

Bidentate Schiff bases derived from (*S*)- α -methylbenzylamine as chiral ligands in the electronically controlled asymmetric addition of diethylzinc to aldehydes

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Abstract

A group of bidentate Schiff bases derived from enantiomerically pure (*S*)- α -methylbenzylamine was synthesized. Crystal structure was determined for three compounds. Schiff bases were used as chiral ligands in the asymmetric addition of Et₂Zn to aldehydes. The obtained enantioselectivity was e.e.=8-94% depending on the substrate and the best was observed for (*S,E*)-2-(1-(1-phenylethylimino)-ethyl)phenol. The enantioselectivity increase was connected with the substituent-induced electronic effects in the substrate molecules. Molecular modeling resulted in the models of the 3D structures of Zn-Zn complex catalysts containing investigated Schiff bases, which were consistent with the reported chirality of the addition product and explained observed e.e. The presented transition state models allow explaining the change of the absolute configuration of diethylzinc addition product in the case of using *ortho*-substituted aldehydes.

Keywords: Bidentate Schiff bases, diethylzinc addition, α -methylbenzylamine derivatives, electronic effects

Introduction

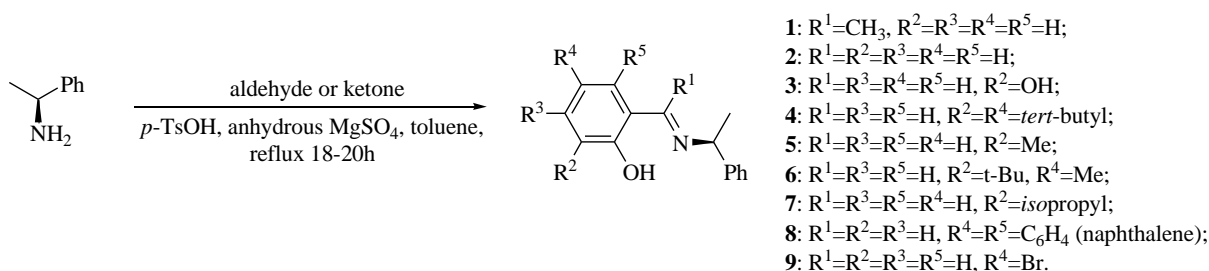
Bidentate chiral salicylidene Schiff bases (SB) derived from (*S*)- α -methylbenzylamine have been of particular interest due to: significant ability of chelation and great stability of metal complexes¹, interesting antifungal activity² and potential use as important intermediates in the synthesis of benzoxazines having antimicrobial³, antitumour⁴ or anthelmintic⁵ activities. Moreover, enantiopure Schiff bases, after chelation with appropriate metals, have been used as

catalysts in such reactions as: cyclopropanation of styrene⁶, trimethylsilylcyanation of aldehydes⁷, Heck or Suzuki coupling reactions⁸. These reactions belong to the group of processes of catalytic asymmetric carbon-carbon bond formation, which is one of the most extensively applied methods in organic chemistry. The use of chiral Schiff bases in the asymmetric synthesis was broadly described in literature⁹. However, only few examples of very effective imines have been presented¹⁰. Bidentate salicylidene SB, obtained from (*S*)- α -methylbenzylamine and its derivatives, can be prepared by solvent-free methods¹¹ and can also be used to obtain efficient aminophenol ligands for the enantioselective addition reactions¹².

Enantioselectivity of catalytic asymmetric reactions has usually been coupled to the steric hindrance effects. By contrast, a concept of *electronic control* or *electronic tuning* in the asymmetric catalysis reactions has been less explored and is still poorly understood. This effect was previously described *e.g.* by Landis *et al.*¹³ in the asymmetric hydrogenation or by Park¹⁴ in the cyclopropanation of alkenes. Zhang *et al.*¹⁵ for the first time observed that the enantioselectivity of diethylzinc addition to aldehydes could depend on the electronic effects related to the nature of the aryl aldehydes and increases with more reactive substrates. In this article we report the synthesis of nine Schiff bases derived from (*S*)- α -methylbenzylamine and their efficiency as chiral ligands. Also, the remarkable findings about electronic effects in the asymmetric addition of diethylzinc to aldehydes are reported.

Results and Discussion

Schiff bases (**1-9**) have been obtained from (*S*)- α -methylbenzylamine in the reaction with respective aromatic aldehydes or ketones with 46-99% yields (Scheme 1). Reactions were performed in toluene according to the procedure reported by Iglesias⁶.



Scheme 1. Synthesis of Schiff base ligands **1-9**.

All products have been purified by crystallization from appropriate solvents (**2-4**, **8**, **9**) or by distillation under reduced pressure (**1**, **5-7**). The compounds similar to ours **1**, **2**, **4**, **8** and **9** have been previously described in Ref. 6,7,16 and 17. The detailed analysis revealed that our compounds have already been synthesized as the same enantiomers (**2**, **4**, **8**)^{6,7}, or as *R*-enantiomers (**1**, **9**)^{16,17} while all our compounds have *S*-configuration. Comparison of our results

with the above references showed that there are some differences between the results of the optical rotation measurements in the case of **1**, **2**, **4**, **8**, **9**. The discrepancy could be caused by: the use of the different solvent for the measurement^{6,16,17} for **2**, **4**, **8**, different enantiomeric purity of α -methylbenzylamine¹⁷ for **9**, or a lack of the Schiff base **1** purification¹⁶. All SB described here were of high purity that was confirmed by the MS analyses.

The UV-Vis absorption spectra were also recorded for all obtained Schiff bases (methanol solutions). Results are presented on Figure 1.

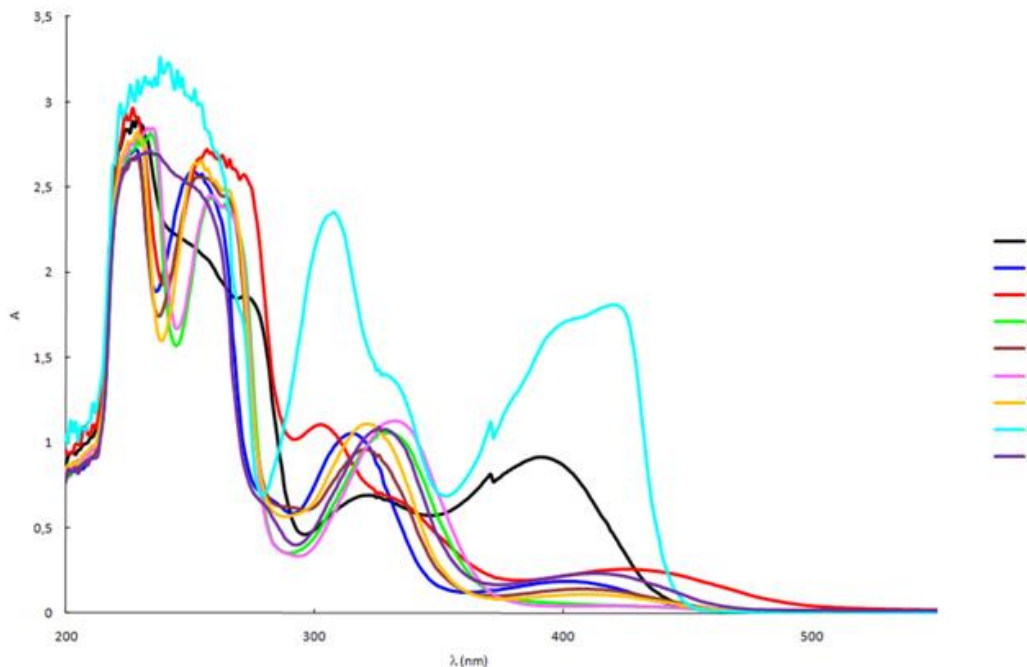


Figure 1. The absorption UV-Vis spectra of Schiff bases **1-9** in methanol solutions ($c = 2.5 \cdot 10^{-5}$ M).

The solution spectra indicated that the electronic properties of SB **1-9** were strongly dominated by the donor-acceptor chromophore (Fig. 1). Electronic absorption spectra of Schiff bases showed the $\pi \rightarrow \pi^*$ transitions related to aromatic rings at about 205-250 nm and $\pi \rightarrow \pi^*$ transitions related to imine group at about 275-350 nm. Moreover, the longer wavelength band at 325-450 nm, characteristic for **1** and **8**, was assigned in accordance with Ref. 18 and 19 to an intramolecular charge transfer involving the whole molecule. This effect could be caused by the probable keto-amine tautomer formation in a methanol solution. The tautomerization of chiral hydroxy SB was described before²⁰ and usually is connected with an intra- and intermolecular hydrogen bond between phenolic hydroxyl and iminium nitrogen.

The crystal structures for imines **2**, **8** and **9** have been determined by the X-ray analysis. Details of the diffraction experiments and structure refinement are presented in Table 1.

Table 1. Crystal data and structure refinement for **2**, **8** and **9**

	2	8	9
Empirical formula	C ₁₅ H ₁₅ NO	C ₁₉ H ₁₇ NO	C ₁₅ H ₁₄ BrNO
Formula weight	225.28	275.34	304.18
Crystal system, space group	Monoclinic, C2	Monoclinic, P2 ₁	Monoclinic, C2
Unit cell dimensions(Å, °)	a = 18.533(3) b = 5.9018(3) c = 14.803(2) β = 129.42(2)	a = 8.8834(11) b = 5.7689(9) c = 14.698(2) β = 102.399(11)	a = 20.890(4) b = 5.7721(8) c = 14.5690(15) β = 129.030(10)
Volume (Å ³)	1250.8(3)	735.67(18)	1364.6(4)
Z, Calculated density (Mg/m ³)	4, 1.196	2, 1.243	4, 1.481
Absorption coefficient (mm ⁻¹)	0.075	0.076	3.000
F(000)	480	292	616
Crystal size (mm)	0.39 x 0.31 x 0.08	0.71 x 0.13 x 0.09	0.67 x 0.24 x 0.14
Theta range for data collection (°)	2.20 to 26.00	2.47 to 27.00	2.51 to 31.38
Reflections collected / unique, R(int)	4015/2168 R(int) = 0.0222	5864/2553 R(int) = 0.0778	6801/2775 R(int) = 0.0509
Completeness, θ _{max}	99.9 %, 26.00	99.8 %, 27.00	99.9 %, 26.00
Max. and min. transmission	0.9937/0.9712	0.9929/0.9480	0.6800/0.2387
Data / restraints / parameters	2168/1/154	2553/1/190	2775/1/163
Goodness-of-fit on F ²	0.890	1.006	1.038
Final R indices [I>2σ(I)]	R1 = 0.0354 wR2 = 0.0848	R1 = 0.0647, wR2 = 0.1634	R1 = 0.0384, wR2 = 0.0884
R indices (all data)	R1 = 0.0529 wR2 = 0.0920	R1 = 0.0983, wR2 = 0.1834	R1 = 0.0558, wR2 = 0.0965
Absolute structure parameter	-0.1(18)	2(3)	-0.001(13)
Largest diff. peak/hole e.Å ⁻³	0.114 / -0.099	0.167 / -0.178	0.225 / -0.570

The molecular structure of **2**, **8** and **9** with the atom numbering scheme is presented on Fig. 2.

The molecular conformation of all investigated compounds **2**, **8** and **9** was determined by almost identical intramolecular hydrogen bonds between O1 hydroxyl group and the imine N1 atom. The presence of the intramolecular O-H...N hydrogen bond was detected in all structures of analogous imines as found with the CSD²¹. In all reported structures **2**, **8** and **9** the molecule had the *E*-conformation.

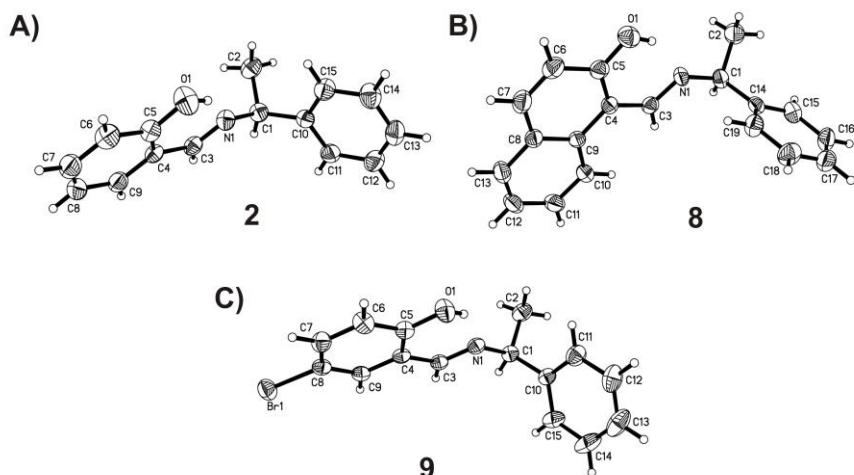


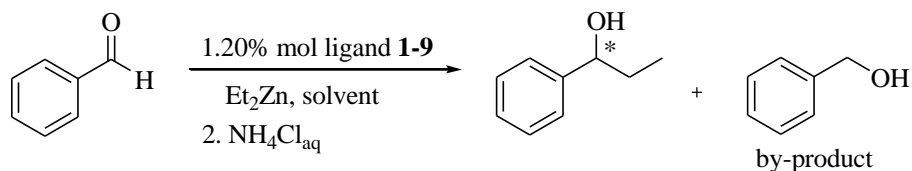
Figure 2. Molecule of A) **2**, B) **8**, C) **9**. The thermal ellipsoids are plotted at 30% probability level.

The presence of bromine atom in **9** allowed determining the absolute configuration as *S* which was consistent with the chirality of the substrate used in the synthesis. For **2** and **8**, the absolute structure could not be determined reliably with the Flack method²². Therefore, the correct chirality was chosen as *S* by the comparison to that determined for **9**.

The inspection of CSD revealed the report on the crystal structure of *R*-enantiomer of **9**²³. Comparison of the structure **9** with that reported for *R*-enantiomer showed that the cell parameters of our structure were of higher precision and the structure determination resulted in the R value lower by 1%. However, some differences in the molecular conformation were found which reflected the opposite configuration on C1. The structure of *S*-enantiomer reported here was similar to that of *S*-enantiomer of the chloro- analog²⁴, for which the two torsion angles described above are 120.7 and 48.2°.

We determined the structure of **2**, to obtain the reference structure of the compound with no additional substituent in the phenolic ring. The CSD search revealed the report on the racemate of **2** crystallizing in the P2(1)/n space group and the optically pure form crystallizing in the C2 space group²⁵.

SB (**1-9**) were tested as chiral ligands in the enantioselective addition of diethylzinc to aldehydes (Scheme 2).



Scheme 2. Asymmetric addition of diethylzinc to benzaldehyde.

In the first stage, ligands (**1-9**) were used in an amount of 20 mol %. Diethylzinc in amount of 2 equiv. in relation to 1 equiv. of benzaldehyde was used according to procedures described before in Ref. 26. Previous reports 27 and 28 showed that the enantioselectivity depends on temperature during the catalyst formation. Therefore, different temperature values were examined for the first step of reaction. All results of studied reactions are summarized in Table 2.

Table 2. Addition of diethylzinc to benzaldehyde in a presence of catalysts containing the Schiff bases **1-9**

Entry	Ligand	Time (h)	Yield of by-product (%) ^d	Yield (%) ^e	E.e. (%) ^f /config. ^g
1	1	24 ^a	22	74	27 (<i>S</i>)
2	1	24 ^b	20	59	27 (<i>S</i>)
3	1	24 ^c	14	79	8 (<i>S</i>)
4	2	24	-	>99	18 (<i>S</i>)
5	3	24	10	41	-
6	4	24	13	64	12 (<i>S</i>)
7	5	24	5	95	18 (<i>S</i>)
8	6	24	8	66	8 (<i>S</i>)
9	7	24	5	95	18 (<i>S</i>)
10	8	24	5	95	8 (<i>S</i>)
11	9	24	9	41	16 (<i>S</i>)

^a Reaction was carried at the temperature range from 0°C to +20°C. ^b Reaction was carried at the temperature range from -20°C to +20°C. ^c Reaction was carried at the temperature range from -70°C to +20°C. ^d Determined by GC using Zebron ZB-5 capillary column (for crude samples). ^e Isolated products. ^f Determined by HPLC using OD-H column. ^g The configuration was determined by the measurement of the optical rotation and by comparison with literature values²⁹.

The best results for investigated SB chiral ligands were observed when both the catalyst formation and addition to benzaldehyde were performed at 0° C (then the reaction was carried at 20° C). The absolute configuration of the product depended on the absolute configuration of the used SB ligand. The obtained results indicated that bidentate ligands (**1-9**) having the *S*-configuration gave (*S*)-1-phenylpropanol as a major product, but only with a weak asymmetric induction in the investigated process. However, relatively good yields of product (41-99%) and poor yields of by-product (<22%) have been achieved.

The modest enantiomeric excesses in the addition Et₂Zn to benzaldehyde, e.e.=8-27% were obtained. The highest enantiomeric excess was observed for ligand **1** (Table 2: entry 1). The results showed that the presence of the methyl moiety (R¹ substituent, Scheme 1), bonded to imine group was a discriminating factor for the substrate orientation. Similar effects of the

methyl substituent on the imine carbon atom for Schiff base ligands derived from 4-hydroxy[2.2]paracyclophane were reported by Danilova *et al.*³⁰.

Based on the crystal structure of **2**, models of the active complex with ligand **1** having opposite *R*-configuration as well as *S*-configuration were proposed. Both models were optimized by Molecular Mechanics method in Arguslab program using UFF force field³¹ and were consistent with the literature examples for chiral bidentate ligands^{26,32,33}. The first model with (*R*)-**1** showed that the addition to *Re* face of the aldehyde was preferred. The bulk of the phenyl ring in the *R*-enantiomer of the ligand enforces binding of benzaldehyde with its *Re* face exposed to ethyl group addition. Therefore, the obtained models suggested the importance of the absolute configuration of ligand for chirality of the addition product.

The model with (*S*)-**1** showed that substituent R¹=CH₃ might have only limited effect on the orientation of the substrate although preference for the *Si* face, which was consistent with observed e.e.=27% (Table 2: entry 1) and *S*-configuration of addition product. It was also noticed that replacement of this methyl group by the bigger group could increase the enantiomeric excess due to the increased bulk near the expected position of benzaldehyde (Fig 3). The presence of the substituent in the ligand phenolic ring also decreased the enantiomeric excess, which was probably connected with either bulk or electronic effects of the substituent. However, Fig. 3 showed that the presence of substituents in phenolic ring, even on C6 (see: Fig. 2), had only secondary importance for the stereochemistry of the end product of Et₂Zn addition to benzaldehyde since they would be positioned too far away from the reaction center in the transition state. Similar effect was described by Parrott II³⁴ and Tanaka³⁵.

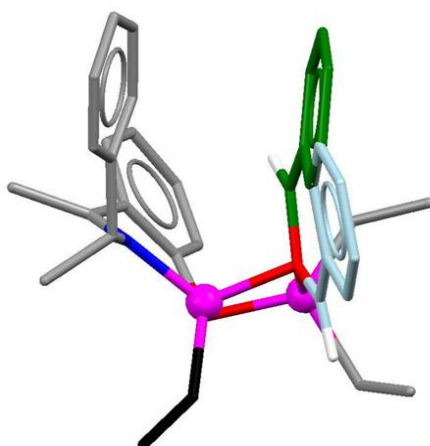


Figure 3. Model of the active complex Zn-Zn formed with ligand **1** with the orientation of the substrate as obtained with MM calculations³¹. The addition to *Si* (green) and *Re* (cyan) faces are equally possible.

The presented model obtained for ligand **1** showed, that there is only a little difference between the addition to *Re* and *Si* faces (Fig. 3). Calculation indicated that in both *Re* and *Si* orientation of the substrate, the π - π stacking interactions could stabilize the transition state. Also,

R¹ substituent might be a factor responsible for slight asymmetric induction. This conclusion was consistent with our experimental data indicating that the absence of –CH₃ group in other investigated ligands resulted in the decrease of enantioselectivity (Table 2: entries 4-11).

In spite of only modest e.e.=27% obtained for ligand **1**, the ligand was examined in a series of reactions with a variety of aromatic and aliphatic aldehydes under optimized conditions (Table 3).

Table 3. Addition of diethylzinc to aldehydes catalyzed by the Schiff base **1**

Entry	Ligand	Aldehyde	Time (h)	Yield (%) ^a	E.e. (%) ^b / config. ^c
1	1	<i>o</i> -methoxybenzaldehyde	72	38	16 (<i>R</i>)
2	1	<i>m</i> -methoxybenzaldehyde	72	78	23 (<i>R</i>)
3	1	<i>p</i> -methoxybenzaldehyde	72	61	39 (<i>S</i>)
4	1	<i>o</i> -chlorobenzaldehyde	72	80	24 (<i>R</i>)
5	1	<i>o</i> -bromobenzaldehyde	72	52	15 (<i>R</i>)
6	1	<i>m</i> -chlorobenzaldehyde	72	92	94 (<i>S</i>)
7	1	<i>p</i> -chlorobenzaldehyde	72	75	53 (<i>S</i>)
8	1	<i>p</i> -bromobenzaldehyde	72	90	96 (<i>S</i>)
9	1	<i>p</i> -dimethylaminobenzaldehyde	72	89	-
10	1	cyclohexanecarbaldehyde	72	94	30 (<i>S</i>)

^a Isolated products. ^b Determined by HPLC using OD-H column or by GC using β-Dex capillary column. ^c The configuration was determined by the measurement of the optical rotation and by comparison to literature values²⁹.

When *o*-, *m*-, *p*-methoxy-, *p*-dimethylamino-, *o*-chloro-, *o*-bromobenzaldehyde and also cyclohexanecarbaldehyde (Table 3: entries 1-5, 9-10) were used, the enantiomeric excesses were lower or at the same level as for benzaldehyde (Table 2: entry 1). However, in the case of *m*-chloro and *p*-chlorobenzaldehyde as well as *p*-bromobenzaldehyde the e.e.'s of addition products were significantly higher (e.e.=94%, 53% and 96%) (Table 3: entries 6-8). The presence of electron-withdrawing substituents in substrates, that caused an increase of Lewis acidity on the carbon atom of carbonyl group, was responsible for increasing reactivity of the substrate. Zhang¹⁵ reported the linear relation between enantioselectivity and the Hammett constant for *para*-substituted substrates using pyridylphenols as ligands. In contrast, in our group of ligands such linear dependence was not so clear. In some reports e.g. Ref. 36 about the electronic effects in the organic reactions, the reasons of this phenomenon were inadequately described. In accordance with mechanism proposed by Zhang¹⁵ for diethylzinc addition and Landis¹³ for asymmetric hydrogenation, the aldehyde binding to zinc complex with Schiff base ligand, involved in the salicylidene moiety the imine bond conjugated with the aromatic ring, led to the formation of transition state that was stabilized by the electron-withdrawing substituents on

para- position. The UV-Vis spectra (Fig. 1) described above revealed the tautomeric equilibrium for the analyzed Schiff base **1**. The tautomerization effect probably also affected the interaction between the substrate and the ligand as well as the geometry of the catalyst complex and the transition state (Fig. 3). The appropriate molecular calculation studies are currently in progress also for other SB ligands³⁷. The tautomerization of Schiff bases was described in literature and is important phenomenon for understanding many physicochemical properties, such as photo- and thermochromism as well as the biological activity³⁸.

For aldehydes with *ortho*- substituents and for *m*-methoxybenzaldehyde, the change from *S* to *R* configuration of the addition product was observed. The *Re* face of the ethyl group addition seems to be stabilized by the π - π interaction between the substrate and the ligand rings as well as the electrostatic interactions between the aldehyde H atom and the imine moiety (Fig. 3). However, these effects give no significant e.e. for the major *R*-product (Table 3). The bulk of investigated *ortho* substituents probably had some influence on the absolute configuration of the product.

The use of diethylzinc addition reaction for the stereoselective synthesis of biologically active compounds is very extensive. Schiff base chiral ligands described in this paper are also during investigation for the application in the synthesis of formoterol³⁹ derivatives that are possible β_2 -adrenergic receptor agonists.

Conclusions

Nine bidentate Schiff bases were synthesized from enantiomerically pure (*S*)- α -methylbenzylamine and were used as chiral ligands in the addition of Et₂Zn to various aldehydes. Due to the characteristic steric position of methyl group in (*S,E*)-2-(1-(1-phenylethylimino)ethyl)phenol **1** this ligand promoted the formation of (*S*)-1-aryl-1-propanol as a predominant product. The average enantiomeric excess was e.e.=27% for benzaldehyde as a substrate. The increase up to e.e.=94% and 96% found for *m*-chlorobenzaldehyde and *p*-bromobenzaldehyde, respectively, was a consequence of the increased Lewis acidity of the carbon atom of the carbonyl group. The probable formation of keto-amine tautomer of **1** observed on the UV-Vis spectra also affected the enantioselectivity. Moreover, the observed change of the absolute configuration of Et₂Zn addition products could be related to the π - π stacking effects between aromatic rings of the substrate with *ortho*- or *meta*-substituents and the ligand as well as to some electrostatic interactions near the imine moiety.

Acknowledgements

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Experimental Section

General. Melting points were determined by a Büchi apparatus in open capillaries and are uncorrected. Optical rotations were measured on PolAAR 3000 automatic polarimeter in a 10 cm cell at 589 nm. Elemental analyses were performed on an Elementary Analysensysteme GmbH Vario MACRO CHN analyzer. The ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200 multinuclear instrument and on Bruker Avance 300 MHz instrument respectively, in CDCl_3 at ambient temperature. Chemical shifts were reported in parts per million (δ scale), coupling constants (J values) were listed in Hertz. UV-Vis spectra were recorded on Helios UNICAM in quartz cuvettes. Infrared spectra were reported in reciprocal centimeters (cm^{-1}) and were measured as a nujol mull or as a neat. EI-HRMS and MS(EI) experiments were performed on Finigan MAT 95 (Bremen, Germany) by Environmental Laboratory of Organic Compounds and Polymer Analysis, Centre of Molecular and Macromolecular Studies, Polish Academy of Science, Łódź. GC was performed on a Perkin–Elmer AutoSystem XL chromatograph using β -Dex 325 capillary column (30m, 0.25mm), or on Shimadzu GC-14A using Zebron ZB-5 capillary column. HPLC analyses were performed on a Shimadzu LC-10AT chromatograph using Chiralcel OD-H column (250 \times 4.6mm). Yellow crystals of **2**, **8** and **9** have been obtained from the hexane-ethyl acetate solution. The X-ray data were collected at 292(2) K with an Oxford Sapphire CCD diffractometer using $\text{MoK}\alpha$ radiation $\lambda = 0.71073 \text{ \AA}$ and ω - 2θ method. The numerical absorption correction was applied with CrysAlis171 package of programs, Oxford Diffraction, 2000⁴⁰. Structures were solved by direct methods and refined with the full-matrix least-squares method on F^2 with the use of SHELX-97 program package⁴¹. The hydrogen atoms have been located from the difference electron density maps and constrained during refinement. The absolute configuration for **9** was determined by the Flack method²² and verified with the prior knowledge on the chirality on C1 of the used substrate. Since the method of synthesis had not inverted the chirality of the existing center, the absolute structure for **2** and **8** was determined by comparison with that of **9**. For all investigated compounds, the (*1S*) configuration was assigned.

The structural data have been deposited with Cambridge Crystallographic Data Centre, the CCDC numbers 782015, 782016 and 782014 for **2**, **8** and **9**, respectively.

Materials. TLC was performed on silica gel Polygram® Sil G/UV₂₅₄ (0.2mm). Regular column chromatography was carried out using Silica Gel 60 (0.06-0.2mm). All solvents were purchased

from POCh Gliwice, Poland. Toluene was distilled from sodium prior to use. Diethylzinc, (*S*)- α -methylbenzylamine (e.e.=99%), aldehydes were purchased from Sigma–Aldrich or Fluka. 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde, 3-*tert*-butyl-5-methyl-2-hydroxybenzaldehyde, 2-hydroxy-3-methylbenzaldehyde and 2-hydroxy-3-isopropylbenzaldehyde were obtained according to literature procedures^{42,43}.

Preparation of Schiff bases 1-9

A 100-ml round-bottom flask equipped with a magnetic stirring bar and reflux condenser was filled with 8.25 mmol (1.0g) of (*S*)- α -methylbenzylamine, 60ml of anhydrous toluene, 8.25 mmol of appropriate aldehydes (or ketone), 20 mg of *p*-toluenesulphonic acid and 6.0 g of anhydrous MgSO₄. The reaction mixture was stirred for 18-20 h at reflux and then, after cooling to room temperature, it was filtered onto Celite pad of 1 cm thickness in a fritted glass funnel. The solvent was stripped and the crude product was either crystallized or purified by distillation under reduced pressure. Yields and physical properties are presented below.

(*S,E*)-2-(1-(1-Phenylethylimino)ethyl)phenol (1). 2-Hydroxyacetophenone as a substrate. Yellow oil (82%). Purified by distillation under reduced pressure. Bp 175-180°C/1 Torr, $[\alpha]_D^{20} = +506$ (*c* 0.70, MeOH) (lit.¹⁶ *R*-enantiomer without purification: $[\alpha]_D^{20} = -275$ (*c* 0.45, CH₂Cl₂)). ¹H NMR (300 MHz, CDCl₃): δ 1.65 (d, *J* = 6.6 Hz, 3H, CH₃), 2.35 (s, 3H, CH₃), 4.95 (q, *J* = 6.6 Hz, 1H, CH), 6.77 (td, *J* = 1.2 Hz, *J* = 8.1 Hz, 1H, CH-aryl), 6.95 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H, CH-aryl), 7.22-7.52 (m, 7H, CH-aryl), 16.76 (br s, 1H, OH). ¹³C NMR (75.5 MHz, CDCl₃): δ 14.63 (CH₃), 25.21 (CH₃), 58.47 (CH), 116.98 (CH), 118.90 (CH), 119.28 (C), 126.29 (2×CH), 127.17 (CH), 128.11 (CH), 128.79 (2×CH), 132.61 (CH), 144.14 (C), 164.29 (C), 170.53 (C). IR (neat): 3028.9, 2971.8, 2554.1, 1613.6, 1578.8, 1503.8, 1449.0, 1375.0, 1303.7, 1257.3, 1161.4, 1133.5, 1085.9, 1014.6, 937.8, 837.1, 754.8, 700.3. MS(EI): *m/z* 239 [M]⁺ (69), 135 (38), 105 (100). EI-HRMS: *m/z* [M]⁺ calcd for C₁₆H₁₇NO, 239.1310; found: 239.1306.

(*S,E*)-2-((1-Phenylethylimino)methyl)phenol (2). 2-Hydroxybenzaldehyde as a substrate. Yellow solid (69%). Purified by re-crystallization from hexane-ethyl acetate (1:1, v/v). Mp 75-77°C (lit.⁶ 72-74°C), $[\alpha]_D^{20} = +175$ (*c* 1.15, MeOH) (lit.⁶ $[\alpha]_D^{20} = +159$ (*c* 0.04, CH₂Cl₂)). ¹H NMR (300 MHz, CDCl₃): δ 1.65 (d, *J* = 6.6 Hz, 3H, CH₃), 4.57 (q, *J* = 6.6 Hz, 1H, CH), 6.88 (td, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H, CH-aryl), 6.98 (d, *J* = 8.4 Hz, 1H, CH-aryl), 7.23-7.41 (m, 7H, CH-aryl), 8.42 (s, 1H, HC=N), 13.56 (br s, 1H, OH). ¹³C NMR (50.3 MHz, CDCl₃): δ 24.71 (CH₃), 68.22 (CH), 116.74 (CH), 118.39 (CH), 118.65 (C), 126.16 (2×CH), 127.02 (CH), 128.45 (2×CH), 131.24 (CH), 132.06 (CH), 143.65 (C), 160.92 (C), 163.27 (CH). IR (nujol mull): 2354.8, 1627.9, 1576.5, 1278.1, 1149.6, 1081.5, 1015.6, 969.2, 851.6, 756.5, 700.3. MS(EI): *m/z* 225 [M]⁺ (64), 121 (46), 105 (100). EI-HRMS: *m/z* [M]⁺ calcd for C₁₅H₁₅NO, 225.1154; found: 225.1154.

(*S,E*)-3-((1-Phenylethylimino)methyl)benzene-1,2-diol (3). 2,3-Dihydroxybenzaldehyde as a substrate. Orange solid (56%). Purified by re-crystallization from ethanol. Mp 92-94°C, $[\alpha]_D^{20} = +266$ (*c* 0.07, MeOH). ¹H NMR (300 MHz, CDCl₃): δ 1.69 (d, *J* = 6.6 Hz, 3H, CH₃), 4.65 (q, *J* =

6.6 Hz, 1H, CH), 6.66 (t, $J = 7.5$ Hz, 1H, CH-aryl), 6.76 (dd, $J = 1.5$ Hz, $J = 8.1$ Hz, 1H, CH-aryl), 6.96 (dd, $J = 1.8$ Hz, $J = 7.5$ Hz, 1H, CH-aryl), 7.27-7.42 (m, 5H, CH-aryl), 8.26 (s, 1H, HC=N), 13.56 (br s, 2H, 2×OH). ^{13}C NMR (50.3 MHz, CDCl_3): δ 24.23 (CH_3), 65.96 (CH), 116.74 (CH), 116.37 (CH), 116.71 (C), 117.38 (CH), 122.08 (CH), 126.36 (2×CH), 127.66 (CH), 128.87 (2×CH), 142.72 (C), 146.03 (C), 153.78 (C), 163.25 (CH). IR (nujol mull): 3160.6, 1635.9, 1197.6, 1018.7, 858.2, 743.9, 696.4. MS(EI): m/z 241 $[\text{M}]^+$ (54), 137 (55), 105 (100). EI-HRMS: m/z $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_2$, 241.1103; found: 241.1099.

(*S,E*)-2,4-Di-*tert*-butyl-6-((1-phenylethylimino)methyl)phenol (4). 3,5-Di-*t*-butyl-2-hydroxybenzaldehyde as a substrate. Yellow solid (79%). Purified by re-crystallization from methanol. Mp 84-85°C, (lit.⁷ 93-94°C), $[\alpha]_{\text{D}}^{20} = +103$ (c 0.314, MeOH) (lit.⁷ $[\alpha]_{\text{D}}^{20} = +119.6$ (c 0.726, CHCl_3)). ^1H NMR (300 MHz, CDCl_3): δ 1.33 (s, 9H, 3× CH_3 : *t*-Bu), 1.49 (s, 9H, 3× CH_3 : *t*-Bu), 1.66 (d, $J = 6.9$ Hz, 3H, CH_3), 4.56 (q, $J = 6.9$ Hz, 1H, CH), 7.11 (d, $J = 2.4$ Hz, 1H, CH-aryl), 7.24-7.43 (m, 7H, CH-aryl), 8.45 (s, 1H, HC=N), 13.84 (br s, 1H, OH). ^{13}C NMR (50.3 MHz, CDCl_3): δ 24.88 (CH_3), 29.49 (3× CH_3), 31.51 (3× CH_3), 34.11 (C), 35.04 (C), 68.48 (CH), 117.98 (C), 126.01 (CH), 126.51 (2×CH), 126.91 (CH), 127.14 (CH), 128.60 (2×CH), 136.68 (C), 140.08 (C), 144.09 (C), 158.04 (C), 164.59 (CH). IR (nujol mull): 1629.4, 1540.2, 1362.0, 1272.2, 1250.3, 1202.8, 1173.4, 1076.1, 1026.1, 976.8, 879.1, 828.7, 764.1, 703.3. MS(EI): m/z 337 $[\text{M}]^+$ (100), 322 (81), 294 (34), 218 (91), 190 (35), 105 (75). EI-HRMS: m/z $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{31}\text{NO}$, 337.2406; found: 337.2397.

(*S,E*)-2-Methyl-6-((1-phenylethylimino)methyl)phenol (5). 2-Hydroxy-3-methylbenzaldehyde as a substrate. Yellow oil (77%). Purified by distillation under reduced pressure. Bp 156-158°C/1 Torr, $[\alpha]_{\text{D}}^{20} = +223$ (c 0.89, MeOH). ^1H NMR (300 MHz, CDCl_3): δ 1.64 (d, $J = 6.6$ Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.56 (q, $J = 6.6$ Hz, 1H, CH), 6.78 (t, $J = 7.5$ Hz, 1H, CH-aryl), 7.11 (dd, $J = 1.5$ Hz, $J = 7.5$ Hz, 1H, CH-aryl), 7.17-7.41 (m, 6H, CH-aryl), 8.41 (s, 1H, HC=N), 13.82 (br s, 1H, OH). ^{13}C NMR (50.3 MHz, CDCl_3): δ 15.43 (CH_3), 24.97 (CH_3), 68.39 (CH), 117.98 (C), 118.09 (CH), 125.82 (C), 126.31 (2×CH), 127.14 (CH), 128.59 (2×CH), 129.01 (CH), 133.21 (CH), 143.87 (C), 159.31 (C), 163.55 (CH). IR (neat): 2972.2, 2867.0, 1626.9, 1491.5, 1452.1, 1308.2, 1269.6, 1123.8, 1084.5, 1033.4, 975.7, 910.5, 846.2, 747.9, 699.2. MS(EI): m/z 239 $[\text{M}]^+$ (78), 135 (76), 105 (100). EI-HRMS: m/z $[\text{M}]^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{NO}$, 239.1310; found: 239.1301.

(*S,E*)-2-*tert*-butyl-4-methyl-6-((1-phenylethylimino)methyl)phenol (6). 3-*tert*-Butyl-2-hydroxy-5-methylbenzaldehyde as a substrate. Yellow oil (61%). Purified by distillation under reduced pressure. Bp 172-174°C/1 Torr, $[\alpha]_{\text{D}}^{20} = +147$ (c 0.89, MeOH). ^1H NMR (200 MHz, CDCl_3): δ 1.44 (s, 3H, 3× CH_3), 1.64 (d, $J = 6.8$ Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.56 (q, $J = 6.8$ Hz, 1H, CH), 6.78 (d, $J = 2.2$ Hz, 1H, CH-aryl), 7.12 (d, $J = 1.8$ Hz, 1H, CH-aryl), 7.25-7.40 (m, 6H, CH-aryl), 8.36 (s, 1H, HC=N), 13.74 (br s, 1H, OH). ^{13}C NMR (75.5 MHz, CDCl_3): δ 20.63 (CH_3), 24.99 (CH_3), 29.41 (3× CH_3), 34.71 (C), 68.56 (CH), 118.42 (C), 126.50 (2×CH), 127.15 (CH), 127.16 (C), 128.61 (2×CH), 129.63 (CH), 130.45 (CH), 137.05 (C), 144.01 (C), 158.03 (C), 164.17 (CH). IR (neat): 2959.0, 2864.9, 1628.5, 1597.7, 1441.2, 1389.8, 1376.7, 1318.2, 1266.4, 1211.0, 1165.2, 1121.6, 1084.1, 1030.1, 975.5, 909.2, 862.3, 789.8, 761.2, 698.9.

MS(EI): m/z 295 $[M]^+$ (93), 280 (30), 252 (33), 190 (29), 176 (71), 148 (50), 105 (100). EI-HRMS: m/z $[M]^+$ calcd for $C_{20}H_{25}NO$, 295.1936; found: 295.1932.

(*S,E*)-2-Isopropyl-6-((1-phenylethylimino)methyl)phenol (7). 2-Hydroxy-3-isopropylbenzaldehyde as a substrate. Yellow oil (71%). Purified by distillation under reduced pressure. Bp 176-178°C/1 Torr, $[\alpha]_D^{20} = +206$ (c 1.39, MeOH). 1H NMR (300 MHz, $CDCl_3$): δ 1.24 (d, $J = 3.6$ Hz, 3H, CH_3 -*iso*-propyl), 1.28 (d, $J = 3.6$ Hz, 3H, CH_3 -*iso*-propyl), 1.64 (d, $J = 6.6$ Hz, 3H, CH_3), 3.42 (sept, $J = 6.9$ Hz, 1H, CH-*iso*-propyl), 4.55 (q, $J = 6.6$ Hz, 1H, CH), 6.85 (t, $J = 5.1$ Hz, 1H, CH-aryl), 7.11 (dd, $J = 1.5$ Hz, $J = 7.7$ Hz, 1H, CH-aryl), 7.24-7.41 (m, 6H, CH-aryl), 8.42 (s, 1H, HC=N), 13.88 (br s, 1H, OH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 22.41 (CH_3), 22.49 (CH_3), 24.96 (CH_3), 26.35 (CH), 68.44 (CH), 118.16 (C), 118.30 (CH), 126.37 (2 \times CH), 127.16 (CH), 128.60 (2 \times CH), 128.60 (CH), 128.94 (CH), 136.22 (C), 143.89 (C), 158.46 (C), 163.79 (CH). IR (neat): 3061.3, 2963.7, 2868.8, 2659.6, 1948.7, 1871.9, 1808.1, 1628.0, 1492.8, 1440.3, 1381.9, 1303.4, 1263.4, 1234.0, 1151.2, 1123.9, 1083.3, 1050.6, 1017.6, 976.4, 911.0, 879.7, 751.9, 699.1, 637.9. MS(EI): m/z 267 $[M]^+$ (44), 162 (100), 148 (27), 105 (66). EI-HRMS: m/z $[M]^+$ calcd for $C_{18}H_{21}NO$, 267.1623; found: 267.1612.

(*S,E*)-1-((1-Phenylethylimino)methyl)naphthalen-2-ol (8). 2-Hydroxy-1-naphthaldehyde as a substrate. Yellow solid (46%). Purified by re-crystallization from hexane-ethyl acetate (1:1, v/v). Mp 112-113°C (lit.⁶ 104-108°C), $[\alpha]_D^{20} = +193$ (c 0.34, MeOH) (lit.⁶ $[\alpha]_D^{20} = +114.87$ (c 0.04, CH_2Cl_2)). 1H NMR (300 MHz, $CDCl_3$): δ 1.75 (d, $J = 6.6$ Hz, 3H, CH_3), 4.77 (q, $J = 6.6$ Hz, 1H, CH), 6.98 (d, $J = 9.3$ Hz, 1H, CH-aryl), 7.21-7.45 (m, 7H, CH-aryl), 7.62 (d, $J = 9.3$ Hz, 1H, CH-aryl), 7.71 (d, $J = 9.3$ Hz, 1H, CH-aryl), 7.82 (d, $J = 8.4$ Hz, 1H, CH-aryl), 8.85 (s, 1H, HC=N), 14.96 (br s, 1H, OH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 24.18 (CH_3), 63.32 (CH), 107.08 (C), 118.02 (CH), 122.78 (CH), 123.90 (CH), 126.25 (2 \times CH), 126.50 (C), 127.74 (CH), 127.77 (CH), 128.92 (2 \times CH), 129.17 (CH), 133.54 (C), 136.65 (CH), 142.51 (C), 158.88 (CH), 173.85 (C). IR (nujol mull): 1610.2, 1537.8, 1185.7, 1106.5, 1067.5, 987.5, 863.5, 832.8, 739.7, 699.4. MS(EI): m/z 275 $[M]^+$ (100), 170 (79), 105 (85). EI-HRMS: m/z $[M]^+$ calcd for $C_{19}H_{17}NO$, 275.1310; found: 275.1306.

(*S,E*)-4-Bromo-2-((1-phenylethylimino)methyl)phenol (9). 5-Bromo-2-hydroxybenzaldehyde as a substrate. Yellow solid (99%). Purified by re-crystallization from hexane-ethyl acetate (1:2, v/v). Mp 131-132°C (lit.¹⁷ 130-132°C), $[\alpha]_D^{20} = +41$ (c 0.24, MeOH) (lit.¹⁷ *R*-enantiomer: $[\alpha]_D^{20} = -54$ (c 0.40, EtOH)). 1H NMR (200 MHz, $CDCl_3$): δ 1.65 (d, $J = 6.6$ Hz, 3H, CH_3), 4.58 (q, $J = 6.6$ Hz, 1H, CH), 6.95 (d, $J = 8.4$ Hz, 1H, CH-aryl), 7.10-7.23 (m, 7H, CH-aryl), 8.32 (s, 1H, HC=N), 13.56 (br s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.68 (CH_3), 68.36 (CH), 109.95 (C), 118.95 (CH), 120.14 (C), 126.36 (2 \times CH), 127.39 (CH), 128.71 (2 \times CH), 132.44 (CH), 134.84 (CH), 143.25 (C), 160.11 (C), 162.15 (CH). IR (nujol mull): 2853.4, 2356.0, 1878.2, 1766.3, 1633.1, 1601.4, 1556.6, 1276.0, 1180.7, 1087.6, 1017.3, 966.1, 914.4, 889.5, 819.8, 767.4, 699.4. MS(EI): m/z 303 $[M]^+$ (29), 198 (29), 135 (38), 105 (100). EI-HRMS: m/z $[M]^+$ calcd for $C_{15}H_{14}BrNO$, 303.0259; found: 303.0255.

General procedure for asymmetric addition of Et₂Zn to aldehydes

Diethylzinc (2 mmol, 2 ml, 1M solution in hexanes) was added to a solution of chiral Schiff base (20 mol %) in dry toluene (5 ml) at appropriate temperature (0°C, -20°C or -70°C-Table 1) in an atmosphere of N₂. After 1 h aldehyde (1 mmol, 1M solution in dry toluene, 1ml) was added and the reaction mixture was turned to room temperature. The mixture was stirred for appropriate time (Tables 4 and 5) and then was quenched with the saturated solution of ammonium chloride (5 ml) and was extracted with ethyl acetate (3 × 10 ml). The organic solution was washed with brine, dried over anhydrous MgSO₄ and gravity filtered. Then, the solvent was stripped to obtain enantiomerically enriched 1-phenyl-1-propanol. Crude samples were analyzed by GC method using ZB-5 capillary column to determine the amount of by-product (appropriate benzyl alcohol). When necessary, the crude product was purified by the column chromatography using appropriate eluents (usually hexane:ethyl acetate=5:1 v/v). The e.e.'s were determined with HPLC using ODH-Chiralcel column or GC analysis using β-Dex capillary column. Yields were determined via GC analysis using ZB-5 capillary column or by isolation of the product (Tables 2 and 3).

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