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A new approach to enantiomerically pure bis-imidazoles derived from *trans*-1,2-diaminocyclohexane

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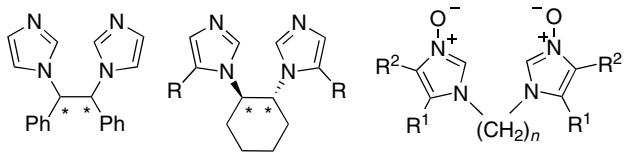
ABSTRACT

Racemic as well as enantiomerically pure *trans*-1,1′-(cyclohexane-1,2-diyl)bis(imidazole N-oxides) were prepared from *trans*-cyclohexane-1,2-bis(methylidenamine) and 1,2-dione monooximes (α-hydroxyiminoketones). The enantiomeric purity of selected products was determined by means of ^{1}H NMR spectroscopy in the presence of (+)-(*R*)-(*tert*-butyl)(phenyl)phosphonothioic acid as a chiral solvating agent. Deoxygenation by treatment with *Raney*-nickel led to the corresponding chiral bis-imidazoles.

1. Introduction

It has been well documented that 2-unsubstituted imidazole N-oxides can be prepared from readily available α-hydroxyimino ketones and *N*-alkyl methanimines (formaldehyde imines).[3–5] Their structure shows a certain similarity with nitrones and, therefore, diverse transformations leading to imidazol-2-ones,[6] imidazole-2-thiones,[7,8] imidazole-2-carbonitriles,[6] and other imidazole derivatives[9] are accessible. Deoxygenation of imidazole N-oxides with *Raney*-Ni yields the corresponding imidazoles,[5] which can be prepared alternatively by using a 1,2-dicarbonyl compound, a primary amine, ammonia and formaldehyde.[10]

In recent years, there has been a growing interest in the synthesis and applications of bis-imidazole derivatives. Especially attractive are their metal complexes as catalysts in organic synthesis.[11,12] Most of the reported compounds are achiral, and the limited availability of optically active bis-imidazoles results from the fact that no general methods are known for their preparation. To the best of our knowledge, there are only two published papers aimed at the preparation of optically active bis-imidazoles. In one case, the co-condensation of (*R*,*R*)- and (*S*,*S*)-1,2-diphenylethane-1,2-diamine with glyoxal, formaldehyde and ammonia gave (*R*,*R*)- and (*S*,*S*)-bis-imidazoles **1**, albeit the yields were rather poor in both cases (ca. 20%). The authors claimed that the products were enantiomerically pure, but no physical data were reported.[13] The second type of optically active bis-imidazoles **2**, which contains the *trans*-1,2-diaminocyclohexane scaffold, was prepared by treatment of the corresponding diimine with tosylmethylisocyanide (TosMIC).[11]



1 **2** **3**

Recently, we described an alternative method for the synthesis of bis(imidazole N-oxides) **3** via condensation of *in situ* prepared alkane-α,ω-bis(methylidenamines) with α-hydroxyimino ketones.[14] In analogy to the previously described 2-unsubstituted imidazole N-oxides, compounds **3** were transformed into imidazole derivatives.[4–7]

Herein, we report the synthesis of bis(imidazole N-oxides) derived from racemic and enantiomerically pure *trans*-1,2-diaminocyclohexane, as well as some transformations of them.

2. Results and discussion

The first experiments were carried out with racemic *trans*-1,2-diaminocyclohexane (*rac*-**4**), which reacted with formaldehyde in methanolic solution at room temperature to yield the dimer *rac*-**6** of the initially formed di-imine *rac*-**5**[15] (Scheme 1). The crystalline product *rac*-**6** reacts with an excess of α-hydroxyimino ketone **7** (dione monooxime) in refluxing ethanol to give the corresponding racemic bis-imidazole N-oxide *rac*-**8** in ca. 30–40% yield.

Optimization of the procedure led to better yields by reacting *rac*-**6** and **7** in glacial acetic acid at room temperature. Using this

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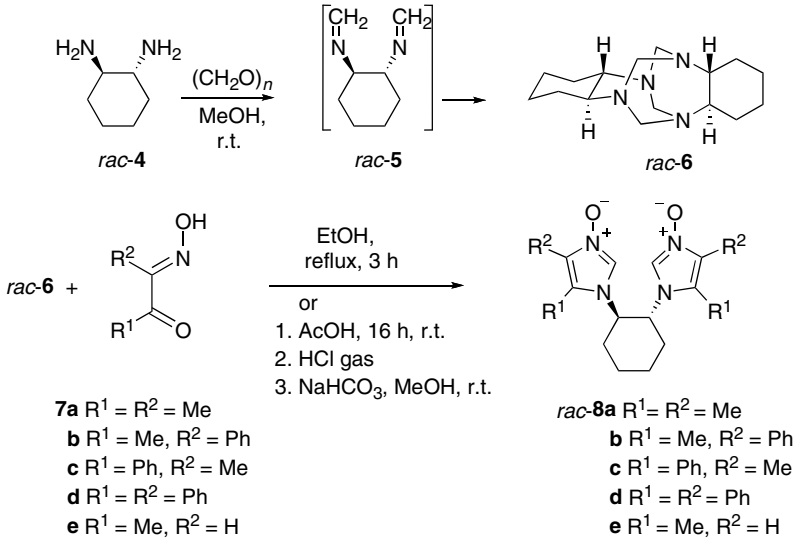


Scheme 1.

method, bis-imidazoles, *rac*-**8**, were obtained in 58–88% yield. The spectroscopic data of the products **8** fit well with previously described imidazole N-oxides.[5,14] The most characteristic feature of the ^{1}H NMR spectra is the signal of H–C(2) at 8.7–8.0 ppm. In the case of *rac*-**8a**, the structure was established by X-ray crystallography (Fig. 1).

The compound in the crystal is racemic. The asymmetric unit contains one zwitterionic molecule **8a** and two water molecules. Each symmetry-independent water molecule acts as a donor for two hydrogen bonds. One water molecule interacts with the oxide O-atom from two different molecules of **8a**, while the second water molecule interacts with an oxide O-atom from a third molecule of **8a** and with the first water molecule. One of the oxide O-atoms accepts one hydrogen bond from each of two different water molecules, while the other oxide O-atom accepts just one hydrogen bond. Only one of the water molecules acts as a hydrogen-bond acceptor. One path generated by these interactions links the two water molecules and a single oxide O-atom into extended chains, which run parallel to the [001] direction and have a graph set motif[17] of $C_2^3(6)$. The interaction between a water molecule and the second oxide O-atom cross-links these chains and thereby forms new chains, which run parallel to the [010] direction and have a graph set motif of $C_3^3(15)$. The interactions combine to link the water and zwitterionic molecules into two-dimensional networks, which lie parallel to the (100) plane.

The two bis(imidazole N-oxides) *rac*-**8b** and *rac*-**8d** were deoxygenated by treatment with *Raney*-Ni in ethanol; after 30 min, the reaction was complete (TLC). Products **9b** and **9d** were obtained in 78% and 85% yields, respectively (Scheme 2). As expected, the signal of H–C(2) is shifted to higher field compared with **8b** and **8d**.

In order to test if the synthesis of bis-imidazole of type **9** can be performed by the co-condensation of *rac*-**4** and diphenylethanedione (benzil) in the presence of formaldehyde and ammonium acetate, the mixture in methanol was heated at reflux for 7 h.

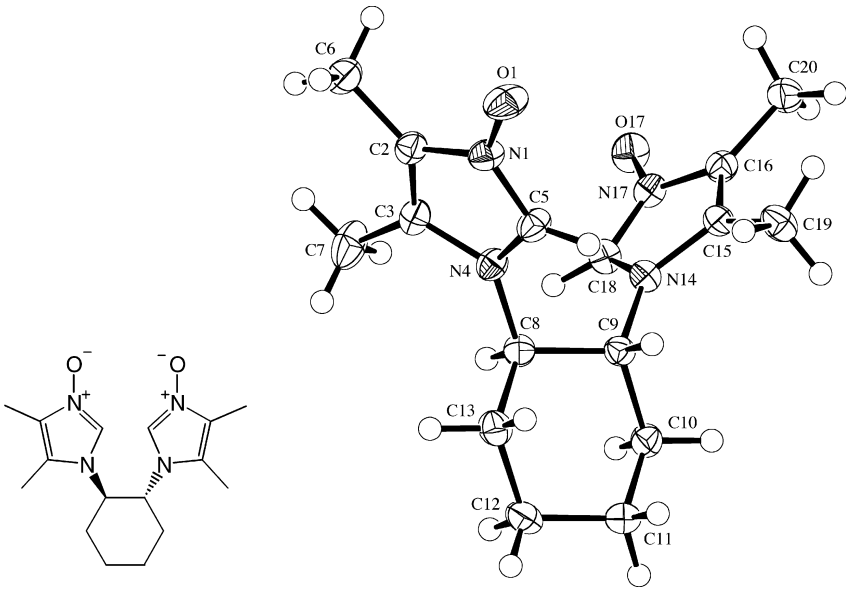
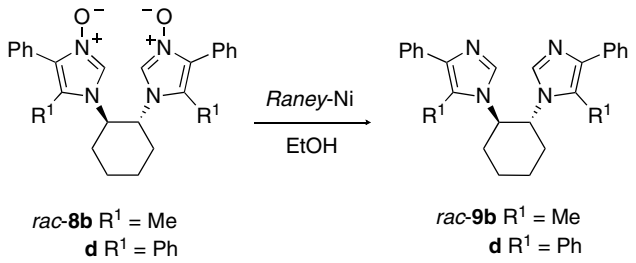


Figure 1. ORTEP plot[16] of the molecular structure of *rac*-**8a** (arbitrary numbering of the atoms, 50% probability ellipsoids).



rac-**8b** R^1 = Me
d R^1 = Ph

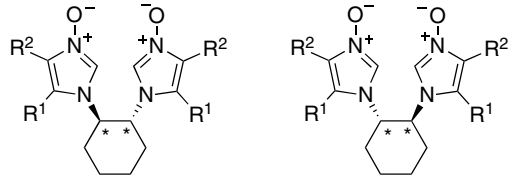
rac-**9b** R^1 = Me
d R^1 = Ph

Scheme 2.

The chromatographic separation gave the known hexahydroquinoxaline **10** and 4,5-diphenylimidazole **11** as the main products. The desired bis-imidazole *rac*-**9d** was isolated in only 14% yield (Scheme 3). This result shows that the condensation of *rac*-**4** with **7** followed by deoxygenation offers a superior access to bis-imidazoles of type **9**.

The successful synthesis of racemic bis(imidazole N-oxides) **8** prompted us to investigate the preparation of enantiomerically pure compounds. For this reason, the enantiomerically pure (*R*,*R*)- and (*S*,*S*)-*trans*-1,2-diaminocyclohexanes [(*R*,*R*)-and (*S*,*S*)-**4**, resp.] were prepared by the resolution of *rac*-**4**. Fractional crystallization of its diastereoisomeric (*R*,*R*)- and (*S*,*S*)-L-tartrates,[18a–c] followed by treatment with HCl in methanol/diethyl ether, gave the hydrochlorides, which after neutralization with NaOH solution[18d] afforded the free bases.

The enantiomerically pure diamines (*R*,*R*)- and (*S*,*S*)-**4** were treated with 2.1 equiv of formaldehyde in methanol in order to prepare the di-imines **5** (Scheme 1). In contrast to the racemic substrate, no crystalline product of type **6** was formed and the crude materials were used for the reactions with α-hydroxyimino ketones **7** in glacial acetic acid. The workup and isolation of (*R*,*R*)- and (*S*,*S*)-bis(imidazole N-oxides) of type **8** were carried out analogously to the procedure applied in the case of *rac*-**8**.



(*R*,*R*)-**8a** $R^1 = R^2$ = Me
b R^1 = Me, R^2 = Ph
c R^1 = Ph, R^2 = Me
d $R^1 = R^2$ = Ph

(*S*,*S*)-**8a** $R^1 = R^2$ = Me
b R^1 = Me, R^2 = Ph
c R^1 = Ph, R^2 = Me
d $R^1 = R^2$ = Ph

Starting with (−)-(*R*,*R*)-**4** and **7a**, the isolated bis(imidazole N-oxide) **8a** showed an $[\alpha]_D$-value of −267.6 (*c* 1.00, MeOH). Based on the reaction mechanism of the formation of **8a**, we assume that the configuration of the product is (*R*,*R*), that is, the stereochemical integrity is preserved.

The enantiomerical purity of (−)-(*R*,*R*)-**8a** was determined by ^{1}H NMR spectroscopy after the addition of 2 equiv of (+)-(*R*)-(*tert*-butyl)(phenyl)phosphonothioic acid ((+)-(*R*)-**12**).[19] Of special diagnostic value is the signal of the H–C(2) of the imidazole rings, which, in the complex of *rac*-**8a** with (+)-(*R*)-**12** appears at 10.2 and 10.4 ppm (Fig. 2). In the corresponding spectrum of (−)-(*R*,*R*)-**8a**, the presence of only one signal at 10.2 ppm confirms that this compound is enantiomerically pure. This result is supported by the presence of only two Me signals between 2.1 and 1.6 ppm.

Similarly, the enantiomeric purity of (−)-(*R*,*R*)-**8b**, (+)-(*S*,*S*)-**8b**, and (+)-(*R*,*R*)-**8d** was determined by ^{1}H NMR spectroscopy.

The treatment of the bis(imidazole N-oxides) (*R*,*R*)- and (*S*,*S*)-**8b**–**d** with *Raney*-Ni in methanol led to the deoxygenated bis-imidazoles (*R*,*R*)-and (*S*,*S*)-**9b**–**d**, respectively.

3. Conclusions

The present study shows that the previously described method for the preparation of bis(imidazole N-oxides) from α,ω-diaminoalkanes and α-hydroxyiminoketones can be successfully applied to the synthesis of optically active derivatives. In this case, enantiomerically pure *trans*-1,2-diaminocyclohexane is used as the chiral substrate. The mild deoxygenation with *Raney*-Ni offers a convenient access to the corresponding optically active bis-imidazoles, which are potentially attractive building blocks for the preparation of chiral metal carbene complexes.

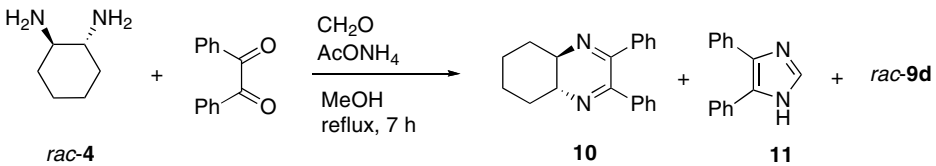
4. Experimental

4.1. General

Melting points were determined on a Melt-Temp. II apparatus (Aldrich) in capillary and are uncorrected. IR spectra were measured on a NEXUS FT-IR spectrophotometer in KBr. ^{1}H and ^{13}C NMR spectra were recorded on a Tesla BS567A (80 and 20 MHz, resp.) or Bruker AC 300 instrument (300 and 75.5 MHz, resp.) in $CDCl_3$, CD_3OD, or DMSO-d_6 as solvent and with TMS as an internal standard. The multiplicity of the ^{13}C signals was deduced from the DEPT spectra. MS (EI, ESI or CI) were registered on Finnigan MAT-90 or Finnigan SSQ-700 instruments. Elemental analyses were performed in the Analytical Laboratory of the University of Zürich.

4.2. Starting materials

α-(Hydroxyimino)ketones **7** were obtained according to known protocols: butane-2,3-dione monooxime **7a**,[20a] 1-phenylpropane-1,2-dione 1-oxime **7b**,[20b] and 1-phenylpropane-1,2-dione 2-oxime **7c**[20c] by nitrosation of the corresponding ketones using isoamyl nitrite, 1,2-diphenylethane-1,2-dione monooxime **7d** (benzil monooxime)[20d] from dibenzoyl and hydroxylamine hydrochloride, and hydroxyiminoacetone **7e** by hydrolysis, nitrosation, and decarboxylation of ethyl acetoacetate by a modified Beech procedure.[20e]



rac-**4** **10** **11** *rac*-**9d**

Scheme 3.

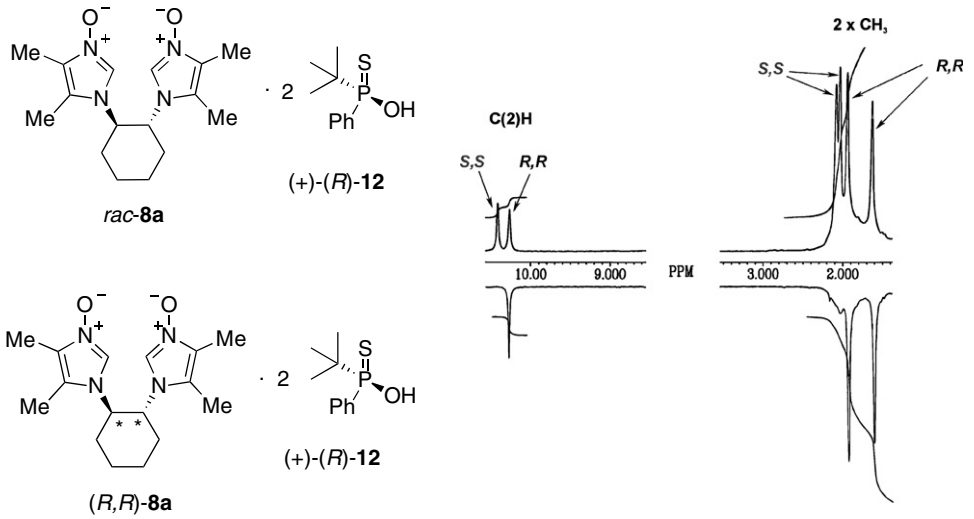


Figure 2. Selected ^{1}H NMR signals of *rac*-**8a** and (*R*,*R*)-**8a** in $CDCl_3$ in the presence of 2 equiv of (+)-(*R*)-(*tert*-butyl)(phenyl)phosphonothioic acid (+)-(*R*)-**12**.

4.3. Synthesis of 1,3,5,7-tetraazapentacyclo[3.3.2.4^{9,10}4^{11,12}]-eicosane *rac*-6

To a solution of racemic *trans*-1,2-diaminocyclohexane *rac*-**4** (5.00 g, 44.0 mmol) in methanol (50 mL), solid formaldehyde (2.78 g, 93.0 mmol) was added, and magnetic stirring was continued overnight. The solvent was removed in vacuo and diethyl ether (30 mL) was added to the resulting solid. After cooling in a fridge, filtration gave a portion of crude product. The filtrate was concentrated and cooled, and a second portion of *rac*-**6** was isolated. The combined crude product was purified by crystallization from a mixture of acetone and dichloromethane to give *rac*-**6** as colorless crystals (3.85 g, 64%). Mp 234–238 °C (Ref. 15 238–239 °C). IR (KBr): *ν* 2937vs (br), 2857m, 1364m, 1273m, 1258s, 1164m, 1071m, 1024s, 1013s, 911m, 661m cm^{-1}. ^{1}H NMR ($CDCl_3$): *δ* 4.07 (AB, *J* = 12.8 Hz, 4H), 3.76 (AB, *J* = 12.8 Hz, 4H), 2.45–2.55 (m, 4H, 4CH), 1.75 (m, 8H, 4CH_2 *c*Hex), 1.28 (m, 8H, 4CH_2 *c*Hex). MS (CI): *m*/*z* 277 (5, [M+1]$^+$), 139 (100, [M/2+1]$^+$). The obtained *rac*-**6** was used as a starting material for the synthesis of racemic bis-imidazole-3-oxides, *rac*-**8**.

4.4. Synthesis of racemic bis(imidazole N-oxides)

Method A: An ethanolic solution of *rac*-**6** (1.0 mmol) and 4.0 mmol of the corresponding dione monoxime **7** was heated at reflux for 3 h. Then, the solvent was removed under reduced pressure, and the resulting deep-orange or deep-yellow oil was washed with acetone until the color disappeared. The obtained solid was purified by crystallization from a mixture of chloroform and acetone. Recrystallization from an appropriate solvent gave analytically pure product as colorless crystals.

4.4.1. *trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4,5-dimethylimidazole)-3,3′-dioxide *rac*-8a

Yield: 191 mg (29%). Colorless crystals. Mp (dec.) 188–194 °C ($CHCl_3$/hexane). IR (KBr): *ν* 3350–2859vs (br), 1626m, 1448m, 1431m, 1408m, 1382m, 1332s, 1219m, 1194s, 1147m, 1086m, 706s, 632m, 582s cm^{-1}. ^{1}H NMR (CD_3OD): *δ* 8.56 (*s*, 2H, HC(2), HC(2′) imidazole), 4.51–4.48 (m, 2H, 2CH *c*Hex), 2.24–1.59 (m, 8H, 4CH_2 *c*Hex), 2.04, 2.00 (2s, 12H, 4CH_3). ^{13}C NMR (CD_3OD): *δ* 126.6, 125.1 (2s, C(4), C(4′), C(5), C(5′) imidazole), 124.1 (d, C(2), C(2′) imidazole), 60.4 (d, 2CH *c*Hex), 34.5, 25.5 (2t, 4CH_2 *c*Hex), 8.3, 6.9 (2q, 4CH_3). MS (CI): *m*/*z* 305 (5, [M+1]$^+$), 289 (28), 273 (100), 271 (49), 261 (7). Anal. Calcd for $C_{16}H_{24}N_4O_2 \cdot 2H_2O$ (340.44): C, 56.45; H, 8.29; N, 16.46. Found: C, 56.43; H, 8.31; N, 15.66. Suitable crystals for an X-ray crystal structure determination were obtained from a solution in chloroform/hexane.

4.4.2. *trans*-1,1′-(Cyclohexane-1,2-diyl)bis(5-methyl-4-phenylimidazole)-3,3′-dioxide *rac*-8b

Yield: 210 mg (41%). Colorless crystals. Mp (dec.) 206–211 °C ($CHCl_3$/hexane). IR (KBr): *ν* 3350–2850vs (br), 1618m, 1497m, 1444m, 1405m, 1342s, 1255m, 1227s, 768m, 715s, 697s, 609m cm^{-1}. ^{1}H NMR (CD_3OD): *δ* 8.77 (s, 2H, HC(2), HC (2′) imidazole), 7.48–7.39 (m, 10H, 10 arom. H), 4.63–4.56 (m, 2H, 2CH *c*Hex), 2.36–1.68 (m, 8H, 4CH_2 *c*Hex), 2.06 (s, 6H, 2CH_3). ^{13}C NMR (CD_3OD): *δ* 131.2, 130.1, 129.5 (3d, 10 arom. CH), 130.4 (s, 2C_q arom.), 129.6, 125.8 (2s, C(4), C(4′), C(5), C(5′) imidazole), 127.5 (d, C(2), C(2′) imidazole), 61.2 (d, 2CH *c*Hex), 33.7, 25.6 (2t, 4CH_2 *c*Hex), 9.3 (q, 2CH_3). MS (EI): *m*/*z* 428 (3, M$^{+\cdot}$), 412 (11), 280 (100), 239 (29), 159 (23), 105 (25), 77 (26). Anal. Calcd for $C_{26}H_{28}N_4O_2 \cdot H_2O$ (446.56): C, 69.93; H, 6.77; N, 12.55. Found: C, 70.31; H, 6.62; N, 12.31.

Method B: A mixture of *rac*-**6** (1.0 mmol) and 4.0 mmol of the corresponding dione monooxime **7** in glacial acetic acid (15 mL) was magnetically stirred overnight at rt. Then, HCl gas was bubbled through the solution for 1 h. In some cases, the product solidified. Then, diethyl ether (ca. 175 mL) was added and the colorless precipitated hydrochloride was filtered, washed with cooled ether (3 × 20 mL), and dried under reduced pressure. The crude hydrochloride was dissolved (or suspended) in methanol (25 mL), solid $NaHCO_3$ (1.64 g) was added, and stirring was continued for 1 h. Evolution of CO_2 was observed. The inorganic salts were filtered off and the solvent was removed (because of partial precipitation of *rac*-**8d**, the solution was warmed before filtration). The crude solid product obtained was recrystallized. Following this procedure, *rac*-**8a** and *rac*-**8b** were prepared with 85% and 89% yields, respectively.

4.4.3. *trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4-methyl-5-phenylimidazole)-3,3′-dioxide *rac*-8c

Yield: 372 mg (77%). Colorless crystals. Mp (dec.) 157–163 °C (CH_2Cl_2/hexane). IR (KBr): *ν* 3150–2850vs (br), 1684m, 1632m, 1444m, 1381m, 1327s, 1170m, 1013m, 766s, 705s cm^{-1}. ^{1}H NMR (CD_3OD): *δ* 8.30 (s, 2H, HC(2), HC(2′) imidazole), 7.58–7.51 (m, 6H, 6 arom. H), 7.19–6.96 (m, 4H, 4 arom. H), 4.28–3.98 (m, 2H, 2CH *c*Hex), 2.18–1.26 (m, 8H, 4CH_2 *c*Hex), 1.90 (s, 6H, 2CH_3). ^{13}C NMR: *δ* 129.8, 129.4, 129.1, 125.0 (4d, 10 arom. CH, C(2), C(2′) imidazole), 126.5, 126.0, 125.7 (3s, 2C_q arom. C(4), C(4′), C(5),

C(5′) imidazole), 59.5 (d, 2CH *c*Hex), 31.8, 23.8 (2t, $4CH_2$ *c*Hex), 7.1 (q, $2CH_3$). HRMS (CI) $C_{26}H_{28}N_4O_2Na$, $[M+Na]^+$: calcd 451.21204; found 451.21045. Anal. Calcd for $C_{26}H_{28}N_4O_2 \cdot 3H_2O$ (482.60): C, 64.71; H, 7.10; N, 11.61. Found: C, 64.75; H, 6.71; N, 11.28.

4.4.4. *trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4,5-diphenylimidazole)-3,3′-dioxide *rac*-8d

Yield: 504 mg (87%). Colorless crystals. Mp (dec.) 260–267 °C (CH_2Cl_2/hexane). IR (KBr): *ν* 3400–2850vs (br), 1636m, 1577m, 1445m, 1405m, 1341m, 1259m, 1221m, 767m, 712m, 695m cm^{-1}. ^1H NMR (CD_3OD): *δ* 8.06 (s, 2H, HC(2), HC(2′) imidazole), 7.51–7.08 (m, 20H, 20 arom. H), 4.11–4.02 (m, 2H, 2CH *c*Hex), 2.22–1.28 (m, 8H, $4CH_2$ *c*Hex). ^{13}C-NMR (CD_3OD): *δ* 130.2, 129.4, 129.0, 128.9, 127.7, 127.6, 124.2 (7d, 20 arom. CH, C(2), C(2′) imidazole), 128.0, 127.1, 126.9, 126.6 (4*s*, $4C_q$ arom., C(4), C(4′), C(5), C(5′) imidazole), 59.3 (d, 2CH *c*Hex), 31.6, 23.8 (2t, $4CH_2$ *c*Hex). HRMS (CI) $C_{36}H_{32}N_4O_2Na$, $[M+Na]^+$: calcd 575.24175; found 575.24384. Anal. Calcd for $C_{36}H_{32}N_4O_2 \cdot 1.5H_2O$ (579.71): C, 74.59; H, 6.09; N, 9.66. Found: C, 74.50; H, 6.03; N, 9.45.

4.4.5. *trans*-1,1′-(Cyclohexane-1,2-diyl)bis(5-methylimidazole)-3,3′-dioxide *rac*-8e

Yield: 160 mg (58%). Colorless solid. Mp (dec.) 220 °C. IR (KBr): *ν* 3150–2850vs (br), 1632m, 1588m, 1450m, 1407s, 1311s, 1297s, 1230m, 1045m, 819m, 693s cm^{-1}. ^1H NMR (CD_3OD): *δ* 8.56 (s, 2H, HC(2), HC (2′) imidazole), 6.71 (s, 2H, HC(4), HC(4′) imidazole), 4.44–4.38 (m, 2H, 2CH *c*Hex), 2.05–1.45 (m, 8H, $4CH_2$ *c*Hex), 1.92 (s, 6H, $2CH_3$). ^{13}C NMR (CD_3OD): *δ* 125.4 (s, C(5), C(5′) imidazole), 123.2, 118.5 (2d, C(2), C(2′), C(4), C(4′) imidazole), 57.6 (d, 2CH *c*Hex), 32.6, 24.0 (2t, $4CH_2$ *c*Hex), 8.5 (q, $2CH_3$). HRMS (EI) $C_{14}H_{20}N_4O_2$, $M^{+\cdot}$: calcd 276.1586; found 276.1586.

4.5. Deoxygenation of racemic bis(imidazole N-oxides)

To a solution of the corresponding bis(imidazole N-oxide) **8** (1.0 mmol) in ethanol (2 mL), an ethanolic suspension of freshly prepared *Raney*-Nickel was added in small portions, and the progress of the reaction was followed by TLC (MeOH/AcOEt 1:3). When the starting N-oxide was completely reduced, the solution was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by crystallization.

4.5.1. *trans*-1,1′-(Cyclohexane-1,2-diyl)bis(5-methyl-4-phenylimidazole) *rac*-9b

Yield: 309 mg (78%). Colorless crystals. Mp 245–246 °C (CH_2Cl_2/hexane). IR (KBr): *ν* 3140–2850vs (br), 1605m, 1498s, 1444m, 1365m, 1242m, 1216s, 932m, 771s, 700vs cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 7.72 (s, 2H, HC(2), HC(2′) imidazole), 7.45–7.43, 7.31–7.28 (2m, 8H, 8 arom. H), 7.22–7.19 (m, 2H, 2 arom. H), 4.03–3.97 (m, 2H, 2CH *c*Hex), 2.35–1.58 (m, 8H, $4CH_2$ *c*Hex), 1.75 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$): *δ* 137.8, 134.9, 124.6 (3*s*, $2C_q$ arom., C(4), C(4′), C(5), C(5′) imidazole), 133.0, 128.2, 127.3, 126.3 (4*d*, 10 arom. CH, C(2), C(2′) imidazole), 60.0 (d, 2CH *c*Hex), 33.0, 25.3 (2t, $4CH_2$ *c*Hex), 8.9 (q, $2CH_3$). HRMS (EI) $C_{26}H_{28}N_4$, $M^{+\cdot}$: calcd 396.2314; found 396.2313.

4.5.2. *trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4,5-diphenylimidazole) *rac*-9d

Yield: 496 mg (85%). Colorless crystals. Mp 277–280 °C (MeOH). IR (KBr): *ν* 3100–2800vs (br), 1603m, 1506s, 1490m, 1443m, 1361w, 1247m, 1040m, 775s, 721m, 698s, 661m cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 7.61–6.96 (m, 22H, 20 arom. H, HC(2), HC(2′) imidazole), 4.14–3.88 (m, 2H, 2CH *c*Hex), 2.24–1.28 (m, 8H, $4CH_2$ *c*Hex). ^{13}C-NMR ($CDCl_3$): *δ* 137.4, 134.2, 130.0, 128.4 (4s, $4C_q$ arom., C(4), C(4′), C(5), C(5′) imidazole), 133.5, 131.2, 129.3, 129.1, 128.0, 126.5, 126.3 (7d, 20 arom. CH, C(2), C(2′) imidazole), 58.1 (d, 2CH *c*Hex), 50.6, 35.3 (2t, $4CH_2$ *c*Hex). HRMS (CI) $C_{36}H_{32}N_4$, $[M+1]^+$: calcd 521.27167; found 521.26997. Anal. Calcd for $C_{36}H_{32}N_4 \cdot 2CH_3OH$ (584.76): C, 78.05; H, 6.89; N, 9.58. Found: C, 77.77; H, 6.81; N, 9.54.

4.6. Attempted synthesis of *trans*-1,1′-(cyclohexane-1,2-diyl)bis(4,5-diphenylimidazole) *rac*-9d from benzil, ammonia, and formaldehyde

A solution of racemic *trans*-1,2-diaminocyclohexane *rac*-**4** (0.57 g, 5.0 mmol), benzil (4.20 g, 20.0 mmol), paraformaldehyde (0.60 g, 20.0 mmol), and ammonium acetate (1.50 g, 20.0 mmol) in methanol (100 mL) was heated at reflux for 7 h. Then, the solvent was evaporated, the resulting mixture was dissolved in CH_2Cl_2 (80 mL) and extracted with 2 M aqueous NaOH solution (200 mL). The separated deep-green organic phase was dried with anhydrous Na_2SO_4 and the solvent was removed. The *trans*-4a,5,6,7,8,8a-hexahydro-2,3-diphenylquinoxaline **10** and 4,5-diphenylimidazole **11** were isolated as the main products. Small amounts of benzil were also detected in the mixture. In addition, the bis-imidazole derivative *rac*-**9d** was isolated after chromatographic workup in 14% yield (SiO_2, MeOH/AcOEt 1:3, $R_f = 0.87$).

4.7. Resolution of 1,2-diaminocyclohexane; (*R*,*R*)- and (*S*,*S*)-*trans*-1,2-diaminocyclohexane

To a magnetically stirred solution of (+)-L-tartaric acid (6.0 g, 40 mmol) in distilled water (17 mL) were added commercially available 1,2-diaminocyclohexane (ca. 90% mixture of *cis*- and *trans*-isomers, 10 mL, 72 mmol) and glacial acetic acid (4.6 mL, 80 mmol). The resulting suspension was magnetically stirred for 2 h at rt, and then in an ice bath for another 2 h. The colorless precipitate of (−)-(*R*,*R*)-1,2-diaminocyclohexane L-tartrate was filtered, washed with distilled water (5 °C) and methanol, and dried in vacuo. The filtrate was magnetically stirred and heated to 80 °C. Then, (+)-L-tartaric acid (15.0 g, 100 mmol) was added. The resulting solution was magnetically stirred overnight at rt, and then cooled in an ice bath. The colorless precipitate of (+)-(*S*,*S*)-1,2-diaminocyclohexane·2L-tartrate was filtered, washed with distilled water (5 °C) and methanol, and dried in vacuo. Calculated yields relate to the total amount of *cis*- and *trans*-1,2-diaminocyclohexane used in the form of a commercial material.

4.7.1. (−)-(*R*,*R*)-1,2-Diaminocyclohexane L-tartrate

Yield: 7.7 g (40%). Colorless crystals. Mp (dec.) 252–267 °C ([lit.[18e]]: mp (dec.) 247–267 °C). $[\alpha]_D^{20} = +12.0$ (*c* 1, H_2O) ([lit.[18e]]: $[\alpha]_D^{20} = +11.6$ (*c* 1, H_2O)).

4.7.2. (+)-(*S*,*S*)-1,2-Diaminocyclohexane·2L-tartrate

Yield: 11.3 g (38%). Colorless crystals. Mp (dec.) 140–150 °C ([lit.[18e]]: mp (dec.) 130–144 °C). $[\alpha]_D^{20} = +25.4$ (*c* 1, H_2O) ([lit.[18e]]: $[\alpha]_D^{20} = +25.8$ (*c* 1, H_2O)).

(−)-(*R*,*R*)-1,2-Diaminocyclohexane L-tartrate (5.0 g, 19 mmol) was dissolved in a minimum amount of 10% HCl in methanol. To this solution was added diethyl ether dropwise until a white precipitate formed. The precipitate was filtered and dried in vacuo, and then dissolved in a minimum amount of saturated NaOH solution. KOH pellets were added to remove water, and the mixture was extracted with diethyl ether (3 × 50 mL). The organic layer was separated, dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure (water/ice bath) to give a colorless precipitate.

(+)-(*S*,*S*)-1,2-Diamiocyclohexane L-tartrate (5.0 g, 12 mol) was dissolved in a minimum amount of saturated NaOH solution. KOH pellets were added to remove water, and the mixture was extracted with diethyl ether (3 × 50 mL). The organic layer was

separated, dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure (water/ice bath) to give a colorless precipitate.

4.7.3. (−)-(*R*,*R*)-*trans*-1,2-Diaminocyclohexane

Yield: 2.0 g (95%). Colorless crystals. $[\alpha]_D^{20} = -20.0$ (*c* 1, 1 M HCl) ([lit.[18e]]: $[\alpha]_D^{20} = -29.7$ (*c* 5, 1 M HCl)).

4.7.4. (+)-(*S*,*S*)-*trans*-1,2-Diaminocyclohexane

Yield 0.9 g (67%). Colorless crystals. $[\alpha]_D^{20} = +17.0$ (*c* 1, 1 M HCl) ([lit.[18e]]: $[\alpha]_D^{20} = +29.7$ (*c* 5, HCl)).

4.8. Synthesis of enantiomerically pure bis(imidazole N-oxides) (*R*,*R*)- and (*S*,*S*)-8

To a stirred solution of (*R*,*R*)- or (*S*,*S*)-*trans*-1,2-diaminocyclohexane (*R*,*R*)- or (*S*,*S*)-**4** (114.0 mg, 1.0 mmol) in methanol (3 mL), solid formaldehyde (63.0 g, 2.1 mmol) was added, the mixture was stirred overnight, and the solvent was removed in vacuo. The resulting oil and 2.1 mmol of the corresponding dione monooxime **7a**–**d** in glacial acetic acid (7 mL) were magnetically stirred overnight at rt. Then, HCl gas was bubbled through the solution for 1.5 h. In some cases, a precipitate was formed. Then, diethyl ether (ca. 50 mL) was added, and the colorless hydrochloride was filtered and dried in vacuo. The crude hydrochloride was dissolved (or suspended) in methanol (25 mL), after which solid $NaHCO_3$ (1.0 g) was added, and stirring was continued for 1.5 h, whereby evolution of CO_2 was observed. Sodium hydrocarbonate was filtered off, and the filtrate was evaporated. The solid obtained was treated with a $CHCl_3$/MeOH mixture (2:1). The undissolved inorganic material was filtered off and the solvent was removed in vacuo. Crude products were triturated with small amounts of acetone to give analytically pure samples. According to this procedure, (*R*,*R*)- and (*S*,*S*)-**8a**–**d** were obtained in 62–85% yield.

4.8.1. (*R*,*R*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4,5-dimethylimidazole)-3,3′-dioxide (*R*,*R*)-8a

Yield: 240 mg (79%). Colorless crystals. Mp (dec.) 210 °C. IR (KBr): *ν* 3420–2865vs (br), 1626m, 1450m, 1429m, 1408m, 1380m, 1332s, 1192s, 1146m, 1084m, 705s, 634m, 583s cm^{-1}. ^1H NMR (CD_3OD): *δ* 8.53 (s, 2H, HC(2), HC(2′) imidazole), 4.53–4.43 (m, 2H, 2CH *c*Hex), 2.25–1.57 (m, 8H, $4CH_2$ *c*Hex), 2.06, 1.91 (2s, 12H, $4CH_3$). ^{13}C NMR (CD_3OD): *δ* 126.7, 124.2 (2s, C(4), C(4′), C(5), C(5′) imidazole), 125.2 (d, C(2), C(2′) imidazole), 60.4 (d, 2CH *c*Hex), 34.5, 25.6 (2t, $4CH_2$ *c*Hex), 8.4, 6.9 (2q, $4CH_3$). MS (ESI): *m*/*z* 327 (39, $[M+Na]^+$), 305 (100, $[M+1]^+$). HRMS (ESI) $C_{16}H_{24}N_4O_2Na$, $[M+Na]^+$: calcd 327.1797; found 327.1798. $[\alpha]_D^{20} = -267.6$ (*c* 1.00, MeOH).

4.8.2. (*S*,*S*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4,5-dimethylimidazole)-3,3′-dioxide (*S*,*S*)-8a

Yield: 253 mg (83%). Colorless crystals. Mp (dec.) 210 °C. IR (KBr): *ν* 3416–2864vs (br), 1627m, 1449m, 1429m, 1408m, 1380m, 1332s, 1192s, 1146m, 1084m, 705s, 634m, 583s cm^{-1}. MS (ESI): *m*/*z* 327 (100, $[M+Na]^+$). HRMS (ESI) $C_{16}H_{24}N_4O_2Na$, $[M+Na]^+$: calcd 327.1797; found 327.1798. $[\alpha]_D^{20} = +241.7$ (*c* 0.90, MeOH).

4.8.3. (*R*,*R*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(5-methyl-4-phenylimidazole)-3,3′-dioxide (*R*,*R*)-8b

Yield: 351 mg (82%). Colorless crystals. Mp (dec.) 230°C. IR (KBr): *ν* 3420–2866vs (br), 1618m, 1497m, 1444m, 1407m, 1343s, 1257m, 1226s, 1047m, 1031m, 847m, 768m, 715s, 697s, 612m cm^{-1}. ^1H NMR (CD_3OD): *δ* 8.77 (s, 2H, HC(2), HC(2′) imidazole), 7.52–7.37 (m, 10H, 10 arom. H), 4.64–4.54 (m, 2H, 2CH *c*Hex), 2.35–1.65 (m, 8H, $4CH_2$ *c*Hex), 2.05 (s, 6H, $2CH_3$). ^{13}C NMR (CD_3OD): *δ* 131.2, 130.1, 129.5 (3d, 10 arom. CH), 130.6 (s, $2C_q$ arom.), 127.5, 125.8 (2*s*, C(4), C(4′), C(5), C(5′) imidazole), 126.4 (*d*, C(2), C(2′) imidazole), 61.2 (*d*, 2CH *c*Hex), 33.7, 25.6 (2*t*, $4CH_2$ *c*Hex), 9.3 (*q*, $2CH_3$). MS (ESI): *m*/*z* 451 (100, $[M+Na]^+$). HRMS (ESI) $C_{26}H_{28}N_4O_2Na$, $[M+Na]^+$: calcd 451.2110; found 451.2111. $[\alpha]_D^{20} = -136.3$ (*c* 0.82, MeOH).

4.8.4. (*S*,*S*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(5-methyl-4-phenylimidazole)-3,3′-dioxide (*S*,*S*)-8b

Yield: 351 mg (82%). Colorless crystals. Mp (dec.) 230 °C. IR (KBr): *ν* 3423–2867vs (br), 1612m, 1576m, 1497m, 1444m, 1407m, 1343s, 1256m, 1226s, 1047m, 1031m, 847m, 769m, 715s, 698s, 611m cm^{-1}. MS (ESI): *m*/*z* 451 (100, $[M+Na]^+$). HRMS (ESI) $C_{26}H_{28}N_4O_2Na$, $[M+Na]^+$: calcd 451.2110; found 451.2109. $[\alpha]_D^{20} = +134.6$ (*c* 0.82, MeOH).

4.8.5. (*R*,*R*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4-methyl-5-phenylimidazole)-3,3′-dioxide (*R*,*R*)-8c

Yield: 291 mg (68%). Colorless crystals. Mp (dec.) 231 °C. IR (KBr): *ν* 3424–2869vs (br), 1698m, 1636m, 1596m, 1443m, 1380m, 1328s, 1177m, 1168m, 1015m, 759m, 708m, 639m. ^1H NMR (CD_3OD): *δ* 7.90 (s, 2H, HC(2), HC(2′) imidazole), 7.70–7.51 (m, 6H, 6 arom. H), 7.18–7.05 (m, 4H, 4 arom. H), 4.28–4.13 (m, 2H, 2CH *c*Hex), 2.30–1.37 (m, 8H, $4CH_2$ *c*Hex), 2.04 (s, 6H, $2CH_3$). ^{13}C NMR (CD_3OD): *δ* 131.4, 131.2, 130.7 (3d, 10 arom. CH), 128.8, 127.9, 127.4 (3s, $2C_q$ arom., C(4), C(4′), C(5), C(5′) imidazole), 125.8 (d, 2H, C(2), C(2′) imidazole), 61.3 (d, 2CH *c*Hex), 34.1, 25.3 (2t, $4CH_2$ *c*Hex), 7.5 (q, $2CH_3$). MS (ESI): *m*/*z* 451 (100, $[M+Na]^+$). HRMS (ESI) $C_{26}H_{28}N_4O_2Na$, $[M+Na]^+$: calcd 451.2110; found 451.2111. $[\alpha]_D^{20} = -127.0$ (*c* 0.84, MeOH).

4.8.6. (*S*,*S*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4-methyl-5-phenylimidazole)-3,3′-dioxide (*S*,*S*)-8c

Yield: 364 mg (85%). Colorless crystals. Mp (dec.) 228 °C. IR (KBr): *ν* 3424–2870vs (br), 1684m, 1578vs, 1443s, 1380m, 1329s, 1178m, 1015m, 759m, 708m, 639m cm^{-1}. MS (ESI): *m*/*z* 451 (100, $[M+Na]^+$). HRMS (ESI) $C_{26}H_{28}N_4O_2Na$, $[M+Na]^+$: calcd 451.2110; found 451.2106. $[\alpha]_D^{20} = +126.2$ (*c* 0.84; MeOH).

4.8.7. (*R*,*R*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4,5-diphenylimidazole)-3,3′-dioxide (*R*,*R*)-8d

Yield: 342 mg (62%). Colorless crystals. Mp (dec.) 209 °C. IR (KBr): *ν* 3424–2867vs (br), 1635m, 1570m, 1506m, 1484m, 1446m, 1405m, 1339s, 1259m, 1222m, 1193m, 767s, 711s, 658m, 636m cm^{-1}. ^1H NMR (CD_3OD): *δ* 8.08 (s, 2H, HC(2), HC(2′) imidazole), 7.65–7.50 (m, 4H, 4 arom. H), 7.38–7.23 (m, 10H, 10 arom. H), 7.18–7.07 (m, 4H, 4 arom. H), 4.37–4.26 (m, 2H, 2CH *c*Hex), 2.38–1.40 (m, 8H, $4CH_2$ *c*Hex). ^{13}C NMR (CD_3OD): *δ* 131.8, 131.4, 131.2, 130.8, 129.9, 129.7 (6d, 20 arom. CH, C(2), C(2′) imidazole), 131.0, 129.6, 127.3 (3s, $4C_q$ arom., C(4), C(4′), C(5), C(5′) imidazole), 61.4 (d, 2CH *c*Hex), 34.0, 25.3 (2t, $4CH_2$ *c*Hex). MS (ESI): *m*/*z* 575 (100, $[M+Na]^+$). HRMS (ESI) $C_{36}H_{32}N_4O_2Na$, $[M+Na]^+$: calcd 575.2423; found 575.2422. $[\alpha]_D^{20} = +6.0$ (*c* 1.02, MeOH).

4.8.8. (*S*,*S*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4,5-diphenylimidazole)-3,3′-dioxide (*S*,*S*)-8d

Yield: 364 mg (66%). Colorless crystals. Mp (dec.) 206 °C. IR (KBr): *ν* 3420–2865vs (br), 1603m, 1577m, 1505m, 1484m, 1445m, 1404m, 1340s, 1258m, 1222m, 1192m, 1077m, 1056m, 766s, 711s, 658m, 636m cm^{-1}. MS (ESI): *m*/*z* 575 (100, $[M+Na]^+$). HRMS (ESI) $C_{36}H_{32}N_4O_2Na$, $[M+Na]^+$: calcd 575.2423; found 575.2418. $[\alpha]_D^{20} = -6.0$ (*c* 1.00, MeOH).

4.9. Deoxygenation of enantiomerically pure bis(imidazole N-oxides) (*R,R*)- and (*S,S*)-9

To a solution of the corresponding (*R,R*)- or (*S,S*)-bis(imidazole N-oxide) (1.0 mmol) in methanol (2 mL), a methanolic suspension of freshly prepared *Raney*-Nickel was added in small portions. The progress of the reaction was followed by TLC (MeOH/CH_3Cl 1:9). When the starting material was completely reduced, the solution was filtered through silica gel and the filtrate was concentrated under reduced pressure.

4.9.1. (*R,R*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(5-methyl-4-phenylimidazole) (*R,R*)-9b

Yield: 317 mg (80%). Colorless crystals. Mp (dec.) 221 °C. IR (KBr): *ν* 3432–2862vs (br), 1632m, 1606s, 1497s, 1448m, 1363m, 1242m, 1216m, 1071m, 1013m, 936m, 773s, 702vs, 645m cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 7.78 (s, 2H, HC(2), HC(2′) imidazole), 7.45–7.20 (m, 10H, 10 arom. H), 4.08–3.98 (m, 2H, 2CH *c*Hex), 2.40–1.55 (m, 8H, $4CH_2$ *c*Hex), 1.74 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$): *δ* 137.7, 134.8, 124.6 (3s, $2C_q$ arom., C(4), C(4′), C(5), C(5′) imidazole), 133.0, 128.2, 127.3, 126.3 (4d, 10 arom. CH, C(2), C(2′) imidazole), 60.0 (d, 2CH *c*Hex), 32.9, 25.2 (2t, $4CH_2$ *c*Hex), 8.8 (q, $2CH_3$). MS (ESI): *m/z* 419 (100, $[M+Na]^+$), 397 (15, $[M+1]^+$). HRMS (ESI) $C_{26}H_{28}N_4Na$, $[M+Na]^+$: calcd 419.2212; found 419.2216. $[\alpha]_D^{20} = +71$ (*c* 1.00, MeOH).

4.9.2. (*S,S*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(5-methyl-4-phenylimidazole) (*S,S*)-9b

Yield: 285 mg (72%). Colorless crystals. Mp (dec.) 220 °C. IR (KBr): *ν* 3416–2817vs (br), 1606s, 1578s, 1497s, 1444m, 1414m, 1363m, 1242m, 1216m, 1034m, 936m, 773s, 702vs, 645m cm^{-1}. MS (ESI): *m/z* 419 (100, $[M+Na]^+$). HRMS (ESI) $C_{26}H_{28}N_4Na$, $[M+Na]^+$: calcd 419.2212; found 419.2218. $[\alpha]_D^{20} = -60.0$ (*c* 1.00, MeOH).

4.9.3. (*R,R*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4-methyl-5-phenylimidazole) (*R,R*)-9c

Yield: 293 mg (74%). Colorless crystals. Mp (dec.) 241 °C. IR (KBr): *ν* 3416–2863vs (br), 1639m, 1607m, 1578m, 1569m, 1492s, 1451m, 1385m, 1227m, 1218m, 1016m, 970m, 785s, 704s, 655m cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 7.48–7.38 (m, 6H, 4 arom. H, HC(2), HC(2′) imidazole), 7.10–6.92 (m, 6H, 6 arom. H), 4.04–3.96 (m, 2H, 2CH *c*Hex), 2.25–1.22 (m, 8H, $4CH_2$ *c*Hex), 2.06 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$): *δ* 134.7, 129.8, 128.3 (3s, $2C_q$ arom., C(4), C(4′), C(5), C(5′) imidazole), 132.6, 130.4, 128.7, 128.1 (4*d*, 10 arom. CH, C(2), C(2′) imidazole), 58.6 (d, 2CH *c*Hex), 35.1, 24.9 (2t, $4CH_2$ *c*Hex), 12.8 (q, $2CH_3$). MS (ESI): *m/z* 419 (100, $[M+Na]^+$). HRMS (ESI) $C_{26}H_{28}N_4Na$, $[M+Na]^+$: calcd 419.2212; found 419.2214. $[\alpha]_D^{20} = -29.8$ (*c* 1.02, MeOH).

4.9.4. (*S,S*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4-methyl-5-phenylimidazole) (*S,S*)-9c

Yield: 293 mg (74%). Colorless crystals. Mp (dec.) 243 °C (MeOH). IR (KBr): *ν* 3420–2863vs (br), 1640m, 1606m, 1578m, 1492s, 1484m, 1450m, 1443m, 1385m, 1227m, 1218m, 1016m, 970m, 785s, 704s, 655m cm^{-1}. MS (ESI): *m/z* 419 (91, $[M+Na]^+$), 397 (100, $[M+1]^+$). HRMS (ESI) $C_{26}H_{28}N_4Na$, $[M+Na]^+$: calcd 419.2212; found 419.2214. $[\alpha]_D^{20} = +28.2$ (*c* 1.02, MeOH).

4.9.5. (*R,R*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4,5-diphenylimidazole) (*R,R*)-9d

Yield: 416 mg (80%). Colorless crystals. Mp (dec.) 224 °C (MeOH). IR (KBr): *ν* 3416–2814vs (br), 1602s, 1578s, 1505s, 1490s, 1443m, 1410m, 1361w, 1247m, 1072m, 1043m, 774s, 721m, 698s, 661s. ^1H NMR ($CDCl_3$): *δ* 7.56–7.48 (m, 6H, 4 arom. H, HC(2), HC(2′) imidazole), 7.38–7.30 (m, 4H, 4 arom. H), 7.18–7.02 (m, 12H, 12 arom. H), 4.08–3.98 (m, 2H, 2CH *c*Hex), 2.38–1.20 (m, 8H, $4CH_2$ *c*Hex). ^{13}C NMR ($CDCl_3$): *δ* 137.3, 134.1, 130.0, 128.5 (4s, $4C_q$ arom., C(4), C(4′), C(5), C(5′) imidazole), 133.5, 131.1, 129.2, 129.1, 128.0, 126.4, 126.3 (7d, 20 arom. CH, C(2), C(2′) imidazole), 58.0 (d, 2CH *c*Hex), 35.2, 24.8 (2t, $4CH_2$ *c*Hex). MS ESI *m/z* 543 (100, $[M+Na]^+$). HRMS (ESI) $C_{36}H_{32}N_4Na$, $[M+Na]^+$: calcd 543.2525; found 543.2531. $[\alpha]_D^{20} = +72.3$ (*c* 0.94, MeOH).

4.9.6. (*S,S*)-*trans*-1,1′-(Cyclohexane-1,2-diyl)bis(4,5-diphenylimidazole) (*S,S*)-9d

Yield: 499 mg (96%). Colorless crystals. Mp (dec.) 228 °C (MeOH). IR (KBr): *ν* 3424–2813vs (br), 1602s, 1576s, 1505s, 1490m, 1443m, 1410m, 1361w, 1247m, 1072m, 1043m, 774s, 721m, 698s, 661s cm^{-1}. MS (ESI): *m/z* 543 (100, $[M+Na]^+$), 521 (30, $[M+1]^+$). HRMS (ESI) $C_{36}H_{32}N_4Na$, $[M+Na]^+$: calcd 543.2525; found 543.2529. $[\alpha]_D^{20} = -70.2$ (*c* 0.94; MeOH).

4.10. X-ray crystal-structure determination of *rac*-8a

All measurements were performed on a Nonius KappaCCD area-diffractometer[21] using graphite-monochromated Mo K*α* radiation (*λ* 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given below[22] and a view of the molecule is shown in Figure 1. Data reduction was performed with HKL DENZO and SCALEPACK.[23] The intensities were corrected for Lorentz and polarization effects, but not for absorption. Equivalent reflections were merged. The structure was solved by direct methods using SIR92,[24] which revealed the positions of all non-H-atoms. The asymmetric unit contains one molecule of *rac*-**8a** and two water molecules. The non-H-atoms were refined anisotropically. The H-atoms of the water molecules were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). The refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Three reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom-scattering factors for non-H-atoms were taken from Ref. 25 and the scattering factors for H-atoms were taken from Ref. 26. Anomalous dispersion effects were included in F_c;[27] the values for *f′* and *f″* were those of Ref. 28. The values of the mass attenuation coefficients are those of Ref. 29. All calculations were performed using the SHELXL97[30] program.

Crystal data for *rac*-**8a**: $C_{16}H_{24}N_4O_2 \cdot 2H_2O$, $M = 340.42$, colorless, prism, crystal dimensions $0.12 \times 0.17 \times 0.22$ mm, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 13.5001(4)$ Å, $b = 9.6212(3)$ Å, $c = 13.8420(3)$ Å, $\beta = 91.625(2)°$, $V = 1797.17(9)$ $Å^3$, $T = 160$ K, $D_X = 1.258$ g cm^{-3}, μ(Mo Kα) = 0.0911 mm^{-1}, scan type ϕ and ω, $2\theta_{(max)} = 60°$, total reflections measured 44007, symmetry independent reflections 5271, reflections with $I > 2\sigma(I)$ 3302, reflections used in refinement 5268, parameters refined 238, $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0521, $wR(F^2)$ [all data] = 0.1442 ($w = [\sigma^2(F_o^2) + (0.0644P)^2 + 0.253P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit 1.023, secondary extinction coefficient 0.006(2), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) = 0.26; −0.28 e $Å^{-3}$.

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