Supporting Information for

Asymmetric one-pot sequential Friedel–Crafts-type alkylation and α -oxyamination catalyzed by a peptide and an enzyme

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General information

¹H and ¹³C NMR spectra were recorded at 400 and 100 MHz respectively on a JEOL JNM-LA400 spectrometer, and chemical shifts were referenced to internal tetramethylsilane (TMS, $\delta = 0.0$ ppm) for ¹H, and the central line of CDCl₃ ($\delta = 77.0$ ppm) for ¹³C. High-resolution FAB mass spectra were obtained on a JEOL JMS-600H mass spectrometer in positive-ionization mode by using 3-nitrobenzyl alcohol as a matrix. Polyethylene glycol 400 was added to the matrix as a mass calibrant. HPLC charts were recorded on a Shimadzu CLASS-VP system with a Chiralpak IA column (25 cm) and IA guard (1 cm), or Chiralpak AS-H column (25 cm) and AS-H guard (1 cm). The resin-supported peptide was synthesized according to our previous report [37]. Laccase was purchased from Sigma-Aldrich (product number: 53739, from Trametes versicolor, 93.6 U/mg) and used as received.

Typical procedure for the sequential FCAA/α-oxyamination (Table 2).

To a mixture of an indole compound (0.10 mmol), an aldehyde (0.15 mmol) and resin-supported TFA·Pro-D-Pro-Aib-(Trp)₂-(Leu-Leu-Aib)₂ (111 mg, 0.02 mmol of the terminal prolyl group) in THF (0.67 mL), was added water (1.34 mL), slowly. After the mixture had been stirred at room temperature for the given time, TEMPO (0.15 mmol) and laccase (0.5 mg) were added. Afterward the mixture was stirred for another 12 h, and then the peptide catalyst was filtered off and washed with diethyl ether. The filtrate solution was washed with water, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the crude product was purified by preparative TLC (hexane/ethyl acetate 2:1) to afford a diastereomeric mixture. Then, the product was dissolved in ethanol (ca. 2 mL), and sodium borohydride (0.3 mmol) was added. Afterward the mixture was stirred for 30 min, and then an aqueous saturated solution of ammonium chloride was added. The resulting solution was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the crude product was purified by preparative TLC (hexane/ethyl acetate 1:1) to afford the corresponding alcohols of syn and anti-isomers separately (in Table 2, entry 4, two isomers could not be separated).



(2*S*,3*S*)-3-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-3-(4-nitrophenyl)-2-(2,2,6,6-tetramethyl-piperidin-1-yloxy)propanol (*syn*-4, Table 2, entry 1).

¹H NMR (CDCl₃) δ 8.14–8.10 (m, 2H), 7.54–7.50 (m, 2H), 7.20–7.17 (m, 2H), 6.85 (dd, J = 8.7, 2.3 Hz, 1H), 6.62 (d, J = 2.8 Hz, 1H), 5.69 (br, 1H), 4.99 (ddd, J = 9.6, 3.7, 1.8 Hz, 1H), 4.49 (d, J = 3.7 Hz, 1H), 3.89 (dd, J = 12.4, 9.6 Hz, 1H), 3.78 (s, 3H), 3.78 (dd, J = 12.4, 1.8 Hz, 1H), 3.71 (s, 3H), 1.62–1.30 (m, 6H), 1.26 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H); ¹³C NMR (CDCl₃) δ 153.79, 149.53, 146.55, 132.07, 129.80, 127.84, 127.82, 123.21, 111.84, 111.43, 110.07, 100.99, 82.72, 66.95, 62.03, 60.22, 55.83, 44.79, 40.53, 40.24, 34.66, 33.05, 32.12, 20.74, 20.31, 16.96; HRMS (FAB) m/z: calculated for C₂₈H₃₈N₃O₅ [M + H]⁺: 496.2811, found 496.2820. Enantiomeric excess was determined by HPLC analysis (Chiralpak IA, hexane/2-propanol 90:10, 1.0 mL min⁻¹): $t_R = 21.7$ min (minor), 30.3 min (major).



(2*R*,3*S*)-3-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-3-(4-nitrophenyl)-2-(2,2,6,6-tetramethyl-piperidin-1-yloxy)propanol (*anti*-4, Table 2, entry 1).

¹H NMR (CDCl₃) δ 8.14–8.10 (m, 2H), 7.56–7.52 (m, 2H), 7.16 (d, J = 8.7 Hz, 1H), 7.10 (s, 1H), 6.87–6.82 (m, 2H), 6.12 (br, 1H), 5.00 (td, J = 9.2, 1.4 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 4.08 (dd, J = 12.4, 9.6 Hz, 1H), 3.91 (dd, J = 12.4, 1.4 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 1.54–1.27 (m, 12H), 0.97 (s, 3H), 0.68 (s, 3H); ¹³C NMR (CDCl₃) δ 153.94, 150.79, 146.23, 132.16, 129.26, 127.27, 126.58, 123.20, 113.01, 111.93, 110.18, 100.81, 82.00, 67.69, 61.95, 60.12, 55.92, 45.03, 40.33, 39.83, 34.61, 33.04, 32.42, 20.70, 20.18, 16.96; HRMS (FAB) *m/z*: calculated for C₂₈H₃₈N₃O₅ [M + H]⁺: 496.2811, found 496.2811. Enantiomeric excess was determined by HPLC analysis (Chiralpak IA, hexane/2-propanol 90:10, 1.0 mL min⁻¹): *t*_R = 31.0 min (minor), 46.6 min (major).



(2*S*,3*S*)-3-(5-Methoxy-1*H*-indol-3-yl)-3-(4-nitrophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanol (*syn*-6, Table 2, entry 2).

¹H NMR (CDCl₃) δ 8.16 (br, 1H), 8.15–8.10 (m, 2H), 7.55–7.50 (m, 2H), 7.36 (s, 1H), 7.25 (d, J = 8.7 Hz, 1H), 6.82 (dd, J = 8.7, 2.3 Hz, 1H), 6.65 (d, J = 2.3 Hz, 1H), 5.77 (br, 1H), 5.01 (ddd, J = 9.6, 4.1, 1.8 Hz, 1H), 4.49 (d, J = 4.1 Hz, 1H), 3.94 (dd, J = 12.4, 9.6 Hz, 1H), 3.77 (dd, J = 12.4, 1.8 Hz, 1H), 3.72 (s, 3H), 1.60–1.30 (m, 6H), 1.25 (s, 3H), 1.12 (s, 3H), 1.12 (s, 3H), 0.98 (s, 3H); ¹³C NMR (CDCl₃) δ 154.02, 149.40, 146.57, 131.00, 129.76, 127.55, 123.25, 123.22, 113.31, 112.31, 111.88, 100.86, 82.78, 67.00, 62.07, 60.26, 55.78, 44.83, 40.52, 40.22, 34.60, 32.14, 20.74, 20.30, 16.93; HRMS (FAB) m/z: calculated for C₂₇H₃₆N₃O₅ [M + H]⁺: 482.2655, found 482.2654. Enantiomeric excess was determined by HPLC analysis (Chiralpak AS-H, hexane/2-propanol 90:10, 1.0 mL min⁻¹): $t_{\rm R} = 31.5$ min (minor), 37.9 min (major).



(2*R*,3*S*)-3-(5-Methoxy-1*H*-indol-3-yl)-3-(4-nitrophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanol (*anti*-4, Table 2, entry 2).

¹H NMR (CDCl₃) δ 8.18 (br, 1H), 8.14–8.10 (m, 2H), 7.57–7.53 (m, 2H), 7.27 (d, J = 1.8 Hz, 1H), 7.23 (d, J = 9.2 Hz, 1H), 6.85–6.81 (m, 2H), 6.21 (br, 1H), 5.04 (td, J = 9.2, 1.4 Hz, 1H), 4.20 (d, J = 9.2 Hz, 1H), 4.09 (dd, J = 11.9, 9.2 Hz, 1H), 3.92 (dd, J = 11.9, 1.4 Hz, 1H), 3.78 (s, 3H), 1.56–1.25 (m, 12H), 0.98 (s, 3H), 0.70 (s, 3H); ¹³C NMR (CDCl₃) δ 154.14, 150.39, 146.32, 131.15, 129.40, 126.93, 123.18, 122.10, 114.89, 112.40, 112.00, 100.72, 81.89, 67.66, 62.01, 60.22, 55.85, 45.10, 40.34, 39.86, 34.55, 32.35, 20.72, 20.23, 16.93; HRMS (FAB) *m*/*z*: calculated for C₂₇H₃₆N₃O₅ [M + H]⁺: 482.2655, found 482.2651. Enantiomeric excess was determined by HPLC analysis (Chiralpak IA, hexane/2-propanol 90:10, 1.0 mL min⁻¹): *t*_R = 36.0 min (minor), 42.4 min (major).



(2*S*,3*S*)-3-(1-Methyl-1*H*-indol-3-yl)-3-(4-nitrophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanol (*syn*-7, Table 2, entry 3).

¹H NMR (CDCl₃) δ 8.13–8.09 (m, 2H), 7.54–7.50 (m, 2H), 7.30 (d, J = 8.2 Hz, 1H), 7.24–7.17 (m, 3H), 7.00 (td, J = 7.6, 0.9 Hz, 1H), 5.69 (br, 1H), 5.04–4.98 (m, 1H), 4.56 (d, J = 3.6 Hz, 1H), 3.93–3.75 (m, 2H), 3.82 (s, 3H), 1.60–1.31 (m, 6H), 1.27 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H); ¹³C NMR (CDCl₃) δ 149.54, 146.56, 136.65, 129.80, 127.50, 127.22, 123.20, 121.94, 119.14, 118.87, 112.03, 109.28, 82.76, 66.93, 62.08, 60.27, 44.78, 40.51, 40.23, 34.61, 32.86, 32.09, 20.73, 20.31, 16.94; HRMS (FAB) *m/z*: calculated for C₂₇H₃₆N₃O₄ [M + H]⁺: 466.2706, found 466.2707. Enantiomeric excess was determined by HPLC analysis (Chiralpak IA, hexane/2-propanol 90:10, 1.0 mL min⁻¹): *t*_R = 10.9 min (minor), 15.7 min (major).



(2*R*,3*S*)-3-(1-Methyl-1*H*-indol-3-yl)-3-(4-nitrophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanol (*anti*-7, Table 2, entry 3).

¹H NMR (CDCl₃) δ 8.13–8.09 (m, 2H), 7.57–7.53 (m, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.20 (t, *J* = 8.2 Hz, 1H), 7.14 (s, 1H), 7.05 (dd, *J* = 8.2, 7.8 Hz, 1H), 6.16 (br, 1H), 5.04 (td, *J* = 9.2, 1.4 Hz, 1H), 4.25 (d, *J* = 9.2 Hz, 1H), 4.08 (dd, *J* = 11.9, 9.2 Hz, 1H), 3.90 (dd, *J* = 11.9, 1.4 Hz, 1H), 3.78 (s, 3H), 1.55–1.28 (m, 12H), 0.98 (s, 3H), 0.69 (s, 3H); ¹³C NMR (CDCl₃) δ 150.79, 146.23, 136.73, 129.27, 126.89, 126.01, 123.21, 122.14, 119.36, 118.59, 113.57, 109.43, 82.06, 67.64, 62.06, 60.26, 45.04, 40.29, 39.80, 34.55, 32.86, 32.36, 20.69, 20.18, 16.93; HRMS (FAB) *m/z*: calculated for C₂₇H₃₆N₃O₄ [M + H]⁺: 466.2706, found 466.2699. Enantiomeric excess was determined by HPLC analysis (Chiralpak IA, hexane/2-propanol 90:10, 1.0 mL min⁻¹): *t*_R = 11.9 min (major), 13.6 min (minor).



3-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-3-(3-nitrophenyl)-2-(2,2,6,6-tetramethylpiperidin-1yloxy)propanol [diastereomeric mixture (ca. 7:3)] (*syn-* and *anti-*8, Table 2, entry 4).

¹H NMR (CDCl₃) δ 8.32 (t, J = 2.1 Hz, 0.7 H), 8.29 (t, J = 2.1 Hz, 0.3 H), 8.06 (ddd, J = 8.2, 2.1, 0.9 Hz, 0.7 H), 8.02 (ddd, J = 8.2, 2.1, 0.9 Hz, 0.3 H), 7.70 (dm, J = 8.2 Hz, 0.3H), 7.64 (dm, J = 8.2 Hz, 0.7H), 7.41 (t, J = 8.2 Hz, 1H), 7.21–7.13 (m. 2H), 6.87–6.83 (m, 1.3H), 6.65 (d, J = 2.7 Hz, 0.7H), 6.11 (br, 0.3H), 5.70 (br, 0.7H), 5.02–4.95 (m, 1H), 4.49 (d, J = 3.7 Hz, 0.7H), 4.18 (d, J = 8.7 Hz, 0.3H), 4.06 (dd, J = 12.4, 9.6 Hz, 0.3H), 3.93–3.85 (m, 1H), 3.80–3.70 (m, 6.7H), 1.53–1.25 (m, 9.9H), 1.15 (s, 2.1H), 1.06 (s, 2.1H), 1.04 (s, 2.1H), 0.97 (s, 0.9H), 0.69 (s, 0.9H); ¹³C NMR (CDCl₃) δ 153.93, 153.80, 147.99, 147.93, 144.88, 144.00, 135.07, 134.76, 132.18, 132.08, 128.83, 128.68, 127.92, 127.86, 127.23, 126.69, 123.94, 123.55, 121.62, 121.26, 113.21, 111.99, 111.86, 111.47, 110.19, 110.09, 100.97, 100.73, 82.62, 81.82, 67.73, 67.00, 62.03, 61.90, 60.21, 60.13, 55.94, 55.86, 44.78, 44.54, 40.58, 40.38, 40.29, 39.89, 34.64, 34.60, 33.06, 32.33, 32.07, 20.68, 20.60, 20.27, 20.08, 16.97; HRMS (FAB) *m/z*: calculated for C₂₈H₃₈N₃O₅ [M + H]⁺: 496.2811, found 496.2814. Enantiomeric excess was determined by HPLC analysis (Chiralpak IA, hexane/2-propanol 90:10, 0.3 mL min⁻¹): $t_{\rm R} = 58.7$ min (syn, minor), 60.9 min (syn, major), 80.3 min (anti, minor), 90.7 min (anti, major).



(2*S*,3*S*)-3-(1-Methyl-1*H*-pyrrol-2-yl)-3-(4-nitrophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanol (*syn*-9, Table 2, entry 5).

¹H NMR (CDCl₃) δ 8.15–8.11 (m, 2H), 7.38–7.34 (m, 2H), 6.54 (dd, J = 2.8, 1.8 Hz, 1H), 6.36 (dd, J = 3.6, 1.8 Hz, 1H), 6.13 (dd, J = 3.6, 2.8 Hz, 1H), 5.63 (br, 1H), 4.91 (ddd, J = 9.6, 4.6, 1.8 Hz, 1H), 4.21 (d, J = 4.6 Hz, 1H), 3.79 (dd, J = 12.4, 9.6 Hz, 1H), 3.69 (dd, J = 12.4, 1.8 Hz, 1H), 3.29 (s, 3H), 1.60–1.23 (m, 9H), 1.17 (s, 3H), 1.15 (s, 3H), 0.97 (s, 3H); ¹³C NMR (CDCl₃) δ 147.63, 146.82, 129.84, 129.73, 123.50, 122.23, 107.98, 106.87, 82.53, 66.70, 62.07, 60.23, 45.39, 40.56, 40.25, 34.60, 34.02, 32.22, 20.64, 20.18, 16.96; HRMS (FAB) *m*/*z*: calculated for C₂₃H₃₄N₃O₄ [M + H]⁺: 416.2549, found 416.2543. Enantiomeric excess was determined by HPLC analysis (Chiralpak IA, hexane/2-propanol 90:10, 1.0 mL min⁻¹): *t*_R = 11.4 min (major), 13.2 min (minor).



(2*R*,3*S*)-3-(1-Methyl-1*H*-pyrrol-2-yl)-3-(4-nitrophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanol (*anti*-9, Table 2, entry 5).

¹H NMR (CDCl₃) $\delta = 8.15-8.11$ (m, 2H), 7.41–7.37 (m, 2H), 6.50 (dd, J = 2.7, 1.6 Hz, 1H), 6.31 (dd, J = 3.7, 1.6 Hz, 1H), 6.11 (dd, J = 3.7, 2.7 Hz, 1H), 6.00 (br, 1H), 4.88 (td, J = 8.7, 2.3 Hz, 1H), 4.02 (dd, J = 11.9, 8.7 Hz, 1H), 3.98 (dd, J = 11.9, 2.3 Hz, 1H), 3.92 (d, J = 8.7 Hz, 1H), 3.31 (s, 3H), 1.52-1.20 (m, 12H), 0.94 (s, 3H), 0.60 (s, 3H); ¹³C NMR (CDCl₃) $\delta = 148.53, 146.49, 130.51, 129.73, 123.24, 122.27, 107.12, 107.02, 81.55, 67.50, 61.94, 60.11, 45.37, 40.30, 39.85, 34.48, 33.85, 32.25, 20.80, 20.13, 16.93; HRMS (FAB)$ *m/z*: calculated for C₂₃H₃₄N₃O₄ [M + H]⁺: 416.2549, found 416.2543. Enantiomeric excess was determined by HPLC analysis (Chiralpak IA, hexane/2-propanol 90:10, 1.0 mL min⁻¹):*t*_R = 9.0 min (minor), 9.9 min (major).

Determination of stereochemistry of products.



In the Friedel–Crafts-type alkylation with peptide catalyst **1** using the substrates shown in the above scheme, the absolute configuration of the major product can be assigned as the *S* form (*Tetrahedron Lett.* **2009,** *50*, 5602–5604). The diastereomers (ca. 75:25) obtained after the next α -oxyamination were reduced to the corresponding alcohols and separated from each other. The analyses by ¹H NMR and NOESY experiments were conducted to determine the relative configuration of the introduced oxyamino group.

With one isomer, a large ${}^{3}J$ coupling constant (9.2 Hz) between the protons shown below (with another isomer, ${}^{3}J = 3.6$ Hz) and the H,H-NOEs between the 4-nitrophenyl group and the tetramethylpiperidinyl moiety were observed. This indicates that this compound is the anti isomer, and the other one is the syn isomer.



major conformation of anti isomer

Based on the mechanistic similarity of the reaction and in analogy with the NMR spectra of other products, the major configurations of all products were assigned as (2S,3S) or (2R,3S).

NOESY spectrum of anti-isomer.





























 1: 220 nm, 8 nm
 area
 area%

 21.749
 482659
 1.12

 30.338
 42698576
 98.88

 Total

 43181235



Chiralpak IA column, hexane/2-propanol 90:10, 1.0 mL min⁻¹





racemic sample



Chiralpak AS-H column, hexane/2-propanol 90:10, 1.0 mL min⁻¹





racemic sample



Chiralpak IA column, hexane/2-propanol 90:10, 1.0 mL min⁻¹



 1: 220 nm, 8 nm
 area
 area%

 36.042
 3895937
 13.42

 42.368
 25126043
 86.58

 Total

 29021980

 100.00



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Chiralpak IA column, hexane/2-propanol 90:10, 1.0 mL min⁻¹





Chiralpak IA column, hexane/2-propanol 90:10, 1.0 mL min⁻¹





racemic sample





Chiralpak IA column, hexane/2-propanol 90:10, 0.3 mL min⁻¹

1: 254 nm. 8 nm		
retention time	e area	area%
58.713	571523	0.85
60.914	46782757	69.59
80.281	3868661	5.76
90.715	15998827	23.80
Total		
	67221768	100.00



racemic sample

Chiralpak IA column, hexane/2-propanol 90:10, 1.0 mL min⁻¹



 retention time
 area
 area%

 11.473
 17303582
 95.68

 13.225
 780891
 4.32

 Total

 18084473
 100.00



racemic sample

Chiralpak IA column, hexane/2-propanol 90:10, 1.0 mL min⁻¹







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