Aminomethylation of BINOL with methyleneiminium salts

Gennady Shustov and Vladimir Khlebnikov

Abstract: A new method for synthesizing chiral 3,3′-bis(*N*,*N*-dialkylaminomethyl)-1,1′-bi-2-naphthols with high enantiomeric excess is described. The procedure consists of bis-lithiation of diprotected (*S*)- or (*R*)-1,1′-bis(2-naphthol) followed by treatment of the intermediate with methyleneiminium salts. Mild reaction conditions prevent racemization and provide 3,3′-bis(*N*,*N*-dialkylaminomethyl)-1,1′-bi-2-naphthols or 3-(*N*,*N*-dialkylaminomethyl)-1,1′-bi-2-naphthols with an enantiomeric excess >99%.

Key words: 3,3′-bis(*N*,*N*-dialkylaminomethyl)-1,1′-bi-2-naphthols, methyleneiminium salts, chiral, enantiomeric excess.

Résumé : On décrit une nouvelle méthode de synthèse des 3,3′-bis(*N*,*N*-dialkylaminométhyl)-1,1′-bi-2-naphthols chiraux avec des excès énantiomères élevés. Le procédé implique une bis-lithiation du (*S*)- ou (*R*)-1,1′-bis(2-naphthol) diprotégé, suivie d'un traitement de l'intermédiaire avec des sels de méthylèneiminium. Les conditions douces de la réaction permettent d'éviter la racémisation et elles permettent d'obtenir les 3,3′-bis(*N*,*N*-dialkylaminométhyl)-1,1′-bi-2-naphthols ou 3-(*N*,*N*-dialkylaminométhyl)-1,1′-bi-2-naphthols avec des excès énantiomères de plus de 99 %.

Mots-clés : 3,3′-bis(*N*,*N*-dialkylaminométhyl)-1,1′-bi-2-naphthols, sels de méthylèneiminium, chiral, excès énantiomère.

[Traduit par la Rédaction]

Introduction

Axial C_2 chirality of 3,3′-bis(*N*,*N*-dialkylaminomethyl)-1,1′-bi-2-naphthols (BINOLAMs (**1**), see Fig. 1) and their capability to form adducts with metals and some organic compounds makes them promising chiral auxiliaries in asymmetric synthesis.[1] The first use of BINOLAMs as chiral catalysts was reported[2] in the Michael addition of 2-(trimethylsilyloxy)furans to oxazolidinone enoates. Later they were used in phase-transfer α-alkylation of iminoesters of amino acids,[3] aldol[4] and nitroaldol[5] condensations, and in asymmetric addition of alkynyl-[6a] and diphenylzincs[6a,6b] to aldehydes and ketones. The major application of BINOLAMs so far is the ability of their complexes with metals to catalyze and induce enantioselectivity in various reactions of cyanosilylation,[6a,7] cyanocarbonylation,[8] and cyano-[9a,9b] or hydroxyphospholylation[9c] of aldehydes (other examples in this area are given in the review by Najera et al.[1c])

Recently, it was reported that BINOLAMs are photocytotoxic to DNA, which makes them effective against certain human tumor cell lines.[10] This BINOLAM action is based on their ability to undergo the elimination of dialkylamines under UV irradiation[11] and form highly reactive methylenequinoid structures; the latter are powerful DNA alkylating and cross-linking agents.[10]

Thus, the development of synthetic methods for producing enantiomerically pure BINOLAMs seems to be quite important. These compounds can be obtained from racemic starting material, for example, via photochemical transamination[11b] using L-proline esters as chiral auxiliaries; however, more often they are synthesized from commercial (*S*)- or (*R*)-1,1′-bis(2-naphthol) (BINOL, **2**).

Starting from BINOL, two basic synthetic approaches are described in the literature to prepare BINOLAMs containing tertiary amines in the side chain. The first one is a multistep route that starts with the introduction of the carboxylic[2a] or aldehyde[8c] groups into the 3,3′ positions of BINOL, followed by the formation of amides or imines that are subsequently reduced (a lengthier procedure from BINOL 3,3′-dialdehyde is sometimes used,[4,10] since it provides higher yields[10]). In isolated examples the required enantiomerically pure BINOL 3,3′-dicarboxylic acid was obtained via resolution[3] or enantioselective oxidative biaryl coupling.[12] Once the appropriate 3,3′-disubstituted BINOL intermediates are produced, the following steps are known to proceed without racemization and provide the enantiomerically pure BINOLAMs in 10%–30% chemical yield. The most recent publication based on this traditional approach describes a newly developed synthesis based on bis-anionic Fries rearrangement[7d] of BINOL carbamates, and it provided BINOLAM (*S*)-**1** (R = Et) with 63% yield in three steps. Unfortunately, this method can hardly be called general, because it was reported[13] that for some substrates migration of the second carbamate group is slow, and a significant amount of mono-rearranged by-product is formed.

The second known approach to the enantiomerically pure BINOLAMs utilizes the direct reaction of aminomethylation of BINOL enantiomers with *N*-hydroxymethylmorpholine (**3**, Fig. 2) at 110 °C, followed by enantiomeric enrichment of

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Fig. 1. Chiral BINOLAMS and parent (*S*)-BINOL.

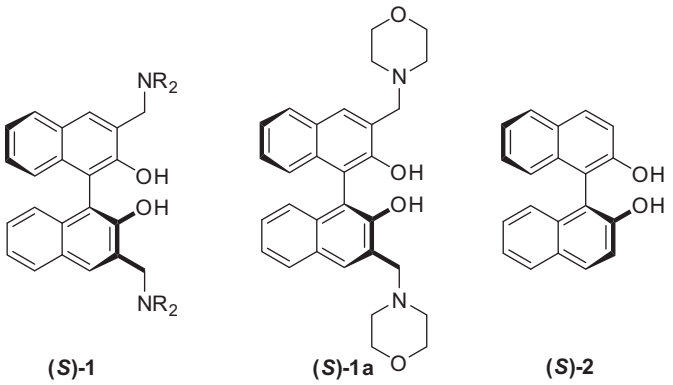
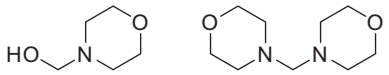


Fig. 2. Aminomethylating agents.



3 **4**

the product by recrystallization.[6a,7c] This is the shortest synthesis of BINOLAMs and hence it looks the most convenient. However, it suffers from several shortcomings.

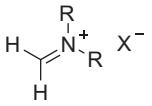
First, the conversion of the starting BINOLs to BINOLAMs in this aminomethylation reaction is not very high, and usually a significant amount of monoaminomethylated product is formed along with the desired BINOLAM. Apparently, the yield in this reaction depends on the purity of the aminomethylating agent **3** and, according to our experience, the reagent **3** (normally prepared by condensation of morpholine with paraformaldehyde) often contains a significant amount of unreactive *N*,*N*-methylene–bismorpholine (**4**). The latter reaction is difficult to control, and the composition of the crude mixture may vary from experiment to experiment. The same is true for preparation of other *N*-hydroxymethyldialkylamines.

Second, since the described direct aminomethylation of BINOL is carried out at elevated temperature (110 °C), noticeable racemization could occur, resulting in the obtained BINOLAM with an ee of about 75%.[6a,7c] These results are understandable and potentially unavoidable because, as it has been demonstrated earlier, the configurational stability of BINOL decreases in the presence of bases.[14] Increasing the ee of (*S*)-**1** by recrystallization as described by other authors[6a,7c] cannot be considered to be a general method applicable to other BINOLAMs, since the recrystallization conditions need to be optimized for each individual compound. This could take significant time and may not be possible in some situations.

Based on these considerations, we thought it would be highly desirable to develop an aminomethylating agent with better reactivity, to make it possible for the aminomethylation reaction to proceed with higher yields and under milder conditions. Since the target aminomethylated BINOLs have useful practical applications and might be required in multigram quantities, we were looking at reagents that could be easily synthesized and purified.

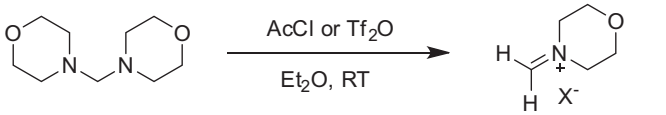
In this study we investigated the possibility of using the methyleneiminium salts **5a**–**5b** (Fig. 3) as such reagents.

Fig. 3. Methyleneiminium salts **5a**–**5d**.



5a R+R = $(CH_2)_2O(CH_2)_2$, X = Cl
5b R+R = $(CH_2)_2O(CH_2)_2$, X = CF_3SO_3
5c R = Me X = Cl
5d R = Me X = I

Scheme 1. Synthesis of methyleneiminium salts **5a** and **5b**.



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5a (X = Cl)
5b (X = CF_3SO_3)

Results and discussion

N,*N*-Dialkylmethyleneiminium salts can be easily generated by a reaction of acyl chlorides or anydrides with methylene–bis(dialkylamines).[15] Thus, chloride **5a** was obtained in 97% yield and triflate **5b** in 99% yield by reacting **4** with acetyl chloride or triflic anhydride accordingly (Scheme 1). Iminium salts **5c** and **5d** are commercially available.

The good reactivity of *N*,*N*-dialkylmethyleneiminium salts in aromatic electrophilic substitution reactions, which was demonstrated for anilines,[16] phenols,[17] furanes,[15c] thiophenes,[18] pyrrols,[19] and various other electron-rich heterocycles,[20] encouraged us to try this approach in the preparation of optically active BINOLAMs.

We started our experiments on BINOL aminomethylation with chloride **5a**, trying to reproduce the conditions that were reported in the literature for 3- and 4-methoxycarbonylphenols.[17] It appeared that the reaction of **2** with iminium salt **5a** in dichloromethane in the presence of K_2CO_3 at room temperature did not occur. Changing the solvent to acetonitrile, increasing the amount of **5a** to 8 equiv, and carrying out the reaction at 60 °C for 19 h did not bring positive results either. No aminomethylation reaction for **2** was observed even when stronger bases were used, such as 1 N NaOH (CH_2Cl_2–H_2O, room temperature, 16 h) or NaH (DMF, room temperature, 19 h).

Based on these results, it was concluded that to make the reaction of methyleneiminium salts with BINOL substrates successful, the increase of nucleophilicity of the latter were required. This can be done, for example, by lithiation of the 3 and 3′ positions of bis-O,O′-diprotected BINOL as described by Snieckus and co-workers.[21]

A series of experiments demonstrated that indeed MOM-protected BINOL **6**, after treatment with *n*-BuLi, reacted smoothly with methyleneiminium salts **5a**–**5d** to produce corresponding BINOLAMs **7a** and **7b** in 54%–88% yields, respectively (Scheme 2 and Table 1). Small amounts of monoaminomethyl derivatives **8a** and **8b** were also formed; however, the yields of these side products were significantly lower then in the case of the reaction of BINOL (**2**) with *N*-hydroxymethylenemorpholine (**3**).[6a,7c]

In a typical aminomethylation procedure, 3.2 equiv of methyleneiminium salt **5** relative to substrate **6** were used.

Scheme 2. Synthesis of **7a** and **7b** and **8a** and **8b**.

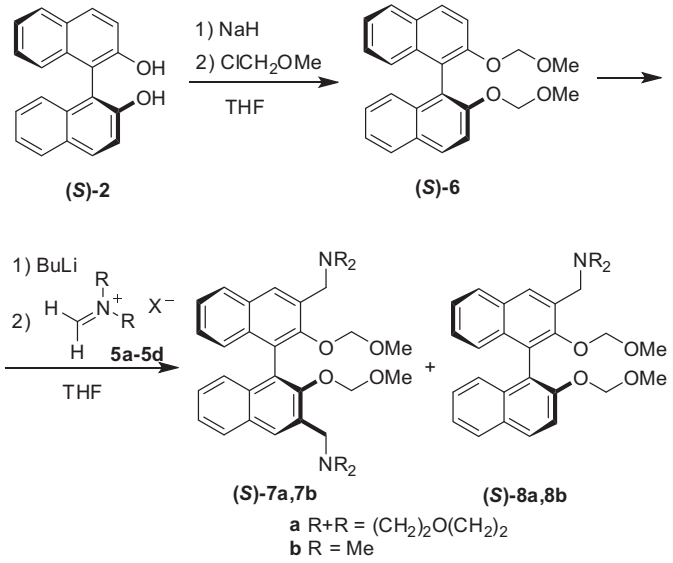


Table 1. Aminomethylation of (*S*)-**6** with methyleneiminium salts **5a**–**5d** (Scheme 2).

Entry	Methyleneiminium salt	Ratio of **7**:**8** (mol/mol)[a]	Yield (%)[b]
1	**5a**	1:0.2	54
2	**5b**	1:0.2	69
3	**5c**	1:0.2	63
4	**5d**	1:0.02	88
5	**5a**	0.2:1	69

Note: The reaction was carried out in THF at –15 °C to room temperature (1 or 2 h) with 2.6 equiv of *n*-BuLi and 3.2 equiv of **5a**–**5d** for entries 1–4 and with 1.3 equiv of *n*-BuLi and 1.6 equiv of **5a** for entry 5.

[a]In the crude mixture.

[b]Isolated yield of the major product.

Reducing this amount to 1.6 equiv allowed the monomethyleneimine compound **8** to be obtained in 69% yield.

Carrying out the reaction under mild conditions (temperature from –20 to 20 °C) helped to avoid the racemization of substrate **6** and its aminomethylated derivatives **7** and **8**. The high ee (>99%) of isolated products (*S*)-**7a** and (*S*)-**7b** and (*S*)-**8a** as well as BINOLAMs (*S*)-**1a** and (*S*)-**1b**, which were obtained after removing the MOM protective groups (Scheme 3), was confirmed by HPLC analysis using a column with a chiral stationary phase.

Conclusion

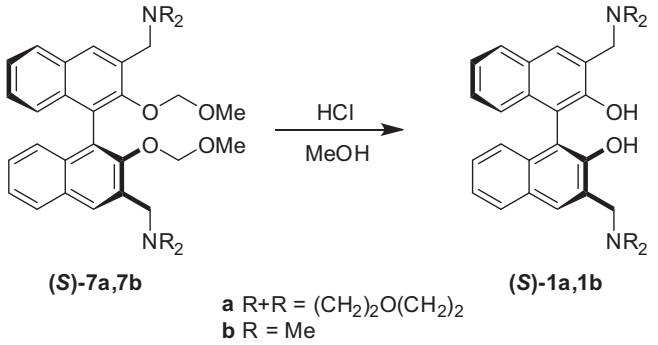
In conclusion, the investigated reaction of lithiated MOM-protected BINOL with methyleneiminium salts can be a convenient and versatile method for the synthesis of BINOLAMs with high enantiomeric excess (>99%).

Experimental

Instrumentation, analysis, and starting materials

All starting materials, solvents, and reagents were used as purchased from commercial suppliers, unless otherwise noted. Anhydrous THF was purchased from Sigma-Aldrich. Reactions were monitored by thin-layer chromatography

Scheme 3. Synthesis of 3,3′-bis(*N*,*N*-dialkylaminomethyl)-1,1′-bi-2-naphthols (BINOLAMs) **1a** and **1b**.



(TLC) carried out on Macherey–Nagel Alugram SIL G/UV254 silica gel 60 plates with a fluorescent indicator using phosphomolybdic acid in ethanol and heat as a developing agent. NMR spectra were recorded on a Varian Mercury 400 NMR instrument (400 MHz frequency for ^{1}H) using residual undeuterated solvent as an internal reference. Low-resolution mass spectra were recorded on a Water Micromass ZQ mass spectrometer with electrospray ionization (ESI). HPLC analyses were performed on a Waters 600 system with a Waters 2996 photodiode array detector using a C-18 reverse-phase column. For the ee determination, a Chiralcel OD-R column was used (MeCN – 0.5 N aq $NaClO_4$, 60:40 as a mobile phase). All dry column chromatography purifications were performed on silica gel 60A with a 5–15 μm particle size.

N-Methylenemorpholinium chloride (5a)

To a stirred solution of acetyl chloride (4.32 g, 55 mmol) in anhydrous Et_2O (100 mL), a solution of methylene–bismorpholine[22] (9.31 g, 50 mmol) in anhydrous Et_2O (50 mL) was added dropwise at 20–24 °C over 1.5 h. The reaction mixture was stirred for an additional 0.5 h at room temperature. The white precipitate was filtered off, washed with anhydrous Et_2O (3 × 40 mL), and dried in vacuum to provide 6.39 g (94%) of *N*-methylenemorpholinium chloride **5a**[15d] as a white powder. ^{1}H NMR (400 MHz) in $(CD_3)_2SO$ δ: 3.90 (4H, t, ^3J = 5.0 Hz, OCH_2), 4.06 (4H, t, ^3J = 5.0 Hz, NCH_2), 8.24 (2H, $^+N{=}CH_2$).

N-Methylenemorpholinium triflate (5b)

To a stirred solution of trifluoromethanesulfonic anhydride (9.93 g, 35.2 mmol) in anhydrous Et_2O (200 mL), a solution of methylene–bismorpholine[22] (5.96 g, 32 mmol) in anhydrous Et_2O (50 mL) was added dropwise at 20–24 °C over 1 h. The reaction mixture was stirred for an additional 2 h at room temperature. The white precipitate was filtered off, washed with anhydrous Et_2O (3 × 40 mL), and dried in vacuum to provide 7.90 g (99%) of *N*-methylenemorpholinium triflate **5b** as a highly hygroscopic white powder.[23] ^{1}H NMR (400 MHz) in $(CD_3)_2SO$ δ: 3.90 (4H, br. t, OCH_2), 4.08 (4H, br. t, NCH_2), 8.21 (2H, $^+N{=}CH_2$).

(*S*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthol (6)

To a stirred cooled (0–5 °C) suspension of NaH (60% in mineral oil, 15.73 g, 0.393 mol) in a mixture of anhydrous THF (660 mL) and anhydrous DMF (330 mL), a solution of **2** (50.41 g, 0.176 mol) in anhydrous THF (200 mL) was

added dropwise at 5–10 °C. The resultant mixture was allowed to warm up to 15 °C and chloromethyl methyl ether (44.73 g, 0.556 mol) was added dropwise at 15–20 °C. The reaction mixture was stirred for 16 h at room temperature, quenched with water (20 mL), concentrated under reduced pressure to a volume of ~400 mL, and diluted with EtOAc (800 mL). The obtained mixture was washed with water (3 × 300 mL), 1 N HCl (300 mL), saturated aqueous $NaHCO_3$ (300 mL), and brine (300 mL) and dried over $MgSO_4$. Filtration through a pad of silica gel and removal of the solvent from the filtrate under reduced pressure provided 72.7 g of a white solid. This solid was suspended in hexanes (300 mL) and the precipitate was filtered off and washed with hexanes (2 × 150 mL). The product **6**[24] (63.2 g, 96%) was obtained as white solid after drying in vacuum. ^{1}H NMR (400 MHz) in $CDCl_3$ δ: 3.14 (6H, OMe), 4.98 (2H, d, ^2J = 6.8 Hz, OCH_A), 5.08 (2H, d, ^2J = 6.8 Hz, OCH_B), 7.15 (2H, d, J = 8.2 Hz), 7.22 (2H, t, J = 8.2 Hz), 7.35 (2H, t, J = 8.2 Hz), 7.58 (2H, d, J = 8.8 Hz), 7.87 (2H, d, J = 8.2 Hz), 7.95 (2H, d, J = 8.8 Hz).

(*S*)-3,3′-Bis(*N*-morpholinomethyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthol (7a)

To a stirred cooled (–5 °C to 0 °C) solution of **6** (1.87 g, 5 mmol) in anhydrous THF (50 mL), a 1.6 mol/L solution of *n*-butyl lithium in hexane (8.13 mL, 13 mmol) was added dropwise at –5 to 0 °C. The reaction mixture was stirred for 2 h at 0–5 °C and cooled to about –15 °C. Avoiding exposure to air, freshly prepared and dried **5b** (3.99 g, 16 mmol) was added portionwise and the reaction mixture was allowed to warm to room temperature. The stirring was continued for an additional 2 h, and the reaction was quenched by addition of water (1 mL). The resultant mixture was concentrated under reduced pressure and the oily residue was dissolved in ethyl acetate (50 mL). The obtained solution was washed with water (2 × 15 mL) and brine (20 mL). After drying over $MgSO_4$, the solution was filtered and concentrated under reduced pressure to provide 3.02 g of a light pink semisolid, which was subjected to dry flash chromatography on silica gel (50% EtOAc–hexanes to 100% EtOAc) to afford 1.98 g (69%) of **7a** as a white solid. Assayed at 98.13% by HPLC. HPLC analysis on a column with a chiral stationary phase showed an enantiomeric excess of >99.5%. ^{1}H NMR (400 MHz) in $CDCl_3$ δ: 2.62 (8H, m, NCH_2), 2.70 (6H, OMe), 3.76 (10H, m, OCH_2 + NCH_A), 3.88 (2H, d, ^2J = 13.6 Hz, NCH_B), 4.57 (2H, d, ^2J = 5.6 Hz, OCH_A), 4.74 (2H, d, ^2J = 5.6 Hz, OCH_B), 7.22 (4H, m), 7.41 (2H, t, J = 8.0 Hz), 7.88 (2H, d, J = 8.0 Hz), 8.00 (2H). MS (electrospray), *m*/*z*: 573 (M^+). Anal. calcd for $C_{34}H_{40}N_2O_6$ (%): C 71.31, H 7.04, N 4.89; found: C 71.38, H 7.10, N 4.90.

(*S*)-3,3′-Bis(*N*,*N*-dimethylaminomethyl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthol (7b)

To a stirred cooled (–5 to 0 °C) solution of **6** (1.87 g, 5 mmol) in anhydrous THF (50 mL), a 1.6 mol/L solution of *n*-butyl lithium in hexane (8.13 mL, 13 mmol) was added dropwise at –5 to 0 °C. The reaction mixture was stirred for 2 h at 0–5 °C and cooled to –15 °C. Solid (*N*,*N*-dimethyl) methyleneammonium iodide (**5d**) (2.96 g, 16 mmol) was added portionwise and the reaction mixture was allowed to warm up to room temperature. The stirring was continued for an additional 2 h and the reaction was quenched by addition of water (1 mL). The resultant mixture was concentrated under reduced pressure and the oily residue was dissolved in ethyl acetate (50 mL). The obtained solution was washed with water (2 × 15 mL), a saturated aqueous solution of $Na_2S_2O_7$ (15 mL), and brine (20 mL). After drying over $MgSO_4$, the solution was filtered and concentrated under reduced pressure to provide 2.61 g of a light yellow oil, which was subjected to dry flash chromatography on silica gel (CH_2Cl_2 to 5% MeOH–CH_2Cl_2) to afford 2.15 g (88%) of **7b** as a colourless viscous oil. Assayed at 97.99% by HPLC. HPLC analysis on a column with a chiral stationary phase showed an enantiomeric excess of >99.5%. ^{1}H NMR (400 MHz) in $CDCl_3$ δ: 2.38 (12H, NMe), 2.76 (6H, OMe), 3.72 (2H, d, ^2J = 14.2 Hz, NCH_A), 3.80 (2H, d, ^2J = 14.2 Hz, NCH_B), 4.51 (2H, d, ^2J = 5.8 Hz, OCH_A), 4.66 (2H, d, ^2J = 5.8 Hz, OCH_B), 7.20 (2H, t, J = 8.2 Hz), 7.25 (2H, d, J = 8.2 Hz), 7.40 (2H, t, J = 8.2 Hz), 7.88 (2H, d, J = 8.2 Hz), 8.04 (2H). MS (electrospray), *m*/*z*: 489 (M^+ + 1). Anal. calcd for $C_{30}H_{36}N_2O_4$ (%): C 73.74, H 7.43, N 5.73; found: C 73.93, H 7.37, N 5.61.

(*S*)-3-*N*-Morpholinomethyl-2,2′-bis(methoxy-methoxy)-1,1′-binaphthol (8a)

To a stirred cooled (–5 to 0 °C) solution of **6** (13.10 g, 35 mmol) in anhydrous THF (350 mL), a 1.6 mol/L solution of *n*-butyl lithium in hexane (28.4 mL, 45.5 mmol) was added dropwise at –5 to 0 °C. The reaction mixture was stirred for 2 h at 0–5 °C and cooled to –15 °C. Solid **5a** (7.59 g, 56 mmol) was added portionwise and the reaction mixture was allowed to warm up to room temperature. The stirring was continued for additional 2 h and the reaction was quenched by addition of water (7 mL). The resultant mixture was concentrated under reduced pressure and the oily residue was dissolved in ethyl acetate (350 mL). The obtained solution was washed with water (2 × 100 mL) and brine (200 mL). After drying over $MgSO_4$, the solution was filtered and concentrated under reduced pressure to provide 16.8 g of a yellow oil, which was subjected to dry flash chromatography on silica gel (30% EtOAc–hexanes to 60% EtOAc–hexanes) to afford 11.50 g (69%) of **8a** as a white solid. Assayed at 96.81% by HPLC. HPLC analysis on a column with a chiral stationary phase showed an enantiomeric excess of >99.5%. ^{1}H NMR (400 MHz) in $CDCl_3$ δ: 2.63 (4H, m, NCH_2), 2.77 (3H, OMe), 3.16 (3H, OMe), 3.57 (4H, m, OCH_2), 3.83 (2H, NCH_2Ar), 4.64 (1H, d, ^2J = 5.6 Hz, OCH_A), 4.71 (1H, d, ^2J = 5.6 Hz, OCH_B), 5.02 (1H, d, ^2J = 7.2 Hz, OCH_A'), 5.11 (1H, d, ^2J = 7.2 Hz, OCH_B'), 7.22 (4H, m), 7.37 (2H, m), 7.58 (1H,d, J = 8.8 Hz), 7.87 (2H, m), 7.96 (2H, d, J = 8.8 Hz), 7.99 (2H). MS (electrospray), *m*/z: 474 (M^+). Anal. calcd for $C_{29}H_{31}NO_5$ (%): C 73.55, H 6.60, N 2.96; found: C 73.81, H 6.72, N 3.07.

(*S*)-3,3′-Bis(*N*-morpholinomethyl)-2,2′-dihydroxy-1,1′-binaphthol (1a)

To a stirred cooled (–5 to 0 °C) solution of **7a** (1.72 g, 3 mmol) in methanol (15 mL), a 4 mol/L solution of HCl in 1,4-dioxane (15 mL, 60 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 16 h. After removal of solvent under reduced pressure, the solid residue was triturated with

Et_2O (2 × 30 mL) and dried in vacuum to provide 1.69 g of a white solid. The isolated solid was suspended in CH_2Cl_2 (80 mL) and saturated aqueous $NaHCO_3$ (40 mL) was added to the resultant suspension. After 15 min of stirring, the organic phase was separated and dried over $MgSO_4$. Filtration and removal of the solvent from the filtrate under reduced pressure provided 1.51 g of a yellow solid, which was subjected to dry flash chromatography on silica gel (2% EtOAc–CH_2Cl_2 to 20% EtOAc–CH_2Cl_2) to afford 1.31 g (90%) of **1a**[7c] as a white solid. Assayed at 96.53% by HPLC. HPLC analysis on a column with chiral stationary phase showed enantiomeranic excess of >99.5%. ^{1}H NMR (400 MHz) in $CDCl_3$ δ: 2.64 (8H, br. m, NCH_2), 3.69 (8H, br. m, OCH_2), 3.89 (2H, d, ^2J = 14.0 Hz, NCH_A), 4.12 (2H, d, ^2J = 14.0 Hz, NCH_B), 7.29–7.12 (6H, m), 7.66 (2H), 7.78 (2H, d, J = 8.4 Hz). MS (electrospray), m/z: 483 ($M^+ - 1$).

(*S*)-3,3′-Bis(*N*,*N*-dimethylaminomethyl)-2,2′-dihydroxy-1,1′-binaphthol (1b)

To a stirred cooled (–5 to 0 °C) solution of **7b** (1.02 g, 2.1 mmol) in methanol (2 mL), a 4 mol/L solution of HCl in methanol (10 mL, 40 mmol) was added dropwise. The reaction mixture was allowed to warm up to room temperature and was stirred for an additional 16 h. After removal of the solvent under reduced pressure, the solid residue was triturated with Et_2O (2 × 20 mL) and dried in vacuum to provide 0.96 g of a white solid. The solid was suspended in CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (25 mL) was added to the resultant suspension. After 15 min of stirring, the organic phase was separated and dried over $MgSO_4$. Filtration and removal of the solvent from the filtrate under reduced pressure provided 0.81 g of a yellow solid, which was subjected to dry flash chromatography on silica gel (CH_2Cl_2 to 6% MeOH–CH_2Cl_2) to afford 0.78 g (93%) of **1b**[2a] as a white solid. Assayed at 97.45% by HPLC. HPLC analysis on a column with a chiral stationary phase showed an enantiomeric excess of >99.5%. ^{1}H NMR (400 MHz) in $CDCl_3$ δ: 2.36 (12H, NMe), 3.76 (2H, d, ^2J = 13.6 Hz, NCH_A), 4.10 (2H, d, ^2J = 13.6 Hz, NCH_B), 7.26–7.13 (6H, m), 7.61 (2H), 7.76 (2H, d, J = 7.6 Hz). MS (electrospray), m/z: 400 (M^+).

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