Asymmetric Oxidative Coupling

Structurally Defined Catalysts for Enantioselective Oxidative Coupling Reactions**

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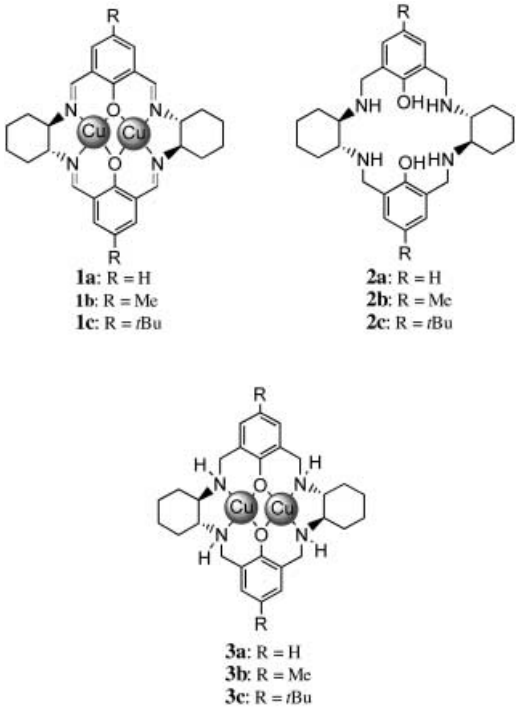
Pure binaphthol enantiomers and their derivatives are important chiral ligands for a wide range of asymmetric syntheses.[1] The facile conversion of binaphthol into 2,2′-(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) is particularly noteworthy because BINAP greatly expanded the synthetic utilities of binaphthol in asymmetric catalysis.[2] In light of the wide-ranging and important applications of these compounds, catalytic asymmetric preparation of chiral binaphthols and improvements in the enantioselectivity of the associated catalysts have continued to attract the attention of many researchers.[3]

Existing catalysts for the asymmetric preparation of chiral binaphthols include copper complexes of chiral amines or their derivatives[4] and chiral $V^{IV}O$ complexes with either one or two stereogenic metal centers.[5] Recently, dimeric copper(II) complexes[4b,e,f] or dinuclear $V^{IV}O$ complexes[5d,e] have been shown to be better catalysts with a high enantioselectivity. In the above reports, the catalytic metal complexes were prepared in situ by reacting a chiral ligand with a desired metal ion (Cu^{I}, Cu^{II}, or $V^{IV}O$). Generally, this method produces at least three species in solution: metal-free ligand, mononuclear, and dinuclear complexes. However, it is not easy to identify the active species that contribute to the overall reaction rate. Furthermore, the X-ray crystal structures of the above catalysts have never been determined, and this has restricted mechanistic investigations aimed at further improving the catalytic enantioselectivity and robustness. Given the success of Jacobsen's salen catalysts[6] in a broad range of asymmetric catalytic reactions, we decided to investigate whether coupled salen complexes would catalyze reactions that require two catalytic centers. Herein we describe the syntheses and crystal structures of a family of dicopper catalysts for the asymmetric oxidative coupling of 2-naphthol.

The reaction of (1*R*,2*R*)-1,2-diaminocyclohexane (*R*,*R*-DACH) with 2,6-diformylphenol or its derivatives in the presence of Cu^{II} gave yellow-green solids of **1a–c** (Scheme 1),



Scheme 1. Structures of Schiff base dicopper(II) complexes **1a–c**, macrocyclic ligands **2a–c**, and polyamino dicopper(II) complexes **3a–c**.

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[+] Sadly, Dr. Arthur E. Martell passed away on October 15, 2003. He was a fine chemist, a stimulating advisor, and always full of ideas. It was our privilege to work with him and we shall always be indebted to him for sharing his scientific insight with us. Along with the chemistry community, we mourn his passing.

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which were recrystallized from DMF/MeOH. X-ray crystal-structure analysis showed that **1b** contains two Cu^{II} centers, each coordinated in a N_2O_2-coordination compartment (Figure 1a). Within the macrocycle, the Schiff-base bonds are essentially coplanar with the adjacent phenolic rings, and the Cu^{II} ions reside in this plane. Each Cu^{II} ion adopts a square-pyramidal geometry with a coordinated methanol molecule in the axial direction. The space-filling representation of the dicationic complex (Figure 1b) exhibits D_2 symmetry and a substantial orbital overlap of the two Cu centers (Cu1–Cu2 distance, 2.8887 Å).

The preparation of **2a–c** was initially attempted by the Schiff-base condensation of *R*,*R*-DACH with the corresponding dialdehyde at room temperature, but this led to an oligomer. After adopting a metal-template approach, followed by hydrogenation, **2a–c** were successfully prepared in high yields (65–85%). ESI MS spectrum of **2b** (Figure 2) (*m*/*z*, [**2b**+H^+] 493.3476; [**2b**+2H^+] 247.1748) shows the correct molecular weight, and ^{1}H NMR and ^{13}C NMR spectra are entirely consistent with the proposed structure. Dicopper(II) complexes **3a–c** were readily prepared by reacting the corresponding macrocyclic ligands with 2 equivalents of Cu^{II} in MeOH.

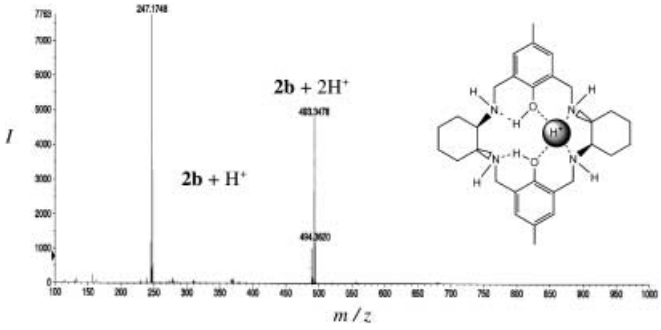


Figure 2. ESI MS spectrum of the macrocyclic ligand **2b**.

By utilizing a similar synthetic approach, Schiff base dicopper(II) complex **1d**, the chiral polyamino macrocycle **2d**, and the corresponding dicopper(II) complex **3d** were successfully prepared (Scheme 2). The X-ray crystal structure of **1d** (Figure 3) shows that the whole molecule adopts a starlike shape with four extended phenyl groups. The C–H bonds from the stereogenic centers in both **1b** and **1d** are essentially perpendicular to the N_4O_2-plane (Figure 4), giving an α,β,α,β-

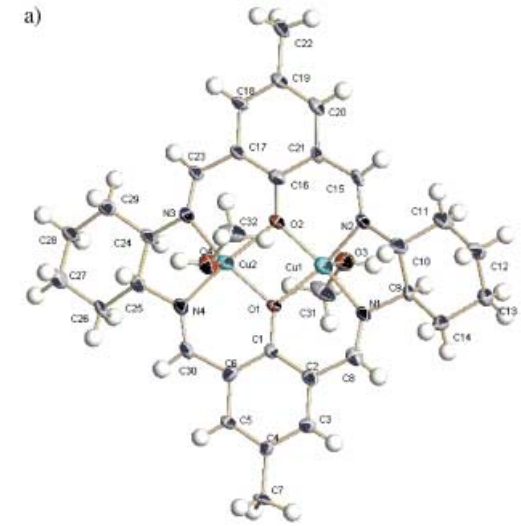
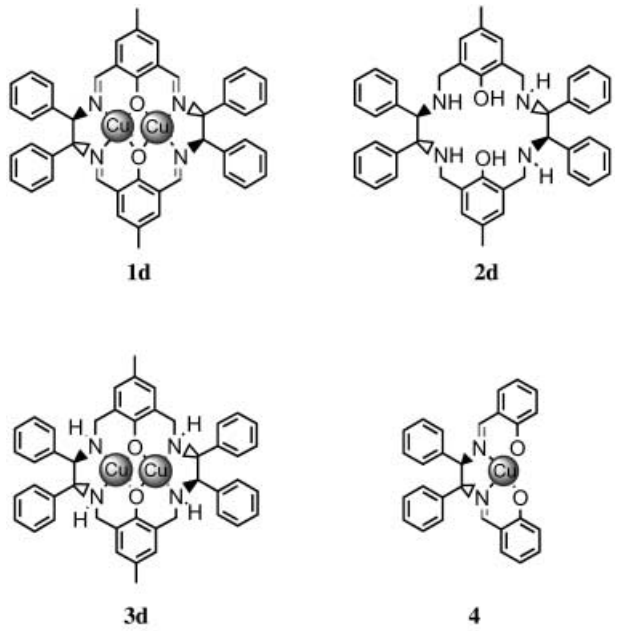


Figure 1. a) ORTEP drawing of **1b**. Selected bond lengths [Å] and angles [°]: Cu(1)-Cu(2) 2.8887(9), Cu(1)-N(1) 1.878(6), Cu(1)-O(1) 1.879(7), Cu(1)-O(2) 1.889(6), Cu(1)-N(2) 1.913(7), Cu(1)-O(3) 2.303(5); N(1)-Cu(1)-O(1) 92.7(3), N(1)-Cu(1)-O(2) 168.1(2), O(1)-Cu(1)-O(2) 81.5(2), N(1)-Cu(1)-N(2) 91.3(3). b) Space-filling representation of **1b**: gray: carbon, red: oxygen, blue: copper.



Scheme 2. Structures of Schiff base dicopper(II) complex **1d**, macrocyclic ligand **2d**, polyamino dicopper(II) complex **3d**, and the control compound **4**.

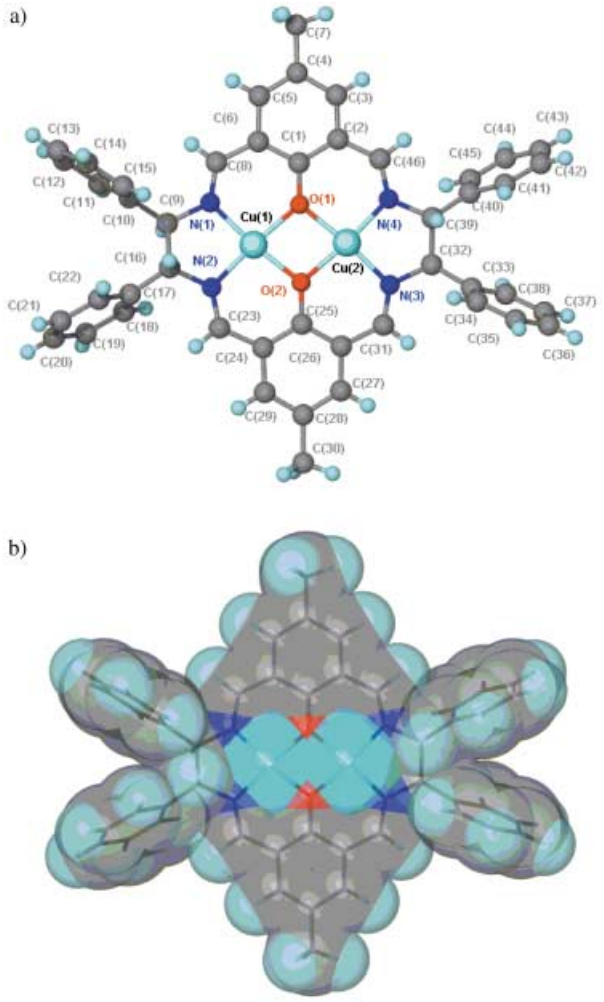
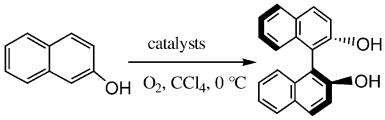


Figure 3. a) ORTEP drawing of **1d**. Selected bond lengths [Å] and angles [°]: Cu(1)-Cu(2) 2.8989(9), Cu(1)-N(1) 1.884(11), Cu(1)-O(1) 1.907(4), Cu(1)-O(2) 1.903(4), Cu(1)-N(2) 1.887(5), Cu(1)-O(1 ме) 2.305(5); N(1)-Cu(1)-O(1) 94.1(2), N(1)-Cu(1)-O(2) 171.9(2), O(1)-Cu(1)-O(2) 80.07(18), N(1)-Cu(1)-N(2) 90.5(3). b) Space-filling representation of **1d**: gray: carbon, red: oxygen, blue: copper.

chiral molecule reminiscent of the chiral porphyrin-amino derivative α,β,α,β-TAPP.[7] Complex **4** was synthesized by condensation of 2 equivalents of salicylaldehyde with 1*R*,2*R*-diphenylethylenediamine (*R*,*R*-DPEN) in the presence of Cu^{II}. This complex serves as a control in the following catalytic experiments.

The oxidative coupling of 2-naphthol was employed as a model reaction to compare the catalytic activity and enantioselectivity of the dicopper(II) macrocycle complexes, **1a–d** and **3a–d**. All reactions were carried in the presence of the catalysts (10 mol%) in CCl_4 at 0°C with molecular oxygen as oxidant (Table 1). The use of complex **1b** resulted in a yield of

Table 1: Catalytic enantioselective coupling of 2-naphthol in the presence of catalysts (10 mol%).[a]



Entry	Catalyst	*T* [°C]	*t* [days]	Yield [%][b]	*ee* [%][c]	Config.
1	**1a**	0	7	75	69	*S*
2	**1b**	0	7	79	82	*S*
3	**1b**	10	5	80	61	*S*
4	**1b**	20	3	89	45	*S*
5	**1c**	0	7	80	84	*S*
6	**1d**	0	7	79	80	*S*
7	**3a**	0	7	92	84	*S*
8	**3b**	0	7	84	86	*S*
9	**3b**	10	5	90	74	*S*
10	**3b**	20	3	93	62	*S*
11	**3c**	0	7	85	87	*S*
12	**3d**	0	7	85	88	*S*

[a] The reaction was carried out at 0, 10 or 20°C in the presence of 10 mol% of catalyst in CCl_4 solution. [b] Yield of isolated product. [c] The enantiomeric excess was determined by HPLC (Chiralpak AD) and the absolute configuration was assigned by comparison to literature.

79% and a moderate enantioselectivity of 82% *ee* (Table 1, entry 2). When polyamino complex **3b** was used (Table 1, entry 8), slightly increases in the *ee* value (86%) and the yield (84%) were observed. In general, polyaza complexes are more robust than their corresponding Schiff base complexes in terms of reproducibility and stability. Catalytic efficiency seems to be insensitive to the bulk of the peripheral groups (compare **1a–c** and **3a–c** series). At higher temperatures, the reaction rate increases, but lower enantioselectivities are observed. For instance, the ee value for **1b** decreased by 37% when the temperature was increased from 0 to 20°C.

Increased bulk of the diamino residues (compare **1b** with **1d** and **3b** with **3d**) does not significantly affect the enantioselectivity. Furthermore, the control compound with one metal center (**4** with C_2 symmetry) leads to a low enantioselectivity at 0°C (only 19% *ee*). These results suggest

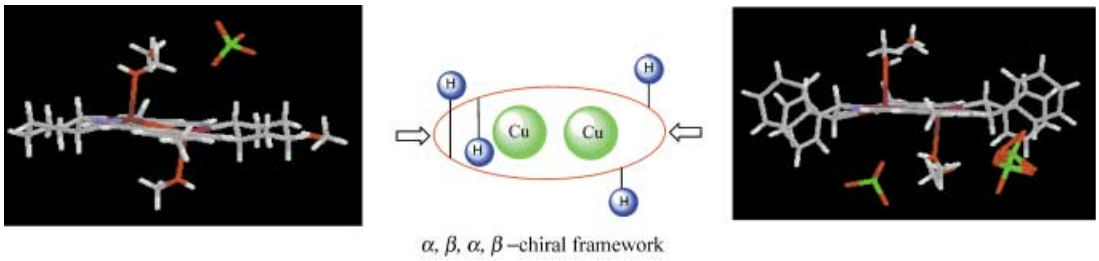


Figure 4. Alternate views of **1b** and **1d**, showing the positions of the chiral C–H bonds.

that a rigid dinuclear platform is essential for high enantioselectivity.

The Cu^{II} complex mediated oxidative coupling can proceed through three mechanistic pathways:[4e,g] 1) homolytic coupling of two radical species, 2) radical insertion of one aryl into the C–H bond of another aryl, and 3) reaction of an anion with a carbocation. For the coupling reaction mediated by **1b** (Figure 5), a substrate molecule may undergo ligand exchange with MeOH (on Cu1) to form a Cu^{II}–substrate complex **5**, which is followed by the generation of a radical intermediate **6**, which results from one-electron transfer from the substrate to Cu^{II}. Simultaneously, the same process may occur on the Cu2 center. Minimization of steric interactions between the radical intermediates and the axial hydrogen atoms of the chiral cyclohexyl rings should favor the orientation shown in Figure 5A. This should produce the *S* product, **8**. The above hypothesis is essentially the same as the pathway 1 mentioned above. This seems to be reasonable given the fact that the two catalytic centers are structurally symmetric. However, more quantitative experiments are required to completely verify our hypothesis or to disprove the remaining two reaction pathways.

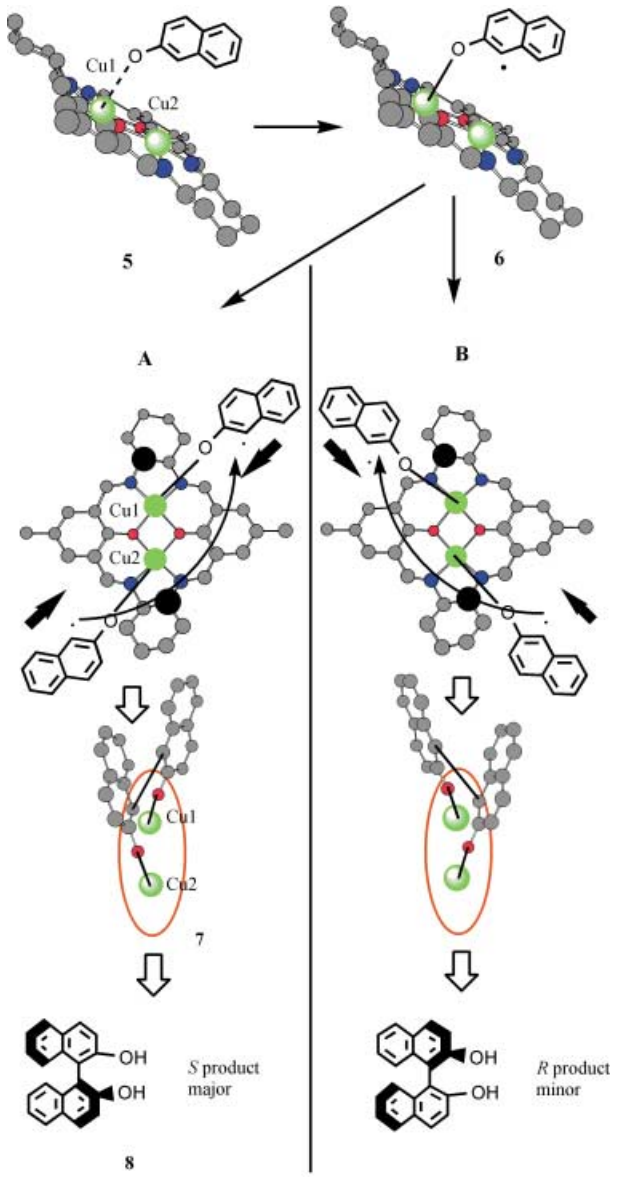


Figure 5. Illustration of enantioselectivity in **1b**-catalyzed oxidative coupling of 2-naphthol. Viewed from above the basal plane of the complex. Hydrogen atoms are omitted for clarity: green: copper, blue: nitrogen, gray: carbon, red: oxygen, black: stereogenic carbon center, which sterically hinders the substrate molecules.

Experimental Section

[**1b**–Cu_2]$(ClO_4)_2 \cdot 4CH_3OH$: A solution of 2-hydroxy-5-methyl-1,3-benzenedicarboxaldehyde (0.1 mmol) was added dropwise to a solution of $Cu(ClO_4)_2$ (0.1 mmol) and *R*,*R*-DACH (0.1 mmol) in EtOH (10 mL). After stirring for 4 h, a yellow-green product was obtained in 56% yield. Elemental analysis: calcd (%) for $C_{34}H_{50}Cl_2Cu_2N_4O_{14}$: C 43.6, H 5.4, N 6.0; found: C 43.6, H 5.5, N 6.0. Green crystals were obtained by diffusion of MeOH into a solution of the sample in *N*,*N*-dimethylformamide. Crystal dimensions: $0.3 \times 0.3 \times 0.02$ mm^3, $C_{34}H_{50}Cl_2Cu_2N_4O_{14}$, $M = 936.76$, monoclinic, space group $P2(1)$, $a = 11.996(3)$ Å, $b = 13.439$ (3) Å, $c = 12.303(3)$ Å, $\alpha = 90.0°$, $\beta = 102.747(5)°$, $\gamma = 90.0°$, $V = 1934.5(8)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.6478$ cm^{-3}, $F(000) = 976$, $T = 110(2)$ K, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å. A total of 7901 independent reflections ($R_{int} = 0.0371$) were obtained. Nonhydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included in the calculated positions refined with isotropic thermal parameters riding on those of the parent atoms. Full-matrix least-squares refinement on F^2 converged to $R_1 = 0.0786$, $wR_2 = 0.2078$ ($I > 2\alpha(I)$) with a goodness of fit $F^2 = 1.060$. CCDC-210825 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[**1d**–$Cu_2(ClO_4)_2$]$\cdot 4CH_3OH$: The complex was prepared by following a similar procedure to that described above (68% yield). Elemental analysis: calcd (%) for $C_{50}H_{54}Cl_2Cu_2N_4O_{14}$: C 53.0, H 4.8, N 5.0; found: C 53.0, H 4.7, N 5.1. Crystal data: green block $0.05 \times 0.2 \times 0.3$ mm^3; $C_{50}H_{54}Cl_2Cu_2N_4O_{14}$, $M = 1132.95$, monoclinic, space group $P2(1)$, $a = 15.8000(2)$ Å, $b = 9.4030$ (12) Å, $c = 16.883(2)$ Å, $\alpha = 90.0°$, $\beta = 98.298(2)°$, $\gamma = 90.0°$, $V = 248.9(6)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.516$ cm^{-3}, $F(000) = 1172$, $T = 110(2)$ K, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å. A total of 5485 independent reflections ($R_{int} = 0.0323$) were obtained. Full-matrix least-squares refinement on F^2 converged to $R_1 = 0.0419$, $wR_2 = 0.0986$ ($I > 2\alpha(I)$) with a goodness of fit $F^2 = 1.020$. CCDC-210826 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

2b: *R*,*R*-DACH (15 mmol) in MeOH (200 mL) was added dropwise to a stirred solution of 2-hydroxy-5-methyl-1,3-benzenedicarboxaldehyde (99%; 2.15 g, 15 mmol) in the presence of $Pb^{II}(OA_C)_2$ in MeOH (300 mL). The yellow solid formed was filtered, washed with MeOH, dried in air, and suspended in MeOH (50 mL). Solid $NaBH_4$ (4.0 g, 100 mmol) was used to reduce the metal complex at 0 °C in an ice bath. The suspension was magnetically stirred for about 2 h at room temperature. Water (5 mL) was added to neutralize excess unreacted $NaBH_4$. The resulting yellow-colored solution was filtered to remove any suspended material. The filtrate was diluted with water (100 mL), acidified (pH 2.0) with H_2SO_4 (8 M), and was then filtered. The filtrate was treated with aqueous ammonia (12.5 ml), and was then extracted with chloroform (3×50 mL). The combined organic layer was washed with water, dried with Na_2SO_4, and the solvent removed on a rotary evaporator nearly to dryness.

The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH ~ 1:1) and was identified as **2b** (75% yield). ESI MS: m/z: 493.3478 $[M+H]^+$; calcd for $C_{30}H_{44}N_4O_2$: 492.3464, m.p. 208 °C; $[\alpha]_D^{25} = -21.7$ ($c = 0.01$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta = 1.17$–1.80 (m, 8H; CH_2 of cyclohexane), 2.31 (m, 3H; CH_3-Ar), 3.79 (s, 2H; CH of cyclohexane), 4.30–4.52 (m, 4H; CH_2-Ar), 7.36 ppm (s, 2H; Ar-H); ^{13}C NMR ($CDCl_3$): $\delta = 20.78$ (CH_2 of cyclohexane), 24.75 (CH_2 of cyclohexane), 44.74 (CH of cyclohexane), 54.81 (CH_2-Ar), 121.86 (Ar-H), 133.75 (C(Ar)-CH_2), 134.36 (C(Ar)-CH_3), 152.10 ppm (C(Ar)-OH). Elemental analysis: calcd (%) for $C_{30}H_{44}N_4O_2$: C 73.13, H 9.00, N 11.37; found: C 73.13, H 9.06, N 11.38%.

2d: Prepared by a similar reaction procedure from *R*,*R*-DPEN as that for **2b**. Yield: 80%; ESI MS: m/z: 689.36 $[M+H]^+$; calcd for $C_{46}H_{48}N_4O_2$: 688.38; m.p. 164 °C; $[\alpha]_D^{25} = +31.3$ ($c = 0.01$, CH_2Cl_2); ^{1}H NMR,($CDCl_3$): $\delta = 2.18$ (s, 3H; CH_3-Ar), 3.80–3.92 (d, 2H; CH-Ar), 4.76 (m, 4H; CH_2-Ar), 7.08–7.42 (m, 12H; Ar-H), 7.78 ppm (s, 1H; OH); elemental analysis: calcd (%) for $C_{46}H_{48}N_4O_2$: C 80.20, H 7.02, N 8.13, found: C 80.11, H 7.06, N 8.10%.

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