*i*Pr), 1.59–1.71 (m, 1H, -CH*H*-*i*Pr), 1.81–1.92 (m, 1H, -C*H*(CH_3)$_2$), 2.25 (br. s, 1H, -O*H*), 2.35 (s, 3H, CH_3), 2.44–2.57 (m, 1H, -C*H*H-CH_2-), 2.58–2.69 (m, 1H, -C*H*H-CH_2-), 2.87–3.20 (m, 4H, -C*H*H-CH_2-), 3.30–3.43 (m, 2H, -C*H*H-CH_2-), 3.64–3.80 (m, 2H, -CH_2OH), 3.94–4.03 (m, 1H, =NC*H*-), 6.15 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.27 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 6.40 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.49 (dd, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.64 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.96 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 16.0 (br. s, 1H, O*H*); MS (70 eV): *m*/*z* (%)=365 (38, M^+), 261 (55), 230 (79), 188 (27), 186 (21), 162 (44), 160 (58), 145 (32), 104 (96). Anal. calcd for $C_{24}H_{31}NO_2$: C, 78.92; H, 8.49; N, 3.83. Found: C, 79.04; H, 8.67; N, 3.74.

(*Rp*,*S*)-12: Yield 77%; mp (orange floss) 97–97.5°C; $[\alpha]_D^{22}$=+646.8 (*c* 0.240, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.85 (d, 3H, ^3J=6.5 Hz, -CHCH_3), 0.92 (d, 3H, ^3J=6.5 Hz, -CHCH_3), 1.41–1.60 (m, 1H, -C*H*(CH_3)$_2$), 1.60 (br. s, 1H, -O*H*), 1.62–1.75 (m, 2H, -CH_2-*i*Pr), 2.35 (s, 3H, CH_3), 2.48–2.60 (m, 1H, -CH_2-CH*H*-), 2.62–2.71 (m, 1H, -C*H*H-CH_2-), 2.84–2.94 (m, 1H, -C*H*H-CH_2-), 2.95–3.20 (m, 3H, -C*H*H-CH_2-), 3.35–3.48 (m, 2H, -C*H*H-CH_2-), 3.75–3.84 (m, 1H, -CH_2OH), 3.88–4.02 (m, 1H, -CH_2OH, 1H, =NC*H*-), 6.22 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.41 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 6.43 (d, 1H, ^3J=7.8 Hz, H-7 or H-8), 6.47 (dd, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.62 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-12 or H-13), 6.97 (dd, 1H, ^3J=7.8, ^4J=1.8 Hz, H-15 or H-16), 15.6 (br. s, 1H, O*H*); MS (70 eV): *m*/*z* (%)=365 (37, M^+), 261 (55), 230 (80), 188 (27), 162 (44), 160 (58), 145 (34), 104 (99). Anal. calcd for $C_{24}H_{31}NO_2$: C, 78.92; H, 8.49; N, 3.83. Found: C, 78.92; H, 8.65; N, 3.70.

3.2. Enantioselective diethylzinc addition to aldehydes catalyzed by iminophenols 8–12

Typical experimental procedure: To a solution of iminoalcohol **8**–**12** (0.007 mmol) in 0.28 ml of toluene, 0.140 ml (0.142 mmol) of Et_2Zn (1 M solution in hexane) was added in one portion at 0°C followed by the aldehyde (0.071 mmol). The resulting yellow solution was warmed to rt and allowed to stir for an additional 15 h. The excess of Et_2Zn was hydrolyzed with 0.25 ml of 1N HCl; the reaction mixture was then diluted with 4 ml of Et_2O and 3 ml of H_2O. The organic layer was separated and the aqueous fraction was additionally extracted with Et_2O (5×4 ml) or CH_2Cl_2. Combined organic fractions were washed with brine (2 ml) and dried over Na_2SO_4. After solvent removal the oily residue, without further purification, was subjected to the GC and chiral GC for the conversion and enantiomeric excess analysis. The conversion was determined by GC (Hewlett–Packard HP 5890 Series II gas chromatograph) on HP-1 (12 m×0.25 mm) with N_2 as carrier gas. Split temperature 200°C, detector FID 250°C, temperature program: 40°C (1 min), flow rate 30°C/min, end temperature 250°C (10 min). Enantiomeric analysis of the product secondary alcohols was performed by GC (Hewlett–Packard HP 5890 Series II gas chromatograph) on CP-Chirasil-Dex CB (25 m×0.25 mm) with N_2 as carrier gas. Temperature data for 1-phenylpropanol: split temperature 200°C, detector FID 250°C, temperature program: 40°C (1 min), flow rate 5°C/min, end temperature 190°C (20 min); the retention times (min) were 26.94 (*S*) and 27.20 (*R*). Temperature data for 1-cyclohexylpropanol: split temperature 200°C, detector FID 250°C, temperature program: 40°C (10 min), flow rate 20°C/min, end temperature 100°C (35 min), flow rate 20°C/min, end temperature 190°C (5 min); the retention times (min) were 16.70 (*S*) and 16.98 (*R*).

3.3. X-Ray crystallographic study of AHPC 2 and iminophenols (*Rp*)-10 and (*Sp*,*S*)-11

X-Ray structure of 2: crystal data: $C_{18}H_{18}O_2$, MW = 266.20 g mol^{-1}, yellow needles, monoclinic, space group $P2_1$, $Z=4$, $a=8.009(16)$, $b=17.799(3)$, $c=9.295(17)$ Å.

X-Ray structure of (*Rp*)-10: crystal data: $C_{20}H_{23}NO_2$, MW = 309.20 g mol^{-1}, orange needles, orthorhombic, space group $P2_12_12_1$, $Z=4$, $a=7.561(2)$, $b=7.877(3)$, $c=27.756(9)$ Å.

X-Ray structure of (*Sp*,*S*)-11: crystal data: $C_{23}H_{29}NO_2$, MW = 351.14 g mol^{-1}, orange needles, monoclinic, space group $C2$, $Z=4$, $a=20.270(2)$, $b=7.598(9)$, $c=14.775(17)$ Å.

Single-crystal X-ray diffraction experiments were carried out with a Bruker SMART 1000 CCD area detector at 293 K for (*Rp*)-**10** and (*Sp*,*S*)-**11**, and a Syntex $P2_1$ diffractometer at 163 K for *rac*-**2** (graphite-monochromated Mo-Kα radiation. The structures were solved by direct method and refined by the full-matrix least-squares against *F*2*hkl* in anisotropic (for non-hydrogen atoms) approximation. All hydrogen atoms in **2** were located from the difference Fourier syntheses and refined in isotropic approximation. For structures **10** and **11** all hydrogen atoms (except the hydrogen atoms in OH groups) were placed in geometrically calculated positions and included in final the refinement using the 'riding' model with the U_{iso}(H) parameters equal to 1.2 U_{eq}(Ci) or 1.5 U_{eq}(Cii), where U(Ci) and U(Cii) are, respectively, the equivalent thermal parameters of the methyne and methylene carbon atoms to which corresponding H atoms are bonded. All calculations were performed on an IBM PC/AT using the SHELXTL software [G. M. Sheldrick, SHELXTL-97, Version 5.10, Bruker AXS Inc., Madison, WI, 53719, USA]. Crystallographic data for structures **2**, **10** and **11** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications (Ref. Numbers CCDC 206295, 206296, 206297, respectively). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK (Fax: (int.) +44-1223/336-033; e-mail: deposit @ccdc.cam.ac.uk.

Acknowledgements

Financial support of Russian authors by *Russian Foundation for Basic Research* (Project Nos. 03-03-32957 and 03-03-32214), and *Funds provided by the EU Descartes Prize* is gratefully acknowledged. The authors are grateful to Dr. E. V. Vorontsov (Moscow, Russia) for NMR spectra analysis and for helpful discussion.

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