Supporting Information for:

Highly Enantioselective L-Thiaproline catalyzed α-Aminoxylation of Aldehydes in Aqueous Media

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**General Information:**

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

Proton nuclear magnetic resonance spectra (\(^1\)H NMR) were recorded on Bruker AMX 400 spectrophotometer (CDCl\(_3\) as solvent). Chemical shifts for \(^1\)H NMR spectra are reported as \(\delta\) in units of parts per million (ppm) downfield from SiMe\(_4\) (\(\delta\) 0.0) and relative to the signal of SiMe\(_4\) (\(\delta\) 0.0, singlet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), dd (doublets of doublet) or m (multiplets). The number of protons (\(n\)) for a given resonance is indicated by nH. Coupling constants are reported as a \(J\) value in Hz. Carbon nuclear magnetic resonance spectra (\(^{13}\)C NMR) are reported as \(\delta\) in units of parts per million (ppm) downfield from SiMe\(_4\) (\(\delta\) 0.0) and relative to the signal of chloroform-d (\(\delta\) 77.03, triplet).

Enantioselectivities were determined by High Performance Liquid Chromatography (HPLC) analysis employing a Daicel Chirapak AD-H (0.46 cm x 25 cm), OD-H (0.46 cm x 25 cm) or OJ-H (0.46 cm x 25 cm) column.

Optical rotations were measured in CHCl\(_3\) on a Schmidt + Haensdch polarimeter (Polartronic MH8) with a 1 cm cell (\(c\) given in g/100 mL). Absolute configuration of the products was determined by comparison with compounds previously published.

Aldehydes \(1i\) and \(1j\) were prepared according to literature procedures.\(^1\)\(^-\)\(^2\) The enantiomers used to determine the ee values were synthesized with DL-proline as catalyst. All other reagents were available from commercial sources and used without further purification.
General experimental procedure for the \( \alpha \)-aminoxylation of aldehydes to nitrosobenzene in the presence of water:

Water (0.10 mL) and tetrabutylammonium bromide (193.4 mg, 0.6 mmol) was added to a 5 mL drum vial containing nitrosobenzene 2 (32.1 mg, 0.3 mmol), corresponding aldehydes 1 (0.9 mmol) and a magnetic stirring bar. After stirring for 5 min at 0 °C, L-thiaproline (8 mg, 0.06 mmol) was then added. The reaction was first stirred at this temperature for about 10 min and then at room temperature until the green solution turned yellow which indicated complete consumption of the nitrosobenzene. As the \( \alpha \)-aminoxy aldehyde product is rather labile, isolation and characterization was performed after conversion to the corresponding \( \alpha \)-aminoxy alcohol 3 by treatment of the reaction mixture with NaBH\(_4\). The excess NaBH\(_4\) was quenched by the addition of water and then extracted with CH\(_2\)Cl\(_2\) (3 x 30 ml). The combined organic extracts were dried with Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The crude oil was purified by flash column chromatography (Hexane:EtOAc = 9/1~7/3) yielding pure \( \alpha \)-aminoxy alcohols 3.

Relative and absolute configurations of the products were compared with the known \(^1\)H NMR, chiral HPLC analysis, and optical rotation values. The compounds in Table 3 are known in the literature.
Experimental data of Compounds 3a-3k

(R)-2-(N-phenylaminoxy)propan-1-ol (3a) ³

\[
\text{OH} \quad \text{N} \quad \text{Ph} \\
\text{O} \quad \text{H} \quad \text{OH}
\]

\(\alpha\)-aminoxy alcohol 3a was prepared according to the general procedure from propanal (0.07 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (42.3 mg, 84% yield) after flash column chromatography on silica gel (Hexane:EtOAc = 9/1~7/3).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.29-7.25 (2H, m), 7.04-6.60 (3H, m), 4.16-4.08 (1H, m), 3.80-3.70 (2H, m), 2.56 (1H, brs), 1.25 (3H, d, \(J = 6.4\) Hz).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 148.5, 129.0, 122.4, 114.7, 80.0, 66.5, 15.4.

HPLC: Chiralpak AD-H (hexane/\(i\)-PrOH, 90/10, flow rate 1 mL/min, \(\lambda = 230\) nm),
\(t_R\) (minor) = 10.6 min, \(t_R\) (major) =12.1 min; 96% ee.

\([\alpha]_D^{25} = + 2.9 \ (c = 1.0, \text{CHCl}_3)\).

(R)-2-(N-phenylaminoxy)butan-1-ol (3b) ³

\[
\text{OH} \quad \text{N} \quad \text{Ph} \\
\text{O} \quad \text{H} \quad \text{OH}
\]

\(\alpha\)-aminoxy alcohol 3b was prepared according to the general procedure from butanal (0.08 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (40.9 mg, 75% yield) after flash column chromatography on silica gel (hexane:EtOAc = 9/1~7/3).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.29-7.25 (2H, m), 7.07-6.95 (2H, m), 3.91-3.74 (3H, m), 2.67 (1H, brs), 1.78-1.53 (2H, m), 1.01 (3H, t, \(J = 7.5\) Hz).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 148.4, 129.0, 122.4, 114.8, 85.3, 64.9, 22.9, 10.1.

HPLC: Chiralpak AD-H (hexane/\(i\)-PrOH, 90/10, flow rate 1 mL/min, \(\lambda = 230\) nm),
\(t_R\) (minor) = 10.2 min, \(t_R\) (major) =11.6 min; 98% ee.

\([\alpha]_D^{23} = + 36.0 \ (c = 1.0, \text{CHCl}_3)\).
(R)-2-(N-phenylaminoxy)pentan-1-ol (3c)

\[
\begin{array}{c}
\text{OH} \\
\text{N} \\
\text{Ph} \\
\text{O} \\
\text{H}
\end{array}
\]

\(\alpha\)-aminoxy alcohol 3c was prepared according to the general procedure from pentanal (0.10 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (46.0 mg, 79% yield) after flash column chromatography on silica gel (hexane:EtOAc = 9/1~7/3).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.28-7.15 (3H, m), 6.98-6.94 (2H, m), 3.94-3.91 (1H, m), 3.85-3.82 (1H, m), 3.75-3.71 (1H, m), 2.93 (1H, brs), 1.67-1.61 (1H, m), 1.54-1.33 (3H, m), 0.97-0.89 (3H, m).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 148.4, 129.0, 122.3, 114.7, 83.7, 65.1, 32.0, 19.0, 14.2.

HPLC: Chiralpak AD-H (hexane/i-PrOH, 90/10, flow rate 1 mL/min, \(\lambda\) = 230 nm),

\(t_R\) (minor) = 10.0 min, \(t_R\) (major) = 11.4 min; 97% ee.

\([\alpha]_D^{23} = + 28.6\ (c = 1.0, \text{CHCl}_3)\).

(R)-2-(N-phenylaminoxy)hexan-1-ol (3d)

\[
\begin{array}{c}
\text{OH} \\
\text{N} \\
\text{Ph} \\
\text{O}
\end{array}
\]

\(\alpha\)-aminoxy alcohol 3d was prepared according to the general procedure from hexanal (0.11 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (46.4 mg, 74% yield) after flash column chromatography on silica gel (hexane:EtOAc = 9/1~7/3).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.29-7.26 (2H, m), 7.06-6.96 (3H, m), 3.98-3.92 (1H, m), 3.87-3.84 (1H, m), 3.79-3.72 (1H, m), 2.68 (1H, brs), 1.69-1.50 (1H, m), 1.47-1.30 (4H, m), 0.92 (3H, \(t, J = 7.1\) Hz).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 148.4, 129.0, 122.5, 114.9, 84.0, 65.4, 29.6, 27.9, 22.0, 14.0.

HPLC: Chiralpak AD-H (hexane/i-PrOH, 90/10, flow rate 1 mL/min, \(\lambda\) = 230 nm),

\(t_R\) (minor) = 9.5 min, \(t_R\) (major) = 11.4 min; 96% ee.

\([\alpha]_D^{23} = + 22.5\ (c = 1.2, \text{CHCl}_3)\).
(R)-3-methyl-2-(N-phenylaminoxy)butan-1-ol (3e)\(^4\)

\[
\begin{array}{c}
\text{O} \\
N \\
\text{Ph} \\
\text{OH}
\end{array}
\]

\(\alpha\)-aminoxy alcohol 3e was prepared according to the general procedure from 3-methybutanal (0.10 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (44.8 mg, 76% yield) after flash column chromatography on silica gel (hexane:EtOAc = 9/1~7/3).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.30-7.26 (2H, m), 7.03-6.99 (3H, m), 3.88-3.87 (2H, m), 3.76-3.74 (1H, m), 2.07-1.99 (1H, m), 1.05 (3H, d, \(J = 6.9\) Hz), 1.01 (3H, d, \(J = 6.9\) Hz).

\(^1\)C NMR (100 MHz, CDCl\(_3\)): 148.3, 129.0, 122.5, 115.0, 88.6, 63.6, 28.7, 18.7, 18.6.

HPLC: Chiralpak AD-H (hexane/\(i\)-PrOH, 90/10, flow rate 1 mL/min, \(\lambda = 230\) nm),
\(t_R\) (minor) = 9.0 min, \(t_R\) (major) =10.1 mins; 97% ee.

\([\alpha]_{D}^{22} = + 33.4 \ (c = 1.0, \text{CHCl}_3)\).

(R)-2-phenyl-2-(N-phenylaminoxy)ethanol (3f)\(^3\)

\[
\begin{array}{c}
\text{O} \\
N \\
\text{Ph} \\
\text{OH}
\end{array}
\]

\(\alpha\)-aminoxy alcohol 3f was prepared according to the general procedure from 2-phenylacetaldehyde (0.11 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (53.5 mg, 78% yield) after flash column chromatography on silica gel (hexane:ether = 9/1~7/3).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.39-7.31 (5H, m), 7.28-7.20 (2H, m), 6.99-6.94 (3H, m), 5.00 (1H, dd, \(J = 3.5, 8.1Hz\)), 3.99-3.92 (1H, m), 3.83-3.78 (1H, m), 2.58 (1H, brs).

\(^1\)C NMR (100 MHz, CDCl\(_3\)): 147.9, 137.7, 129.0, 128.7, 128.5, 127.0, 122.5, 115.0, 86.4, 66.4.

HPLC: Chiralpak OD-H (hexane/\(i\)-PrOH, 95/5, flow rate 1 mL/min, \(\lambda = 230\) nm),
\(t_R\) (major) = 25.8mins, \(t_R\) (minor) =30.2 min; 93% ee.

\([\alpha]_{D}^{24} = - 85.5 \ (c = 1.1, \text{CHCl}_3)\).
(R)-3-phenyl-2-(N-phenylaminoxy)propan-1-ol (3g) ³

α-aminoxy alcohol 3g was prepared according to the general procedure from 3-phenylpropanal (0.12 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (55.9 mg, 77% yield) after flash column chromatography on silica gel (hexane:ether = 9/1~7/3).

¹H NMR (400 MHz, CDCl₃): δ 7.32-7.18 (6H, m), 7.08 (1H, brs), 6.94 (1H, t, J = 7.3 Hz), 6.82 (2H, d, J = 8.0 Hz), 4.16-4.10 (1H, m), 3.85 (1H, d, J = 11.8 Hz), 3.04 (1H, dd, J = 6.8, 13.7 Hz), 2.84 (1H, dd, J = 7.0, 13.7 Hz), 2.62 (1H, brs).

¹³C NMR (100 MHz, CDCl₃): 148.3, 137.8, 129.4, 128.9, 128.5, 126.4, 122.3, 114.6, 85.0, 64.1, 36.4.

HPLC: Chiralpak OD-H (hexane/i-PrOH, 91/9, flow rate 1 mL/min, λ = 230 nm),

$t_R$ (major) = 57.9 min, $t_R$ (minor) = 62.4 min; >99% ee.

$[\alpha]_D^{22} = +55.2$ (c = 1.3, CHCl₃).

(R)-2-(N-phenylaminoxy)pent-4-en-1-ol (3h) ⁴

α-aminoxy alcohol 3h was prepared according to the general procedure from 4-pentenal (0.09 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (51.0 mg, 88% yield) after flash column chromatography on silica gel (hexane:EtOAc = 9/1~7/3).

¹H NMR (400 MHz, CDCl₃): δ 7.29-7.26 (2H, m), 7.06-6.96 (3H, m), 5.93-5.82 (1H, m), 5.18-5.11 (2H, m), 4.05-4.00 (1H, m), 3.87-3.75 (2H, m), 2.54-2.32 (3H, m), 1.66 (1H, brs).

¹³C NMR (100 MHz, CDCl₃): 148.3, 134.0, 129.0, 122.5, 117.8, 114.8, 83.3, 64.6, 34.6.

HPLC: Chiralpak AD-H (hexane/i-PrOH, 90/10, flow rate 1 mL/min, λ = 230 nm),

$t_R$ (minor) = 10.5 min, $t_R$ (major) = 12.5 min; 96% ee.

$[\alpha]_D^{23} = -22.9$ (c = 1.0, CHCl₃).
(R)-4-(benzyloxy)-2-(N-phenylaminoxy)butan-1-ol (new compound) (3i)

\[
\begin{align*}
\text{BnO} & \quad \text{O} \quad \text{N} \quad \text{Ph} \\
\text{OH} & \quad \text{N} \\
\end{align*}
\]

\(\alpha\)-aminoxy alcohol 3i was prepared according to the general procedure from 4-(benzyloxy)butanal (0.16 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (73.8 mg, 86% yield) after flash column chromatography on silica gel (hexane:EtOAc = 9/1–7/3).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.34-7.23 (6H, m), 7.05 (1H, brs), 6.98-6.94 (3H, m), 4.54-4.52 (2H, m), 4.14-4.11 (1H, m), 3.93-3.87 (1H, m), 3.81-3.77 (1H, m), 3.66 (2H, \(t, J = 5.7\ Hz\)), 2.81 (1H, \(t, J = 5.9\ Hz\)), 2.06-1.89 (2H, m).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 148.3, 138.0, 129.0, 128.5, 127.8, 122.4, 116.1, 114.8, 81.5, 73.2, 66.7, 64.8, 30.3.

HPLC: Chiralpak AD-H (hexane/i-PrOH, 91/9, flow rate 1 mL/min, \(\lambda = 230\ nm\)), 
\(t_R\) (minor) = 18.8 min, \(t_R\) (major) = 24.1 min; 97% ee.

\([\alpha]_{D}^{22}\) = +15.5 (c = 1.1, CHCl\(_3\)).

HRMS (ESI) calcd for C\(_{17}\)H\(_{21}\)NO\(_3\), m/z 288.1600, found 288.1599.

(R)-tert-butyl 3-hydroxy-2-(N-phenylaminoxy)propylcarbamate (new compound) (3j)

\[
\begin{align*}
\text{Boc} & \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{Ph} \\
\text{OH} & \quad \text{N} \\
\end{align*}
\]

\(\alpha\)-aminoxy alcohol 3j was prepared according to the general procedure from tert-butyl-3-oxopropylcarbamate (0.16 mL, 0.9 mmol) to provide the title compound as a pale yellow liquid (67.2 mg, 79% yield) after flash column chromatography on silica gel (hexane:EtOAc = 9/1–7/3).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.32-7.24 (3H, m), 6.98-6.94 (2H, m), 5.02 (1H, brs), 3.94-3.92 (1H, m), 3.80 (2H, s), 3.50-3.36 (2H, m), 1.45 (9H, s).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 157.1, 148.3, 129.0, 122.4, 114.6, 82.4, 80.0, 61.3, 39.6, 28.3.

HPLC: Chiralpak OJ-H (hexane/i-PrOH, 95/5, flow rate 1 mL/min, \(\lambda = 230\ nm\)),
\( t_R \) (minor) = 24.8 min, \( t_R \) (major) = 26.6 min; 93% ee.

\([\alpha]_D^{22} = -8.2 \ (c = 1.3, \text{CHCl}_3)\).

HRMS (ESI) calcd for \( \text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_4 \), m/z 282.1658, found 282.1659.

\((R)-2-(p\text{-toluidinoxy})\text{propan-1-ol} \) (new compound) (3k)

\( \alpha \)-aminoxy alcohol 3k was prepared according to the general procedure from propanal (0.07 mL, 0.9 mmol) and nitrosotoluene (36.3 mg, 0.3 mmol) to provide the title compound as a pale yellow liquid (45.0 mg, 83% yield) after flash column chromatography on silica gel (hexane:EtOAc = 9/1~7/3).

\(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.07 (2H, d, \( J = 8.1 \) Hz), 6.99 (1H, brs), 6.88 (2H, d, \( J = 8.3 \) Hz), 4.13-4.07 (1H, m), 3.78-3.68 (2H, m), 2.28 (3H, s), 1.22 (3H, d, \( J = 6.5 \) Hz).

\(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): 145.8, 132.0, 129.5, 115.3 79.8, 66.6, 20.6, 15.4.

HPLC: Chiralpak AD-H (hexane/i-PrOH, 90/10, flow rate 1 mL/min, \( \lambda = 230 \) nm),

\( t_R \) (minor) = 10.9 min, \( t_R \) (major) = 12.4 min; 97% ee.

\([\alpha]_D^{25} = +5.5 \ (c = 1.5, \text{CHCl}_3)\).

HRMS (ESI) calcd for \( \text{C}_{10}\text{H}_{16}\text{NO}_2 \), m/z 182.1181, found 182.1181.

References:
$^1$H and $^{13}$C NMR Spectra of Compounds 3a-3n
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![NMR spectra](image)

3b

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HPLC Spectra of Compounds 3a-3n

Supplementary Material (ESI) for Green Chemistry
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