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Synthesis of (2*S*,2′*S*)-bimorpholine *N*,*N*′-quaternary salts as chiral phase transfer catalysts

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Abstract—(2*S*,2′*S*)-Bimorpholine was synthesized starting from (*R*,*R*)-tartaric acid ester acetal in six steps in 50% of the total yield. Key steps include: cyanide catalyzed amidation and one-step cyclization with *p*-toluenesulfonyl imidazole. Derivatization of *N*,*N*′-dibenzyl bimorpholine afforded quaternary bimorpholinium salts, which were used as chiral phase transfer alkylation catalysts.

1. Introduction

Asymmetric organocatalysis has become an important approach to stereoselective organic synthesis over the last decade.[1] The necessary organocatalysts are natural products selected from the chiral pool (such as amino acids, especially proline)[2] or are synthetic. There are practically no limits to synthetic catalyst structure: one can design and synthesize sterically and electronically tunable catalysts.[3] Compounds containing nitrogen have a special place among catalysts because of their unique properties. Chiral amines as donating ligands to metal catalysts are widely applied in asymmetric hydrogenation and hydride transfer reactions.[4] Asymmetric aminocatalysis via enamine or iminium intermediates has matured to become a widely used methodology.[5] Furthermore, quaternarization of the enantiomerically pure amines gives rise to the chiral ammonium compounds that are used as asymmetric phase transfer catalysts (PTC).[6]

Alkylation of glycine imine ester in the presence of a PTC as a model reaction has been investigated in detail. In addition to cinchonidine derivatives,[7] spiro ammonium salts[8] and two-centered tartaric acid derivatives[9] are found to be the most efficient catalysts for this reaction (Fig. 1).

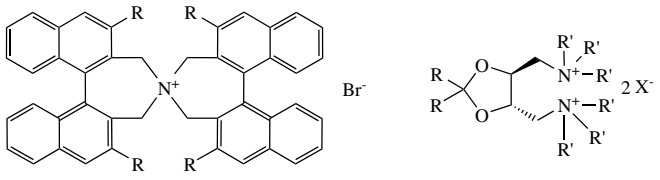
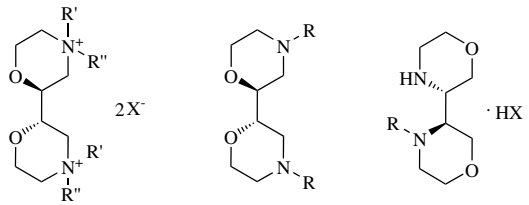


Figure 1.

We have now designed new dicationic catalysts **1a** and **1b**, where the tartaric acid backbone is converted into a C_2-symmetric heterocycle (Fig. 2). In this new catalyst, nitrogen atoms are fixed into a more rigid cyclic two-centered diammonium structure. We have previously shown that a similar principle (incorporation of a nitrogen atom into a



1a R′=Me R″=Bn X=I
1b R′=R″=Bn X=Br

2a R=H
2b R=Bn

3

Figure 2.

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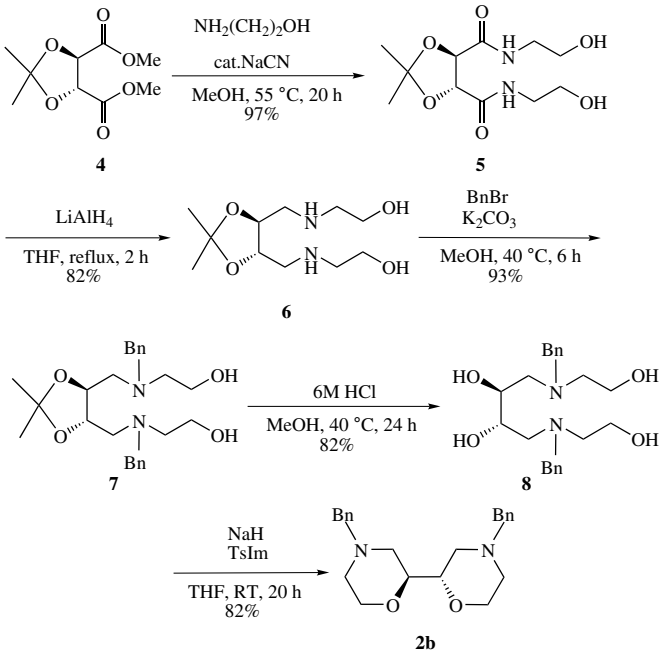
cyclic compound and the remaining tartaric acid skeleton) works efficiently in the case of some organocatalytic reactions. Thus, 3,3′-bimorpholine derivative **3** catalyzed Michael addition and also intramolecular aldol condensation proceed stereoselectively, affording the corresponding products in high ee (up to 95%).[10] Additionally, 3,3′-bimorpholine has been used as a ligand in transition-metal mediated asymmetric reductions.[11] We expected that the addition of sterically demanding substituents to the nitrogen atoms in 2,2′-bimorpholine **2a** would afford ammonium compounds with valuable asymmetric PTC properties. Herein, we report a new efficient method for the synthesis of (2*S*,2′*S*)-bimorpholine **2a**, its derivative **2b** and their quaternarization and our preliminary results of asymmetric alkylation of glycine imine ester in the presence of the new PTC.

2. Results and discussion

The synthesis of (2*S*,2′*S*)-bimorpholine **2a** has previously been reported by our group.[12] The key steps of the synthesis are: introduction of nitrogen-containing functionality into the tartaric acid derivative, chain lengthening via O-alkylation of hydroxyl groups and intramolecular cyclization. Nitrogen functionality was introduced into the molecule using a two-step procedure, which involves mesylation of the hydroxyl groups, followed by their azidation with sodium azide (Scheme 1). The target compound was obtained over 10 steps in a 15% overall yield.

Now we have developed a considerably shorter and more efficient route to (2*S*,2′*S*)-bimorpholine **2a**, outlined in Scheme 2. Cyanide-catalyzed amidation of (*R*,*R*)-tartaric acid ester acetal **4** with 2-aminoethanol enables us to introduce nitrogen and construct a necessary skeleton for cyclization in one step in order to obtain the morpholine ring.

First, cyanide-catalyzed amidation[13] of acetal **4** with 2-aminoethanol gave the desired amide **5** in an almost quantitative yield (97%). Amide **5** was reduced to amine **6** with $LiAlH_4$ in an 82% yield. Tertiary amine **7** was synthesized via direct N-alkylation of secondary amine **6** with benzyl bromide in a 93% yield. Deacetalization of compound **7** with 6 M HCl afforded tetraol **8** in an 82% yield. A key step in the synthesis of dibenzyl bimorpholine **2b** is cyclization of tetraol **8**. Mesylation or tosylation of the primary hydroxyl groups in tetraol **8** led to a multicomponent mixture. However, tetraol **8** was cyclized in a one-step procedure with *p*-toluenesulfonyl imidazole in THF, affording *N*,*N*′-dibenzyl (2*S*,2′*S*)-bimorpholine **2b**.[14] The yield of this intramolecular cyclization depends considerably on the concentration. Decrease in the concentration from 0.1 to

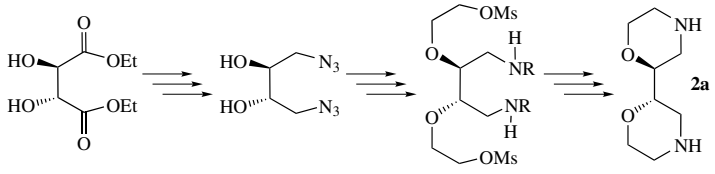


Scheme 2.

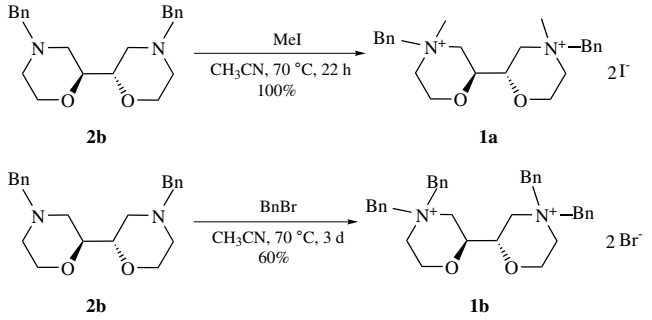
0.013 M led to the increase of the reaction yield from 23% to 82%. Thus *N*,*N*′-dibenzyl (2*S*,2′*S*)-bimorpholine **2b** was synthesized in five steps in 50% yield. (If unsubstituted bimorpholine is required, the debenzylation of **2b** with ammonium formate, affording desired (2*S*,2′*S*)-bimorpholine **2a** in a 70% yield, is used.)

(2*R*,2′*R*)-Bimorpholine **2b** was synthesized according to the same synthetic route starting from (*S*,*S*)-tartaric acid derivative. Chiral HPLC analysis on Chiralcel OD-H column of both enantiomers revealed their high enantiomeric purity (ee 99%).

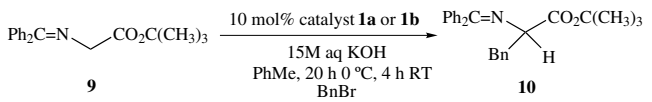
In order to perform PTC assisted alkylation of glycine imine ester **9**, we synthesized quaternary ammonium salts **1a** and **1b** from *N*,*N*′-dibenzyl (2*S*,2′*S*)-bimorpholine **2b** (Scheme 3). First, N-alkylation of tertiary amine **2b** with methyl iodide resulted in ammonium salt **1a** in quantitative yield as a single diastereoisomer (de >98% by NMR configurations at the two stereogenic N centres not determined). PTC-mediated alkylation of imine **9** in the presence of catalyst **1a** gave a racemic product **10** (Scheme 4). Since the efficient PTCs, which has been previously used[7–9] is more sterically hindered than catalyst **1a**, we assumed that by introducing more bulky groups into compound **2b**, the PTC-mediated alkylation of imine **9** could proceed with a higher selectivity.



Scheme 1.



Scheme 3.



Scheme 4.

Derivatization of compound **2b** with benzyl bromide afforded quaternary tetrabenzyl bimorpholinium salt **1b** (in a 60% yield after crystallization). The sterically hindered salt was thereafter used in the PTC-mediated alkylation of imine **9**. Catalyst **1b** revealed certain enantioselection in the alkylation; however, the selectivity was quite low and compound **10** was obtained with 18% ee. The catalyst might need further modification in order to increase steric hinderance at the ammonium site.

3. Conclusions

A high-yield synthetic scheme in six steps, starting from tartaric ester, to obtain the enantiomeric 2,2′-bimorpholine **2b** was developed. Although the corresponding bimorpholinium salts were found to be inefficient catalysts for the alkylation of the glycine imine ester, further investigations to widen the synthetic scope of this potential organocatalyst in other reactions are in progress.

4. Experimental

4.1. Materials and methods

Chemicals were purchased from either Aldrich Chemical Co. or Alfa Aesar and used as received. THF was distilled over $LiAlH_4$. Precoated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography silica gel KSK40-100 μm was used. Full assignment of ^1H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a Bruker AMX500 instrument. Solvent peaks ($CHCl_3$ $\delta = 7.27$, DMSO-d_5 $\delta = 2.50$, CHD_2OD $\delta = 3.30$, $CDCl_3$ $\delta = 77.00$, DMSO-d_6 $\delta = 39.50$, CD_3OD $\delta = 49.00$) were used as chemical shift references. IR spectra were measured on a Perkin–Elmer Spectrum BX FTIR spectrometer. Mass spectra were recorded on a Hitachi M80B spectrometer using EI (70 eV) or CI (isobutane) mode or on a Shimadzu GCMS-QP2010 spectrometer using EI (70 eV). Elemental analyses were performed on a Perkin–Elmer C, H, N, S-Analyzer 2400. Optical rotations were obtained using a Krüss Optronic GmbH Polarimeter P 3002. Chiral HPLC was performed using an Agilent Technologies 1200 Series chromatograph equipped with a Chiralcel OD-H column. All the reactions sensitive to moisture or oxygen were carried out under an Ar atmosphere in oven-dried glassware.

4.2. (4*R*,5*R*)-*N*,*N*′-Bis(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide 5

2-Aminoethanol (1.42 mL, 23.5 mmol) and sodium cyanide (58 mg, 1.17 mmol) was added to a solution of (*R*,*R*)-tartaric acid ester acetal **4** (2.561 g, 11.7 mmol) in MeOH (25 mL). The reaction mixture was stirred at 55 °C for 20 h. MeOH was evaporated and the crude mixture was purified by the column chromatography on silica gel (15% MeOH in CH_2Cl_2), to afford amide **5** as a yellow oil (yield 3.133 g, 97%). ^1H NMR (DMSO-d_6, 500 MHz): δ 1.39 (6H, s, 2-CH_3), 3.17 (4H, q, $J = 3 \times 5.8$ Hz, CH_2N), 3.41 (4H, dt, $J = 5.4$, 2×5.8 Hz, CH_2OH), 4.49 (2H, s, H-4,5), 4.69 (2H, t, $J = 5.4$ Hz, OH), 7.97 (2H, t, $J = 5.8$ Hz, NH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 26.21 (2-CH_3), 41.37 (CH_2N), 59.55 (CH_2OH), 77.60 (CHO), 111.73 (C-2), 169.11 (CO). IR: $\nu = 3338$, 3092, 2990, 2940, 2881, 1670, 1537, 1385, 1260, 1214, 1082 cm^{-1}. $[\alpha]_D^{22} = -20.9$ (*c* 2.40, MeOH). MS *m*/*z*: 277 (M^++1), 246, 218, 188, 130. Anal. Calcd for $C_{11}H_{20}N_2O_6$ (276.29): C, 47.82; H, 7.30; N, 10.14. Found: C, 47.60; H, 7.29; N, 9.94.

4.3. 2,2′-{[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]bis(methyleneimino)}diethanol 6

Amide **5** (9.097 g, 0.033 mol) in THF (100 mL) at 0 °C was added to a suspension of $LiAlH_4$ (7.50 g, 0.20 mol) in THF (50 mL). After refluxing for 2 h, water (7.7 mL), 15% NaOH solution (7.7 mL) and water (23 mL) were added at 0 °C. The mixture was filtered and washed with THF. The inorganic precipitate was extracted with THF (200 mL) in a Soxhlet apparatus. The combined THF extracts were dried over Na_2SO_4. After filtration, the solvents were evaporated and the residue was purified by column chromatography on silica gel (7% MeOH/NH_3 in CH_2Cl_2), affording amine **6** as a yellow oil (yield 6.688 g, 82%). ^1H NMR ($CDCl_3$, 500 MHz): δ 1.37 (6H, s, 2-CH_3), 2.75 and 2.78 (4H, m, OCHCH_2N), 2.80 and 2.82 (4H, m, NCH_2CH_2), 2.9 (4H, br s, OH and NH), 3.63 (4H, br t, $J = 5.2$ Hz, CH_2OH), 3.87 (2H, br t, $J = 3.0$ Hz, CHO). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.10 (2-CH_3), 51.54 (OCH*C*H_2N), 51.58 (N*C*H_2CH_2), 60.86 (*C*H_2OH), 78.96 (C-4,5), 108.74 (C-2). IR: $\nu = 3310$, 2932, 2985, 1674, 1456, 1375, 1080 cm^{-1}. $[\alpha]_D^{23} = -28.0$ (*c* 2.63, MeOH). MS (10 eV) *m*/*z*: 249 (M^++1), 233, 217, 188, 144, 116.

4.4. 2,2′-{[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]bis[methylene(benzylimino)]}diethanol 7

Amine **6** (399 mg, 1.61 mmol) was dissolved in MeOH (15 mL), K_2CO_3 (666 mg, 4.82 mmol) and benzyl bromide (573 μL, 4.82 mmol) were added. The reaction mixture was stirred at 40 °C for 6 h. MeOH was evaporated and the crude mixture was purified by column chromatography on silica gel (5% MeOH/NH_3 in CH_2Cl_2), affording benzyl-

ated amine **7** as a yellow oil (yield 643 mg, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.36 (6H, s, 2-CH_3), 2.63 (4H, d, $J = 3.0$ Hz, OCHCH_2N), 2.66 and 2.72 (4H, td, $J = 2 \times 5.3$ and 13.4 Hz, NCH_2CH_2), 3.45 (2H, br s, OH), 3.58 (4H, br t, $J = 5.3$ Hz, CH_2OH), 3.63 and 3.70 (4H, both d, $J = 13.5$ Hz, BnCH_2), 3.73 (2H, br t, $J = 3.0$ Hz, CHO), 7.24–7.33 (10H, m, Ar). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.07 (2-CH_3), 56.01 (OCH*C*H$_2$N), 56.26 (N*C*H$_2$CH$_2$), 59.23 (*C*H$_2$OH), 59.50 (Bn*C*H$_2$), 78.37 (C-4,5), 109.10 (C-2), 127.18 (*p*-Ar), 128.27 (*m*-Ar), 129.05 (*o*-Ar), 138.29 (*s*-Ar). IR: $\nu = 3426$, 3029, 2985, 2936, 2825, 1602, 1495, 1454, 1371, 1251, 1214, 1170, 1046 cm^{-1}. $[\alpha]_D^{23} = -8.4$ (*c* 2.37, MeOH). MS *m*/*z*: 413 ($M^+ - CH_3$), 410, 319, 262, 206, 164, 134, 91. Anal. Calcd for $C_{25}H_{36}N_2O_4$ (428.58): C, 70.06; H, 8.47; N, 6.54. Found: C, 69.83; H, 8.58; N, 6.48.

4.5. (2*S*,3*S*)-1,4-Bis[(2-hydroxyethyl)(benzyl)amino]butane-2,3-diol 8

To a solution of benzylated amine **7** (6.615 g, 15.4 mmol) in MeOH (50 mL) 6 M HCl solution (40 mL) was added and the mixture was heated at 40 °C for 21 h. In an ice-water bath 10 M NaOH solution was added until pH ~ 8–9. After the addition of satd NaCl solution (30 mL), the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography on silica gel (5% MeOH/NH_3 in CH_2Cl_2), affording tetraol **8** as a yellow oil which solidifies in a freezer (yield 4.893 g, 82%). ^{1}H NMR (CD_3OD, 500 MHz): δ 2.59 and 2.67 (4H, m, NCH_2CH_2), 2.64 (4H, m, OCHCH_2N), 3.57 and 3.58 (4H, m, CH_2OH), 3.63 and 3.71 (4H, both d, $J = 14.0$ Hz, BnCH_2), 3.67 (2H, br t, $J = 3.0$ Hz, H-2,3), 7.29 (2H, m, *p*-Ar), 7.27 (4H, m, *m*-Ar), 7.32 (4H, m, *o*-Ar). ^{13}C NMR (CD_3OD, 125 MHz): δ 57.69 (OCH*C*H$_2$N), 58.58 (N*C*H$_2$CHO), 60.84 (*C*H$_2$OH), 60.97 (Bn*C*H$_2$), 70.87 (C-4,5), 128.10 (*p*-Ar), 129.29 (*m*-Ar), 130.23 (*o*-Ar), 140.34 (*s*-Ar). IR: $\nu = 3369$, 3062, 3028, 2829, 1602, 1494, 1453, 1372, 1132, 1028 cm^{-1}. $[\alpha]_D^{22} = -25.2$ (*c* 4.87, MeOH). MS *m*/*z*: 389 (M^++1), 224, 206, 194, 164, 134, 91. Anal. Calcd for $C_{22}H_{32}N_2O_4$ (388.51): C, 68.01; H, 8.30; N, 7.21. Found: C, 67.98; H, 8.33; N, 7.21.

4.6. (2*S*,2′*S*)-4,4′-Dibenzyl-2,2′-bimorpholine 2b

Tetraol **8** (2.127 g, 5.47 mmol) in THF (400 mL) was added to NaH (1.095 g, 27.37 mmol) at 0 °C, under an argon atmosphere. The mixture was stirred at 0 °C for 5 min and at rt for 1 h. The reaction mixture was cooled to 0 °C and 1-(*p*-toluenesulfonyl)imidazole (2.434 g, 10.95 mmol) was added. After stirring for 15 min at 0 °C the reaction mixture was allowed to warm to rt and stirred for 20 h. The reaction suspension was cooled to 0 °C, and the reaction was quenched by the dropwise addition of satd NH_4Cl solution (20 mL). THF was evaporated, satd NaCl and satd $NaHCO_3$ solutions were added and the mixture was extracted with EtOAc (3 × 15 mL). The organic phase was dried over Na_2SO_4 and solvent was evaporated. The residue was purified by column chromatography on silica gel (1.5% MeOH/NH_3 in CH_2Cl_2), affording **2b** as a yellow oil (yield 1.573 g, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.19 (4H, br t, $J = 11$ Hz, H-3a,3′a,5a,5′a), 2.63 (4H, br d, $J = 11$ Hz, H-3e,3′e,5e,5′e), 3.48 and 3.52 (4H, d, $J = 13.0$ Hz, BnCH_2), 3.52 (2H, br m, H-2,2′), 3.64 (2H, br t, $J = 11$ Hz, H-6a,6′a), 3.91 (2H, br d, $J = 11$ Hz, H-6e,6′e), 7.27 (2H, m, *p*-Ar), 7.32 (8H, m, *o*,*m*-Ar). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 52.82 (C-5,5′), 54.61 (C-3,3′), 63.30 (Bn*C*H$_2$), 66.97 (C-6,6′), 76.48 (C-2,2′), 127.07 (*p*-Ar), 128.20 (*m*-Ar), 129.06 (*o*-Ar), 137.72 (*s*-Ar). IR: $\nu = 3027$, 2909, 2857, 2816, 1602, 1494, 1453, 1349, 1118, 1088, 1047, 1019 cm^{-1}. $[\alpha]_D^{23} = +49.4$ (*c* 6.36, MeOH). MS *m*/*z*: 352 (M^+), 261, 206, 175, 164, 134, 91. Anal. Calcd for $C_{22}H_{28}N_2O_2$ (352.48): C, 74.97; H, 8.01; N, 7.95. Found: C, 74.80; H, 8.11; N, 7.89.

4.7. (2*R*,2′*R*)-4,4′-Dibenzyl-2,2′-bimorpholine 2b

Compound **2b** was synthesized using the same synthetic scheme, starting from (*S*,*S*)-tartaric acid derivative **4**. $[\alpha]_D^{22} = -47.9$ (*c* 1.84, MeOH). HPLC analysis: t_R for (*R*,*R*)-**2b** 9.8 min; t_R for (*S*,*S*)-**2b** 19.3 min (hexane/*i*PrOH 95:5, 0.8 mL/min).

4.8. (2*S*,2′*S*)-2,2′-Bimorpholine 2a

To a solution of bimorpholine **2b** (294 mg, 0.83 mmol) in MeOH (10 mL) 10% Pd/C (441 mg) and ammonium formate (263 mg, 4.17 mmol) was added under an Ar atmosphere. After heating the reaction mixture at 60 °C for 7 h, the mixture was filtered and washed with MeOH. The MeOH was evaporated and the crude mixture was purified by column chromatography on silica gel (7% MeOH/NH_3 in CH_2Cl_2), affording bimorpholine **2a** as a white solid (yield 101 mg, 70%). The spectroscopic data were in agreement with the published data.[12]

4.9. (2*S*,2′*S*)-4,4′-Dibenzyl-4,4′-dimethyl-2,2′-bimorpholinium diiodide 1a

To a solution of bimorpholine **2b** (206 mg, 0.58 mmol) in CH_3CN (6 mL) methyl iodide (364 μL, 5.84 mmol) was added. The mixture was stirred at 70 °C for 22 h. CH_3CN was evaporated and the crystals were washed with EtOAc, affording quaternary ammonium salt **1a** as yellow crystals (yield 372 mg, 100%). ^{1}H NMR (CD_3OD, 500 MHz): δ 3.24 (6H, s, NCH_3), 3.42 (2H, br d, $J = 12.5$ Hz, H-5e,5′e), 3.56 (2H, br d, $J = 12.5$ Hz, H-3e,3′e), 3.67 (2H, br t, $J = 12.5$ Hz, H-5a,5′a), 3.77 (2H, br t, $J = 12.5$ Hz, H-3a,3′a), 4.09 (2H, br d, $J = 12.5$ Hz, H-6e,6′e), 4.18 (2H, br t, $J = 12.5$ Hz, H-6a,6′a), 4.36 (2H, br d, $J = 12.5$ Hz, H-2a,2′a), 4.79 (4H, br s, BnCH_2), 7.51–7.57 (6H, m, *m*,*p*-Ar), 7.67 (4H, m, *o*-Ar). ^{13}C NMR (CD_3OD, 125 MHz): δ 45.48 (NCH_3), 59.83 (C-5,5′), 60.51 (C-3,3′), 61.75 (C-6,6′), 70.21 (C-2,2′), 73.32 (Bn*C*H$_2$), 127.54 (*s*-Ar), 130.39 (*m*-Ar), 132.02 (*p*-Ar), 134.55 (*o*-Ar). IR: $\nu = 4042$, 3449, 2965, 2883, 1989, 1623, 1497, 1472, 1430, 1357, 1257, 1102 cm^{-1}. $[\alpha]_D^{22} = +41.2$ (*c* 4.74, MeOH). MS *m*/*z*: 637 (M^++1). Mp 165–168 °C.

4.10. (2*S*,2′*S*)-4,4,4′,4′-Tetrabenzyl-2,2′-bimorpholinium dibromide 1b

To a solution of bimorpholine **2b** (225 mg, 0.64 mmol) in CH_3CN (6 mL), benzyl bromide (456 μL, 3.83 mmol) was

added. The mixture was refluxed for 31 h. CH_3CN was evaporated and the crude product was crystallized in CH_3CN, affording quaternary ammonium salt **1b** as white crystals (yield 267 mg, 60%). ^1H NMR (CD_3OD, 500 MHz): δ 3.21 (2H, br t, $J = 13$ Hz, H-5a,5′a), 3.37 (2H, br t, $J = 13$ Hz, H-3a,3′a), 3.47 (2H, br d, $J = 13$ Hz, H-5e,5′e), 3.74 (2H, br d, $J = 13$ Hz, H-3e,3′e), 3.97 (2H, br d, $J = 13$ Hz, H-6e,6′e), 4.54 (2H, br t, $J = 13$ Hz, H-6a,6′a), 4.55 and 4.60 (4H, d, $J = 12.8$ Hz, $BnCH_2$), 4.55 (2H, br d, $J = 13$ Hz, H-2a,2′a), 5.20 and 5.23 (4H, d, $J = 13.3$ Hz, $BN'CH_2$), 7.45–7.52 (10H, m, *o*,*m*,*p*-Ar), 7.60 (6H, m, *m*′,*p*′-Ar), 7.75 (4H, m, *o*′-Ar). ^{13}C NMR (CD_3OD, 125 MHz): δ 54.75 (C-5,5′), 55.88 (C-3,3′), 61.44 (C-6,6′), 63.27 ($BN'CH_2$), 68.53 ($BnCH_2$), 69.87 (C-2,2′), 127.57 (*s*-Ar), 128.23 (*s*′-Ar), 130.40 (*m*-Ar), 130.78 (*m*′-Ar), 132.06 (*p*-Ar), 132.15 (*p*′-Ar), 134.69 (*o*′-Ar), 135.04 (*o*-Ar). IR: $\nu = 3629$, 3411, 3033, 2978, 2950, 2892, 2709, 2613, 1985, 1616, 1496, 1454, 1214, 1102, 760, 734, 704 cm^{-1}. $[\alpha]_D^{22} = -53.7$ (*c* 2.5, MeOH). Mp 170–173 °C.

4.11. Alkylation of imine 9

A solution of quaternary salt **1b** (13 mg, 0.019 mmol) and imine **9** (55 mg, 0.19 mmol) in toluene (6 mL), was cooled to 0 °C, degassed and placed under an argon atmosphere. Benzyl bromide (27 μL, 0.22 mmol) and degassed 15 M KOH were added. The mixture was stirred for 20 h. In addition, to complete the reaction, the mixture was stirred at rt for 4 h. H_2O (10 mL) was added and the mixture was extracted with EtOAc (2×7 mL) and dried (Na_2SO_4). Solvent was evaporated and the residue was purified by column chromatography (3% EtOAc in petroleum ether), affording imine **10** as a colourless oil (yield 21 mg, 29%). $[\alpha]_D^{24} = +40$ (*c* 1.84, CH_3Cl) ($[\alpha]_D^{22} = -185.3$ (*c* 1.0, CH_3Cl) for 85% ee imine **10**).[7c] Ee of the product was also determined by chiral HPLC (column Chiralcel OD-H, eluent: hexane–*i*PrOH = 99.5:0.5, 0.6 mL/min).

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References

1. Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis-From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005.
2. List, B. *Tetrahedron* **2002**, *58*, 5573–5590.
3. (a) Chen, J.-R.; Li, X.-Y.; Xing, X.-N.; Xiao, W.-J. *J. Org. Chem.* **2006**, *71*, 8198–8202; (b) Chen, J.-R.; Lu, H.-H.; Li, X.-Y.; Cheng, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543–4545; (c) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem. Eur. J.* **2005**, *11*, 7024–7029; (d) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21–24.
4. (a) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022; (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.
5. For recent reviews see: (a) List, B. *Chem. Commun.* **2006**, 819–824; (b) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492; (c) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558–569.
6. (a) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517; (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525; (c) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028.
7. (a) Lygo, B.; Allbutt, B. *Synlett* **2004**, 326–328; (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415; (c) Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 1515–1517; (d) Yoo, M.-S.; Jeong, B.-S.; Lee, J.-H.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2005**, *7*, 1129–1131; (e) Yu, H.; Takigawa, S.; Koshima, H. *Tetrahedron* **2004**, *60*, 8405–8410.
8. (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520; (b) Yu, H.; Takigawa, S.; Koshima, H. *Tetrahedron* **2004**, *60*, 8405–8410; (c) Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R. *Tetrahedron Lett.* **2003**, *44*, 8677–8680; (d) Hashimoto, T.; Maruoka, K. *Tetrahedron Lett.* **2003**, *44*, 3313–3316; (e) Kano, T.; Konishi, S.; Shirakawa, S.; Maruoka, K. *Tetrahedron: Asymmetry* **2004**, *15*, 1243–1245; (f) Shirakawa, S.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2004**, *6*, 1429–1431.
9. (a) Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7743–7754; (b) Rueffer, M. E.; Fort, L. K.; MacFarland, D. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3297–3300; (c) Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206–11207; (d) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539–9543.
10. (a) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559–2562; (b) Kriis, K.; Kanger, T.; Laars, M.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synlett* **2006**, 1699–1702.
11. (a) Kriis, K.; Kanger, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 2271–2275; (b) Kriis, K.; Kanger, T.; Lopp, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2687–2691.
12. (a) Kriis, K.; Kanger, T.; Pehk, T.; Lopp, M. *Proc. Estonian Acad. Sci. Chem.* **2001**, *50*, 173–179; Kriis, K.; Kanger, T.; Pehk, T.; Lopp, M. *Chem. Abstr.* **2002**, *136*, 118420; (b) Kanger, T.; Kriis, K.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2002**, *13*, 857–865.
13. (a) Kang, S. H.; Kim, M. *J. Am. Chem. Soc.* **2003**, *125*, 4684–4685; (b) Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033–2036.
14. Lanman, B. A.; Myers, A. G. *Org. Lett.* **2004**, *6*, 1045–1047.