Asymmetric aldol reaction via memory of chirality

Hidetoshi Watanabe, Tomoyuki Yoshimura, Shimpei Kawakami, Takahiro Sasamori, Norihiro Tokitoh, and Takeo Kawabata*

Institute for Chemical Researches, Kyoto University

Electronic Supplementary Information

General Procedure .............................................................................................................. 2
General Procedure for Table 1 ................................................................................................ 2
Synthesis of compound 3 ..................................................................................................... 5
Synthesis of compound 4 ..................................................................................................... 5
Synthesis of compound 5 ..................................................................................................... 6
Synthesis of compound 6 ..................................................................................................... 7
Synthesis of compound 7 ..................................................................................................... 8
Synthesis of compound 8 ..................................................................................................... 9
Conversion of 2 into 10 ...................................................................................................... 10
ORTEP representation of 10 ............................................................................................. 11
Synthesis of compound 11 ................................................................................................ 11
Aldol reaction between 11 and benzaldehyde ................................................................. 12
Aldol reaction between 13 and benzaldehyde ................................................................. 13
Spectral data .................................................................................................................... 15
General Procedure. \(^1\)H NMR were measured in CDCl\(_3\) solution and referenced from TMS (0.00 ppm) using JEOL ECX-400 or JEOL AL-400 (400 MHz) spectrophotometers, unless otherwise noted. \(^{13}\)C NMR were measured in CDCl\(_3\) solution and referenced to CDCl\(_3\) (77.5 ppm) using JEOL ECX-400 or JEOL AL-400 (100 MHz) spectrophotometers, unless otherwise noted. Chemical shifts are reported in ppm. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet; br, broadened. IR spectra were recorded on JASCO FT/IR-4200 spectrometer. Mass spectra were obtained on JEOL JMS-700. Elemental analyses were performed with CHN J-science-lab. Microcoder JM10. Optical rotations were determined on HORIBA SEPA-200. Melting points were measured with Yanagimoto Micro Melting Point Apparatus PM-500 and are uncorrected. Enantiomeric excess was determined by HPLC analysis using Shimadzu LC-10AS liquid chromatograph with Chiralpak AD-H or Chiracel OD-H as chiral stationary phase. Flash column chromatography was performed on Silica Gel (SilicaFlash\textsuperscript{®} 60F\textsubscript{245}) and compounds were visualized with UV light and \(p\)-anisaldehyde stain, phosphomolybdic acid stain or ninhydrin stain. Preparative thin layer chromatography was performed on precoated plates (0.5 mm, silica gel Merck Kieselgel 60F\textsubscript{245}) and visualized with UV light. All reactions were conducted in oven-dried glassware under argon atmosphere. Dehydrated solvents were purchased from Kanto Kagaku or Wako Chemicals and pre-treated with activated MS4Å for 1 day or longer.

General Procedure for Table 1

Procedure I

KHMDS (1.1 eq.) was added to a solution of \(1\) (1.0 eq.) in toluene/THF at \(-78^\circ\)C. After being stirred for 30 min, benzaldehyde (3.0 eq) was added dropwise at same temperature. The resulting mixture was stirred for 2.5 hr and poured into sat. NH\(_4\)Cl aq. and extracted with AcOEt. The extracts were washed with sat. NaHCO\(_3\)aq. and brine, and dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/Et\(_2\)O=1/1) to give an oil, which was further purified by PTLC (hexane/1,4-dioxane=4/1) to obtain \(2\).

Procedure II

A solution of \(1\) (1.0 eq.) was added to a solution of benzaldehyde (3.0 eq.) and KHMDS (1.1 eq.) in toluene/THF at the temperature shown in Table 1. After being stirred for 10 min, the mixture was poured into sat. NH\(_4\)Cl aq. and extracted with AcOEt. The extracts were washed with sat. NaHCO\(_3\)aq. and brine, and dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/Et\(_2\)O=1/1) to give an oil, which was further purified by PTLC (hexane/1,4-dioxane=4/1) to obtain \(2\).

Procedure III

Benzaldehyde (0.13 mL, 1.25 mmol) was added to a mixture of \(1\) (84 mg, 0.25 mmol) in toluene (1.5 mL) at rt and the mixture was cooled to the temperature shown in Table 1. KHMDS (0.37-0.41 M in toluene, 1.83-2.02 mL, 0.75 mmol) was added to this solution and the resulting mixture was stirred for the time shown in Table 1 at the same temperature. The reaction mixture was poured into sat. NH\(_4\)Cl aq. and extracted with AcOEt. The
extracts were washed with sat. NaHCO₃ aq. and brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/Et₂O=1/1) to give an oil, which was further purified by PTLC (hexane/1,4-dioxane=4/1) to obtain 2.

2-(4S,5S)-Ethyl 4-benzyl-3-(methoxymethyl)-2-oxo-5-phenyloxazolidine-4-carboxylate

Colorless oil; [α]D²⁰ +2.8 (c 1.0, CHCl₃, 87% ee); ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.26 (m, 10H), 5.38 (s, 1H), 4.83 (ABq, ΔυAB=0.32 Hz, J=11.6 Hz, 2H), 3.71 (q, J=7.2 Hz, 2H), 3.52 (ABq, ΔυAB=0.031 Hz, J=15.6 Hz, 2H), 3.47 (s, 3H), 0.94 (t, J=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 169.7, 158.5, 134.4, 134.3, 131.4, 129.3, 129.2, 128.6, 128.0, 126.3, 78.9, 76.3, 73.1, 62.4, 57.6, 37.4, 13.8; IR (neat) cm⁻¹: 2935, 1774, 1739, 1496, 1455, 1455, 1433, 1233, 1078, 1028, 744, 701; MS (EI) m/z (rel intensity) 369 (M⁺, 5), 338 (10), 296 (40), 278 (100), 220 (20), 202 (40), 158 (20), 130 (20), 91 (60); HRMS (EI) m/z Calcd for C₂₁H₂₃NO₅ (M⁺): 369.1576 Found 369.1581; Anal. Calcd for C₂₁H₂₃NO₅: C, 68.28; H, 6.28; N, 3.79 Found: C, 68.02; H, 6.36; N, 3.77; HPLC conditions: Daicel Chiralcel OD-H, hexane:2-propanol=95:5, flow 0.5 mL/min, tR=32 (4R,5R), 37 (4S,5S) min.

Table 1, entry 13

Table 1, entry 13

To a solution of 1-t-Bu (91 mg, 0.25 mmol) and benzaldehyde (0.13 mL, 1.25 mmol) in t-BuOMe (1.5 mL) was added dropwise KHMDS (0.37 M in PhMe, 2.02 mL, 0.75 mmol) at –50 °C. After being stirred for 12 hr, the reaction mixture was poured into sat. NH₄Cl aq. and the resulting mixture was extracted with AcOEt. The extracts were washed with sat. NaHCO₃ aq. and brine, and dried over Na₂SO₄, filtered and concentrated. The residue was chromatographed on silica gel (hexane/Et₂O=1/1) to give an oil, which was further purified by PTLC (hexane/1,4-dioxane=4/1) to obtain 2-t-Bu (31 mg, 31%, 89% ee).

2-t-Bu: tert-Butyl 4-benzyl-3-(methoxymethyl)-2-oxo-5-phenyloxazolidine-4-carboxylate

Colorless oil; [α]D²⁰ +1.9 (c 1.0, CHCl₃, 86% ee); ¹H NMR (400 MHz, CDCl₃): δ 7.43-7.30 (m, 10H), 5.38 (s, 1H), 4.82 (ABq, ΔυAB=0.27 Hz, J=11.6 Hz, 2H), 3.50 (s, 2H), 3.48 (s, 3H) 1.07 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 168.5, 158.7, 135.0, 134.7, 131.5, 129.3, 129.1, 128.8, 128.0, 126.4, 83.8, 78.6, 76.4, 73.0, 57.8, 38.1, 27.6; IR (neat) cm⁻¹: 2930, 1771, 1732, 1454, 1370, 1251, 1081, 1040, 745, 701; MS (EI) m/z (rel intensity) 397 (M⁺, 1), 306 (60), 296 (100), 250 (60), 220 (30), 174 (25), 130 (20), 91 (40), 57 (10); HRMS (EI) m/z Calcd for C₂₃H₂₇NO₅ (M⁺): 397.1889 Found 397.1875; Anal. Calcd for C₂₃H₂₇NO₅: C, 68.50; H, 6.85; N, 3.52%. Found: C, 69.29; H, 7.02; N, 3.49%; HPLC conditions: Daicel Chiralcel OJ-H, hexane:2-propanol=95:5, flow 0.6 mL/min, tR=14 (major), 22 (minor) min.
To a solution of 1Bn (100 mg, 0.25 mmol) and benzaldehyde (0.13 mL, 1.25 mmol) in t-BuOMe (1.50 mL) was added dropwise KHMDS (0.30 M in PhMe, 2.50 mL, 0.75 mmol) at –50 °C. After being stirred for 12 hr, the reaction mixture was poured into sat. NH₄Cl aq. and the resulting mixture was extracted with AcOEt. The extracts were washed with sat. NaHCO₃ aq. and brine, and dried over Na₂SO₄, filtered and concentrated. The residue was chromatographed on silica gel (hexane/Et₂O=1/1) to give an oil, which was further purified by PTLC (hexane/1,4-dioxane=4/1) to give 2Bn (106 mg, 99%, 82% ee).

2Bn: Benzyl 4-benzyl-3-(methoxymethyl)-2-oxo-5-phenyloxazolidine-4-carboxylate

Colorless oil; [α]D²⁰ +22 (c 1.0, CHCl₃, 91% ee); ¹H NMR (400 MHz, CDCl₃): δ 7.42-7.24 (m, 13H), 7.12-7.09 (m, 2H), 5.39 (s, 1H), 4.80 (ABq, ΔνAB=0.33 Hz J=11.6 Hz, 2H), 4.63 (ABq, ΔνAB=0.035 Hz J=12.4 Hz, 2H) 3.52 (ABq, ΔνAB=0.024 Hz J=15.6 Hz, 2H) 3.39 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 169.7, 158.5, 134.6, 134.2, 134.2, 131.5, 129.4, 129.3, 128.8, 128.1, 126.4, 79.1, 76.4, 73.4, 68.3, 57.7, 37.4; IR (neat) cm⁻¹: 3064, 2934, 1770, 1742, 1455, 1374, 1078, 1078, 910, 698; MS (EI) m/z (rel intensity) 431 (M⁺, 1), 400 (5), 340 (100), 296 (60), 220 (50), 130 (20); HRMS (EI) m/z Calcd for C₂₆H₂₅NO₅ (M⁺): 431.1733 Found 431.1725

Anal. Calcd for C₂₆H₂₅NO₅: C, 72.37; H, 5.84; N, 3.25%. Found: C, 72.37; H, 5.90; N, 3.06%; HPLC conditions: Daicel Chiralcel OD-H, hexane: 2-propanol=90:10, flow 0.6 mL/min, tR=27 (major), 33 (minor) min.
Table 2, entry 2

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Et} \\
\text{Boc} & \quad \text{MOM} \\
\text{Me} & \quad \text{CHO} \\
\rightarrow \\
\text{Ph} & \quad \text{CO}_2\text{Et} \\
\text{MOM} & \quad \text{N} \\
\end{align*}
\]

\(p\)-Tolualdehyde (0.15 mL, 1.25 mmol) was added to a solution of 1 (84 mg, 0.25 mmol) in \(t\)-BuOMe (1.5 mL) and the mixture was cooled to \(-60\) °C and KHMD (0.40 M in toluene, 1.88 mL, 0.75 mmol) was added slowly. After being stirred for 12 hr at same temperature, the reaction mixture was poured into sat. NH\(_4\)Cl aq. and extracted with AcOEt and the extracts were washed with sat. NaHCO\(_3\) aq. and brine, and dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/AcOEt=7/1) to give an oil, which was further purified by PTLC (hexane/AcOEt=3/1) to give 3 (65 mg, 67%, 88% ee).

**3: Ethyl 4-benzyl-3-(methoxymethyl)-2-oxo-5-\(p\)-tolyloxazolidine-4-carboxylate**

Colorless oil; [\(\alpha\)]\(_{D}\)\(^{20}\) = -9.9 (c 1.1, CHCl\(_3\), 86% ee); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.44 - 7.31 (m, 5H), 7.15 (s, 4H), 5.34 (s, 1H), 4.82 (ABq, \(\Delta\nu_{AB}=0.32\) Hz, \(J=11.5\) Hz, 2H), 3.75 (q, \(J=7.3\) Hz, 2H), 3.49 (ABq, \(\Delta\nu_{AB}=0.034\) Hz, \(J=15.6\) Hz, 2H), 3.46 (s, 3H), 2.33 (s, 3H), 0.98 (t, \(J=7.2\) Hz, 3H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 169.9, 158.8, 139.3, 134.5, 131.6, 131.4, 129.4, 129.3, 128.1, 126.4, 79.2, 76.5, 73.3, 62.5, 57.7, 37.5, 21.6, 14.0; IR (neat) cm\(^{-1}\): 2930, 1773, 1740, 1373, 1232, 1039, 704; MS (EI) \(m/z\) (rel intensity) 383 (M\(^+\), 5), 351 (10), 310 (20), 292 (100), 234 (20), 216 (90), 144 (30), 91 (50); HRMS (EI) \(m/z\) Calcd for C\(_{22}\)H\(_{25}\)NO\(_5\) (M\(^+\)): 383.1733 Found 383.1739 Anal. Calcd for C\(_{22}\)H\(_{25}\)NO\(_5\): C, 68.91; H, 6.57; N, 3.65 Found C, 68.70; H, 6.53; N, 3.56; HPLC conditions: Daicel Chiralcel OD-H, hexane:2-propanol=93:7, flow 0.8 mL/min, \(t_R=13\) (minor), 16 (major) min.

Table 2, entry 3

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Et} \\
\text{Boc} & \quad \text{MOM} \\
\text{Me} & \quad \text{CHO} \\
\rightarrow \\
\text{Ph} & \quad \text{CO}_2\text{Et} \\
\text{MOM} & \quad \text{N} \\
\end{align*}
\]

\(p\)-Anisaldehyde (0.15 mL, 1.25 mmol) was added to a solution of 1 (84 mg, 0.25 mmol) in \(t\)-BuOMe (1.5 mL) and the mixture was cooled to \(-60\) °C and KHMD (0.38 M in toluene, 1.97 mL, 0.75 mmol) was added slowly. After being stirred for 6 hr at same temperature, the reaction mixture was poured into sat. NH\(_4\)Cl aq. and extracted with AcOEt and the extracts were washed with sat. NaHCO\(_3\) aq. and brine, and dried over Na\(_2\)SO\(_4\),
filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/AcOEt=7/1) to give an oil, which was further purified by PTLC (hexane/1,4-dioxane=4/1) to obtain 4 (66 mg, 66%, 88% ee).

4: Ethyl 4-benzyl-3-(methoxymethyl)-5-(4-methoxyphenyl)-2-oxooxazolidine-4-carboxylate
Colorless oil; $[\alpha]_D^{20}$ –14 (c 1.1, CHCl$_3$, 87% ee); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44-7.30 (m, 5H), 7.18 (d, $J$=8.8 Hz, 2H), 6.86 (d, $J$=8.8 Hz, 2H), 5.33 (s, 1H), 4.82 (ABq, $\Delta\nu_{AB}$=0.32 Hz $J$=11.2 Hz, 2H), 3.78 (s, 3H), 3.77 (q, $J$=7.2 Hz, 2H), 3.48 (ABq, $\Delta\nu_{AB}$=0.031 Hz $J$=15.6 Hz, 2H), 3.46 (s, 3H), 1.01 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 169.9, 160.4, 158.6, 134.4, 131.5, 129.2, 128.0, 127.8, 126.2, 114.0, 79.1, 76.4, 73.3, 62.5, 57.6, 55.6, 37.5, 14.0; IR (neat) cm$^{-1}$: 2935, 1769, 1741, 1516, 1254, 1032, 704; MS (EI) m/z (rel intensity) 399 (M+, 40), 308 (100), 264 (90), 232 (90), 191 (30), 151 (30), 135 (20); HRMS (EI) m/z Calcd for C$_{22}$H$_{25}$NO$_6$: 399.1682 Found 399.1681; Anal. Calcd for C$_{22}$H$_{25}$NO$_6$: C, 66.15; H, 6.31; N, 3.51 Found C, 65.85; H, 6.38; N, 3.28; HPLC conditions: Daicel Chiralpak AD-H, hexane:2-propanol=85:15, flow 1.0 mL/min, $t_R$=33 (minor), 40 (major) min.

Table 2, entry 4

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>CO$_2$Et</td>
<td>Boc</td>
<td>MOM</td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>CHO</td>
<td>Ph</td>
<td>CO$_2$Et</td>
<td></td>
</tr>
</tbody>
</table>

A mixture of 1 (84 mg, 0.25 mmol) and p-bromobenzaldehyde (231 mg, 1.25 mmol) was dissolved in toluene (4.5 mL) and the resulting mixture was cooled to –50 °C. KHMDS (0.37 M in t-BuOMe, 2.03 mL, 0.75 mmol) was added dropwise slowly to this solution. After being stirred for 6 hr at same temperature, the reaction mixture was poured into sat. NH$_4$Cl aq. and extracted with AcOEt. The extracts were washed with sat. NaHCO$_3$ aq. and brine, and dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/1,4-dioxane=5/1) to give an oil, which was further purified by PTLC (hexane/AcOEt=3/1) to obtain 5 (72 mg, 64%, 78% ee).

5: Ethyl 4-benzyl-5-(4-bromophenyl)-3-(methoxymethyl)-2-oxooxazolidine-4-carboxylate
Colorless oil; $[\alpha]_D^{20}$ –23 (c 1.1, CHCl$_3$, 78% ee); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.47 (d, $J$=8.2 Hz, 2H), 7.42-7.33 (m, 5H), 7.12 (d, $J$=8.2 Hz, 2H), 5.32 (s, 1H), 4.83 (ABq, $\Delta\nu_{AB}$=0.30 Hz $J$=11.4 Hz, 2H), 3.77 (q, $J$=6.8 Hz, 2H), 3.49 (ABq, $\Delta\nu_{AB}$=0.024 Hz $J$=15.6 Hz, 2H), 3.42 (s, 3H), 0.99 (t, $J$=6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 169.7, 158.3, 134.2, 133.6, 131.9, 131.5, 129.4, 128.3, 128.1, 123.5, 78.4, 76.4, 72.9, 62.7, 57.8, 37.5, 14.0; IR (neat) cm$^{-1}$: 2935, 1773, 1739, 1373, 1254, 1081, 1040, 704; MS (EI) m/z (rel intensity) 449
A mixture of 1 (84 mg, 0.25 mmol) and \( p \)-phenylbenzaldehyde (228 mg, 1.25 mmol) was dissolved in toluene (4.5 mL) and the resulting mixture was cooled to \(-50^\circ\text{C}\). KHMS (0.37 M in \( t \)-BuOMe, 2.03 mL, 0.75 mmol) was added slowly. After being stirred for 12 hr at same temperature, the reaction mixture was poured into sat. NH\(_4\)Cl aq. and extracted with AcOEt. The extracts were washed with sat. NaHCO\(_3\) aq. and brine, and dried over Na\(_2\)SO\(_4\), filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/AcOEt=6/1) to give an oil, which was further purified by PTLC (hexane/AcOEt=4/1) to obtain 6 (106 mg, 95%, 80% ee).

**6: Ethyl 4-benzyl-5-(biphenyl-4-yl)-3-(methoxymethyl)-2-oxooxazolidine-4-carboxylate**

Colorless oil: \([\alpha]_D^{20}\) = -58 (c 1.0, CHCl\(_3\), 85% ee); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.59-7.55 (m, 4H), 7.47-7.32 (m, 10H), 5.43 (s, 1H), 4.85 (ABq, \(\Delta\nu_{AB}=0.31\) Hz, \(J=11.4\) Hz, 2H), 3.75 (q, \(J=7.3\) Hz, 2H), 3.54 (ABq, \(\Delta\nu_{AB}=0.043\) Hz, \(J=15.1\) Hz, 2H), 3.48 (s, 3H), 0.95 (t, \(J=7.3\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 169.9, 158.6, 142.3, 140.6, 134.4, 133.5, 131.6, 129.4, 129.3, 128.2, 128.1, 127.5, 127.4, 126.9, 79.0, 76.5, 73.3, 62.6, 57.8, 37.6, 14.0; IR (neat) cm\(^{-1}\): 2933, 1772, 1739, 1373, 1233, 1082, 1038, 764, 700; MS (EI) \(m/z\) (rel intensity) 445 (M\(^+\), 10), 354 (100), 310 (20), 278 (95), 165 (30), 91 (40); HRMS (EI) \(m/z\) Calcd for C\(_{27}\)H\(_{27}\)NO\(_5\) (M\(^+\): 445.1889 Found 445.1882; Anal. Calcd for C\(_{27}\)H\(_{27}\)NO\(_5\): C, 72.79; H, 6.11; N, 3.14 Found C, 72.59; H, 6.30; N, 3.06; HPLC conditions: Daicel Chiralpak AD-H, hexane:2-propanol=80:20, flow 1.0 mL/min, \(t_R=20\) (minor), 47 (major) min.
o-Anisaldehyde (0.15 mL, 1.25 mmol) was added to a solution of 1 (84 mg, 0.25 mmol) in t-BuOMe (1.5 mL) and the mixture was cooled to −50 °C and KHMDS (0.44 M in toluene, 1.70 mL, 0.75 mmol) was added slowly. After being stirred for 12 hr at same temperature, the reaction mixture was poured into sat. NH₄Cl aq. and extracted with AcOEt. The extracts were washed with sat. NaHCO₃ aq. and brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/AcOEt=7/1) to give an oil, which was further purified by PTLC (hexane/1,4-dioxane=7/1) to obtain 7 (67 mg, 67%, 89% ee).

7: Ethyl 4-benzyl-3-(methoxymethyl)-5-(2-methoxyphenyl)-2-oxooxazolidine-4-carboxylate

Colorless oil; [α]D<sup>20</sup> +9.0 (c 1.1, CHCl₃, 89% ee); <sup>1</sup>H NMR (400 MHz, CDCl₃): δ 7.45 (d, J=7.2 Hz, 2H), 7.39-7.26 (m, 5H), 6.95 (t, J=8.2 Hz, 1H), 6.87 (d, J=8.2 Hz, 1H), 5.86 (s, 1H), 4.81 (ABq, Δυ<sub>AB</sub>=0.31 Hz J=11.6 Hz, 2H), 3.91 (s, 3H), 3.61 (q of ABq, Δυ<sub>AB</sub>=0.095 Hz J<sub>AB</sub>=10.8 Hz, J<sub>AX</sub>=7.2 Hz, 2H), 3.55 (ABq, Δυ<sub>AB</sub>=0.27 Hz J=15.4 Hz, 2H), 3.42 (s, 3H), 0.92 (t, J=7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl₃): δ 170.0, 158.7, 156.7, 153.5, 131.6, 130.3, 129.0, 127.8, 127.8, 124.2, 120.9, 110.5, 76.3, 75.3, 73.0, 62.3, 57.7, 55.6, 37.6, 13.9; IR (neat) cm<sup>−1</sup>: 2937, 1768, 1738, 1495, 1378, 1250, 1036, 756, 704; MS (EI) m/z (rel intensity) 399 (M⁺, 10), 368 (10), 308 (100), 276 (10), 264 (10), 232 (40), 151 (20), 135 (10); HRMS (EI) m/z Calcd for C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub> (M⁺): 399.1682 Found 399.1675; Anal. Calcd for C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub>: C, 66.15; H, 6.31; N, 3.51 Found C, 66.00; H, 6.31; N, 3.39; HPLC conditions: Daicel Chiralcel OD-H, hexane:2-propanol=95: 5, flow 0.8 mL/min, t<sub>R</sub>=20 (minor), 23 (major) min.
A mixture of 1 (84 mg, 0.25 mmol) and 2-naphthaldehyde (195 mg, 1.25 mmol) was dissolved in toluene (4.5 mL) and the resulting mixture was cooled to –50 °C. KHDMDS (0.37 M in t-BuOMe, 2.03 mL, 0.75 mmol) was added slowly to this solution. After being stirred for 6 hr at same temperature, the reaction mixture was poured into sat. NH₄Cl aq. and extracted with AcOEt. The extracts were washed with sat. NaHCO₃ aq. and brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/AcOEt=3/1) to give an oil, which was further purified by PTLC (hexane/1,4-dioxane=5/1) to obtain 8 (46 mg, 44%, 86% ee).

**8: Ethyl 4-benzyl-3-(methoxymethyl)-5-(naphthalen-2-yl)-2-oxooxazolidine-4-carboxylate**

Colorless oil; [α]D20 −59 (c 1.0, CHCl₃, 86% ee); ¹H NMR (400 MHz, CDCl₃): δ 7.82-7.78 (m, 3H), 7.72 (s, 1H), 7.52-7.47 (m, 4H), 7.44-7.32 (m, 4H), 5.56 (s, 1H), 4.86 (ABq, ΔυAB=0.32 Hz, J=11.6 Hz, 2H), 3.60 (q, J=7.2 Hz, 2H), 3.57 (ABq, ΔυAB=0.087 Hz, J=15.6 Hz, 2H), 3.48 (s, 3H), 0.79 (t, J=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 169.9, 158.7, 134.5, 133.7, 133.1, 131.8, 129.4, 128.5, 128.5, 128.2, 128.1, 127.1, 126.1, 123.6, 79.3, 76.5, 73.3, 62.6, 57.8, 37.8, 13.8; IR (neat) cm−¹: 2934, 1771, 1739, 1376, 1227, 1083, 1040, 704; MS (EI) m/z (rel intensity) 419 (M⁺, 30), 284 (20), 270 (20), 252 (60), 91 (60); HRMS (EI) m/z Calcd for C₂₅H₂₅NO₅ (M⁺): 419.1733 Found 419.1749; Anal. Calcd for C₂₅H₂₅NO₅: C, 71.58; H, 6.01; N, 3.34 Found C, 71.48; H, 6.12; N, 3.24; HPLC conditions: Daicel Chiralcel OD-H, hexane:2-propanol=90:10, flow 0.5 mL/min, tR=25 (minor), 29 (major) min.
Determination of Absolute configuration

LiOH•H₂O (82 mg, 1.95 mmol) was added to a solution of 2 (239 mg, 0.65 mmol, 85% ee) in H₂O/EtOH/THF (18 mL, 1/1/1, v/v/v) at 0 °C. The resulting mixture was warmed to 50 °C and stirred for 3 hr. After being cooled to rt, the mixture was diluted with AcOEt and 1 M HCl was added. The aqueous layer was extracted with AcOEt and the extracts were washed with brine and dried over Na₂SO₄, filtered, and concentrated. The residue was dissolved in CH₂Cl₂ (6.5 mL) and cooled to 0 °C. To this solution were added O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 373 mg, 0.98 mmol), 1-hydroxy-7-benzotriazole (HOAT, 133 mg, 0.98 mmol), (S)-(–)-(1-naphthyl)ethylamine (0.21 mL, 1.30 mmol), and i-Pr₂NEt (0.34 mL, 1.95 mL), successively. After being stirred at rt for 48 hr, the mixture was diluted with AcOEt and washed with aqueous 10% citric acid solution, sat. NaHCO₃ aq., and brine and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/AcOEt=4/1) to give 9 (277 mg, 89%). Trifluoroacetic acid (6 mL) was added to a solution of 9 (200 mg, 0.40 mmol) in CH₂Cl₂ (2.0 mL) at 0 °C. The resulting mixture was refluxed for 2 hr. After removal of volatiles, the residue was purified through flash silica gel column chromatography (hexane/AcOEt=3/1) to give 10 (157 mg, 85%) as colorless crystals.

10: (1S,10αS)-N-((S)-1-(naphthalen-1-yl)ethyl)-3-oxo-1-phenyl-3,5,10,10α-tetrahydro-1H-oxazolo[3,4-b]-isoquinoline-10α-carboxamide

Colorless crystal; mp. 210-213 °C (recrystallized from 1,4-dioxane/petroleum ether) [α]_D^20 +15.0 (c 0.39, CHCl₃, >99% ee); ¹H NMR (400 MHz, CDCl₃): δ 7.78 (d, J=8.3 Hz, 1H), 7.73 (d, J=8.3 Hz, 1H), 7.46-7.43 (m,
3H), 7.39-7.31 (m, 4H), 7.25-7.21 (m, 2H), 7.18-7.14 (m, 3H), 6.91-6.87 (m, 1H), 6.62 (d, J=7.8 Hz, 1H), 5.84 (br d, J=7.8 Hz, 1H), 5.54 (s, 1H), 5.22 (dq, J=7.3 Hz, 6.8 Hz, 1H), 4.64 (d, J=17.0 Hz, 1H), 4.06 (d, J=14.7 Hz, 1H), 3.59 (d, J=17.0 Hz, 1H), 3.08 (d, J=14.7 Hz, 1H), 0.80 (d, J=6.8 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 165.7, 158.7, 136.8, 135.3, 134.1, 131.3, 131.2, 130.1, 129.7, 129.2, 129.1, 127.7, 127.6, 127.1, 126.7, 126.6, 126.1, 125.3, 123.1, 123.0, 84.1, 68.4, 45.09, 44.0, 18.2; IR (neat) cm⁻¹: 2925, 1754, 1668, 1401, 1220, 1004, 776; MS (EI) m/z (rel intensity) 431 (M⁺, 20), 264 (80), 263 (40), 220 (100), 218 (30), 155 (20); HRMS (EI) m/z Calcd for C₃₀H₂₆N₂O₃ (M⁺): 462.1943 Found 462.1941.

Crystal data for 10+[1/2 1,4-dioxane], found C₃₂H₃₀N₂O₄, FW=506.58, T=103 (2) K, Wavelength 0.71069 Å Crystal system triclinic, Space group P1 (#1), Unit cell dimensions a=9.1521 (3) Å α=97.7195 (13)°. b=14.3285 (4) Å β=97.2737 (19)°. c=20.2138 (6) Å γ=89.468 (2)°. Volume=2605.51 (14) Å³, Z=4, Density (calculated)=1.291 Mg/m³, Absorption coefficient=0.085 mm⁻¹, F (000)=1072, Crystal size=0.35 x 0.10 x 0.05 mm³, Reflections collected 23140, Independent reflections 17122 [R (int)=0.0499], Completeness to theta=25.50° 99.4 %, Final R indices [I>2sigma (I)] R₁=0.0551, wR₂=0.1210 R indices (all data) R₁=0.0762, wR₂=0.1297. CCDC 867310 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.ac.uk/data_request/cif.

Preparation of precursor 11

KHMDS (0.32 M in THF, 8.31 mL, 2.66 mmol) was added dropwise slowly to a solution of known S1 (1.0 g, 2.96 mmol) at –78 °C. The resulting mixture was stirred for 30 min and MOMCl (0.90 mL, 11.8 mmol) was added slowly. After being stirred for 17 hr, the reaction mixture was poured into sat. NH₄Cl aq. and extracted with AcOEt. The extracts were washed with sat. NaHCO₃ aq. and brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/1,4-dioxane=20/1) to give 11 (870 mg, 86%, >99% ee).

A 2/3 mixture of rotamers of 11;(S)-Ethyl 2-(tert-butoxycarbonyl(methoxymethyl)amino)-3-(4-ethoxyphenyl)propanoate

Colorless oil; [α]D²⁰ =−127 (c 0.96, CHCl₃, >99% ee); ¹H NMR (400 MHz, CDCl₃): δ 7.09, 7.06 (two d, J=8.7
Hz and J=8.7 Hz, ratio=2:3, 2H), 6.80 (d, J=8.7 Hz, 2H), 4.73, 4.60 (two d, J=11.0 Hz and J=11.0 Hz, ratio=3:2, 2H), 4.27-4.12 (m, 2.4 H), 4.07 (dd, J=11.0 Hz, 5.0 Hz, 3/5 H), 4.02-3.97 (m, 12/5 H), 3.81 (d, J=11.0 Hz, 3/5H), 3.32, 3.28 (two d, J=5.0 Hz and J=5.0 Hz, ratio=2:1, 1H), 3.23, 3.17 (two s, ratio=3:2, 1H), 1.49, 1.48 (two s, ratio=3:2, 9H), 1.40 (t, J=7.3 Hz, 3H), 1.30, 1.25 (two t, J=7.3 Hz and J=7.3 Hz, ratio=3:2, 3H); 13C NMR (100 MHz, CDCl3): δ 171.5, 158.0 and 157.9 (rotamer), 155.3 and 154.7 (rotamer), 130.6, 130.4 and 130.2 (rotamer), 114.9 and 114.7 (rotamer), 81.5 and 81.1 (rotamer), 79.8, 63.7, 61.1 and 61.4 (rotamer), 61.2 and 60.9 (rotamer), 56.2 and 55.8 (rotamer), 35.7 and 34.8 (rotamer), 28.6, 15.2, 14.5; IR (neat) cm⁻¹: 2930, 1740, 1705, 1512, 1243, 1175, 1091, 913, 863; MS (EI) m/z (rel intensity) 381 (M+, 10), 276 (10), 250 (20), 220 (100), 135 (90), 107 (50), 57 (50); HRMS (EI) m/z Calcd for C20H31NO6 (M+): 381.2151 Found 381.2160 Anal. Calcd for C20H31NO6: C, 62.97; H, 8.91; N, 3.67 Found C, 62.88; H, 8.22; N, 3.85; HPLC conditions: Daicel Chiralcel OD-H, hexane:2-propanol=98:2, flow 0.4 mL/min, tR=18 (R), 20 (S) min.

Procedure for aldol reaction between 11 and benzaldehyde

Benzaldehyde (0.13 mL, 1.25 mmol) was added to a solution of 11 (95 mg, 0.25 mmol) in t-BuOMe (1.5 mL) and the mixture was cooled to – 40 °C and KHMS (0.39 M in toluene, 1.92 mL, 0.75 mmol) was added dropwise slowly. After being stirred for 6 hr at same temperature, the reaction mixture was poured into sat. NH₄Cl aq. and extracted with AcOEt. The extracts were washed with sat. NaHCO₃ aq. and brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/Et₂O=1/1) to give an oil, which was further purified by PTLC (hexane/1,4-dioxane=4/1) to obtain 12 (98 mg, 95%, 85% ee).

12: Ethyl 4-(4-ethoxybenzyl)-3-(methoxymethyl)-2-oxo-5-phenyloxazolidine-4-carboxylate
Colorless oil; [α]D²⁰ –6.6 (c 1.2, CHCl₃, 91% ee); ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.30 (m, 5H), 7.09 (ABq, ΔνAB=0.37 Hz J=8.4 Hz, 4H), 5.39 (s, 1H), 4.82 (ABq, ΔνAB=0.32 Hz J=11.4 Hz, 2H), 4.04 (q, J=7.2 Hz, 2H), 3.70 (q, J=7.6 Hz, 2H), 3.46 (s, 3H), 3.44 (ABq, ΔνAB=0.043 Hz J=15.6 Hz, 2H), 1.42 (t, J=7.2 Hz, 3H), 0.93 (t, J=7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 169.8, 158.8, 158.6, 134.6, 132.5, 129.3, 128.7, 126.4, 125.9, 115.1, 79.0, 76.3, 73.3, 63.8, 62.4, 57.6, 36.7, 15.2, 13.9; IR (neat) cm⁻¹: 2934, 1770, 1739, 1513, 1248, 913, 733; MS (EI) m/z (rel intensity) 413 (M⁺, 20), 382 (5), 278 (10), 202 (5), 135 (100), 107 (60); HRMS (EI) m/z Calcd for C₂₃H₂₇NO₆ (M⁺): 413.1838 Found 413.1844; Anal. Calcd for C₂₃H₂₇NO₆: C, 66.81; H, 6.58; N, 3.39 Found C, 66.80; H, 6.68; N, 3.34; HPLC conditions: Daicel Chiralpak AD-H, hexane:2-propanol=90:10, flow 0.6 mL/min, tR=53 (minor), 59 (major) min.
Procedure for aldol reaction between 13 and benzaldehyde

Benzaldehyde (0.13 mL, 1.25 mmol) was added to a solution of 13 (76 mg, 0.25 mmol) in t-BuOMe (1.5 mL) and the mixture was cooled to –40 °C and KHMDS (0.44 M in toluene, 1.70 mL, 0.75 mmol) was added dropwise slowly. After being stirred for 12 hr at same temperature, the reaction mixture was poured into sat. NH₄Cl aq. and extracted with AcOEt. The extracts were washed with sat. NaHCO₃ aq. and brine, and dried over Na₂SO₄, filtered, and concentrated. The residue was purified through flash silica gel column chromatography (hexane/AcOEt=6/1) to give an oil, which was further purified by PTLC (hexane/1,4-dioxane=4/1) to obtain 14 (70 mg, 83%, 94% ee).

14: Ethyl 4-isobutyl-3-(methoxymethyl)-2-oxo-5-phenyloxazolidine-4-carboxylate
Colorless oil; [α]D²⁰ +19 (c 1.2, CHCl₃, 98% ee); ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.30 (m, 5H), 5.58 (s, 1H), 4.74 (ABq, ΔυAB=0.29 Hz, J=11.8 Hz, 2H), 3.61 (q of ABq, ΔυAB=0.080 Hz JAB=10.8 Hz, JAX=7.2 Hz, 2H), 3.42 (s, 3H), 2.08 (d of ABq, ΔυAB=0.18 Hz, J=15.2 Hz, JAX=6.0 Hz, 2H), 2.05 (br sept, J= 6.0 Hz, 1H), 1.20 (d, J=6.0 Hz, 3H), 1.04 (d, J=6.0 Hz, 3H), 0.87 (t, J=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.0, 158.8, 134.5, 129.5, 128.8, 126.4, 80.2, 76.0, 73.2, 62.2, 57.4, 40.3, 25.9, 24.5, 23.6, 13.9; IR (neat) cm⁻¹: 2960, 2940, 1772, 1745, 1574, 1455, 1374, 1299, 1082, 1029, 751, 697; MS (EI) m/z (rel intensity) 335 (M⁺, <1), 304 (1), 278 (1), 262 (100), 232 (10), 218 (10), 186 (15); HRMS (EI) m/z Calcd for C₁₈H₂₅NO₅ (M⁺): 335.1733 Found 335.1736; Anal. Calcd for C₁₈H₂₅NO₅: C, 64.46; H, 7.51; N, 4.18 Found C, 64.46; H, 7.64; N, 4.27; HPLC conditions: Daicel Chiralcel OD-H, hexane:2-propanol=90:10, flow 0.5 mL/min, tR=14 (minor), 19 (major) min.
Electronic Supplementary Material (ESI) for Chemical Communications

This journal is © The Royal Society of Chemistry 2012

--- PROCESSING PARAMETERS ---

de_balance : 5 : FALSE
amp : [2.0000] : 0.0000
trimSpin : [4.0000] : 10.0000
trunc : 10 : 512
fwhm : 1 : TRUE
nadingphase : ppm
Derived from: TN-766 13C-1.5df

Filename : TN-766 13C-4.jdf
Author : delta
Experiment : single pulse decouple
sample_id : ZM3863
solute : CHCl3
spinning : 22.050-22.055, 22.055-22.060
Contact : single pulse decouple
Data_format : 2D COMPLEX
Site_size : 32768
Site_resolution : 0.0034
Site : [2] COMPLEX
Spectrometer : 400G NMR
Field_strength : 9.49994625 (400MHz)

X_ppm : 0.04933333
X_ppm : 180.00300000
X_offset : 100.00
X_points : 1024
X_resolution : 4
X_signal : 0.954184
X_resolution : 0.407508

Decoupling : TRUE
Initial_wait : 112
NMR : TRUE
NMR_time : 236
sequence : 1024
Relaxation_delay : 2.0
Repetition_time : 1.04313312

Temp: 27.7[°C]
Electronic Supplementary Material (ESI) for Chemical Communications
This journal is © The Royal Society of Chemistry 2012

--- PROCESSING PARAMETERS ---
 acqui_balance : 0 : TRUE
 acqui : 2.0[ms] ; 0.0[ms]
 turbo : 100% ; 50%
 fem : 1 ; fem : fem
 nmz_time : 100
 ppm
 Derived from: TN-435 pure 13C-1.jdf

Filename : TN-435 pure 13C-1.jdf
Author : delta
Experiment : simple pulse decoupl
Sample_id : #819704
Sample : CHLOROMETH-D
Creation_time : 14.06.2008 19:46:00
Revision_time : 23-MAY-2007 11:56:47
T1_time : 23-MAY-2007 11:57:13

Content : single pulse decoupling
Data_format : ID COMPLEX
Dim_time : 200ms
Dim_spectra : 2
Dim_metas : 2
Dim_spectra : 2
Spectrometer : BRUKER 400P

Field_strength : 9.40076[MHz] ; 400[MHz]
E_h[sec] : 1.04133[ms]
E_width : 100.0[Hz]
E_fine : 2
Phase : 4
Phase_resonance : 0 ; 0.0584866[Hz]
T1_time : 6.40705[ms]
Tr[sec] : 18
Tr_fine : 399.7603186[ms]
Tr[sec] : 5[ms]
Clipped : FALSE
Mod_return : 3
Acquire : 256
Total_acquire : 256
E_fine : 2
E_width : 10.2[Hz]
E_phase : 0
E_time : 1.043153[ms]
E_width : 3.8[ms]
T1_time : 6.3[ms]
T2_time : 10.0[ms]
Decoupling : TRAM
Initial_wait : 1.0[ms]
Mix : TRAM
Mix_time : 2.0[ms]
Inversion : 21.0[ms]
Repulatation_time : 3.0433333[ms]
Temp[deg] : 14.2[°C]

Ph
MOM-N
O
CO₂Et
O
Me
Electronic Supplementary Material (ESI) for Chemical Communications
This journal is © The Royal Society of Chemistry 2012
Electronic Supplementary Material (ESI) for Chemical Communications
This journal is © The Royal Society of Chemistry 2012