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Planar-chiral salen and hemisalen [2.2]paracyclophane ligands for asymmetric diethylzinc addition to aldehydes

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Abstract—Fourteen multistereogenic symmetric and asymmetric salens based on a [2.2]paracyclophane skeleton have been tested as catalysts for the enantioselective addition of diethylzinc to aldehydes affording the corresponding alcohols in up to 94% enantiomeric excess. Chiral [2.2]paracyclophane hemisalens are applied for the first time as chiral ligands in the Et_2Zn addition to benzaldehyde.

1. Introduction

Despite various salen types of ligands with both central and axial chirality being used for many enantioselective reactions,[1,2] there has only been one report on the synthesis and application of symmetric salens based on a planar-chiral analogue of the salicyl aldehyde, 5-formyl-4-hydroxy[2.2]paracyclophane[3] **1** (FHPC, Fig. 1).[4] As part of our ongoing study of chiral cyclophanes in asymmetric synthesis, we have previously described the novel planar-chiral compound, *ortho*-acylhydroxy[2.2]-paracyclophanes,[5] 4-acetyl-5-hydroxy-**2** (AHPC) and 4-benzoyl-5-hydroxy[2.2]paracyclophane **3** (BHPC) (Fig. 1).

Very recently we reported a unique collection of enantiomerically pure symmetric and unsymmetric salens[6] and hemisalens[6] obtained by a combination of ketones, **2**, **3**, and aldehyde **1**, with different diamines. Herein, we report the use of a model reaction to test these as chiral ligands in the enantioselective addition of diethylzinc to aldehydes.

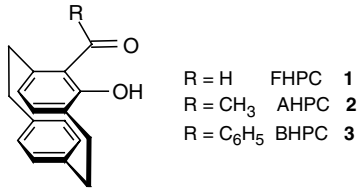

Figure 1.

2. Results and discussion

The chiral salens **4**–**10** (Figs. 2–5) were obtained by using enantiomerically pure **1**–**3** and achiral ethylenediamine (EDA) or chiral (1*R*,2*R*)-diaminocyclohexane [(1*R*,2*R*)-CHDA] as starting materials, via both direct and stepwise approaches.[6] The prepared salens are classified by the structural and configurational features of their carbonyl components into four different types:[6]

Type I: Structurally and configurationally symmetric salens (Fig. 2).
Type II: Structurally asymmetric, configurationally symmetric salens (Fig. 3).
Type III: Structurally and configurationally asymmetric salens (Fig. 4).
Type IV: Structurally symmetric, configurationally asymmetric salens (Fig. 5).

Herein, we will also describe the X-ray crystallographic structures of salens, **5** and **10a** (Fig. 6).

Despite their usefulness for numerous applications, there are only two reports of salen applications for the promoting of asymmetric Et_2Zn addition to aldehydes.[7,8] Thus, the Jacobsen salen, [(*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine],[7] with two stereogenic centers in its diamine moiety, along with

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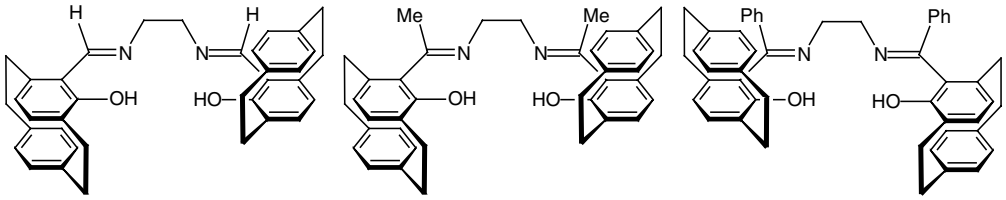
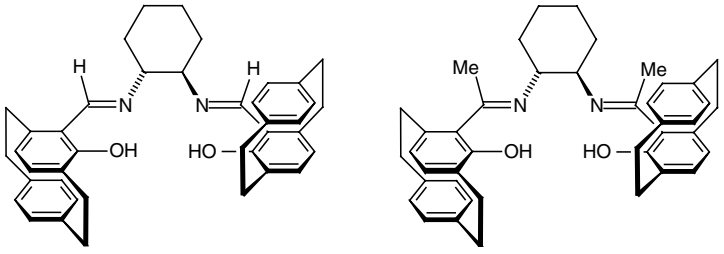
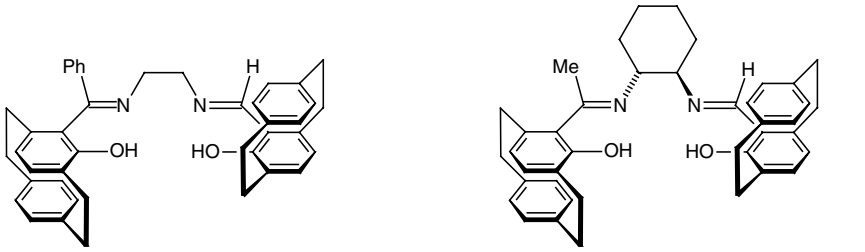


[(*S*)-FHPC]$_2$ EDA **4** [(*S*)-AHPC]$_2$ EDA **5** [(*R*)-BHPC]$_2$ EDA **6**



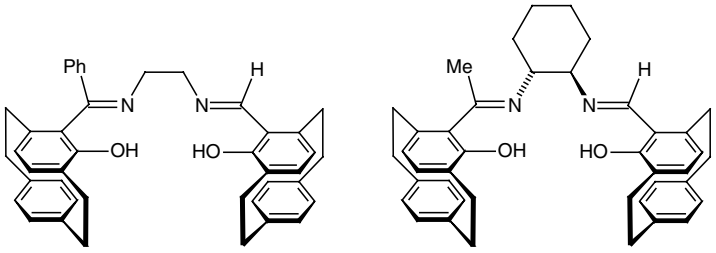
[(*S*)-FHPC]$_2$ (1*R*,2*R*)-CHDA **7a** [(*S*)-AHPC]$_2$ (1*R*,2*R*)-CHDA **8a**
[(*R*)-FHPC]$_2$ (1*R*,2*R*)-CHDA **7b** [(*R*)-AHPC]$_2$ (1*R*,2*R*)-CHDA **8b**

Figure 2.



[(*S*)-BHPC][(*S*)-FHPC] EDA **9a** [(*S*)-AHPC][(S)-FHPC] (1*R*,2*R*)-CHDA **10a**
[(*R*)-AHPC][(R)-FHPC] (1*R*,2*R*)-CHDA **10b**

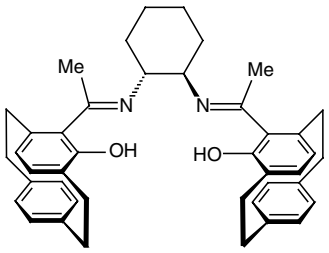
Figure 3.



[(*S*)-BHPC][(*R*)-FHPC] EDA **9b** [(*S*)-AHPC][(*R*)-FHPC] (1*R*,2*R*)-CHDA **10c**
[(*R*)-AHPC][(*S*)-FHPC] (1*R*,2*R*)-CHDA **10d**

Figure 4.

an axially chiral salen,[8] constructed from (*Ra*)-2,2′-dihydroxy-[1,1′]-binaphthyl-3-carbaldehyde and (*Ra*)-1,1′-binaphthyl-2,2′-diamine, were used as the ligands. The highest stereoinduction (83% ee) was achieved with *p*-chlorobenzaldehyde as the substrate. The evaluation of the salen ligands **4**–**10** was performed in the reaction of diethylzinc with aromatic benzaldehyde and aliphatic cyclohexane carbaldehyde, since it has been shown that these sets of substrates are recognized in a different manner by various ligands. In a standard experiment, the chiral zinc catalyst was prepared first by stirring equivalent quantities of diethylzinc and the chiral salen in toluene at room temperature. The enantioselective addition reaction was carried out by the successive addition of 2 equiv of diethylzinc and 1 equiv of the aldehyde to 0.1 equiv of the catalyst in toluene at 0 °C. The reaction mixture was then stirred at room temperature for 15 h. The excess Et_2Zn was then destroyed by the addition of 1 N HCl. After a standard workup, the conversion and enantiomeric excess of the resultant



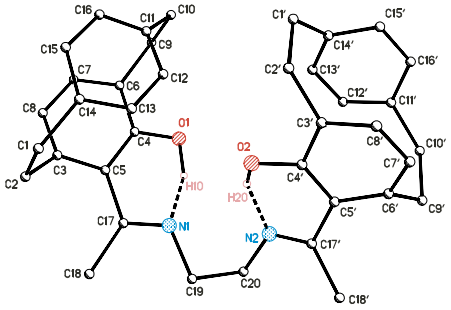
[(*S*)-AHPC][(*R*)-AHPC] (1*R*,2*R*)-CHDA **8c**

Figure 5.

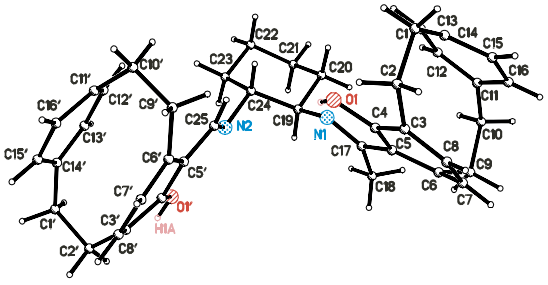
secondary alcohols (1-phenylpropanol **11**, 1-cyclohexylpropan-1-ol **12**) were determined by GC and Chiral GC analysis (Table 1).

At the conclusion of the reactions, about 83–90% of the starting aldehydes were converted to give the corresponding secondary alcohols, **11** and **12**. As with most reactions using benzaldehyde, it was observed that a trace amount of benzyl alcohol was formed due to reduction of the aldehyde by Et_2Zn.

In the series of salens, which were constructed from two planar-chiral [2.2]paracyclophane moieties and achiral EDA (Table 1, entries 1–5), C_2-symmetric salens, **4** and **6** (Table 1, entries 1, 3), based on FHPC and BHPC, were ineffective. But the C_2-symmetric salens, **9a** and **9b** (Table 1, entries 4, 5), also obtained from the FHPC and BHPC fragments, significantly increased the enantioselectivity. Moreover, both diastereomers produced (*S*)-1-phenylpropanol with remarkably similar enantioselectivities (Table 1, entries 4, 5). This clearly supports the view that the configuration of an FHPC fragment does not influence the stereoselectivity of the process. The best result of the series (72% ee), was observed by



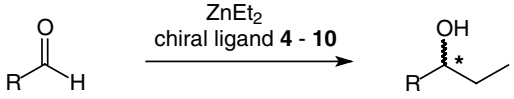
Crystal structure of **5**



Crystal structure of **10a**

Figure 6.

Table 1. The enantioselective addition of Et_2Zn to aldehydes catalyzed by the in situ formation of zinc-complexes of salens **4**–**10** (toluene, 25 °C, 10 mol% of chiral ligand)



R = C_6H_5 **11**

C_6H_{11} **12**

Entry	Chiral salen	Aldehyde	Conversion[a] (%)	Ee[b] (%)
1	[(*S*)-FHPC]EDA **4**	PhCHO	89	13 (*R*)
2	[(*S*)-AHPC]EDA **5**	PhCHO	87	72 (*S*)
3	[(*R*)-BHPC]EDA **6**	PhCHO	89	11 (*S*)
4	[(*S*)-BHPC][(*S*)-FHPC]EDA **9a**	PhCHO	86	46 (*S*)
5	[(*S*)-BHPC][(*R*)-FHPC]EDA **9b**	PhCHO	86	48 (*S*)
6	[(*S*)-FHPC](1*R*,2*R*)-CHDA **7a**	PhCHO	83	41 (*S*)
7	[(*R*)-FHPC](1*R*,2*R*)-CHDA **7b**	PhCHO	87	0
8	[(*S*)-AHPC](1*R*,2*R*)-CHDA **8a**	PhCHO	83	13 (*R*)
9	[(*S*)-AHPC][(*R*)-AHPC](1*R*,2*R*)-CHDA **8c**	PhCHO	86	58 (*R*)
10	[(*R*)-AHPC]$_2$(1*R*,2*R*)-CHDA **8b**	PhCHO	86	68 (*R*)
11	[(*S*)-AHPC][(*S*)-FHPC](1*R*,2*R*)-CHDA **10a**	PhCHO	86	29 (*R*)
12	[(*S*)-AHPC][(*R*)-FHPC](1*R*,2*R*)-CHDA **10b**	PhCHO	90	53 (*S*)
13	[(*R*)-AHPC][(*R*)-FHPC](1*R*,2*R*)-CHDA **10c**	PhCHO	88	60 (*R*)
14	[(*R*)-AHPC][(*S*)-FHPC](1*R*,2*R*)-CHDA **10d**	PhCHO	88	72 (*R*)
15	[(*S*)-AHPC]EDA **5**	$C_6H_{11}CHO$	90	70 (*R*)
16	[(*R*)-AHPC][(*S*)-FHPC](1*R*,2*R*)-CHDA **10d**	$C_6H_{11}CHO$	88	94 (*S*)

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

[b] The absolute configurations of alcohols **11** and **12** were determined by the elution order on GC analysis using a chiral stationary phase in comparison with standard samples.[9,10]

salen **5** (Table 1, entry 2), which was derived from AHPC. Earlier, it was observed that bidentate[5] and tridentate iminophenols with an AHPC backbone were also beneficial catalysts for asymmetric Et_2Zn additions to aldehydes[9–11] and imines,[12,13] as compared to their FHPC and BHPC analogues.

For multistereogenic salens, which were constructed from two planar-chiral [2.2]paracyclophane moieties, chiral (1*R*,2*R*)-CHDA, and have four stereogenic elements (Table 1, entries 6–14), the in-depth interpretation of the influence of every stereogenic element on the stereoselectivity of the reaction is very difficult. Herein, therefore, we are only pointing out the basic trends, which are clear from the results that we have obtained.

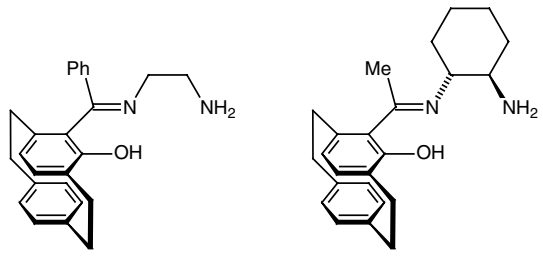
While using the aldimine ligand, **7b**, which is based from (*R*)-FHPC (Table 1, entry 7), no enantioselection is observed. Its diastereomer, **7a**, however, from (*S*)-FHPC, significantly enhances the enantioselectivity (41% ee, Table 1, entry 6). For the diastereomeric salens constructed from AHPC fragments **8a** < **8c** < **8b** the enantioselectivity increases along the line 13 (*R*) < 58 (*R*) < 68 (*R*), respectively (Table 1, entries 8–10). The best results were obtained for salens having the (*R*)-AHPC fragment (Table 1, entries 9, 10).

A similar regularity was observed for the diastereomeric salens, **10a**–**d**, constructed from AHPC and FHPC fragments (Table 1, entries 11–14). In this group, the enantioselectivity changes along the line **10a** < **10b** < **10c** < **10d** from 29 (*R*) < 53 (*S*) < 60 (*R*) < 72 (*R*), respectively. Better results were also obtained for salens including an (*R*)-AHPC fragment (Table 1, entries 13, 14). Interestingly, only one salen in this series, which combines (*S*)-AHPC and (*R*)-FHPC fragments, produces (*S*)-**11** with a reasonable ee (Table 1, entry 12).

In conclusion, we have demonstrated that the enantioselectivity of the addition reaction is strongly dependent on both structural and configurational features of chiral salens. Thus, in the series of salens with EDA, the presence of an AHPC fragment in a ligand provides the optimal asymmetric induction (ee up to 72%). In the series of salens with chiral (1*R*,2*R*)-CHDA, ligands including at least one (*R*)-AHPC fragment were found to be more effective. Such combination of stereogenic elements generates the (*R*)-configuration of the product 1-phenylpropanol.

The salens **5** and **10d**, which demonstrated the best results in the benzaldehyde series, were also tested as chiral ligands for the Et_2Zn addition to the more sterically hindered cyclohexane carbaldehyde. The enantioselectivity remained practically the same for salen **5** (Table 1, entry 15), but increased up to a remarkable 94% enantiomeric excess for **10d** (Table 1, entry 16). The inversion of the configuration of the product carbinol, **12**, was observed in both cases. The analogous inversion of configuration was noticed earlier, when tridentate Schiff bases of AHPC with different β-aminoalcohols were used in the same reaction.[11]

Moreover, we recently synthesized, isolated, and characterized the first chiral hemisalens **13** and **14** in the [2.2]paracyclophane series (Fig. 7), which were then used as precursors for the corresponding asymmetric salens.[6]



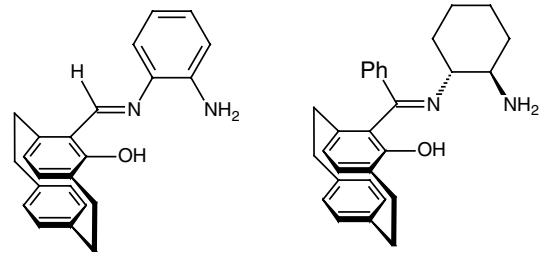
[(*S*)-BHPC] EDA **13**

[(*S*)-AHPC] (1*R*,2*R*)-CHDA **14a**

[(*R*)-AHPC] (1*R*,2*R*)-CHDA **14b**

Figure 7.

However, the stability of the aforementioned hemisalens, in contrast to the reported examples of their aromatic analogues,[14,15] allowed us to consider them as a novel type of N,O-ligand. To the best of our knowledge, this type of ligand has never been used in asymmetric synthesis before. Herein, using analogous methods,[6] we synthesized three new hemisalens, **15**, **16a**, and **16b** (Fig. 8), and tested them as well as **14a** in the model reaction of the Et_2Zn addition to benzaldehyde.



[(*S*)-BHPC] PHDA **15**

[(*S*)-BHPC] (1*R*,2*R*)-CHDA **16a**

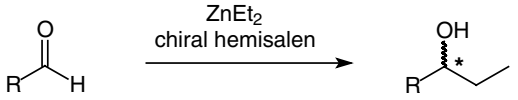
[(*R*)-BHPC] (1*R*,2*R*)-CHDA **16b**

Figure 8.

The standard experiment includes the successive addition of 2 equiv of Et_2Zn and 1 equiv of benzaldehyde to a solution of the hemisalen catalyst (10 mol%) in toluene at 0 °C, followed by stirring at room temperature for 15 h. The excess Et_2Zn was then destroyed by the addition of 1 N HCl. After a standard workup, the enantiomeric excess of the resultant secondary alcohol was determined as described for salens. The results obtained are summarized in Table 2.

The hemisalen, **15**, from aldehyde **1**, with a sterically hindered *ortho*-phenylenediamine (PHDA), results in 1-phenylpropanol (*R*)-**11** with moderate ee (Table 2, entry 1). The hemisalen based on (*S*)-AHPC and (1*R*,2*R*)-CHDA, **14a**, produces (*S*)-**11** with a good ee, although the analogous ligand, **16a**, from BHPC shows almost no enantioselectivity (Table 2, entries 2, 3). The diastereomeric hemisalen, **16**, demonstrates the cooperative effect of the three stereogenic elements. Thus, in

Table 2. Enantioselective addition of Et_2Zn to benzaldehyde catalyzed by in situ formed zinc-complexes of hemisalens **14a**, **15**, and **16** (toluene, 25 °C, 10 mol % of chiral ligand)



R = C_6H_5 **11**

Entry	Ligand	Conversion[a] (%)	Ee[b] (%)
1	[(*S*)-FHPC]PHDA **15**	89	46 (*R*)
2	[(*S*)-AHPC](1*R*,2*R*)-CHDA **14a**	87	60 (*S*)
3	[(*S*)-BHPC](1*R*,2*R*)-CHDA **16a**	89	5 (*R*)
4	[(*R*)-BHPC](1*R*,2*R*)-CHDA **16b**	87	65 (*R*)

[a] The conversion was determined by GC of reaction mixtures after standard workup.
[b] The absolute configuration of 1-phenylcarbinol **11** was determined by the elution order of Chiral GC analysis in comparison with standard samples.[9,10]

contrast with the 'mismatched' **16a** [(*R*)-**11**, 5% ee], hemisalen **16b** showed the best result of the series (ee up to 65%, Table 2, entry 4).

In summary, we report the first example of the application of hemisalen type ligands in a model reaction of an asymmetric diethylzinc addition to benzaldehyde. The high resistance of the salens, **4**–**10**, as well as hemisalens, **14**–**16**, to acidic hydrolysis at the reaction mixture workup conditions allowed us to recover them by preparative chromatography in high chemical yields and unchanged enantiomeric and diastereomeric purities. Thus, they could be reused in the same reaction.

3. Conclusion

In this manuscript we demonstrated the evident potential of planar-chiral salens and the first stable hemisalens of [2.2]paracyclophane series as chiral ligands, as in the example of an asymmetric diethylzinc addition reaction to aldehydes. Further investigations on other asymmetric transformations with the presented ligands are in progress in our laboratories.

4. Experimental

Toluene was distilled over Na before use. Et_2O was distilled from sodium benzophenone ketyl under argon before use. Ethylenediamine (EDA) was distilled over Na before use. (1*R*,2*R*)-(+)-1,2-Diaminocyclohexane [(1*R*,2*R*)-CHDA], *ortho*-phenylenediamine (PHDA), and Et_2Zn (1 M solution in hexane) were purchased from Fluka and used without purification. Benzaldehyde and cyclohexane carbaldehyde were purchased from Aldrich, stored, and used under an argon atmosphere without further purification. TLC analyses were performed on the silica gel precoated plates 'SORBFIL' PTLC-A-UV. Column chromatography was performed on silica gel 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 salens, **4**–**10**, and hemisalen **14a** were obtained according to procedures described in the literature.[6] All reactions of asymmetric addition of diethylzinc to aldehydes were carried out with dry glassware under an argon atmosphere.

4.1. Preparation of hemisalens 15, 16

4.1.1. [(*S*)-FHPC]PHEDA 15. A solution of 0.200 g (0.790 mmol) of (*S*)-FHPC **1** and 0.250 g (2.380 mmol) of *o*-phenylenediamine in 8 ml of toluene was refluxed for 10 h. After cooling the solution and removing the solvent, the crude product was purified by column chromatography on SiO_2 (toluene/EtOH 20/1 to 5/1 as eluents) yielding 0.230 g (85%) of (*S*)-**15** as an orange powder. Mp 136.5–137 °C. $[\alpha]_D^{22} = -794.4$ (*c* 0.220, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.55–2.67 (m, 1H, –CH_2–C*H*–, 2H, –NH_2), 2.74–2.85 (m, 1H, –C*H*H–CH_2–), 2.86–3.00 (m, 1H, –C*H*H–CH_2–), 3.03–3.15 (m, 1H, –C*H*H–CH_2–), 3.18–3.28 (m, 1H, –C*H*H–CH_2–), 3.32–3.43 (m, 1H, –CH_2–C*H*–), 3.53–3.67 (m, 2H, –CH_2–C*H*–), 6.24 (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}), 6.48 (dd, 1H, $^3J = 7.8$, $^4J = 1.8$ Hz, H^{12} or H^{13}), 6.57 (d, 1H, $^3J = 7.8$ Hz, H^7 or H^8), 6.64 (dd, 1H, $^3J = 7.8$, $^4J = 1.8$ Hz, H^{12} or H^{13}), 7.17–7.22 (m, 2H, arom H), 7.33–7.37 (m, 2H, arom H), 7.40 (dd, 1H, $^3J = 7.8$, $^4J = 1.8$ Hz, H^{15} or H^{16}). Anal. Calcd for $C_{23}H_{22}N_2O$ (342.25): C, 80.72; H, 6.43; N, 8.18. Found: C, 81.10; H, 6.58; N, 8.14.

4.1.2. Preparation and separation of diastereomeric hemisalens [BHPC](1*R*,2*R*)-CHDA 16. The dark orange suspension of 0.200 g (0.50 mmol) of *rac*-BHPC **3**, 0.260 g (2.26 mmol) (1*R*,2*R*)-CHDA, and 0.250 ml (0.42 g, 2.260 mmol) of $TiCl_4$ was refluxed with a Dean–Stark trap apparatus, filled with anhydrous $MgSO_4$ for 12 h. After solvent removal, the crude red oil was chromatographed on SiO_2 (toluene/EtOH 20/1). From the combined fractions with R_f 0.4, 0.080 g (50%) of [(*R*)-BHPC](1*R*,2*R*)-CHDA **16b** was collected as an orange oil. $[\alpha]_D^{22} = +210.9$ (*c* 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.90–1.02 (m, 1H, –CH_2– CHDA), 1.18–1.38

(m, 4H, –CH_2– CHDA), 1.50–1.60 (m, 1H, –CH_2– CHDA), 1.62–2.95 (m, 3H, –CH_2– CHDA, 2H, NH_2), 2.16–2.22 (m, 1H, –CH_2–C*H*–), 2.30–2.40 (m, 1H, –C*H*–CH_2–), 2.50–2.60 (m, 1H, –C*H*H–CH_2–), 2.78–2.86 (m, 1H, –C*H*H–CH_2–), 2.96–3.06 (m, 1H, –C*H*H–CH_2–), 3.14–3.22 (m, 2H, –C*H*H–CH_2–), 3.33–3.52 (m, 2H, –C*H*H–CH_2–), 6.02 (d, 1H, $^3J = 7.8$ Hz, H^7 or H^8), 6.40–6.48 (m, 3H, PC arom H), 6.52 (dd, 1H, $^3J = 7.8$, $^4J = 1.8$ Hz, H^{15} or H^{16}), 7.04 (dd, 1H, $^3J = 7.8$, $^4J = 1.8$ Hz, H^{12} or H^{13}), 7.40–7.50 (m, 5H, arom H). Anal. Calcd for $C_{29}H_{32}N_2O{\cdot}0.25C_7H_8$ (447.22): C, 82.61; H, 7.54; N, 6.26. Found: C, 82.90; H, 7.68; N, 6.05; MS (70 eV): m/z (%) = 424 (M^+, 29), 320 (69), 312 (20), 104 (100).

From combined fractions with R_f 0.25, 0.12 g (75%) of [(*S*)-BHPC](1*R*,2*R*)-CHDA **16a** was collected as orange semisolid compound. $[\alpha]_D^{22} = -642.9$ (*c* 0.316, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.90–1.02 (m, 1H, –CH_2– CHDA), 1.23–1.50 (m, 2H, –CH_2– CHDA, 2H, NH_2), 1.68–1.78 (m, 2H, –CH_2– CHDA), 1.82–1.95 (m, 3H, –CH_2– CHDA), 2.02–2.12 (m, 1H, –CH_2– CHDA), 2.15–2.40 (m, 1H, –C*H*–CH_2–, 1H, –CH_2– CHDA), 2.50–2.60 (m, 1H, –C*H*H–CH_2–), 2.78–2.92 (m, 2H, –C*H*H–CH_2–), 2.93–3.25 (m, 3H, –C*H*H–CH_2–), 3.40–3.52 (m, 1H, –C*H*H–CH_2–), 6.01 (d, 1H, $^3J = 7.8$ Hz, H^7 or H^8), 6.40–6.48 (m, 3H, PC arom H), 6.52 (dd, 1H, $^3J = 7.8$, $^4J = 1.8$ Hz, H^{15} or H^{16}), 7.04 (dd, 1H, $^3J = 7.8$, $^4J = 1.8$ Hz, H^{12} or H^{13}), 7.24–7.33 (m, 2H, arom H), 7.40 (m, 3H, arom H). Anal. Calcd for $C_{29}H_{32}N_2O{\cdot}0.38C_8H_7$ (459.22): C, 82.95; H, 7.64; N, 6.10. Found: C, 83.22; H, 7.68; N, 6.07; MS (70 eV): m/z (%) = 424 (M^+, 15), 320 (79), 312 (13), 104 (100). The absolute configurations of the diastereomers of **16a** and **b** were determined by chemical transformation of (*R*)-**3** to [(*R*)-BHPC](1*R*,2*R*)-CHDA **16b**, which was found having positive rotation, and hence the configuration of the diastereomer **16a** with negative rotation angle was assigned as [(*S*)-BHPC](1*R*,2*R*)-CHDA.

4.1.3. Preparation of hemisalen [(*R*)-BHPC](1*R*,2*R*)-CHDA 16b. The dark orange suspension of 0.050 g (0.125 mmol) of (*R*)-BHPC[16] (ee 92%), 0.065 g (0.565 mmol) (1*R*,2*R*)-CHDA, and 0.063 ml (0.100 g, 2.570 mmol) of $TiCl_4$ in 5 ml of toluene was refluxed equipped with Dean–Stark trap filled with anhydrous $MgSO_4$ for 12 h. After solvent removal, the crude red oil was passed from short column filled with SiO_2 (toluene/EtOH 20/1) to remove the traces of corresponding salen. The resulted hemisalen [(*R*)-BHPC](1*R*,2*R*)-CHDA (de 92%) 0.030 g (75%) was collected as orange oil. $[\alpha]_D^{22} = +195.3$ (*c* 0.32, $CHCl_3$).

4.2. Enantioselective diethylzinc addition to aldehydes catalyzed by salens 4–10

4.2.1. Typical experiment procedure. To a suspension of salen (0.005 mmol) in 0.2 ml of toluene, 0.005 mmol of Et_2Zn (15% solution in hexane, $d = 0.720$) was added and the resulting yellow or orange mixture was stirred for 1 h at room temperature. The resulting mixture was cooled to 0 °C and 0.12 ml (0.102 mmol) of Et_2Zn (15% solution in hexane, $d = 0.720$) was added in one aliquot. After 5 min, 0.051 mmol of aldehyde was added dropwise and the mixture was warmed to room temperature and then allowed to stir for an additional 15 h. The excess Et_2Zn was hydrolyzed with 0.25 ml of 1 N HCl. The reaction mixture was then diluted with 4 ml of ether and 3 ml of water. The organic layer was separated and aqueous fraction was additionally extracted with Et_2O (5×4 ml) or CH_2Cl_2. The combined organic fractions were washed with brine (2 ml) and dried over Na_2SO_4. After solvent removal, the oily residue was subjected to the GC and Chiral GC, without further purification, 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 secondary product 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-cyclohexylpropan-ol: 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 44.90 (*S*) and 45.50 (*R*).

4.3. Enantioselective diethylzinc addition to aldehydes catalyzed by hemisalens 14a, 15, and 16

4.3.1. Typical experimental procedure. To a solution of hemisalen (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 dropwise addition of the aldehyde (0.071 mmol). The resulting yellow solution was warmed to room temperature and allowed to stir for additional 15 h. The excess Et_2Zn was hydrolyzed with 0.25 ml of 1 N HCl. The reaction mixture was then diluted with 4 ml of Et_2O and 3 ml of H_2O. Organic layer was separated and the aqueous fraction was additionally extracted with Et_2O (5×4 ml) or CH_2Cl_2. The 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 secondary alcohols product 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 the carrier gas. Temperature data

for 1-phenylpropan-ol: 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-cyclohexylpropan-ol: 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*).

4.4. X-ray crystallographic study of salens 5 and 10a

X-ray structure of **5**. Crystal data: $C_{38}H_{40}N_2O_2$, $MW = 556.10\,g\,mol^{-1}$, orange needles, monoclinic, space group $P2_1$, $Z = 4$, $a = 16.891(2)$, $b = 9.210(1)$, $c = 24.003(7)$ Å, $\beta = 98.82(1)°$, $R_1 = 0.0578$.

X-ray structure of **10a**. Crystal data: $C_{41}H_{44}N_2O_2{\cdot}CHCl_3$, $MW = 716.28\,g\,mol^{-1}$, orange plates, monoclinic, space group $P2_12_12_1$, $Z = 4$, $a = 7.9304(16)$, $b = 9.4494(19)$, $c = 47.082(9)$ Å, $\beta = 128.417(2)°$, $R_1 = 0.0446$.

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 **5**, **10a** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications (reference nos CCDC 216188 and 218779, respectively). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK [Fax: (internat.) +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

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