Asymmetric Epoxidation of Enones by Peptide-Based Catalyst: a Strategy Inverting Juliá–Colonna Stereoselectivity

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**General information.**

$^1$H and $^{13}$C NMR spectra were recorded at 400 and 100 MHz respectively on a JEOL JNM-LA400 spectrometer, and chemical shifts were referenced to internal tetramethysilane (TMS, $\delta = 0.0$ ppm) for $^1$H, and the central line of CDCl$_3$ ($\delta = 77.0$ ppm) for $^{13}$C. High-resolution FAB mass measurements were performed on a JEOL JMS-600H mass spectrometer in a positive ionization mode with 3-nitrobenzyl alcohol or 2-nitrophenyl octyl ether as a matrix. Polyethylene glycol 400 was added to the matrix as an internal mass calibrant. HPLC traces were recorded on a Shimadzu CLASS-VP system using Chiralcel OJ-H column (25 cm) and OJ-H guard (1 cm), or Chiralcel OD-H column (25 cm) and OD-H guard (1 cm).

**Preparation of peptide catalysts.**

Resin-supported peptides were synthesized according to a standard Fmoc solid phase peptide synthesis$^{[1,2]}$ using TentaGel S-NH$_2$ (AnaSpec, Inc., product number: 22798, 0.29 mmol/g amine loading). The resin was added to an empty column with a filter at the bottom, and the following manipulations were performed. First, the resin was swollen with dichloromethane for 15 min, and washed with DMF (5x). In a different vessel, to a suspension of an Fmoc-amino acid (3 equiv.), $O$-$(7$-azabenzotriazol-1-yl)-$N,N,N',N'-$tetramethyluronium hexafluorophosphate (HATU, 3 equiv.), and $1$-hydroxy-$7$-azabenzotriazole (HOAt, 3 equiv.) in DMF, was added diisopropylethylamine (6 equiv). This solution was transferred to the column that contained the resin, and the column was mixed every 5 min with a vortex mixer. After 30 min, the resin was washed with DMF (5x), and the completion of the coupling reaction of the Fmoc-amino acid was checked by the Kaiser test or the chloranil test. The resin was then washed with 20 vol% piperidine solution in DMF (1x), and this solution was added again to remove the Fmoc group. After the reaction ran for 20 min with mixing every 5 min by a vortex mixer, the resin was washed with DMF (10x). This cycle, the coupling of an Fmoc-protected amino acid and the removal of the Fmoc group, was repeated until the intended sequence was introduced onto the resin. After the Fmoc group of the terminal residue was removed, the resin was washed successively with DMF (5x) and dichloromethane (5x), and then dried under reduced pressure.

**Preparation of substrates 2h and 2i.**

![Chemical structure](image)

A flask that contained 2,4-dinitrobenzaldehyde (98 mg), a trifluoroacetic acid salt of morpholine (63 mg), and 2-butanone (5 mL) was heated to 90 °C. After stirring the mixture for 24 h, the flask was cooled to room temperature, and an aqueous saturated solution of ammonium chloride was added. The resulting mixture was
stirred for 5 min, and extracted with chloroform. After the organic layer was dried over anhydrous magnesium sulfate and removed under reduced pressure, the residue was purified by preparative TLC (hexanes/ethyl acetate 2:1) to afford enone 2h (47 mg, 37%). For the synthesis of 2i, 2-pentanone (2.5 mL) was used instead of 2-butano.

(E)-1-(2,4-Dinitrophenyl)pent-1-en-3-one (2h)

\[\text{C_13H_9O_3N_2} \, \text{[M+H]^+} : 251.0668, \text{found 251.0658.}\]

(E)-1-(2,4-Dinitrophenyl)hex-1-en-3-one (2i)

\[\text{C_14H_11O_3N_2} \, \text{[M+H]^+} : 265.0824, \text{found 265.0832.}\]

Typical procedure for peptide-catalyzed epoxidation.

Water (200 µL) was added slowly with stirring to a round-bottom flask that contained enone 2f (0.03 mmol), resin-supported Ala(1-Pyr)-Pro-(Leu-Leu-Aib)₂ (54 mg, 0.012 mmol of the N-terminal amino group), benzoic acid (0.006 mmol), and THF (100 µL). Urea-hydrogen peroxide (1.5 mmol) was added, and the flask was warmed to 40 °C. After stirring the mixture for 48 h, an aqueous saturated solution of ammonium chloride was added. The resulting mixture was stirred for 5 min, and peptide catalyst was filtered off and washed with chloroform. The filtrate 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 residue was purified by preparative TLC (hexanes/ethyl acetate 2:1) to afford epoxy ketone 3f. The amounts of the catalyst and benzoic acid, and the reaction time varied depending on a substrate (see, the footnotes of Table 2). Products 3a, b, d, e, and f were isolated as a mixture with starting substrate 2.

The spectral data for 3a, b, and d were reported. The absolute configuration of the major isomer of 3a was determined according to the literature. For other products, the major configurations were assigned as the same ones, based on the mechanistic similarity for the peptide-catalyzed reaction.
(3S,4R)-Epoxy-4-(2,4-dinitrophenyl)butan-2-one (3c)

\[ \text{H NMR (CDCl}_3\delta 9.07 (d, J = 2.3 \text{ Hz}, 1H), 8.56 (dd, J = 8.7, 2.3 \text{ Hz}, 1H), 7.88 (d, J = 8.7 \text{ Hz}, 1H), 4.69 (d, J = 2.1 \text{ Hz}, 1H), 3.46 (d, J = 2.1 \text{ Hz}, 1H), 2.32 (s, 3H); } \]

\[ \text{\textsuperscript{13}C NMR (CDCl}_3\delta 201.59, 147.88, 147.42, 138.61, 128.93, 128.68, 120.55, 61.61, 55.67, 25.27; } \]

HRMS (FAB) m/z: calculated for C\textsubscript{10}H\textsubscript{8}N\textsubscript{2}O\textsubscript{6} [M+H]\textsuperscript{+}: 253.0460, found 253.0467. Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H, hexane/2-propanol = 70:30, 0.8 mL min\textsuperscript{-1}): \( t_R = 36.9 \text{ min (major), 48.4 min (minor).} \)

(3S,4R)-Epoxy-4-(4-bromophenyl)butan-2-one (3e)

\[ \text{H NMR (CDCl}_3\delta 7.53-7.48 (m, 2H), 7.18-7.13 (m, 2H), 3.98 (d, J = 1.8 \text{ Hz}, 1H), 3.45 (d, J = 1.8 \text{ Hz}, 1H), 2.20 (s, 3H); } \]

\[ \text{\textsuperscript{13}C NMR (CDCl}_3\delta 203.82, 134.07, 131.89, 127.29, 123.04, 63.35, 57.13, 24.81; } \]

HRMS (FAB) m/z: calculated for C\textsubscript{10}H\textsubscript{10}Br\textsubscript{2} [M+H]\textsuperscript{+}: 240.9864, found 240.9869. Enantiomeric excess was determined by HPLC analysis (Chiralcel OJ-H, hexane/2-propanol = 95:5, 1.0 mL min\textsuperscript{-1}): \( t_R = 24.1 \text{ min (major), 37.4 min (minor).} \)

(3S,4R)-Epoxy-4-(3,5-dichlorophenyl)butan-2-one (3f)

\[ \text{H NMR (CDCl}_3\delta 7.35 (t, J = 1.8 \text{ Hz}, 1H), 7.17 (d, J = 1.8 \text{ Hz}, 2H), 3.97 (d, J = 1.8 \text{ Hz}, 1H), 3.43 (d, J = 1.8 \text{ Hz}, 1H), 2.20 (s, 3H); } \]

\[ \text{\textsuperscript{13}C NMR (CDCl}_3\delta 203.09, 138.60, 135.54, 129.16, 124.16, 63.03, 56.31, 24.96; } \]

HRMS (FAB) m/z: calculated for C\textsubscript{10}H\textsubscript{9}Cl\textsubscript{2} [M+H]\textsuperscript{+}: 230.9979, found 230.9979. Enantiomeric excess was determined by HPLC analysis (Chiralcel OJ-H, hexane/2-propanol = 95:5, 1.0 mL min\textsuperscript{-1}): \( t_R = 20.3 \text{ min (major), 22.1 min (minor).} \)

(3S,4R)-Epoxy-4-(3,5-dibromophenyl)butan-2-one (3g)[6]

\[ \text{H NMR (CDCl}_3\delta 7.65 (t, J = 1.8 \text{ Hz}, 1H), 7.37 (d, J = 1.8 \text{ Hz}, 2H), 3.95 (d, J = 1.8 \text{ Hz}, 1H), 3.43 (d, J = 1.8 \text{ Hz}, 1H), 2.20 (s, 3H); } \]

\[ \text{\textsuperscript{13}C NMR (CDCl}_3\delta 203.04, 139.08, 134.63, 127.49, 123.36, 63.04, 56.10, 24.97. } \]

Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H, hexane/2-propanol = 70:30, 0.8 mL min\textsuperscript{-1}): \( t_R = 36.9 \text{ min (major), 48.4 min (minor).} \)
Enantiomeric excess was determined by HPLC analysis (Chiralcel OJ-H, hexane/2-propanol = 95:5, 1.0 mL min⁻¹): $t_R = 25.7$ min (major), 28.4 min (minor).

\[
\text{O}_2\text{N} - \text{O} - \text{nitro} \quad \text{Epoxy-1-(2,4-dinitrophenyl)pentan-3-one (3h)}
\]

$^1$H NMR (CDCl₃) $\delta$ 9.06 (d, $J = 2.3$ Hz, 1H), 8.55 (dd, $J = 8.7$, 2.3 Hz, 1H), 7.88 (d, $J = 8.7$ Hz, 1H), 4.66 (d, $J = 1.8$ Hz, 1H), 3.49 (d, $J = 1.8$ Hz, 1H), 2.69 (dq, $J = 18.3$, 7.3 Hz, 1H), 2.59 (dq, $J = 18.3$, 7.3 Hz, 1H), 1.18 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (CDCl₃) $\delta$ 204.02, 147.83, 147.42, 138.81, 128.97, 128.64, 120.52, 61.14, 55.95, 31.84, 7.04; HRMS (FAB) $m/z$: calculated for C₁₁H₁₁N₂O₆ [M+H]⁺: 267.0617, found 267.0620. Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H, hexane/2-propanol = 70:30, 0.8 mL min⁻¹): $t_R = 34.3$ min (major), 49.7 min (minor).

\[
\text{O}_2\text{N} - \text{O} - \text{nitro} \quad \text{Epoxy-1-(2,4-dinitrophenyl)pentan-3-one (3i)}
\]

$^1$H NMR (CDCl₃) $\delta$ 9.06 (d, $J = 2.3$ Hz, 1H), 8.55 (dd, $J = 8.7$, 2.3 Hz, 1H), 7.88 (d, $J = 8.7$ Hz, 1H), 4.65 (d, $J = 2.1$ Hz, 1H), 3.47 (d, $J = 2.1$ Hz, 1H), 2.63 (dt, $J = 17.4$, 7.3 Hz, 1H), 2.53 (dt, $J = 17.4$, 7.3 Hz, 1H), 1.73 (sext, $J = 7.3$ Hz, 2H), 1.00 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (CDCl₃) $\delta$ 203.58, 147.84, 147.45, 138.83, 128.96, 128.64, 120.53, 61.28, 55.83, 40.23, 16.55, 13.62; HRMS (FAB) $m/z$: calculated for C₁₁H₁₁N₂O₆ [M+H]⁺: 281.0773, found 281.0770. Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H, hexane/2-propanol = 70:30, 0.8 mL min⁻¹): $t_R = 29.9$ min (major), 43.5 min (minor).
$^1$H and $^{13}$C NMR spectra.$^7$
HPLC traces.

Chiralcel OJ-H, hexane/2-propanol = 70:30, 0.8 mL min⁻¹

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racemic sample
Chiralcel OJ-H, hexane/2-propanol = 70:30, 0.8 mL min⁻¹

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racemic sample
Chiralcel OD-H, hexane/2-propanol = 70:30, 0.8 mL min\(^{-1}\)

![Chiral resolution diagram]

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racemic sample

![Chiral resolution diagram]
Chiracel OJ-H, hexane/2-propanol = 95:5, 1.0 mL min^{-1}

1: 230 nm, 8 nm

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racemic sample
Chiralcel OJ-H, hexane/2-propanol = 95:5, 1.0 mL min\(^{-1}\)

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racemic sample
Chiralcel OJ-H, hexane/2-propanol = 95:5, 1.0 mL min$^{-1}$

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racemic sample
Chiralcel OJ-H, hexane/2-propanol = 95:5, 1.0 mL min⁻¹

![Chiralcel OJ-H, hexane/2-propanol](image)

**Retention Time** | **Area**     | **Area %**
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**Total**

Area 8975113

**Total Area % 100.00**

race sample
Chiracel OD-H, hexane/2-propanol = 70:30, 0.8 mL min\(^{-1}\)

![Graph showing the chromatogram of the racemic sample.](image)

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racemic sample
Chiracel OD-H, hexane/2-propanol = 70:30, 0.8 mL min$^{-1}$

1: 254 nm, 8 nm

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racemic sample
References.


[7] In the case that remaining substrate 2 could not be separated from product 3, epoxidation was completed with Na$_2$CO$_3$·1.5H$_2$O in 1,2-dimethoxyethane/MeOH/H$_2$O or a 30% H$_2$O$_2$ aqueous solution in Et$_3$N/THF to obtain clear spectra.