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A Practical One-Pot Synthesis of Enantiopure Unsymmetrical Salen Ligands

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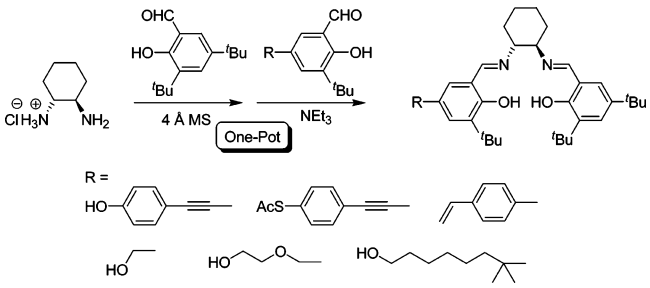


A practical, one-pot synthesis of enantiopure unsymmetrical salen ligands is described, using a 1:1:1 molar ratio of a chiral diamine and two different salicylaldehydes. The new synthetic protocol can be readily performed in good yields (60−85%) on a multigram scale with good tolerance toward various functional groups.

Metal complexes of chiral salen ligands (e.g., **1**, Figure 1) are among the most versatile asymmetric catalysts that have been applied successfully in a wide range of highly reactive and enatioselective catalytic reactions.[1−5] Whereas the vast majority of preparative and catalytic studies on this family of compounds has been dedicated to salen ligands with C_2 symmetry, recent studies have demonstrated that unsymmetrical salen ligands, in terms of two distinct substituents on the two aromatic rings,[6] hold important advantages.[7−12] For instance, immobilized salen catalysts are usually prepared by attaching

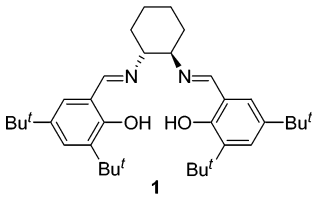
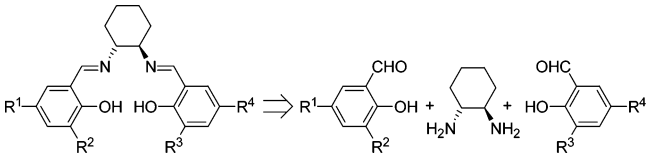


FIGURE 1. Jacobsen's salen ligand **1**.

SCHEME 1. Retrosynthetic Analysis of Unsymmetrical Salen Ligands



salicylidene moieties to supports.[13] The use of symmetrical salens would lead to a bigrafted, bridged geometry.[14] This often restricts the accessibility to catalytic centers and, hence, results in reduced activities and enantioselectivities. In contrast, studies from several groups have shown that the immobilization of monofunctionalized unsymmetrical salen ligands can generate the supported metal complexes in a more flexible fashion, often resulting in more desirable catalytic properties.[7−10]

Moreover, the desymmetrization of the salen core would introduce more structural variations that allows a deliberate optimization of both steric and electronic properties of the ligands. Finally, it has been reported that metal complexes derived from unsymmetrical salen ligands could exhibit better enantioselectivities for several reactions in comparison with their symmetrical counterparts.[11,12]

The condensation of a diamine and 2 equiv of a salicylaldehyde has been generally practiced as the standard method for the preparation of symmetrical salen ligands in high yields.[4,15] However, the synthesis of unsymmetrical salens has proven to be challenging (Scheme 1).[11,16−18] Although the direct condensation of an unprotected diamine with two different salicylaldehydes has been reported to work in several cases,[19−21] a number of research groups have reported problems associated with this methodology.[11,22,23] Since the condensations of the two amino groups often proceed with comparable rates, the reaction

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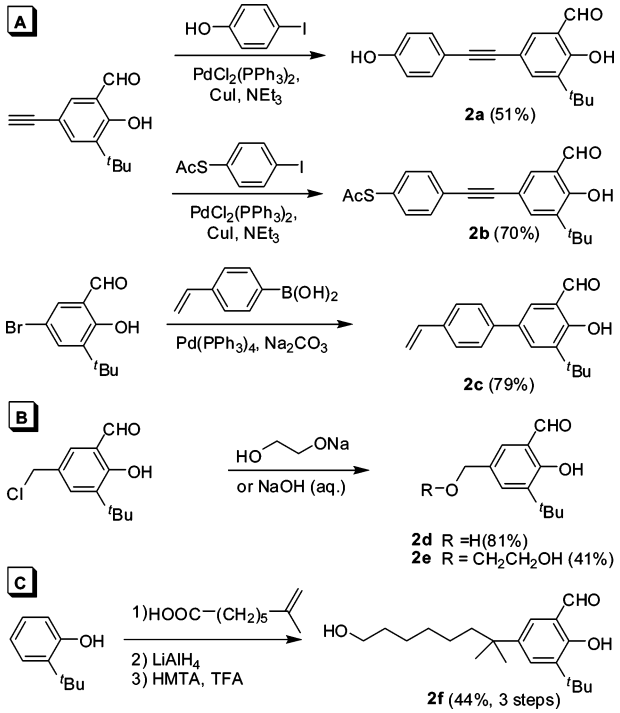
SCHEME 2. Synthesis of the Salicylaldehydes 2

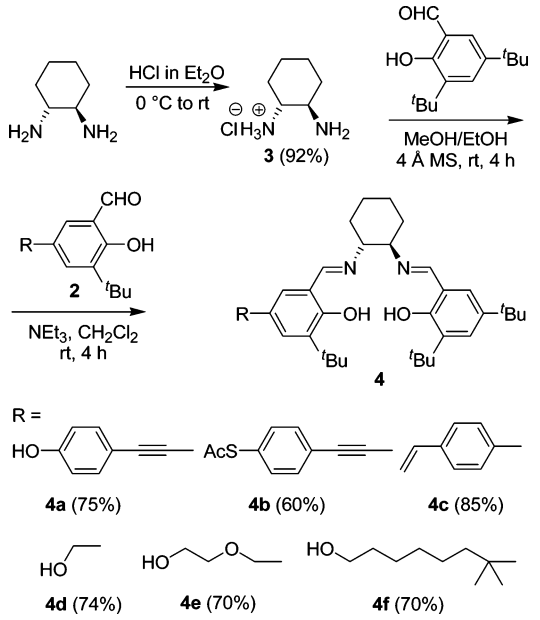


produces, inevitably, a statistical mixture of an aimed unsymmetrical salen and two undesired symmetrical salens.[7,24]

A more efficient approach is to protect one amino group of the employed diamine and to isolate the monoimine intermediate after the first condensation step. Acids including hydrogen chloride,[16] (+)-tartaric acid,[11] and *O*,*O*′-dibenzoyl-D-tartaric acid (DBTA)[11] have been applied to generate diamine monoammonium salts that can undergo stepwise condensations. Unfortunately, while this method has been reported with reasonably good yields for the synthesis of racemic unsymmetrical salens, poor yields were obtained when enantiopure diamines were used as a result of the disproportionation of the salicylidene moieties.[11] The origin for this difference between enantiopure and racemic compounds is still not understood. In this context, the development of a general and reliable preparative protocol for this important family of ligands, especially in nonracemic forms, is needed. Herein, we describe such a protocol by introducing a straightforward one-pot synthesis of enantiopure unsymmetrical salen ligands that can be performed in high yields on multigram scales.

Our efforts are focused on the preparation of nonracemic unsymmetrical salen ligands that can be attached to a variety of supports such as organic polymers, silica, and metallic nanoparticles. For this purpose, we have synthesized several salicylaldehydes functionalized with an immobilizing group (−OH, −SAc, or −CH═CH_2) and either a rigid (phenylacetylene or phenylene) or a flexible spacer (alkyl or ethylene glycol) as building blocks for the synthesis of unsymmetrical salen ligands. The synthetic pathway towards these building blocks is outlined in Scheme 2. First, for the syntheses of the rigid linker-based compounds, we employed Pd-catalyzed Sonogashira or Suzuki coupling reactions to yield **2a**−**c** (path A).[14] Both coupling reactions showed good tolerance to the presence

SCHEME 3. One-Pot Synthesis of Unsymmetrical Salen Ligands



of hydroxy, acetylsulfanyl, vinyl, and/or formyl functional groups. Second, salicylaldehydes **2d** and **2e** were produced by nucleophilic substitutions of 3-*tert*-butyl-5-chloromethylsalicylaldehyde[8,25] with RONa (R = −H, $-CH_2CH_2OH$) (path B). Last, the Friedel−Crafts alkylation of 2-*tert*-butylphenol with 7-methyl-7-octenoic acid, followed by the reduction of the carboxylic acid with $LiAlH_4$ and the acid-catalyzed formylation reaction, produced **2f** with a long alkyl chain (path C).

At the outset of this project, it became clear that a one-pot condensation reaction would be superior to the known stepwise route[11,16] for the preparation of enantiopure unsymmetrical salen ligands (Scheme 3). A one-pot approach would avoid the isolation step of the monoimine intermediate that is prone to the undesired disproportionation reaction.

We chose hydrogen chloride as the acid to protect one amine group of the diamine. The monoammonium salt **3** was prepared in almost quantitative yield from a 1:1 molar ratio of (*R*,*R*)-diaminocyclohexane and 2.0 M hydrogen chloride in ether.[16] The first condensation between **3** and 3,5-di-*tert*-butylsalicylaldehyde was carried out in a 1:1 (v/v) mixture of anhydrous methanol and ethanol at ambient temperature. It is crucial to use activated 4 Å molecular sieves to remove the water that is formed during the reaction. This significantly reduced the reaction time to 4 h and, more importantly, depressed the exchange of the salicylidene moieties. After the first condensation was complete, a solution of the functionalized salicylaldehyde **2** in dichloromethane was added to the reaction system, followed by the slow addition of an excess of anhydrous triethylamine as a deprotective base. The TLC analysis and ^{1}H NMR spectra showed that the second condensation was completed within 4 h and only traces of symmetrical salens were detected.

The target unsymmetrical salen ligands **4** were isolated in 60−85% yields as light yellow solids by means of column chromatography on silica gel pretreated with methanol or

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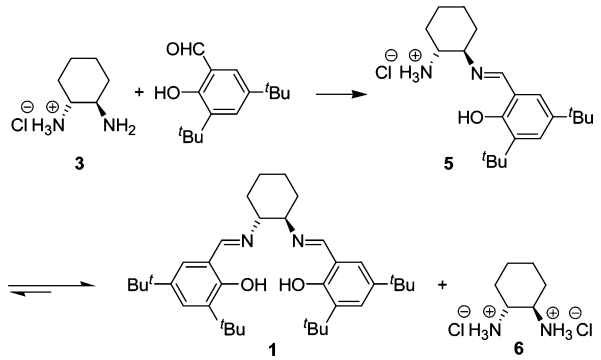
SCHEME 4. Disproportionation of the Monoimine Intermediate



methanol/triethylamine. The reaction is very efficient in terms of time and reproducibility and can easily be scaled up and carried out on a multigram scale. For instance, we prepared and isolated 5 g of the styryl-substituted salen **4c** within 2 days.

To compare our one-pot protocol to the stepwise synthesis developed by other groups,[11,16] we attempted to synthesize and separate the monoimine intermediate **5**. Unfortunately, we were unable to obtain **5** in reasonable yields (typical yields were less than 30%). It was found that a considerable amount of symmetrical salen **1** was formed during the workup (Scheme 4). A similar phenomenon was observed by Gilheany and coworkers, who employed (+)-tartaric acid instead of hydrogen chloride as the protective acid.[11] In addition, a ^{1}H NMR spectroscopic study revealed that **5** was unstable in solution and disproportionated quantitatively into **1** and **6** in acetone-d_6 at ambient temperature within 24 h. This observation clearly demonstrates the advantages of the one-pot strategy over the previously employed stepwise approach for the preparation of enantiopure unsymmetrical salen ligands.

In conclusion, we have developed a straightforward one-pot protocol for the synthesis of monofunctionalized enantiopure unsymmetrical salen ligands, using a 1:1:1 molar ratio of a hydrogen chloride-protected chiral diamine and two different salicylaldehydes. This new synthetic method allows for the synthesis of unsymmetrical salen ligands in good to excellent yields and can be readily performed on the large scale. While we have successfully tested this methodology in the synthesis of monofunctionalized unsymmetrical salens suitable for immobilization, this one-pot methodology can also be applied as a general and practical method for the preparation of other unsymmetrical salens.

Experimental Section

(*R*,*R*)-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-[3-*tert*-butyl-5-(4′-hydroxyphenylethynyl)salicylidene]-1,2-cyclohexanediamine (4a). (*R*,*R*)-1,2-Diaminocyclohexane mono(hydrogen chloride) (108 mg, 0.72 mmol), 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (168 mg, 0.72 mmol), and 4 Å molecular sieves (100 mg) were charged into a 25 mL flask equipped with a magnetic stir bar and a septum. Anhydrous ethanol (3 mL) and anhydrous methanol (3 mL) were added, and the bright yellow solution was stirred at room temperature for 4 h. A solution of 5-(4′-hydroxyphenylethynyl)-3-*tert*-butyl-2-hydroxybenzaldehyde (211 mg, 0.72 mmol) in anhydrous CH_2Cl_2 (6 mL) and anhydrous NEt_3 (0.20 mL, 1.44 mmol) was added. The red solution was stirred at room temperature for an additional 4 h. The reaction mixture was filtered through a short pad of dry silica gel, and the silica gel was flushed with CH_2Cl_2. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexanes = 1:5) to afford **4a** (323 mg, 75%) as a yellow-orange powder. R_f (SiO_2, ethyl acetate/hexanes = 1:5) = 0.13. $[\alpha]^{20}_D$: −136 (*c* 0.5, DCM). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 1.44 (s, 9 H), 1.46 (s, 9 H), 1.40−1.53 (m, 2 H), 1.82−1.93 (m, 2 H), 1.66−1.81 (m, 2 H), 1.93−2.05 (m, 2 H), 3.25−3.77 (m, 4H), 6.81 (d, J = 8.7 Hz), 7.00 (d, J = 2.5 Hz), 7.19 (d, J = 2.0 Hz, 1 H), 7.35 (d, J = 2.5 Hz, 1 H), 7.40 (d, J = 8.7 Hz, 2 H), 7.41 (d, J = 2.0 Hz, 1 H), 8.22 (s, 1 H), 8.28 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.4, 29.4, 29.6, 31.5, 33.1, 33.2, 35.0, 34.2, 35.1, 72.0, 2.2, 87.2, 88.3, 112.5, 115.7, 115.6, 117.7, 118.4, 126.1, 127.3, 132.7, 133.1, 133.2, 136.7, 137.9, 140.1, 155.7, 158.4, 161.5, 165.2, 166.2. MS (ESI): m/z (I_{rel}) = 607 (56, $[M + 1]^+$), 291 (84, $C_{25}H_{31}N_2O_2^+$). HRMS (ESI): calcd for $C_{40}H_{51}N_2O_3$ ($[M + 1]^+$) 607.3899, found 607.3888. Anal. Calcd for $C_{40}H_{50}N_2O_3$ (606.38): C, 79.17; H, 8.30; N, 4.62; O, 7.91. Found: C, 78.61; H, 8.26; N, 4.63; O, 8.03.

(*R*,*R*)-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-[5-(4′-acetylsulfanylphenylethynyl)-3-*tert*-butylsalicylidene]-1,2-cyclohexanediamine (4b). (*R*,*R*)-1,2-Diaminocyclohexane mono(hydrogen chloride) (128 mg, 0.85 mmol), 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (199 mg, 0.85 mmol,), and 4 Å molecular sieves (100 mg) were charged into a 25 mL flask equipped with a magnetic stir bar and a septum. Anhydrous ethanol (3 mL) and anhydrous methanol (3 mL) were added, and the bright yellow solution was stirred at room temperature for 4 h. A solution of 3-*tert*-butyl-5-(4′-acetylsulfanylphenylethynyl)-2-hydroxybenzaldehyde (300 mg, 0.85 mmol) in anhydrous CH_2Cl_2 (6 mL) and anhydrous NEt_3 (0.27 mL, 1.9 mmol) were added. The red solution was stirred at room temperature for an additional 4 h. The reaction mixture was filtered through a short pad of dry silica gel, and the silica gel was flushed with CH_2Cl_2. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexanes = 1:10) to afford **4b** (339 mg, 60%) as a yellow powder. R_f (SiO_2, ethyl acetate/hexanes = 1:5) = 0.47. $[\alpha]^{20}_D$: −144 (*c* 0.5, DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 9 H), 1.42 (s, 9 H), 1.43 (s, 9 H), 1.43−1.60 (m, 2 H), 1.84−1.94 (m, 2 H), 1.66−1.83 (m, 2 H), 1.94−2.08 (m, 2 H), 2.43 (s, 3 H), 3.24−3.44 (m, 2 H), 6.96 (d, J = 2.4 Hz, 1 H), 7.21 (d, J = 2.0 Hz, 1 H), 7.32 (d, J = 2.4 Hz, 1 H), 7.37 (d, J = 8.4 Hz, 2 H), 7.40 (d, J = 2.4 Hz, 1 H), 7.51 (d, J = 8.4 Hz, 1 H), 8.26 (s, 4 H), 8.28 (s, 4H), 13.60 (br s, 1 H), 14.33 (br s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 24.4, 29.3, 29.6, 30.4, 31.6, 33.1, 33.3, 34.2, 35.0, 35.1, 72.4, 72.5, 86.7, 91.6, 111.9, 117.8, 118.6, 125.2, 126.0, 127.1, 127.5, 132.1, 134.3, 132.7, 133.5, 136.6, 137.9, 140.2, 158.0, 161.5, 165.0, 166.2, 193.8. MS (ESI): m/z (I_{rel}) = 665 (59, $[M + 1]^+$), 449 (69, $C_{27}H_{33}N_2O_2S^+$), 331 (100, $C_{21}H_{35}N_2O$). Anal. Calcd for $C_{42}H_{52}N_2O_3S$ (664.37): C, 75.86; H, 7.88; N, 4.21; O, 7.22. Found: C, 75.79; H, 7.93; N, 4.06; O, 7.19.

(*R*,*R*)-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-[3-*tert*-butyl-5-(4′-vinylbenzene)salicylidene]-1,2-cyclohexanedediamine (4c). A 250 mL flask was charged with (1*R*,2*R*)-1,2-diaminocyclohexane monohydrochloride salt (1.51 g, 10 mmol), activated 4 Å molecular sieves (4.0 g), anhydrous methanol (40 mL), and anhydrous ethanol (40 mL). 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (2.34 g, 10 mmol) was added in one portion, and the reaction mixture was stirred at room temperature for 4 h. After complete consumption of the aldehyde as monitored by TLC, a solution of 3-*tert*-butyl-2-hydroxy-5-(4′-vinylphenyl)benzaldehyde (2.74 g, 10 mmol) in dichloromethane (80 mL) was added to the reaction system, followed by the slow addition of triethylamine (2.8 mL, 20 mmol). The reaction mixture was stirred at room temperature for an additional 4 h followed by the removal of the solvents. The residue was dissolved in dichloromethane (100 mL), washed with aqueous hydrochloric acid (1 M, 50 mL) and water (2 × 50 mL), and dried with magnesium sulfate. Flash chromatography of the crude product with (ether/hexanes = 1:50) afforded **4c** (5.05 g, 85%) as a yellow solid. Mp: 177−178 °C. $[\alpha]^{20}_D$: −156 (*c* 0.5, DCM). ^{1}H NMR (400

MHz, $CDCl_3$): δ = 1.22 (s, 9 H), 1.42 (s, 9 H), 1.44−1.51 (m, 2 H), 1.46 (s, 9 H), 1.70−1.84 (m, 2 H), 1.88−1.91 (m, 2 H), 1.97−2.02 (m, 2 H), 3.30−3.38 (m, 2 H), 5.25 (d, J = 11.0 Hz, 1 H), 5.77 (d, J = 17.6 Hz, 1 H), 6.74 (dd, J = 11.0, 17.6 Hz, 1 H), 6.97 (d, J = 2.5 Hz, 1 H), 7.21 (d, J = 2.5 Hz, 1 H), 7.31 (d, J = 2.5 Hz, 1 H), 7.40−7.45 (m, 4 H), 7.49 (d, J = 2.5 Hz, 1 H), 8.30 (s, 1 H), 8.35 (s, 1 H), 13.69 (s, br, 1 H), 14.01 (s, br, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 24.5, 24.6, 29.5, 29.6, 31.6, 33.3, 33.4, 34.2, 35.1, 35.2, 72.6, 113.6, 118.0, 119.0, 126.2, 126.7, 126.9, 127.1, 128.2, 128.3, 130.5, 136.0, 136.6, 136.7, 137.8, 140.2, 140.7, 158.2, 160.2, 165.8, 166.2. IR: ν = 3082, 2999, 2952, 2933, 2860, 1628, 1467, 1440, 1390, 1271, 1252, 1171, 840 cm^{-1}. UV−vis (THF): λ = 262, 300, 340 nm. MS (FAB): m/z (I_{rel}) = 592 (100, M^+). Anal. Calcd for $C_{40}H_{52}N_2O_2$ (592.85): C, 81.04; H, 8.84; N, 4.73. Found: C, 81.06; H, 8.95; N, 4.72.

(*R*,*R*)-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-[3-*tert*-butyl-5-(hydroxymethyl)salicylidene]-1,2-cyclohexanediamine (4d). A 100 mL flask was charged with (1*R*,2*R*)-1,2-diaminocyclohexane monohydrochloride salt (151 mg, 1.0 mmol), activated 4 Å molecular sieves (200 mg), and anhydrous methanol (10 mL). 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (234 mg, 1.0 mmol) was added in one portion, and the reaction mixture was stirred at room temperature for 4 h. A solution of 3-*tert*-butyl-2-hydroxy-5-(hydroxymethyl)benzaldehyde (208 mg, 1.0 mmol) in dichloromethane (10 mL) was added to the reaction mixture, followed by the slow addition of triethylamine (0.27 mL, 2.0 mmol). The reaction mixture was stirred at room temperature for an additional 4 h followed by the removal of the solvents. The residue was dissolved in dichloromethane (20 mL), washed with water (2 × 20 mL), and dried with magnesium sulfate. Flash chromatography of the crude product on silica gel (ether/hexanes = 1:4 to 1:1) afforded **4d** (0.39 g, 75%) as a light yellow solid. $[\alpha]^{20}_D$: −318 (*c* 0.5, DCM). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 9 H), 1.41 (s, 9 H), 1.42 (s, 9 H), 1.43−1.51 (m, 2 H), 1.70−1.80 (m, 2 H), 1.88−1.92 (m, 2 H), 1.96−2.02 (m, 2 H), 3.29−3.38 (m, 2 H), 4.52 (s, 2 H), 6.96 (d, J = 2.2 Hz, 1 H), 7.01 (d, J = 2.0 Hz, 1 H), 7.25 (d, J = 2.0 Hz, 1 H), 7.31 (d, J = 2.4 Hz, 1 H), 8.28 (s, 1 H), 8.29 (s, 1 H), 13.68 (s br, 1 H), 13.97 (s br, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 24.5, 24.6, 29.5, 29.6, 31.6, 33.3, 33.4, 34.2, 35.0, 35.2, 65.6, 72.60, 72.61, 118.0, 118.5, 126.2, 127.0, 129.0 (2 overlapping lines), 130.1, 136.6, 137.7, 140.1, 158.1, 160.3, 165.5, 166.1. MS (EI): m/z (I_{rel}) = 520 (100, M^+). Anal. Calcd for $C_{33}H_{48}N_2O_3$: C, 76.11; H, 9.29; N, 5.38. Found: C, 76.19; H, 9.51; N, 5.07.

(*R*,*R*)-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-[3-*tert*-butyl-5-(2′-hydroxyethoxymethyl)salicylidene]-1,2-cyclohexanediamine (4e). (*R*,*R*)-1,2-Diaminocyclohexane mono(hydrogen chloride) (276 mg, 1.83 mmol), 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (460 mg, 1.83 mmol), and 4 Å molecular sieves (200 mg) were charged into a 50 mL flask equipped with a magnetic stir bar and a septum. Anhydrous ethanol (5 mL) and anhydrous methanol (5 mL) were added, and the bright yellow solution was stirred at room temperature for 4 h. A solution of 3-*tert*-butyl-2-hydroxy-5-(2′-hydroxyethoxymethyl)benzaldehyde (460 mg, 1.83 mmol) in anhydrous CH_2Cl_2 (10 mL) and anhydrous NEt_3 (0.51 mL, 3.66 mmol) were added. The red solution was stirred at room temperature for an additional 4 h. The reaction mixture was filtered through a short pad of dry silica gel, and the silica gel was flushed with CH_2Cl_2. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexanes = 1:3) to afford **4e** (725 mg, 70%) as a yellow powder. R_f (SiO_2, ethyl acetate/hexanes = 1:3) = 0.23. $[\alpha]^{20}_D$: −262 (*c* 0.5, DCM). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (s, 9 H), 1.41 (s, 9 H), 1.42 (s, 9 H), 1.43−1.55 (m, 2 H), 1.83−1.92 (m, 2 H), 1.61−1.81 (m, 2 H), 1.93−2.08 (m, 2 H), 2.01 (br s), 3.28−3.38 (m, 2 H), 3.54 (m, 2 H), 3.72 (br s, 2 H), 4.40 (s, 2 H), 6.98 (d, J = 2.3 Hz, 1 H), 7.01 (d, J = 1.6 Hz, 1 H), 7.22 (d, J = 1.6 Hz, 1 H), 7.31 (d, J = 2.3 Hz, 1 H), 8.29 (s, 1 H), 8.30 (s, 1 H), 13.70, (br s, 1 H), 14.00 (br s,1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 24.3, 29.4, 29.5, 31.5, 33.3, 34.2, 34.9, 35.1, 63.0, 71.2, 72.5, 72.6, 73.4, 117.9, 118.4, 126.1, 126.8, 126.9, 129.6, 129.8, 136.5, 137.4, 140.0, 158.1, 160.3, 165.3, 166.0. MS (ESI): m/z (I_{rel}) = 565 (13, $[M + 1]^+$), 349 (48, $C_{20}H_{33}N_2O_3^+$), 331 (100, $C_{21}H_{35}N_2O^+$). HRMS (ESI): calcd for $C_{35}H_{53}N_2O_4$ ($[M + 1]^+$) 565.4005, found 565.4001. Anal. Calcd for $C_{35}H_{52}N_2O_4$ (564.39): C, 74.43; H, 9.28; N, 4.96. Found: C, 74.38; H, 9.30; N, 4.85.

(*R*,*R*)-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-[3-*tert*-butyl-5-(7′-hydroxy-1′,1′-dimethylheptyl)salicylidene]-1,2-cyclohexanediamine (4f). (*R*,*R*)-1,2-Diaminocyclohexane mono(hydrogen chloride) (59 mg, 0.39 mmol), 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (92 mg, 0.39 mmol), and 4 Å molecular sieves (200 mg) were charged into a 25 mL flask equipped with a magnetic stir bar and a septum. Anhydrous methanol (5 mL) was added, and the bright yellow solution was stirred at room temperature for 4 h. A solution of 3-*tert*-butyl-2-hydroxy-5-(7′-hydroxy-1′,1′-dimethylheptyl)benzaldehyde (125 mg, 0.39 mmol) in anhydrous CH_2Cl_2 (10 mL) and anhydrous NEt_3 (0.15 mL, 0.90 mmol) were added. The red solution was stirred at room temperature for an additional 4 h. The reaction mixture was filtered through a short pad of dry silica gel, and the silica gel was flushed with ethyl acetate. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexanes = 1:3) to afford **4f** (208 mg, 84%) as a bright yellow powder. $[\alpha]^{20}_D$: −200 (*c* 0.5, DCM). ^1H NMR (300 MHz, $CDCl_3$): δ =1.00−1.15 (m, 2 H), 1.16−1.31 (m, 2 H), 1.25 (s, 6 H), 1.23 (s, 9 H), 1.28 (s, 9 H), 1.42 (s, 9 H), 1.43−1.59 (m, 6 H), 1.70−1.80 (m, 2 H), 1.88−1.92 (m, 2 H), 1.93−2.08 (m, 4 H), 2.01 (s, 1H), 3.29−3.38 (m, 2 H), 3.54 (t, 2 H), 6.98 (d, J = 2.2 Hz, 1 H), 7.01 (d, J = 1.8 Hz, 1 H), 7.25 (d, J = 2.0 Hz, 1 H), 7.31 (d, J = 2.4 Hz, 1 H), 8.29 (s, 1 H), 8.31 (s, 1 H), 13.71 (s br, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 24.6, 24.8, 25.7, 29.1, 29.2, 29.3, 29.6, 29.7, 30.3, 31.6, 31.7, 33.0, 33.4, 33.5, 33.6, 34.3, 35.2, 37.2, 44.6, 63.2,72.6, 76.8, 77.3, 77.7, 118.1, 126.2, 126.9, 127.0, 136.5, 136.6, 138.7, 140.1, 158.1, 158.2, 165.9, 166.0, 166.1, 220.2. MS (ESI): m/z (I_{rel}) = 635.6 (13, $[M + 1]^+$). HRMS (ESI): calcd for $C_{41}H_{64}N_2O_3$ ($[M + 1]^+$) 633.4996, found 633.4995. Anal. Calcd for $C_{41}H_{64}N_2O_3$ (633.49): C, 77.80; H, 10.19; N, 4.43. Found: C, 77.88; H, 10.20; N, 4.39.

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Supporting Information Available: Detailed experimental procedures and characterization data are presented. This material is available free of charge via the Internet at http://pubs.acs.org.

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