**Enantioselective direct aldol reaction “in the presence of water”
promoted by chiral organic catalysts.**

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General Methods. TLC was performed on silica gel 60 TLC plates F254 and visualized using UV or phosphomolibdic acid. Flash chromatography was carried out on silica gel (230-400 mesh). ^1H NMR were recorded at 300 MHz with the indicated solvent. ^{13}C NMR were obtained at 75 MHz. Chemical shifts were determined relative to tetramethylsilane (for hydrogen atoms) and residual solvent peaks (for carbon atoms). Optical rotations were obtained on a polarimeter at 589 nm. HPLC for ee determination was performed under the conditions reported below.

Synthesis of Catalyst 6.

To a solution of (R)-*N*-acetyl binaphthyl diamine (0.700 g, 2.1 mmol) in dry DMF (7 mL), K_2CO_3 (0.400 g, 3.15 mmol) and 1-dodecyl iodide (2.24 g, 7.55 mmol) were added. After the reaction mixture was stirred at 130°C for 20 hours, it was cooled down to room temperature; water (10 mL) and ethyl acetate (30 mL) were added, the organic phase was separated, washed twice with water (5 mL each), dried over Na_2SO_4 and evaporated. A purification through a short plug of silica gel (9/1 hexanes/ethyl acetate) allowed to obtain the bis *N,N*-alkyl derivative in 98% yield, that was used as such in the next step. $[\alpha]^{23}_{\text{D}}$ -65.3.3 (c 0.48 in DCM); ^1H NMR (300 MHz, CDCl_3): δ 8.50 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 7.9 Hz, 2H), 7.87 (m, 2H), 7.97 (m, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.30 (m, 2H), 7.28 (s, 1H), 7.20-7.10 (m, 3H), 6.95 (d, J = 7.5 Hz, 1H), 2.75 (m, 4H), 1.85 (s, 3H), 1.40-1.05 (m, 40H), 0.90 (m, 6H). The product (1.0 g, 1.5 mmol) was hydrolysed by reacting with 37% HCl (50 mL) in ethanol (70 mL) at 70°C for 15 hours. The product was obtained in quantitative yield and used without further purification. $[\alpha]^{23}_{\text{D}}$ +0.07 (c 0.11 in DCM); ^1H NMR (300 MHz, CDCl_3): δ 7.97-7.62 (m, 4H), 7.49 (d, J = 7.8 Hz, 1H), 7.30-6.90 (m, 7H), 3.60 (bs, 2H), 2.83 (m, 4H), 1.40-1.10 (m, 40H), 0.91 (m, 6H).

To a stirred solution of (S)-Boc-proline (0.085 g, 0.39 mmol) in dry CHCl_3 (2 mL) EDC (0.075 g, 0.39 mmol) and HOBT (0.053 g, 0.039 mmol) were added and the reaction mixture was cooled to 0°C. After (R)-*N,N*-bisdodecyl binaphthyl diamine (0.130 g, 0.21 mmol) in CHCl_3 (1 mL) was added the resulting mixture was allowed to stir at RT for 40 hours. The reaction was quenched by the addition of a saturated aqueous solution of NaHCO_3 (3 mL), the organic phase was separated, washed with water, dried over Na_2SO_4 , filtered, and concentrated under vacuum at room temperature to afford the crude product, that was purified by flash chromatography with 8/2 hexanes:ethyl acetate mixture as eluant. (Yield 75%) The deprotection of Boc group was accomplished by stirring the prolinamide in DCM/TFA (1/1 2mL) at RT for 15 hours. The mixture was cooled at 0°C, diluted with DCM (5 mL) and washed with a saturated aqueous solution of NaHCO_3 until pH was basic. The aqueous phase was extracted twice with DCM and all the organic

phases were dried over Na₂SO₄, filtered, and concentrated under vacuum at room temperature to afford the product in >98% yield.

6 waxy solid, $[\alpha]^{23}_{\text{D}} +0.03$ (c 0.21 in DCM); IR(DCM): ν 1667, 1595, 1455, 1427, 1260 cm⁻¹ ¹H NMR (300 MHz, CDCl₃): δ 9.55 (bs, 1H), 8.67 (d, J = 8.0 Hz, 1H), 8.00-7.80 (m, 4H), 7.50 (d, J = 7.7 Hz, 1H), 7.33 (m, 3H), 7.18 (m, 3H), 7.00 (d, J = 7.5 Hz, 1H), 3.45 (m, 1H), 2.80-2.60 (m, 5H), 2.30 (m, 1H), 1.95 (m, 1H), 1.70 (m, 1H), 1.40 (m, 2H), 1.25-1.05 (m, 40H), 0.80 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 173.0, 150.1, 134.6, 134.5, 133.6, 131.5, 129.5, 129.0, 128.3, 127.9, 127.7, 126.5, 126.4, 125.9, 125.0, 124.4, 123.9, 121.2, 120.5, 60.9, 52.9, 46.7, 31.9, 30.6, 29.6, 29.5, 29.4, 29.3, 27.8, 27.0, 25.8, 22.7, 14.1. MS-ESI⁺: m/z 719 [M+H]⁺, Elem. anal. calcd. for C₄₉H₇₁N₃O: C, 81.95; H, 9.97; N, 5.85. Found: C, 81.63; H, 9.93; N, 5.87.

Synthesis of Catalyst 7. To a stirred solution of (S)-Boc-proline (0.085 g, 0.39 mmol) in dry CHCl₃ (2 mL) EDC (0.075 g, 0.39 mmol) and HOBt (0.053 g, 0.039 mmol) were added and the reaction mixture was cooled to 0°C. After biphenyl diamine (0.030 g, 0.15 mmol) in CHCl₃ (1 mL) was added the resulting mixture was allowed to stir at RT for 20 hours. The reaction was quenched by the addition of a saturated aqueous solution of NaHCO₃ (3 mL), the organic phase was separated, washed with water, dried over Na₂SO₄, filtered, and concentrated under vacuum at room temperature to afford the crude product, that was purified by flash chromatography with 8/2 hexanes:ethyl acetate mixture as eluant. (Yield 65%) The deprotection of Boc group was accomplished by stirring the prolinamide in DCM/TFA (1/1 2 mL) at RT for 35 minutes. The mixture was cooled at 0°C, diluted with DCM (5 mL) and washed with a saturated aqueous solution of NaHCO₃ until pH was basic. The aqueous phase was extracted twice with DCM and all the organic phases were dried over Na₂SO₄, filtered, and concentrated under vacuum at room temperature to afford the product in 80% yield.

7 pale yellow solid, m.p. 167°C, $[\alpha]^{23}_{\text{D}} -14.9$ (c 0.21 in DCM); IR(DCM): ν 1672, 1578, 1470, 1427 cm⁻¹ ¹H NMR (300 MHz, CDCl₃): δ 9.75 (bs, 1H), 8.45 (d, J = 7.5 Hz, 1H), 8.27 (d, J = 8.1 Hz, 1H), 7.53 (m, 2H), 7.30 (m, 4H), 3.65 (m, 2H), 2.72 (m, 2H), 2.50 (m, 1H), 2.35 (m, 1H), 2.10 (m, 4H), 1.85 (m, 2H), 1.55 (m, 4H). ¹³C NMR (75 MHz, CDCl₃): δ 173.9, 130.4, 129.0, 128.4, 124.3, 121.4, 120.4, 60.9, 46.8, 30.7, 25.8. MS-ESI⁺: m/z 379 [M+H]⁺, Elem. anal. calcd. for C₂₂H₂₆N₄O₂: C, 69.82; H, 6.92; N, 14.80. Found: C, 69.81; H, 6.90; N, 14.85.

Aldol reaction. General procedure: To a stirred suspension of catalyst (0.02 mmol) in water (0.8 mL) (or acetone/CHCl₃ 1/1 mixture) at given temperature after 15 min. the aldehyde (0.2 mmol) was added. The mixture was allowed to stir for given time, then solvent was evaporated and the crude product analysed. If necessary, the crude products were purified by flash chromatography with different hexanes:ethyl acetate mixture as eluants. Yields and ee for each reaction are indicated in the Tables. The assignment of the absolute configuration to the predominant isomer formed in each reaction rests on comparison of sign of optical rotation with those reported in the literature.

(R)-4-(4-nitro-phenyl)-4-hydroxy-2-butanone This product was purified with a hexanes:ethyl acetate 7:3 mixture as eluant. It had ^1H NMR data in agreement with those reported in the literature. The enantiomeric excess was determined by HPLC on a Chiracel OJ column (hexane:isopropanol 70:30; flow rate 0.8 ml/min; λ 220 nm): $t_R = 11.6$ min, $t_S = 12.9$ min.

(R)-4-(4-nitro-phenyl)-4-hydroxy-2-pentanone This product was purified with a hexanes:ethyl acetate 7:3 mixture as eluant. It had ^1H NMR data in agreement with those reported in the literature. The enantiomeric excess was determined by HPLC on a Chiracel OJ-H column (hexane:isopropanol 80:20; flow rate 0.8 ml/min; λ 220 nm): $t_R = 16.3$ min, $t_S = 18.9$ min.

(R)-4-(4-nitro-phenyl)-4-hydroxy-2-nonanone This product was purified with a hexanes:ethyl acetate 8:2 mixture as eluant. It had ^1H NMR data in agreement with those reported in the literature. The enantiomeric excess was determined by HPLC on a Chiracel OD column (hexane:isopropanol 90:10; flow rate 0.8 ml/min; λ 267 nm): $t_R = 11.9$ min, $t_S = 12.8$ min.

(R,R)-2-[1-(4-nitrophenyl)-hydroxymethyl]-cyclohexanone It had ^1H NMR data in agreement with those reported in the literature. The diastereoisomeric ratio was determined by NMR on the crude reaction mixture and confirmed after chromatographic purification. The enantiomeric excess was determined by HPLC on a Chiracel OJ-H column (hexane:isopropanol 70:30; flow rate 0.8 ml/min; λ 230 nm): $t_{\text{anti major}} = 10.5$ min, $t_{\text{syn major}} = 12.3$ min; $t_{\text{anti min}} = 11.3$ min, $t_{\text{syn min}} = 16.8$ min.

(R,R)-2-[1-phenyl-hydroxymethyl]-cyclohexanone It had ^1H NMR data in agreement with those reported in the literature. The diastereoisomeric ratio was determined by NMR on the crude reaction mixture and confirmed after chromatographic purification. The enantiomeric excess was determined by HPLC on a Chiracel OD column (hexane:isopropanol 99:1; flow rate 1.0 ml/min; λ 210 nm): $t_{\text{syn major}} = 19.4$ min; $t_{\text{syn min}} = 23.1$ min; $t_{\text{anti major}} = 33.0$ min; $t_{\text{anti min}} = 60.3$ min,

(R,R)-2-[1-(2-chlorophenyl)-hydroxymethyl]-cyclohexanone It had ^1H NMR data in agreement with those reported in the literature. The diastereoisomeric ratio was determined by NMR on the crude reaction mixture and confirmed after chromatographic purification. The enantiomeric excess was determined by HPLC on a Chiracel OD column (hexane:isopropanol 95:5; flow rate 0.8 ml/min; λ 210 nm): $t_{\text{anti major}} = 11.5$ min, $t_{\text{anti min}} = 13.3$ min.

(R,R)-2-[1-(4-methoxyphenyl)-hydroxymethyl]-cyclohexanone It had ^1H NMR data in agreement with those reported in the literature. The diastereoisomeric ratio was determined by NMR on the crude reaction mixture and confirmed after chromatographic purification. The enantiomeric excess was determined by HPLC on a Chiracel OD column (hexane:isopropanol 90:10; flow rate 0.8 ml/min; λ 220 nm): $t_{\text{syn major}} = 10.6$ min, $t_{\text{syn min}} = 11.4$ min; $t_{\text{anti major}} = 12.1$ min, $t_{\text{anti min}} = 14.9$ min.

(R,R)-2-[1-pentafluorophenyl-hydroxymethyl]-cyclohexanone It had ^1H NMR data in agreement with those reported in the literature. The diastereoisomeric ratio was determined by NMR on the crude reaction mixture and confirmed after chromatographic purification. The enantiomeric excess was determined by HPLC on a Chiracel AD column (hexane:isopropanol 90:10; flow rate 0.8 ml/min; λ 220 nm): $t_{\text{anti min}} = 7.8$ min, $t_{\text{anti major}} = 8.9$ min.

compound 6 - ¹³C MNR

TU 389

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compound 7 - 1-H NMR

8a

CH₃ → 4.6

2184.09
2178.51
2171.46

MP 1.6

1599.07

compound 7 - ¹³C NMR

97.4%