Supporting Information

“Highly Enantioselective α -Aminoxylation of Aldehydes and Ketones with a Polymer-Supported Organocatalyst”

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General Information

All reactions were conducted under air unless otherwise stated. Synthesis grade DMF, anhydrous CHCl_3 , nitrosobenzene, ketones **2a-2e** and aldehydes **4a-4h** were used as received (Aldrich). Solution ^1H NMR, ^{13}C NMR and PENDANT¹ experiments were performed with a Bruker Avance 400 Ultrashield spectrometer in CDCl_3 at room temperature. TMS served as internal standard ($\delta = 0$ ppm) for ^1H NMR and CDCl_3 ($\delta = 77$ ppm) for ^{13}C NMR and PENDANT spectra. Chemical shifts are given in δ and coupling constants in Hz. IR spectra were recorded on a Tensor 27 Bruker FT-IR or on a Thermo Nicolet 5700 using KBr pellets and are reported in wavenumbers (cm^{-1}). Mass spectra were measured on a Waters LCT Premier instrument operated in ESI mode. Optical rotations were measured at room temperature on a Jasco P-1030 polarimeter. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Series 1100 and 1200), using Chiralcel AD-H and OD-H columns and AD-H and OD-H guard columns as noted. Racemic standard products were prepared using DL-proline as catalyst according to reported procedures² in order to establish HPLC conditions.

Typical procedure for the enantioselective α -aminoxylation of ketones 2a-e catalyzed by resin 1.

Resin **1** (83.3 mg, 0.05 mmol, *f*: 0.6 mmol/g) was placed in a vial with DMF (1 mL) and 0.5 mmol of ketone at room temperature. The resin was swelled for 10 minutes under vigorous stirring. Then, a solution of nitrosobenzene in DMF (0.5 M; 0.25 mmol) was slowly added with a syringe pump over 3 h, and the mixture was stirred for an additional 30 minutes period. In some experiments, mesitylene (0.072 mmol) was added as standard for NMR quantification at this stage. The yellow-orange mixture was

filtered and the resin was rinsed with ethyl acetate (3 x 1 mL). The solvents were removed under reduced pressure, DMF being azeotropically distilled at 30 °C with toluene (3 x 2 mL). Purification by short-path column chromatography on silica gel, eluting with hexane/ethyl acetate mixtures afforded the pure α -aminoxylation products.

Typical procedure for the tandem α -aminoxylation and O-N cleavage of 2a

Resin **1** (83.3 mg, 0.05 mmol, *f*: 0.6 mmol/g) was placed in a vial with DMF (1 mL) and 0.5 mmol of **2a** at room temperature. The resin was swelled for 10 minutes under vigorous stirring and then a solution of nitrosobenzene in DMF (0.5 M; 0.25 mmol) was slowly added with a syringe pump over 3 h. After 30 minutes of additional stirring, mesitylene (0.072 mmol) was added as standard for NMR quantification (**3a**: 18.6 mmol; 74% yield). The resin was removed by filtration and rinsed with dichloromethane (2 x 2 mL). Nitrosobenzene (0.5 mmol) was added in one portion to the combined organic phase and the mixture was stirred at room temperature for 2.5 h. The ^1H NMR spectrum of the reaction mixture showed the cleavage of the O-N bond in a quantitative manner (azoxybenzene: 19.9 mmol; 2-hydroxycyclohexanone: the H^2 signal is overlapped with that of water):

Comparison of the ^1H NMR spectra of the reaction crude of the tandem process: (a) α -aminoxylation of **2a**; (b) O-N bond heterolysis of **3a**.

^1H NMR (DMF- d_7 , 400 MHz)

Typical procedure for the enantioselective α -aminoxylation of aldehydes 4a-h catalyzed by resin 1.

Resin **1** (77.8 mg, 0.047 mmol, *f*: 0.6 mmol/g) was placed in a vial with anhydrous chloroform (2 mL) and swelled at 0-4 °C (ice bath) for 10 minutes. Addition of nitrosobenzene (50.3 mg, 0.47 mmol) in one portion turned the suspension green. Finally the aldehyde (1.4 mmol) was added and the reaction was vigorously stirred at 0-4 °C until the solution became yellow (1-3 h). When the reaction was complete, the resin was removed by filtration and rinsed with dichloromethane (2 x 2 mL). The reaction mixture was added to a previously cooled ethanol suspension (2 mL) of NaBH₄ (26.0 mg, 0.68 mmol) at 0 °C. After 20 minutes, the reaction mixture was treated with saturated aqueous NaHCO₃ solution (5 mL) and extracted with dichloromethane (3 x 5 mL). The organic fraction was dried over MgSO₄ and concentrated under reduced pressure, adding excess toluene to azeotropically remove the excess of primary alcohol arising from the reduction of the aldehyde. The crude β -aminoxylated alcohol **6** was then purified by flash chromatography on silica gel with hexane/ethyl acetate mixtures as eluent.

Test of recycling and reuse of resin 1.

After performing the α -aminoxylation of propanal (103 μ L, 1.37 mmol) with PhNO (0.45 mmol) in the presence of resin **1** (10%; 77.8 mg; *f*: 0.6 mmol/g;) for 1.5 h in CHCl₃ at 0-4 °C, the resin was separated by filtration, rinsed with CH₂Cl₂ (2 x 2 mL), dried at 40 °C under vacuum and reused in a following run.

Cycle	Yield (%)	Ee (%)
1	81	99
2	75	98
3	75	99

Characterization of new compounds

(R)-2-(N-Phenyl-aminooxy)undec-10-en-1-ol (6c)

Prepared according to the general procedure from undecylenic aldehyde (289 μ L, 1.37 mmol) for 1 h to provide the title compound as an oil (90 mg, 75% yield, 98% ee)

after silica gel chromatography (hexane / ethyl acetate gradients from 50/1 to 4/1).

$[\alpha]_D^{29} + 15.0$ (c 1.16, CHCl_3). IR (ATR): 3385, 3260, 3080, 2922, 2850, 1645, 1600, 1497, 1470, 998, 916, 742, 693 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz) δ : 1.20-1.73 (m, 13H), 2.02-2.07 (m, 2H), 2.48 (s, 1H), 3.77 (dd, $J = 11.0, 6.0$ Hz, 1H), 3.84-3.88 (m, 1H), 3.94-3.99 (m, 1H), 4.91-5.02 (m, 1H), 5.76-5.86 (m, 1H), 6.97-7.00 (m, 3H), 7.25-7.30 (m, 2H) ppm. ^{13}C NMR (CDCl_3 , 100.6 MHz) δ : 25.7 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 29.9 (CH_2), 33.8 (CH_2), 65.5 (CH_2), 83.9 (CH), 114.2 (CH), 114.9 (2CH), 122.5 (CH), 129.1 (2CH), 139.2 (CH), 148.4 (C) ppm. HRMS (ES⁺): m/z calcd for $\text{C}_{17}\text{H}_{27}\text{NNaO}_2$: 300.1939; found: 300.1931 $[\text{M}+\text{Na}]^+$

(R)-3-(Methylthio)-2-(N-Phenylaminooxy)propan-1-ol (6e)

Prepared according to the general procedure from 3-methylthiopropionaldehyde (133 μ L, 1.40 mmol) for 15 h to provide the title compound as an oil (89 mg, 83% yield, 99% ee) after silica gel chromatography (hexane / ethyl acetate gradients from 50/1 to 4/1). $[\alpha]_D^{28} + 82.8$ (c 0.87, CHCl_3). IR (ATR): 3420, 3260, 2930, 1600, 1497, 1470, 1200, 998, 925 cm^{-1} . ^1H -RMN (400 MHz, CDCl_3) δ : 2.19 (s, 3H), 2.71-2.76 (dd, $J = 13.6, 7.1$ Hz, 1H), 2.84-2.89 (dd, $J = 13.6, 5.8$ Hz, 1H), 3.84-3.89 (dd, $J = 12.2, 5.8$ Hz, 1H), 3.96-4.00 (dd, $J = 12.2, 3.0$ Hz, 1H), 4.08-4.13 (m, 1H), 6.97-7.02 (m, 3H), 7.25-7.30 (m, 2H) ppm. ^{13}C -RMN (100.6 MHz, CDCl_3) δ : 16.58 (CH_3), 33.86 (CH_2), 63.80 (CH_2), 83.01 (CH), 114.78 (2CH), 122.61

(CH), 129.07 (2CH), 148.29 (C) ppm. HRMS (ES⁺): m/z calcd for C₁₀H₁₅NO₂NaS: 236.0721; found: 236.0727 [M+Na]⁺.

(R)-2-(N-Phenyl-aminoxy)-3,3-dimethyl butan-1-ol (6h)

Prepared according to the general procedure from 3,3'-dimethylbutanal (177 μ L, 1.41 mmol) for 70 minutes to provide the title compound as an oil (34 mg, 35% yield, 99% ee) after silica gel chromatography (gradient from hexane to hexane/ethyl acetate 10/1). $[\alpha]_D^{29} + 5.8$ (c 0.86, CHCl₃). IR (KBr) cm⁻¹: 3449, 3251, 2959, 1602, 1494, 1474, 1365, 1088, 1051, 1025, 993, 923, 766, 748, 692. ¹H NMR (CDCl₃, 400 MHz): 1.03 (s, 9H), 3.19 (br s, 1H), 3.72 (m, 1H), 3.94 (m, 2H), 7.03 (m, 3H), 7.29 (m, 2H) ppm. ¹³C NMR (CDCl₃, 100.6 MHz): 27.0 (3CH₃), 65.0 (CH₂), 91.6 (CH), 115.8 (2CH), 122.5 (CH), 129.4 (2CH), 148.0 (C) ppm. HRMS (ES⁺): m/z calcd for C₁₂H₁₉NO₂Na: 232.1313; found: 232.1324 [M+Na]⁺.

HPLC data for α -aminoxylation products

(R)-2-(N-Phenyl-aminoxy)cyclohexanone (3a):³ Daicel CHIRALCEL AD-H, Hexane/2-propanol 98:2, 1 mL/min, $\lambda = 244$ nm, $t_r(\text{minor})$: 36.4 min., $t_r(\text{major})$: 45.0 min. $[\alpha]_D^{28} + 92$ (c 0.30, CHCl₃).

(R)-7-(N-Phenyl-aminoxy)-1,4-dioxaspiro[4.5]decan-8-one (3b):^{2a} Daicel CHIRALCEL OD-H, Hexane/2-propanol 90:10, 0.5 mL/min, $\lambda = 244$ nm, $t_r(\text{major})$: 21.4 min, $t_r(\text{minor})$: 24.5 min.

(R)-2-(N-Phenyl-aminoxy)-4,4-dimethylcyclohexanone (3c):^{2a} Daicel CHIRALCEL OD-H, Hexane/2-propanol 98:2, 1 mL/min, $\lambda = 254$ nm, $t_r(\text{major})$: 13.0 min, $t_r(\text{minor})$: 17 min.

(R)-3-(N-Phenyl-aminooxy)tetrahydro-pyran-4-one (3d):^{2a} Daicel CHIRALCEL AD-H, Hexane/2-propanol 91:9, 1 mL/min, λ =254 nm, $t_r(\text{major})$: 20.1 min, $t_r(\text{minor})$: 26.3 min.

(R)-3-(N-Phenyl-aminooxy)-1-methylpiperidin-4-one (3e):^{2a} Daicel CHIRALCEL AD-H, Hexane/2-propanol 90:10, 1 mL/min, λ =254 nm, $t_r(\text{major})$: 18.6 min, $t_r(\text{minor})$: 24.5 min.

(R)-2-(N-Phenyl-aminooxy)propan-1-ol (6a):⁵ Daicel CHIRALCEL AD-H column, Hexane/2-propanol 95:5, 1 mL/min, λ =254 nm, t_r (minor): 22.5 min, $t_r(\text{major})$: 25.8 min. $[\alpha]_D^{29} + 2.2$ (c 0.27, CHCl₃).

(R)-2-(N-Phenyl-aminooxy)pent-4-en-1-ol (6b):^{2b} Daicel CHIRALCEL AD-H, Hexane/2-propanol 95:5, 1 mL/min, λ = 244 nm, t_r (minor): 22.6 min, $t_r(\text{major})$: 28.3 min. $[\alpha]_D^{29} + 14.9$ (c 0.10, CHCl₃).

(R)-2-(N-Phenyl-aminooxy)undec-10-en-1-ol (6c): Daicel Chiralcel AD-H column, Hexane/2-propanol 95:5, 1 mL/min, λ = 254 nm, $t_r(\text{minor})$: 14.3 min; $t_r(\text{major})$: 17.1 min. $[\alpha]_D^{29} + 15.0$ (c 1.16, CHCl₃).

(R)-(N-Phenyl-aminooxy)heptan-1-ol (6d):⁴ Daicel CHIRALCEL AD-H, Hexane/2-propanol 95:5, 1 mL/min, λ =254 nm, $t_r(\text{minor})$: 16.8 min, $t_r(\text{major})$: 21.2 min. $[\alpha]_D^{29} + 20.0$ (c 1.5, CHCl₃).

(R)-3-(Methylthio)-2-(N-Phenylaminooxy)propan-1-ol (6e): Daicel Chiralcel AD-H column, Hexane/2-propanol 95:5, 1 mL/min, λ = 230 nm, $t_r(\text{minor})$: 37.7 min; $t_r(\text{major})$: 45.0 min. $[\alpha]_D^{28} + 82.8$ (c 0.87, CHCl₃).

(R)-3-Phenyl-2-(N-Phenyl-aminooxy)propan-1-ol (6f):⁵ Daicel Chiralcel AD-H, Hexane/2-propanol 95:5, 1 mL/min, λ = 254 nm, $t_r(\text{minor})$: 34.3 min; t_r (major): 44.8 min.

(R)-3-Methyl-2-(N-phenyl-aminoxy)butan-1-ol (6g):⁵ Daicel Chiralcel AD-H, Hexane/2-propanol 90:10, 1 mL/min, $\lambda = 230$ nm, $t_r(\text{minor}) = 8.9$ min; $t_r(\text{major})$: 10 min. $[\alpha]_D^{29} + 25$ (c 0.88, CHCl₃).

(R)-2-(N-Phenyl-aminoxy)-3,3-dimethyl butan-1-ol (6h): Daicel Chiralcel AD-H column, Hexane/2-propanol 98:2, 1 mL/min, λ 230 nm, $t_r(\text{minor})$. 28.4 min; $t_r(\text{major})$: 30.1 min. $[\alpha]_D^{29} + 5.8$ (c 0.86, CHCl₃).

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¹H NMR (400 MHz, CDCl₃)

(R)-3-(Methylthio)-2-(N-Phenylaminoxy)propan-1-ol (6e)

^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3):

(R)-2-(N-Phenyl-aminoxy)-3,3-dimethyl butan-1-ol (6h)

^1H NMR (400 MHz, CDCl_3)

PENDANT (100 MHz, CDCl_3):