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Synthesis and Structural Analysis of Chiral Bis-dihydro[1,3]-naphthoxazines and Imidazolidine Derivatives Prepared by Three-Component Mannich-Type Condensation

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Abstract: Enantiomerically pure (*S*)-1-phenylethan-1-amine has been applied in Mannich-type condensation between formaldehyde and naphthalenediols leading to the synthesis of chiral bis-dihydro[1,3] naphthoxazines in excellent yields. Salen-type structures have been synthesized, applying *R*,*R*- or *S*,*S*-cyclohexane-1,2-diamines in condensation with formaldehyde and naphthalene-2-ol. The obtained chiral imidazolidine derivatives of the type 1,1′-(((3a,7a)-hexahydro-1*H*-benzo[*d*]imidazole-1,3(2*H*)diyl)bis(methylene))bis(naphthalen-2-ol) were evaluated as pre-catalysts for the addition of diethyl zinc to aldehydes. The structures of the newly synthesized compounds were elucidated using ^{1}D and ^{2}D NMR experiments (COSY, HMBC, HSQS), elemental analysis, mass spectrometry (HRMS spectra) and single-crystal X-ray diffraction (SCXRD). The products were further characterized with powder X-ray diffraction (PXRD) and thermal analysis (DSC).

Keywords: Mannich condensation; bis-dihydro[1,3]naphthoxazines; *R*,*R*- or *S*,*S*-cyclohexane-1,2-diamine; chiral ligand; enantioselectivity; X-ray crystallography

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1. Introduction

Multicomponent reactions are an attractive tool for creating complex polyfunctional organic compounds [1,2]. The synthesis of dihydrooxazines by three-component Mannich-type condensation of naphthol, amine and formaldehyde has a high potential for obtaining an important class of heterocyclic compounds. Structurally diverse dihydro[1,3]oxazines have demonstrated a broad range of biological activities (bactericides, fungicides, anti-inflammatory, antitumor, anti-HIV) and have found applications in materials science [3,4].

The synthesis of dihydro[1,3]oxazines occurs most commonly through one-pot condensation between aromatic alcohol, formaldehyde and amine applying different solvents or in some examples under solvent-free conditions [3]. The use of readily available chiral amines offers the opportunity for synthesis of chiral dihydrooxazines. To date, there are only a limited number of examples describing the synthesis of enantiopure dihydro[1,3]naphthoxazine using chiral amines. These compounds are employed as intermediates in the synthesis of *N*-substituted aminobenzylnaphthols and demonstrate a significant activity in asymmetric catalysis [5]. In our previous studies, we demonstrated a practicable approach for the synthesis of 1,3-naphthoxazines through a three-component condensation involving naphthalene-2-ol, formaldehyde and a series of chiral amines. The subsequent reduction obtained the corresponding *N*-methyl derivatives in a convenient way [6]. In a

similar synthetic approach, we applied 2,6-, 2,3- and 1,5-dihydroxy naphthalenes in the condensation reaction (Betti reaction) with aromatic aldehydes and (*S*)-(−)-1-phenylethane-1-amine, synthesizing chiral aminobenzylnaphthols in good yields [7].

In this study, we present the synthesis of bis-dihydro[1,3]naphthoxazines applying 2,3- and 2,6-dihydroxy naphthalenes, (*S*)-(−)-1-phenylethane-1-amine and formaldehyde. Of further interest was the condensation of cyclohexane-1,2-diamine, naphthalene-2-ol and formaldehyde due to the opportunity to obtain salen-type structures [8,9]. The structural elucidation of isolated chiral compounds applying advanced NMR and X-ray crystallographic experiments was of particular importance for understanding the possible catalyst applications of the compounds. Some of the synthesized structures were preliminarily evaluated in a model catalytic reaction.

2. Materials and Methods

2.1. Chemistry (General Methods)

All reagents were of commercial grade and were used without additional purification. Aluminum sheets precoated with silica gel 60 F_{254} (Merck, Darmstadt, Germany) were used for performing thin-layer chromatography (TLC) while silica gel 60 (230–400 mesh, Merck, Rahway, NJ, USA) was used for flash chromatography. Optical rotation $[\alpha]_D^{20}$ measurements were performed using a JASCO P2000 polarimeter, Jasco Inc., Hachioji, Japan. The NMR spectra were recorded on a Bruker Avance II+ 600 spectrometer (600 MHz for ^{1}H, 150 MHz for ^{13}C NMR) in $CDCl_3$ with TMS as the internal standard for chemical shifts (δ, ppm). The NMR data for ^{1}H and ^{13}C were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constants (*J*, Hz) and identification. The assignment of the ^{1}H and ^{13}C NMR spectra was made on the basis of DEPT, COSY, HSQC, HMBC and NOESY experiments. All assignments marked with an asterisk are tentative. Mass spectra (MS) were recorded on a QSTAR pulsar I mass spectrometer (AB/MDS Sciex) by electrospray ionization (ESI) and were reported as fragmentation in *m*/*z* with relative intensities (%) in parentheses. The mass spectra were recorded on Thermo Scientific (Waltham, MA, USA) UHPLC system coupled with a Q Exactive Plus Hybrid Quadrupole-Orbitrap Mass Spectrometer Thermo Scientific (HESI HRMS). The spectra were processed by the Xcalibur Free Style program.

2.2. Synthesis of Bis-dihydro[1,3]naphthoxazines

2.2.1. Synthesis of 3,10-Bis((*S*)-1-phenylethyl)-2,3,4,9,10,11-hexa-hydronaphtho[1,2-*e*:4,3-e′]bis([1,3]oxazine) (**3**)

To a mixture of naphthalene-2,3-diol (0.100 g, 0.62 mmol, **1**) and (*S*)-(−)-1-phenylethane-1-amine (0.159 g, 1.30 mmol, **2**) in ethanol (5 mL), paraformaldehyde (0.094 g, 3.10 mmol) was added. The mixture was stirred at 50 °C for 3 h. After evaporation of the solvent, the crude product was column chromatographed (CH_2Cl_2/MeOH = 100:1) to provide 0.275 g (98%) of **3**. mp 206–211 °C. $[\alpha]_D^{20}$ = +121 (c 1.014, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.53 (d, 6H, *J* = 6.6 Hz, H-14, H-14′), 4.07–4.12 (m, 4H, H-13, H-13′, H*-11), 4.39 (d, 2H, *J* = 16.4 Hz, H*-11′), 5.06* (d, 2H, *J* = 10.2 Hz, H-21), 5.34* (dd, 2H, *J* = 10.2, 0.8 Hz, H-21′), 7.24–7.27 (m, 4H, H-7, H-8, H-18, H-18′), 7.30–7.33 (m, 4H, H-17, H-17′, H-19, H-19′), 7.35–7.36 (m, 4H, H-16, H-16′, H-20, H-20′), 7.37–7.38 (m, 2H, H-6, H-9); ^{13}C NMR (150.92 MHz, $CDCl_3$) δ 21.68 (2q, C-14, C-14′), 46.00 (2t, C-11, C-11′), 58.26 (2d, C-13, C-13′), 80.37 (2t, C-21, C-21′), 111.70 (2s, C-1, C-4), 121.43 (2d, C-6, C-9), 123.94 (2d, C-7, C-8), 126.35 (2s, C-5, C-10), 127.19 (2d, C-18, C-18′), 127.22 (4d, C-16, C-16′, C-20, C-20′), 128.51 (4d, C-17, C-17′, C-19, C-19′), 143.52 (2s, C-2, C-3), 144.78 (2s, C-15, C-15′); MS (ESI) *m*/*z* (rel. int.): 451 ([M + H]$^+$, 34). HRMS (ESI$^+$) *m*/*z* calcd. for $C_{30}H_{30}N_2O_2^+$ [M + H]$^+$ 451.2381, found 451.2238. Anal. calcd. for $C_{30}H_{30}N_2O_2$ (450.58): C, 79.97; H, 6.71; N, 6.22. Found: C, 80.21; H, 6.82; N, 6.25.

2.2.2. Synthesis of
3,9-Bis((*S*)-1-phenylethyl)-2,3,4,8,9,10-hexahydronaphtho[1,2-*e*:5,6-*e*′]bis([1,3]oxazine) (**5**)

To a mixture of naphthalene-2,6-diol (0.100 g, 0.62 mmol, **4**) and (*S*)-(−)-1-phenylethane-1-amine (0.159 g, 1.30 mmol, **2**) in ethanol (3 mL), 37% aq. solution of formaldehyde (calculated to provide 5 equiv. of formaldehyde) was added. The mixture was stirred at 50 °C for 1h. After evaporation of the solvent, the crude product was column chromatographed (petroleum ether/MTBE = 20:1) to provide 0.265 g (94%) of **5**. mp 183–185 °C. $[\alpha]_D^{20}$ = +29 (c 1.005, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.49 (d, 6H, *J* = 6.6 Hz, H-14, H-14′), 4.03 (q, 2H, *J* = 6.6 Hz, H-13, H-13′), 4.13* (d, 2H, *J* = 16.8 Hz, H-11), 4.38* (d, 2H, *J* = 16.8 Hz, H-11′), 4.88* (d, 2H, *J* = 10.1 Hz, H-21), 5.13* (dd, 2H, *J* = 10.1, 1.2 Hz, H-21′), 6.98 (d, 2H, *J* = 9.1 Hz, H-3, H-8), 7.24–7.36 (m, 12H, H-18, H-18′, H-4, H-9, H-17, H-17′, H-19, H-19′, H-16, H-16′, H-20, H-20′); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.63 (2q, C-14, C-14′), 46.19 (2t, C-11, C-11′), 58.18 (2d, C-13, C-13′), 79.79 (2t, C-21, C-21′), 113.38 (2s, C-1, C-6), 118.61 (2d, C-3, C-8), 120.82 (2d, C-4, C-9), 127.08 (2s, C-5, C-10), 127.22 (2d, C-18, C-18′), 127.27 (4d, C-16, C-16′, C-20, C-20′), 128.52 (4d, C-17, C-17′, C-19, C-19′), 144.72 (2s, C-15, C-15′), 150.91 (2s, C-2, C-7); HRMS (ESI$^+$) *m*/*z* calcd. for $C_{30}H_{30}N_2O_2^+$ $[M + H]^+$ 451.2381, found 451.2238. Anal. calcd. for $C_{30}H_{30}N_2O_2$ (450.58): C, 79.97; H, 6.71; N, 6.22. Found: C, 80.18; H, 6.93; N, 6.04.

2.3. Synthesis of Cyclohexane-1,2-diamine Derivatives

2.3.1. Synthesis of 1,1′-(((3a*R*,7a*R*)-Hexahydro-1H-benzo[d]imidazole-1,3(2*H*)-diyl)-bis(methylene))bis(naphthalen-2-ol) ((*R*,*R*)-**9**)

To a solution of naphthalene-2-ol (0.375 g, 2.20 mmol, **7**) in methanol (5 mL), paraformaldehyde (0.071 g, 2.00 mmol) and *R*,*R*-cyclohexane-1,2-diamine (0.135 g, 1.00 mmol, **6**) were added. The mixture was refluxed for 2 h, whereby a white precipitate was formed. The reaction mixture was cooled to room temperature and the product was collected by filtration and washed with MeOH to provide 0.245 g (47%) of (*R*,*R*)-**9**. mp 190–192 °C. $[\alpha]_D^{20}$ = +83 (c 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.25–1.35 (m, 2H, H-15, H-15′), 1.40–1.50 (m, 2H, H-14, H-14′), 1.82–1.90 (m, 2H, H-15, H-15′), 2.09–2.17 (m, 2H, H-14, H-14′), 2.48–2.56 (m, 2H, H-13, H-13′), 3.66 (s, 2H, H-16), 4.21 (d, 2H, *J* = 14.5 Hz, H-11, H-11′), 4.38 (d, 2H, *J* = 14.5 Hz, H-11, H-11′), 7.03 (d, 2H, *J* = 8.9 Hz, H-3, H-3′), 7.22–7.26 (m, 2H, H-7, H-7′), 7.38–7.44 (m, 2H, H-8, H-8′), 7.62 (d, 2H, *J* = 8.9 Hz, H-4, H-4′), 7.69 (d, 2H, *J* = 8.0 Hz, H-6, H-6′), 7.76 (d, 2H, *J* = 8.6 Hz, H-9, H-9′), 11.98 (br s, 2H, HO-(C-2, C-2′)); ^{13}C NMR (600 MHz, $CDCl_3$) δ 23.99 (2t, C-15, C-15′), 28.94 (2t, C-14, C-14′), 51.52 (2t, C-11, C-11′), 69.42 (2d, C-13, C-13′), 76.53 (t, C-16), 111.09 (2s, C-1, C-1′), 118.93, (2d, C-3, C-3′), 120.90 (2d, C-9, C-9′), 122.58 (2d, C-7, C-7′), 126.48 (2d, C-8, C-8′), 128.43 (2s, C-5, C-5′), 128.80 (2d, C-6, C-6′), 129.42 (2d, C-4, C-4′), 132.02 (2s, C-10, C-10′), 155.96 (2s, C-2, C-2′); MS (ESI) *m*/*z* (rel. int.): = 439 ($[M + H]^+$, 67). HRMS (ESI$^+$) *m*/*z* calcd. for $C_{29}H_{30}N_2O_2^+$ $[M + H]^+$ 439.2382, found 439.2376. Anal. Calcd. for $C_{29}H_{30}N_2O_2$ (438.57): C, 79.42; H, 6.89; N, 6.39. Found: C, 79.14; H, 6.88; N, 6.41

2.3.2. Synthesis of 1,1′-(((3a*S*,7a*S*)-Hexahydro-1H-benzo[d]imidazole-1,3(2*H*)-diyl)-bis(methylene))bis(naphthalen-2-ol) ((*S*,*S*)-**9**)

(1*S*,2*S*)-(−)-cyclohexane-1,2-diamine (as tartrate) (0.5 g, 1.9 mmol, **6**) was mixed with 3 mL water and K_2CO_3 (0.525, 3.8 mmol). A mixture of paraformaldehyde (0.114 g, 3.8 mmol) and naphthalene-2-ol (0.6 g, 4.2 mmol, **7**) in ethanol (10 mL) was added. The reaction mixture was stirred at 50 °C for 24 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and washed with water (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was column chromatographed (petroleum ether/CH_2Cl_2 = 1:5) to provide 0.260 g (31%) of ((*S*,*S*)-**9**) mp 186–188 °C; $[\alpha]_D^{20}$ = −86 (c 1.00, $CHCl_3$); The NMR data are identical to those of enantiomer (*R*,*R*)-**9**. HRMS (ESI$^+$) *m*/*z* calcd. for $C_{29}H_{30}N_2O_2^+$ $[M + H]^+$ 439.2382, found 439.2379.

2.4. General Procedure for Enantioselective Addition of Diethylzinc to Aldehydes

To a solution of the corresponding ligand ((*R*,*R*)-**9** or (*S*,*S*)-**9**) (3 mol %) in toluene (4 mL), Et_2Zn (1.7 mmol, 1M solution in hexane) was added dropwise at 0 °C in an Ar atmosphere. The mixture was stirred for 30 min at 0 °C and then the corresponding aldehyde (1.0 mmol) was added at −20 °C. The reaction mixture was stirred at 20 °C and monitored by TLC (petroleum ether/MTBE = 5:1) until the aldehyde was consumed. The mixture was quenched (aq. NH_4Cl), extracted with Et_2O and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (petroleum ether/MTBE = 5:1).

2.5. Powder X-ray Diffraction (PXRD)

Powder XRD patterns were determined for the powdered compounds **3**, (*R*,*R*)-**9** and (*S*,*S*)-**9** to establish crystalline properties, purity and eventual presence of polymorphs. Powder samples of the synthesized compounds were analyzed on an Empyrean Powder X-ray diffractometer (Malvern Panalytical, Almelo, The Netherlands) in the 2–50° 2θ range using Cu radiation (λ = 1.5406 Å) and a PIXcel3D detector. The diffraction patterns of the crystals were compared with those of starting compounds and the computed from SCXRD pattern to confirm the presence or absence of additional phases.

2.6. Single-Crystal X-ray Diffraction (SCXRD)

Single crystals of compounds **3** and (*R*,*R*)-**9** with suitable size (~0.3 × 0.3 × 0.3 mm^3) and diffracting quality were mounted on nylon loops. Diffraction data for **3** were collected on a SupernovaDual diffractometer equipped with an Atlas CCD detector while diffraction data for (*R*,*R*)-**9** were collected on a Bruker D8 Venture diffractometer equipped with a PHOTON II CPAD detector. Both diffractometers operate with a micro-focus sealed X-ray source, generating Mo$K\alpha$ radiation with λ = 0.71073 Å. The collected data were processed with CrysAlisPro [10] (for **3**) or APEX4 [11] (for (*R*,*R*)-**9**) programs. The structures were solved with intrinsic phasing methods and refined by the full-matrix least-squares method of F^2 using ShelxT [12]and ShelxL [13] as implemented in the OLEX2-ver.1.5 graphical interface [14]. All non-hydrogen atoms were located successfully from Fourier map and were refined anisotropically. Hydrogen atoms were placed on calculated positions riding on the parent carbon atoms (U_{eq} = 1.2 for C-$H_{aromatic}$ = 0.93 Å and C-$H_{methylenic}$ = 0.97 Å) while those riding on a heteroatoms were refined from electron density maps. Ortep-3v2 software [15] was used to prepare the figures visualizing the compounds in the asymmetric unit. Complete crystallographic data for the structure of compounds **3** and (*R*,*R*)-**9** reported in this paper have been deposited in the CIF format with the Cambridge Crystallographic Data Center as 2294902 and 2294903, respectively. These data, last accessed on 14 September 2023, can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

2.7. Thermal Analysis (DSC)

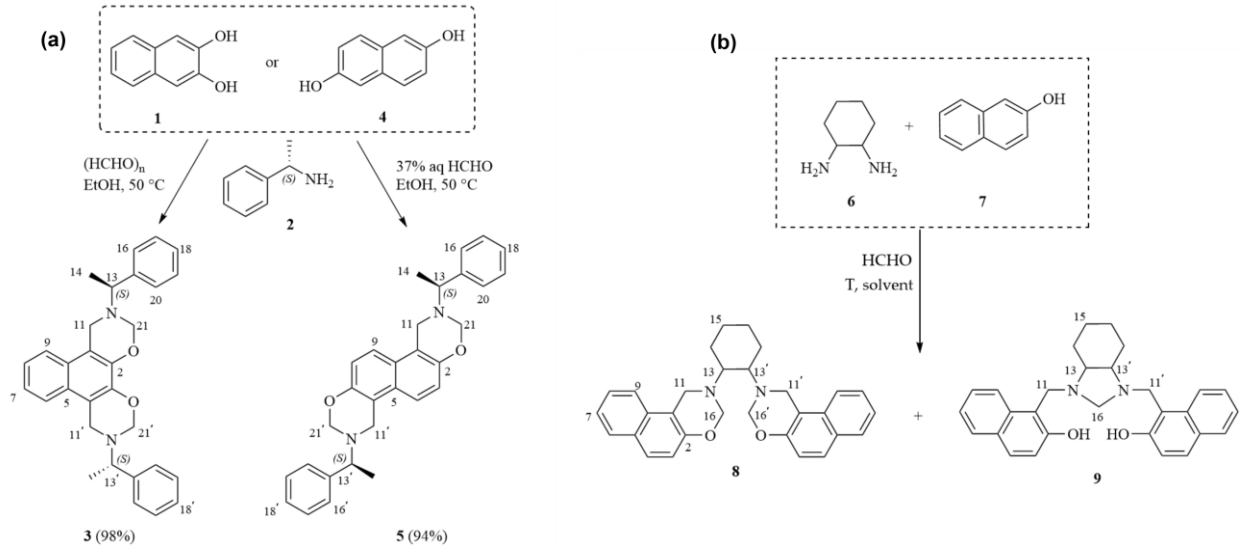
Differential scanning calorimetry was conducted to estimate thermotropic properties and thermal behaviors of the new compounds. DSC analyses were performed on a Discovery DSC250 (TA instruments, New Castle, DE, USA). Samples weighing between 1 and 5 mg were heated in aluminum pans from 30 to 250 °C (10 °C·min^{-1}) in nitrogen (flow rate 25 mL·min^{-1}). Endothermic/exothermic effects of solvent evaporation, melting point and decomposition of the synthesized compounds were determined from the DSC experiments.

3. Results and Discussion

3.1. Synthesis

The condensation reactions of naphthalene-2,3-diol (**1**) or naphthalene-2,6-diol (**4**), (*S*)-(−)-1-phenylethane-1-amine (**2**) and formaldehyde (applied as formalin, 37% aq. solution or paraformaldehyde) were performed in ethanol at 50 °C as shown in Scheme 1a. The products **3** and **5** were isolated in high yields (98% and 94%, respectively) after short reaction times (1–3 h) and purification by column chromatography. As the next step,

preparation the corresponding *N*-methyl derivatives through reduction with $LiAlH_4$ was attempted [6]. Surprisingly, all reduction experiments applying different conditions and reducing agents ($LiAlH_4$ or $NaBH_4$) were unsuccessful and even traces of the desired *N*-methylated compounds could not be detected.



Scheme 1. Condensation of (**a**) naphthalene-diols **1** or **4** and (*S*)-(−)-1-phenylethane-1-amine (**2**) and (**b**) cyclohexane-1,2-diamine (**6**) and naphthalene-2-ol (**7**) with formaldehyde.

The condensation of cyclohexane-1,2-diamine (**6**), naphthalene-2-ol (**7**) and formaldehyde (Scheme 1b) was of particular interest, since the formation of a salen-type structure was expected. Salen ligands are described as efficient catalysts in certain enantioselective processes [8]. The initial condensation experiments were performed with racemic cyclohexane-1,2-diamine (**6**) in ethanol as a solvent at room temperature (Scheme 1b). An aqueous solution of formaldehyde (37%) was used in large excess and the reaction outcome was monitored by TLC. The formation of the expected bis-dihydro[1,3]naphthoxazine **8** was recognized in the crude reaction mixture by NMR spectroscopy (Figure 1, Table 1). The amine **6** was consumed over the course of a 3 h reaction time (Table 2, entry 1). Besides this, an additional compound with similar structure was identified and determined as imidazolidine **9** (Scheme 1b). The experiments for separation and isolation (column chromatography, crystallization) of products **8** and **9** in pure form were unsuccessful. However, it was possible to distinguish the two compounds in a mixture and to determine undoubtedly the structures by using NMR and HRMS experiments. In Figure 1, representative ^1H NMR spectra of **8** and **9** are shown and in Table 1 the characteristic chemical shifts of the individual compounds are introduced.

Table 1. Characteristic chemical shifts (in ppm) of selected protons allowing one to distinguish between compounds **8** and **9** in mixtures.

Some Characteristic Protons	8	9
	^1H NMR (Number of Protons)	^1H NMR (Number of Protons)
C(H)-11	4.36 (4H)	4.21 (2H) 4.39 (2H)
C(H)-13	3.01–3.16 (2H)	2.45–2.60 (2H)
C(H)-16	4.98 (4H)	3.66 (2H)

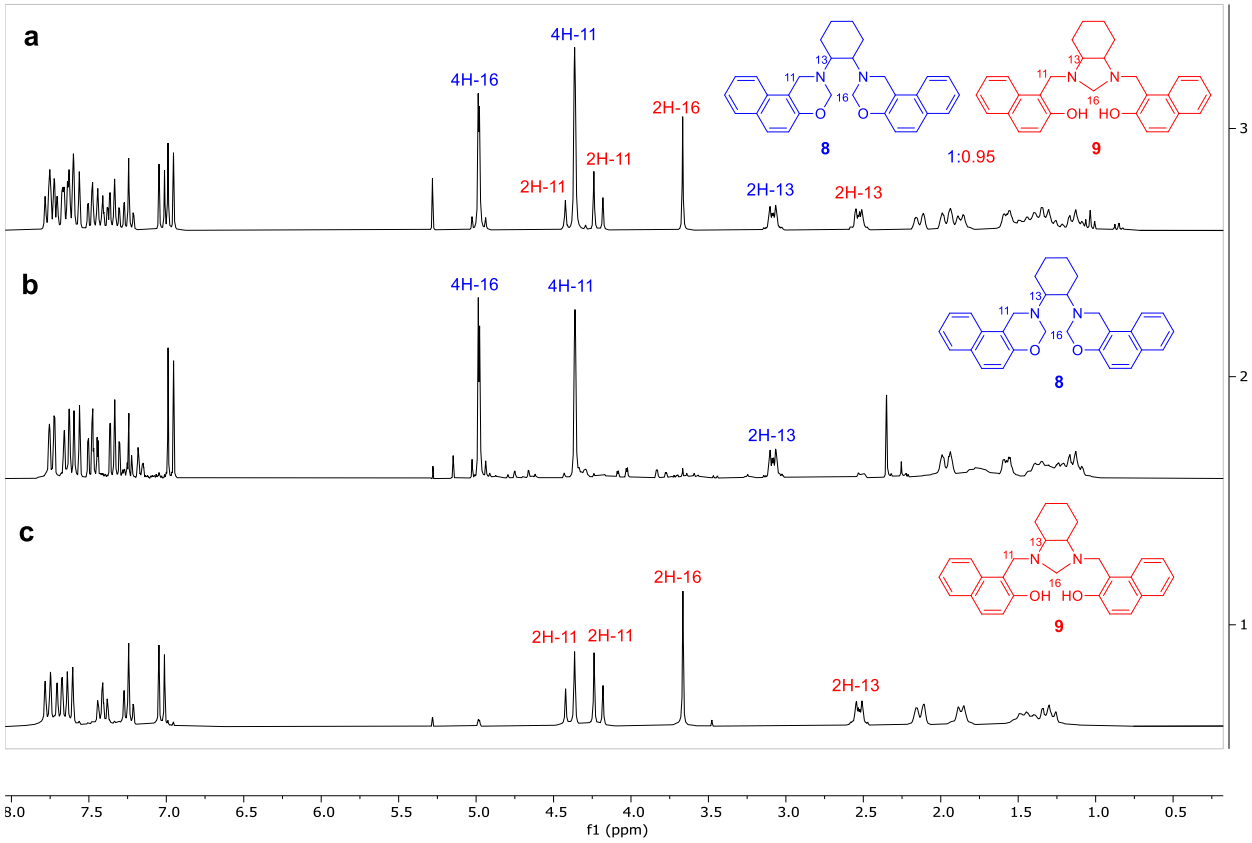


Figure 1. Comparison of ^{1}H NMR spectra ($CDCl_3$ at 298 K) of (**a**) a mixture of **8** (blue) and **9** (red) (20:19 ratio); (**b**) crude product **8** (contains 16% of **9**) and (**c**) pure compound **9**.

Table 2. Optimization the condensation of cyclohexane-1,2-diamine (**6**) in racemic form, naphthalen-2-ol (**7**) and formaldehyde with the purpose to alter the ratio of **8**:**9**.

№	HCHO (Equivalent)	Solvent	Time (h)	T (°C)	Molar Ratio 8:9 [3]	Yield [5] of 9 (%)
1	10 [1]	EtOH	3	20	5:2	-
2	10 [1]	EtOH	5	20	2:1	-
3	10 [1]	EtOH	1	50	5:2	-
4	10 [1]	EtOH	6	50	2:1	-
5	10 [1]	EtOH	18	50	20:19 [4]	-
6	10 [2]	EtOH	24	50	7:10	34 [6]
7	10 [1]	EtOH	2.5	reflux	2:5	-
8	10 [2]	toluene	24	50	5:1	-
9	2 [1]	MeOH	2	reflux	0:1	50 [7]
10	2 [2]	MeOH	2	reflux	0:1	46 [7]
11	2 [2]	EtOH	2	reflux	0:1	34 [7]
12	2 [2]	EtOH	24	50	0:1	63 [6]

[1] A 37% aq. solution of formaldehyde; [2] paraformaldehyde; [3] molar ratio determined by ^{1}H NMR spectroscopy of crude mixture; [4] ratio determined after washing the crude reaction mixture with acetonitrile; [5] yields of isolated compound; [6] after column chromatography; [7] after filtration of the crystallized **9** from the reaction mixture.

In order to optimize the formation of compound **8** preferentially, a series of experiments have been performed (Table 2). In general, prolonged reaction time and heating up to 50 °C promotes the formation of compound **9** (compare entries 1 to 6). If the mixture is refluxed for 2.5 h, compound **9** is formed preferentially (entry 7). The result introduced in entry 5 needs some comment. In fact, the ratio **8**:**9** after 18 h at 50 °C was 10:7. After washing the crude mixture with acetonitrile, the ratio was shifted in favor of **9** (**8**:**9** =

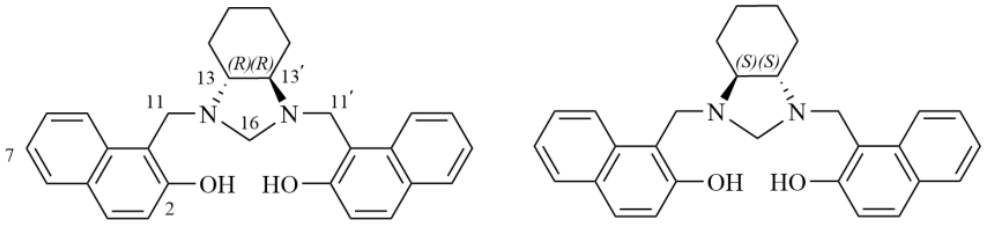
20:19). However, pure **8** could not be isolated from the filtrate (due to stability problems, vide infra).

When toluene was used as solvent and the mixture heated at 50 °C for 24 h, the ratio of the two products **8** and **9** formed was 5:1 (entry 8, Table 1). Even at this ratio, the isolation of bis-dihydro[1,3]naphthoxazine **8** in pure form was impossible. All attempts to purify **8** by crystallization using various solvents and mixtures of solvents did not lead to a positive result. Furthermore, **8** is unstable under column chromatography conditions even when the silica gel is deactivated with Et_3N. On standing, bis-dihydro[1,3]naphthoxazine **8** is transformed slowly into **9**, detected by its increased fraction in the ratio. Pure **9** is stable at room temperature; however, if mixed with formaldehyde, the formation of **8** was observed in a short time, forming nearly a 1:1 ratio of **8**:**9**. It is important to emphasize that reduction experiments for treatment of mixtures of **8** and **9** with $LiAlH_4$ or $NaBH_4$ led to destruction of **8**, whereas **9** remained almost unchanged.

It is interesting to note that the synthesis of compound **8** was recently described (racemic diamine **6** was used) [9]. The structural proof was reported based on elemental analysis and IR spectroscopy and no NMR data were presented. However, the compound described as **8** was further used as a ligand to prepare salen-type complexes with the transition metal Mn, which were characterized by single-crystal X-ray crystallography. Consequently, based on the published results of [9] and our results, it is possible to assume that salen-type metal complexes could be formed from mixtures of **8** and **9** under suitable conditions.

In further experiments, the formation of **9** could be optimized (entries 9–12). In refluxing mixtures of diamine **6**, naphthalene-2-ol and formaldehyde (37 aq. solution or paraformaldehyde, 2 equivalent), the reaction outcome was exclusively shifted to the formation of compound **9**. Conveniently, the imidazolidine **9** crystalize in the reaction mixture and could be isolated by filtration. The highest yield of pure **9** (63% after column chromatography) was realized by heating the reaction mixture at 50 °C for 24 h (entry 12).

The optimized conditions (entry 12) were applied for the synthesis of the corresponding chiral derivatives (Figure 2) applying (*R*,*R*)-**6** (in free base form) and (*S*,*S*)-**6** (as tartrate salt). The yields of pure compounds we could realize were 47% for (*R*,*R*)-**9** (isolated by crystallization) and 31% for (*S*,*S*)-**9** (isolated by column chromatography).

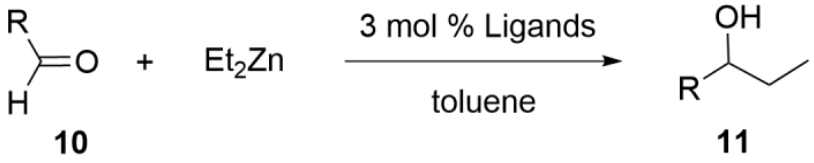


(*R*,*R*)- **9** (47%) (*S*,*S*)- **9** (31%)

Figure 2. Structures and configuration of (*R*,*R*)-**9** and (*S*,*S*)-**9**.

3.2. Enantioselective Addition of Et_2Zn to Aldehydes Catalyzed by Ligands (R,R)-9 and (S,S)-9

The imidazolidine derivatives (*R*,*R*)-**9** and (*S*,*S*)-**9** possess suitable structure and properties to be used as ligands in the model reaction for the enantioselective addition of diethylzinc to aldehydes by using a standard procedure (Scheme 2). The imidazolidine derivatives of **9** were applied in 3 mol % quantity by using of standard conditions described in the literature (see Section 2) [7,16–18]. A series of aromatic aldehydes were tested in the addition reaction, leading to the chiral secondary alcohols of type **11**. The yields obtained (Table 3) ranged from moderate to very good; however, in several cases (entries 4–6 and 10), this was after prolonged reaction times. The enantioselectivities achieved were moderate. The prolonged reaction times indicates the relatively low efficiency of the chiral catalyst formed in situ in respect to the enantioselectivity, although the chemical yields were acceptable and, in some cases, even very high.



10 **11**

Scheme 2. The enantioselective addition of Et_2Zn to aldehydes.

Table 3. Catalytic activity and efficiency of (*R*,*R*)-**9** and (*S*,*S*)-**9** as ligands in the enantioselective addition of Et_2Zn to aldehydes.

Entry	Aldehyde	Ligands	Time (h)	Yield 11 (%) [1]	*ee* (%) Configuration
1	2-Methoxybezaldehyde	(*R*,*R*)-9	72	66	53 (*R*) [2]
2	2-Methoxybezaldehyde	(*S*,*S*)-9	24	80	58 (*S*) [2]
3	1-Naphthaldehyde	(*R*,*R*)-9	52	45	39 (*R*) [3]
4	1-Naphthaldehyde	(*S*,*S*)-9	120	54	30 (*S*) [3]
5	4-Chlorobenzaldehyde	(*R*,*R*)-9	144	90	49 (*R*) [3]
6	4-Chlorobenzaldehyde	(*S*,*S*)-9	120	30	50 (*S*) [3]
7	Cyclohexanecaboxaldehyde	(*R*,*R*)-9	24	46	38 (*S*) [2]
8	Cyclohexanecaboxaldehyde	(*S*,*S*)-9	24	49	40 (*R*) [2]
9	Ferrocenecarboxaldehyde	(*R*,*R*)-9	48	79	38 (*R*) [3]
10	Ferrocenecarboxaldehyde	(*S*,*S*)-9	120	74	42 (*S*) [3]

[1] The yield of isolated products in pure form after column chromatography; [2] enantiomeric excess was determined by GC analyses; [3] enantiomeric excess was determined by HPLC analyses.

The best asymmetric induction was achieved by the addition reaction of diethylzinc to 2-methoxybenzaldehyde catalyzed by ligands (*R*,*R*)-**9** and (*S*,*S*)-**9** (53% and 58% *ee*, respectively, Table 3).

3.3. Crystal Structure Description

Single crystals of compounds **3** and (*R*,*R*)-**9** were obtained by slow evaporation from a hot methanol solution. Compounds **3** and (*R*,*R*)-**9** crystallize in non-centrosymmetric monoclinic $P2_1$ and orthorhombic $P2_12_12_1$ space groups with one molecule in the asymmetric unit (ASU) and two and four molecules in the unit cell, respectively (Table S1). The ORTEP view of the molecules in the ASU of compounds **3** and (*R*,*R*)-**9** with appropriate labeling scheme is shown in Figure 3. Selected bond lengths and angles from the single-crystal X-ray diffraction experiment are provided in Table 4 and they are comparable with other similar structures in the Cambridge structural database (ref. codes PAFCEH [19], OWEHEE [20], VESHAD [21], SOVYOR [22], HAJWUO [23], CAXJEU [24] and AFIHII [25]).

The molecule of compound **3** (Figure 3a) can be divided into two main fragments—a central 2,3,4,9,10,11-hexahydronaphtho[1,2-*e*:4,3-*e*′]bis([1,3]oxazine) core covalently bonded with two ethyl benzene side chains. Furthermore, the 2,3,4,9,10,11-hexahydronaphtho[1,2-*e*:4,3-*e*′]bis([1,3]oxazine) core can be divided into a fused naphthalene and two 1,3-oxazinane rings sharing the common C1–C2 and C3–C4 carbon atoms. The naphthalene ring is planar with an rmsd of 0.012 Å while the two 1,3-oxazinane rings are non-planar (rmsd ~0.200 Å) and have a "half-chair" conformation. The two N atoms from the 1,3-oxazinane rings (namely N12 and N22) are covalently bonded to the α-carbon atoms—labeled C13 or C24—of the ethylbenzene moieties. The angle between the normal of the mean planes of the benzene rings C15–C16–C17–C18–C19–C20 and C26–C27–C28–C29–C30–C31 from the ethylbenzene fragments and the naphthalene fragment are 135.77(13)° and 140.33(14)°, respectively. The twist/fold angles between the C15–C16–C17–C18–C19–C20/naphthalene and C26–C27–C28–C29–C30–C31/naphthalene fragments are 126.02(16)°/112.35(19)° and 133.67(17)°/117.20(20)°, respectively.

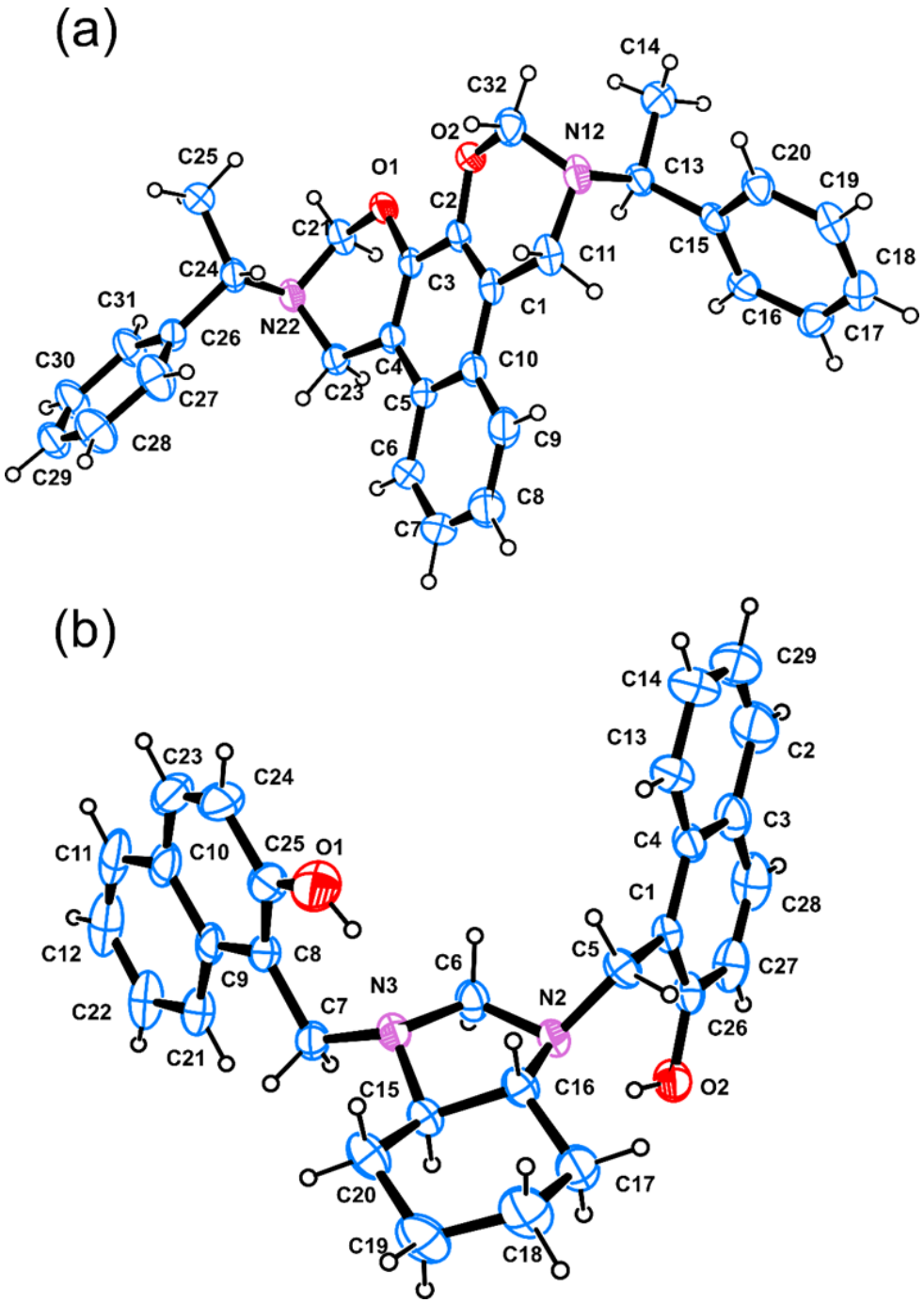


Figure 3. ORTEP [15] view of the molecules present in the ASU of (**a**) **3**, (**b**) (*R*,*R*)-**9**, with appropriate labeling scheme. The thermal ellipsoids are given with 50% probability level.

Table 4. Selected bond lengths and angles for compounds **3** and (*R*,*R*)-**9**.

Compound 3						**Compound (*R*,*R*)-9**					
Bond Lengths, Å						Bond Lengths, Å					
Atom	Atom	Å	Atom	Atom	Å	Atom	Atom	Å	Atom	Atom	Å
O1	C3	1.373(5)	N22	C23	1.466(5)	O1	C25	1.360(4)	C1	C5	1.510(3)
O2	C2	1.363(5)	N12	C13	1.491(6)	O2	C26	1.357(3)	C7	C8	1.511(3)
C3	C2	1.420(6)	N22	C24	1.490(6)	N2	C5	1.468(3)	C9	C10	1.422(4)
O1	C21	1.456(6)	C3	C4	1.362(6)	N3	C7	1.475(3)	C3	C4	1.419(4)
O2	C32	1.456(6)	C2	C1	1.367(6)	N2	C6	1.476(3)	C15	C16	1.508(3)
N12	C32	1.429(6)	C7	C8	1.381(9)	N3	C6	1.468(3)	C19	C20	1.523(5)
N12	C11	1.467(6)	C24	C25	1.528(7)	N3	C15	1.467(3)	C17	C18	1.527(4)
N22	C21	1.431(5)	C13	C14	1.521(6)	N2	C16	1.471(3)	C18	C19	1.524(5)
Bond Angles, °						Bond Angles, °					
	Atom	Atom	Atom	°			Atom	Atom	Atom	°	
	C2	O2	C32	113.6(4)			C6	N3	C7	113.0(2)	
	C3	O1	C21	114.0(3)			C6	N2	C5	113.1(2)	
	N12	C32	O2	113.7(4)			N3	C6	N2	106.1(2)	
	N12	C11	C1	111.9(4)			N3	C15	C20	117.3(2)	
	C32	N12	C11	108.3(3)			N2	C16	C17	118.0(2)	
	N12	C13	C15	109.0(4)			C25	C8	C7	121.6(3)	
	N22	C23	C4	111.2(3)			C26	C1	C5	118.7(2)	
	C21	N22	C23	107.9(3)			C16	C17	C18	107.6(3)	
	N22	C24	C26	110.3(4)			C15	C20	C19	108.8(3)	

The molecule of compound (*R*,*R*)-**9** (Figure 3b) consists of a central octahydro-1*H*-benzo[*d*]imidazole fragment that is connected with two 1-methylnaphthalen-2-ol side chains via N–C covalent bonds (N3–C7 and N2–C5). Furthermore, the octahydro-1*H*-benzo[*d*]imidazole moiety (rmsd = 0.207 Å) is built up by fused six-membered cyclohexane and five-membered imidazolidine aliphatic rings sharing the C15 and C16 carbon atoms. The cyclohexane and the imidazolidine rings are non-planar (rmsd = 0.239 Å and 0.200 Å) and have "chair" and "half-chair" conformation, respectively. The 1-methylnaphthalen-2-ol side chains are planar with an rmsd of 0.040 Å (for the N3-bonded one) and 0.015 Å (for N2-bonded one). The angles between the normal of the mean planes of the N3-bonded and N2-bonded 1-methylnaphthalen-2-ol fragments and the central octahydro-1*H*-benzo[*d*]imidazole fragment are 81.99° and 100.24° and the twist/fold angles are 82.19°/168.6° and 98.85°/29.75°, respectively.

The molecule of **3** lacks proton-donating groups (like C–OH, NH, NH_2); therefore, typical hydrogen bonding interactions are not expected. The packing of the molecules in the crystal structure is governed by weak C–H. . .O and C–H. . .π interactions. On the other hand, the molecule of (*R*,*R*)-**9** has two proton-donating hydroxyl groups (–OH) and two N atoms from the imidazole moiety acting as proton acceptors. Thus, formation of intramolecular hydrogen bonding interactions of the O–H. . .N type is expected and detected (Figure 4, Table 5). The crystal structure of (*R*,*R*)-**9** is further stabilized by weak C-H. . .O interactions (π...π interactions are not detected).

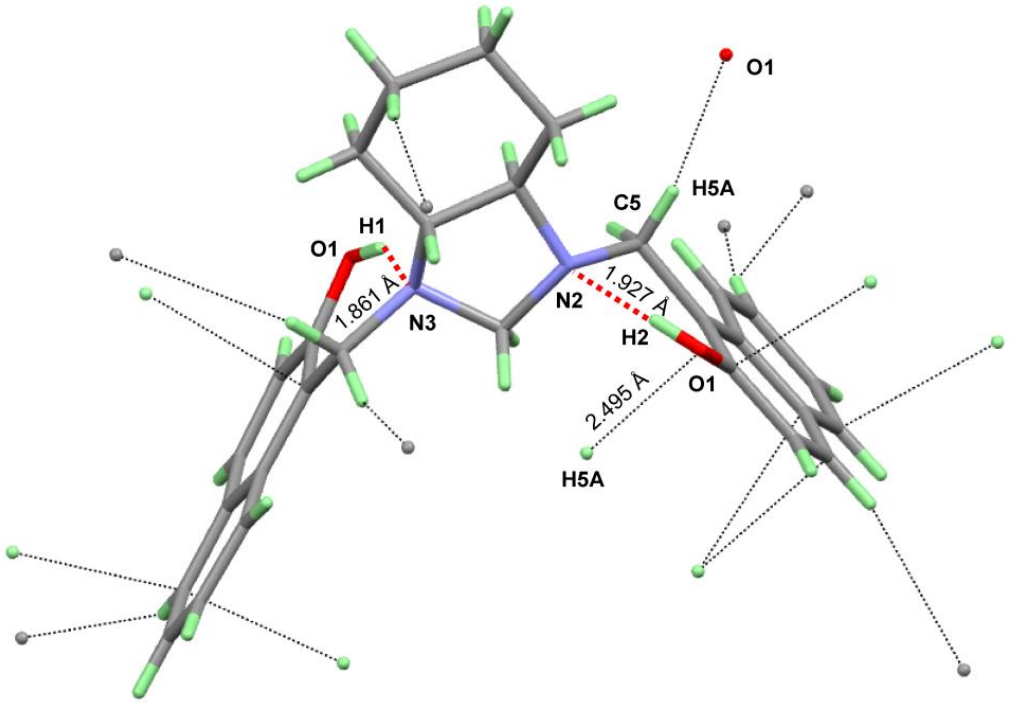


Figure 4. Visualization of the detected hydrogen-bonding interactions of the O–H. . .N type (red dots), weak C–H. . .O interactions (the strongest one is labeled, e.g., C5–H5A. . .O1, 2.495 Å) and short contacts stabilizing the crystal structure of compound (*R*,*R*)-**9**.

Table 5. Observed hydrogen bonds and weak interactions in (*R*,*R*)-**9.**

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O1	H1	N3	0.82	1.86	2.596(3)	148.4
O2	H2	N2	0.82	1.93	2.650(3)	146.4
C5	H5A	O2 [1]	0.97	2.49	3.223(3)	131.7

Symmetry operation: [1] $-1/2 + x, 1/2 - y, 1 - z$.

The thermal stability of compounds **3**, **5**, (*R*,*R*)-**9** and (*S*,*S*)-**9** was evaluated using differential scanning calorimetry in the temperature region of 30–250 °C. The DSC thermograms of compound **3,** (*R*,*R*)-**9** and (*S*,*S*)-**9** (Figure 5a,c,d) disclose a similar thermal comportment, e.g., a sharp *endothermic* effect followed by sharp *exothermic* effect. For all **3,** (*R*,*R*)-**9** and (*S*,*S*)-**9** compounds, the *endothermic* effect is related to the melting of the compounds while the immediately following *exothermic* effect is associated with the decomposition of the compounds. According to the DSC data, the melting behavior for (*R*,*R*)-**9** and (*S*,*S*)-**9** is similar, with maximums at 191 and 188 °C, respectively (Figure 5c,d). The thermal comportment of **5** features also an *endothermic* and an *exothermic* effect (Figure 5b). For compound **5,** the melting is observed at ~185 °C while the decomposition is delayed with ~40 °C after the melting has finished.

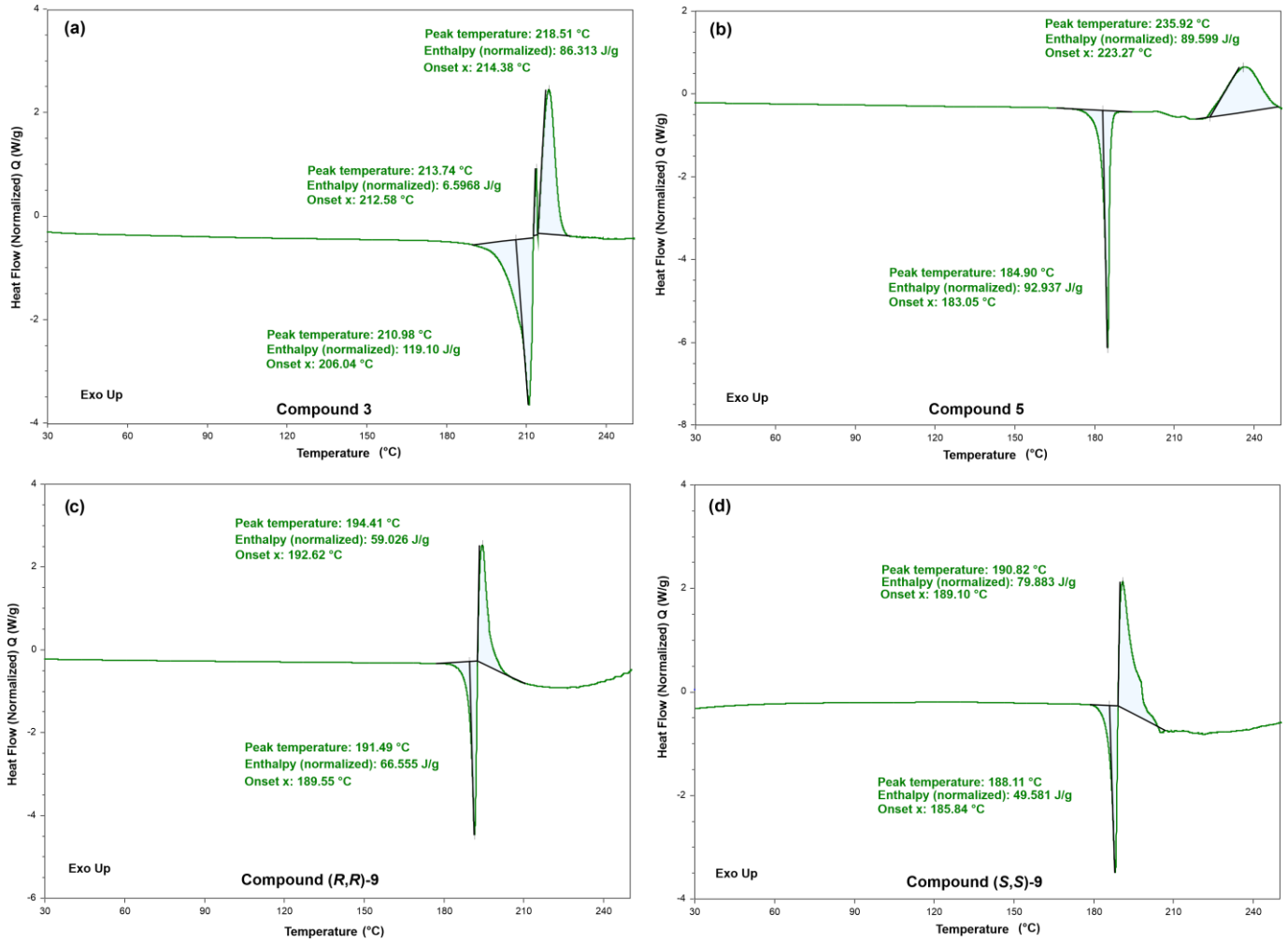


Figure 5. DSC thermograms of (**a**) **3**, (**b**) **5**, (**c**) (*R*,*R*)-**9**, (**d**) (*S*,*S*)-**9**.

Overall, the DSC characterization of compounds **3**, **5**, (*R*,*R*)-**9** and (*S*,*S*)-**9** reveals their high purity and stability up to and above 180 °C (no decomposition or phase transitions are observed). The purity and the lack of polymorphs or isomerization in compounds **3** and (*R*,*R*)-**9** are also confirmed by comparing the powder diffraction patterns of the bulk samples (in blue, Figure 6) and those generated from the single-crystal structural analysis (in red, Figure 6).

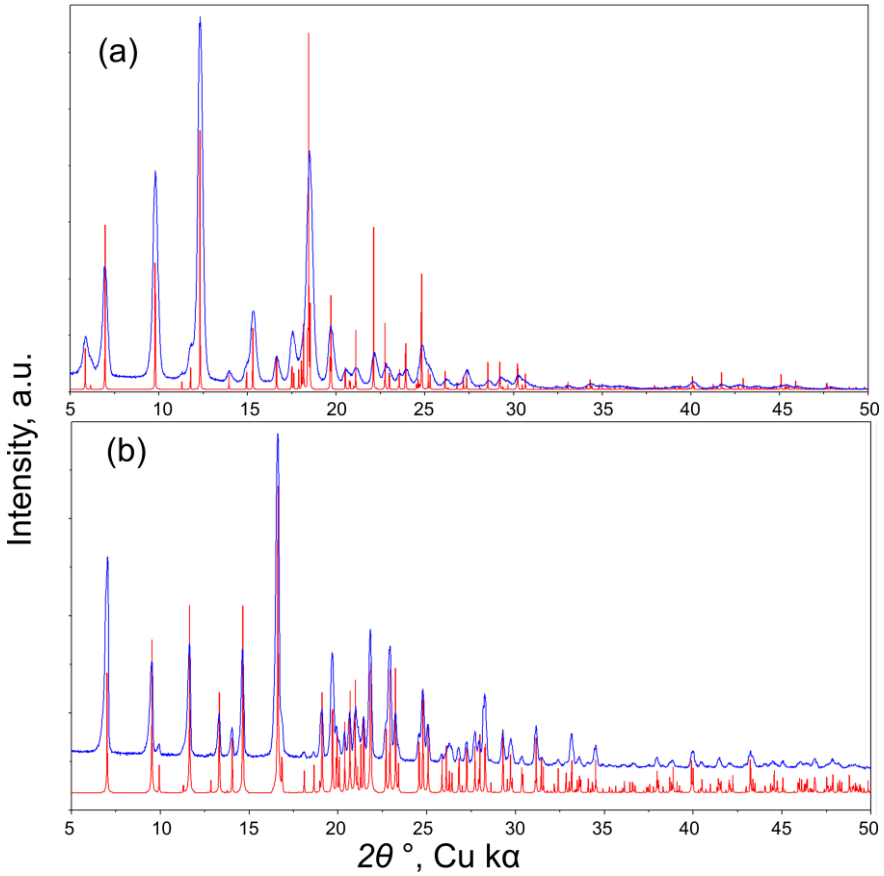


Figure 6. Comparison between the collected powder X-ray diffraction data (in blue color) and that calculated from single crystal (in red color) for (**a**) compound **3** and (**b**) compound (*R*,*R*)-**9**.

4. Conclusions

The three-component Mannich-type condensation of naphthalene-2-ol and isomeric naphthalenediols, formaldehyde and chiral amines is an excellent tool for the synthesis in excellent yields of enantiomerically pure substituted bis-dihydro[1,3]naphthoxazines (compounds **3** and **5**). The properly optimized condensation reaction of naphthalene-2-ol, formaldehyde and chiral cyclohexane-1,2-diamine (both enantiomers, *R*,*R*- and *S*,*S*-configuration) leads to the unusual structure of 1,1′-(((3a,7a)-hexahydro-1*H*-benzo[*d*]imidazole-1,3(2*H*)-diyl)-bis(methylene))bis(naphthalen-2-ol), compound **9**, of which the two enantiomers were isolated. The latter were evaluated as pre-catalysts for enantioselective addition of diethylzinc to aldehydes showing moderate asymmetric induction.

In compound **3**, the naphthalene ring is planar, while the 1,3-oxazinane rings have a "half-chair" conformation. In (*R*,*R*)-**9**, the cyclohexane and imidazolidine rings have a non-planar "chair" and "half-chair" conformation, respectively. Compound **3** lacks proton-donating groups and, therefore, typical hydrogen bonding interactions are not expected in its crystal structure. In contrast, (*R*,*R*)-**9** has two proton-donating hydroxyl groups (–OH) and two N atoms from the imidazole moiety acting as proton acceptors; thus intramolecular hydrogen bonding interactions of the O–H. . .N type stabilize the molecular and crystal structure.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cryst13101495/s1, Figures S1–S6. The NMR spectra of compound **3**; Figure S7. The HRMS spectrum of compound **3**; Figures S8–S13. The NMR spectra of compound **5**; Figure S14. The HRMS spectrum of compound **5**; Figure S15. The ^{1}H NMR spectrum of compound **8**; Figure S16. The ^{1}H NMR spectrum of a mixture of compounds **8** and **9** (1:0.95 ratio); Figure S17. The HRMS spectrum of a mixture of compounds **8** and **9**; Figures S18–S23. The NMR spectra of

compound (*R*,*R*)-**9**; Figure S24. The HRMS spectrum of compound (*R*,*R*)-**9**; Table S1. Most important data collection and refinement parameters for compounds **3** and (*R*,*R*)-**9**.

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