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<td>Author(s)</td>
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Diastereoselective arylation of L-proline derivatives at the 5-position

Osamu Onomura,* Peter G. Kirira, Toshimitsu Tanaka, Shinsuke Tsukada, Yoshihiro Matsumura, Yosuke Demizu

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

Abstract- Diastereoselective introduction of nucleophiles into L-proline derivatives at the 5-position was achieved with suitable selection of N-protecting group. N-Methoxycarbonylated or benzyloxy carbonylated L-proline derivatives reacted with arene to give cis-arylated products. On the other hand, N-benzo ylated L-proline derivative preferentially gave trans-arylated product which could be easily transformed into optically active C2-symmetrical pyrrolidine derivative. Such derivative 5, worked well as an organic activator in the asymmetric reduction of aromatic imines by Cl3SiH.

Keywords: Diastereoselective; Organocatalysis; Asymmetric reduction of imines; C2-Symmetrical pyrrolidine; Proline derivative

1. Introduction

Optically active 2,5-disubstituted pyrrolidines are key intermediates for preparation of pharmaceuticals or natural products1 as well as organocatalysts for asymmetric reactions.2 Electrochemical oxidation of L-proline derivatives 1 is a useful tool for their synthesis (Eq. 1).3

*Corresponding author, Tel +81-95-819-2429, Fax +81-95-819-2476, E-mail: onomura@nagasaki-u.ac.jp
Recently, we have reported that cis-5-arylated N-formyl-L-proline 4 worked well as an organic activator in the enantioselective reduction of ketones with Cl$_3$SiH$^5$ in high enantioselectivities (Eq. 2). However, it was difficult to prepare 4 for practical use because diastereoselectivity in arylation reaction of 2a (PG=CHO) was very low. We wish herein to report diastereoselective introduction of nucleophiles into L-proline derivatives at the 5-position. In addition, synthesis of compound 4 and C$_2$-symmetrical pyrrolidine derivative 5 derived from cis- and trans-arylated products, and its application to asymmetric reduction of aromatic imines with Cl$_3$SiH$^6$ are presented.

\[
\begin{align*}
\text{Ar} & \text{Cl}_3\text{SiH} (3.0 \text{ equiv}) \\
\text{R} & \text{4} (0.1 \text{ equiv})
\end{align*}
\]

up to 99% ee

2. Results and discussion

2.1. Diastereoselective introduction of nucleophiles into L-proline derivatives at the 5-position
First, we investigated introduction of trimethylbenzene and triethylbenzene into 5-methoxylated L-proline derivatives 2a-d\(^7\) protected with various N-acyl groups in the presence of Lewis acids (Eq. 3). The results are shown in Table 1. N-Formylated proline 2a gave the corresponding arylated product 3a as a diastereomer mixture (cis/trans = 43/57, entry 1),\(^4\) while N-methoxycarbonylated 2b and N-benzoxycarbonylated 2c gave compounds 3b and 3c as a single isomer (cis/trans = 100/0, entries 2 and 3). In the case of N-benzoylated 2d, trans-3d\(^8\) was mainly obtained along with small amount of cis-3d (cis/trans = 11/89, entry 4). Using SnCl\(_4\) instead of TiCl\(_4\) did not affect the diastereoselectivity though the former had relatively poor yield (entry 5). Triethylbenzene as a nucleophile gave similar results to that of trimethylbenzene (entries 6-9), but in the case of N-benzoylated proline 2d did not afford 5-arylated product 6d (entry 10).

![Reaction Scheme](image)

**Table 1. Arylation of proline derivative 2a-d at the 5-position**

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>Lewis acid</th>
<th>R</th>
<th>Yield (%)</th>
<th>cis/trans</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>CHO</td>
<td>TiCl(_4)</td>
<td>Me</td>
<td>3a</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>CO(_2)Me</td>
<td>TiCl(_4)</td>
<td>Me</td>
<td>3b</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>Cbz</td>
<td>TiCl(_4)</td>
<td>Me</td>
<td>3c</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>Bz</td>
<td>TiCl(_4)</td>
<td>Me</td>
<td>3d</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Bz</td>
<td>SnCl(_4)</td>
<td>Me</td>
<td>3d</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>CHO</td>
<td>SnCl(_4)</td>
<td>Et</td>
<td>6a</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>CO(_2)Me</td>
<td>SnCl(_4)</td>
<td>Et</td>
<td>6b</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>Cbz</td>
<td>SnCl(_4)</td>
<td>Et</td>
<td>6c</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>Cbz</td>
<td>TiCl(_4)</td>
<td>Et</td>
<td>6c</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td>Bz</td>
<td>SnCl(_4)</td>
<td>Et</td>
<td>6d</td>
<td>0</td>
</tr>
</tbody>
</table>
Allylation of 5-methoxylated L-proline derivatives 2b and 2d showed similar tendency to their arylation (Eq. 4). That is, \(N\)-methoxycarbonylated 2b mainly gave \(cis\)-allylated proline 7b (\(cis/trans = 73/27\)),\(^7c\) while \(N\)-benzoylated proline 2d preferentially changed into \(trans\)-allylated proline 7d (\(cis/trans = 13/87\)).\(^9\)

Key intermediates in these reactions are carbenium and iminium ions illustrated in Scheme 1. Since the carbonyl group of carbamates (PG= CO\(_2\)Me or Cbz) can coordinate to Lewis acid, carbenium ion will be preferable to iminium ion. On the other hand, carbonyl group of amide (PG=Bz) might not coordinate to Lewis acid. Therefore, the iminium ion will be predominantly generated. The \(cis\)-selectivity in the carbenium ion intermediate is illustrated in Scheme 1 (Carbamate) in which PG (CO\(_2\)Me or Cbz) is oriented in \(trans\) position with respect to 2-CO\(_2\)Me substituent. Nucleophiles may approach the intermediate preferentially from the \(trans\) direction with respect to PG.\(^7c\)

The \(trans\)-selectivity (PG=Bz) in the iminium ion intermediate is illustrated in Scheme 1 (Amide) in which Bz and iminium groups exist on the same plane. Nucleophiles can approach the intermediate preferentially from the \(trans\) direction with respect to 2-CO\(_2\)Me substituent.
2.2. *Synthesis of an organic activator 4 and C₂-symmetrical pyrrolidine derivative 5*

An organic activator 4 for the enantioselective reduction of ketones was synthesized from 6c after hydrogenation, N-formylation followed by alkaline hydrolysis in 58% yield (Eq. 5).

\[
\begin{align*}
\text{Compound 6c} & \quad \xrightarrow{1) \text{Pd-C, H₂, Et₃N, MeOH}} \quad \text{Compound 4} \quad \text{58\% yield} \\
& \quad \xrightarrow{2) \text{Ac₂O, HCO₂H}} \quad \text{Compound 5} \\
& \quad \xrightarrow{3) \text{NaOH, H₂O/THF}} \quad \text{Compound 8} \\
& \quad \text{C₂-Symmetrical pyrrolidine derivative 5} \quad \text{was prepared from N-benzoylated proline 3d as follows (Scheme 2); Alkaline hydrolysis of 3d followed by recrystallization from CHCl₃/hexane afforded carboxylic acid 8 in 54\% yield as a single isomer (cis/trans = 0/100). Electrochemical decarboxylative methoxylation of 8 in methanol afforded methoxylated compound 9, which reacted with mesitylene in the presence of TiCl₄ to} 
\end{align*}
\]
exclusively afford *trans*-2,5-biarylated pyrrolidine 10 in high yield. By reduction of
*N*-benzoyl group of 10, successive deprotection of *N*-benzyl group of 11, and
*N*-picolynoylation of 12, desired pyrrolidine 5 was obtained in enough yield.

2) Recrystallization from CHCl₃/hexane
BH₃-THF (2.0 equiv), THF, reflux

N<sub>Bz</sub>CO₂H₈, 54% yield
cis/trans = 11/89

N<sub>Bz</sub>OMe₉, 73% yield

N<sub>Bz</sub>Ar₉, 88% yield
cis/trans = 0/100

1) NaOH (2.0 equiv), H₂O/THF, rt
2,6-lutidine (1.3 equiv), C(+)–Pt(−), -2e
MeOH, 0°C

N<sub>H</sub>Ar₉, 81% yield (from 10)

N<sub>Bn</sub>Ar₁₁, 81% yield (from 10)

N<sub>H</sub>Ar₅, 93% yield

Scheme 2

2.3. Asymmetric reduction of aromatic imines catalyzed by 5 with Cl₃SiH

Catalytic activation of Cl₃SiH with compound 5 was applicable to asymmetric
reduction of aromatic imines 13a-f (Eq. 6). The results are summarized in Table 2,
which also shows the results of asymmetric reduction using 15<sup>6c</sup> for comparison. In all
cases, compound 5 could play the role of an activator to afford (S)-amines 14a-f<sup>6</sup> with
good yield and enantioselectivity just like that of 15 (entries 1-6).
3. Conclusion

We have accomplished diastereoselective introduction of nucleophiles into L-proline derivatives at the 5-position. \(N\)-Methoxycarbonylated or \(N\)-benzyloxy carbonylated L-proline 2b or 2c were exclusively transformed into \(cis\)-arylated products 3b,c or 6b,c, while \(N\)-benzoylated L-proline derivative 2d mainly gave \(trans\)-arylated product 3d. \(C_2\)-Symmetrical pyrrolidine derivative 5 derived from 3d worked well as an organic activator in the reduction of aromatic imines to the corresponding optically active amines with high enantioselectivity by Cl3SiH.

4. Experimental Section

4.1. General
Electrochemical reactions were carried out using DC Power Supply (GP 050-2) of Takasago Seisakusho, Inc. $^1$H NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. $^{13}$C NMR spectra were measured on a Varian Gemini 400 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Mass spectra were obtained on a JEOL JMS-DX 303 instrument. Elemental analyses were performed on Perkin Elmer 2400II.

All reagents and solvents were used as supplied without further purification.

4.2. Methyl N-protected 5-methoxy-L-prolinate 2a-d

N-Protected 5-methoxy-L-prolinates 2a,$^7c$ 2b,$^7a$ 2c,$^7d$ and 2d$^7b$ were known compounds.

4.3. General procedure for arylation or allylation of methyl N-protected-5-methoxy-L-prolinate 2a-d

Under an argon atmosphere, TiCl$_4$ (55 μL, 0.5 mmol) was added dropwise to the solution of 2a (109 mg, 0.5 mmol) and 1,3,5-trimethylbenzene (209 μL, 1.5 mmol) in CH$_2$Cl$_2$ (5 mL) at -78°C. The resulting mixture was stirred for 12 h and allowed to stand until it warmed to room temperature. The solution was poured in ice water (10 mL) and extracted with CHCl$_3$ (10 mL x 3). The combined organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography ($n$-hexane : AcOEt = 10 : 1) to afford 3a as a colorless oil (93 mg, 61%). Arylation with 1,3,5-triethylbenzene and allylation with allyltrimethylsilane were carried out according to this same procedure.
4.3.1. Methyl cis-N-formyl-5-(2,4,6-trimethylphenyl)-L-prolinate (cis-3a)\(^4\)

Colorless oil; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.85 (s, 1H), 6.88 (s, 2H), 5.04 and 5.06 (d, \(J = 11.0\) Hz, 1H), 4.53 (t, \(J = 5.4\) Hz, 1H), 3.80 (s, 3H), 2.55-1.95 (m, 13H).

4.3.2. Methyl trans-N-formyl-5-(2,4,6-trimethylphenyl)-L-prolinate (trans-3a)\(^4\)

Colorless oil; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.81 (s, 1H), 6.85 (s, 2H), 5.37 (t, \(J = 8.0\) Hz, 1H), 4.56 (t, \(J = 7.5\) Hz, 1H), 3.75 (s, 3H), 2.42-1.99 (m, 13H).

4.3.3. Methyl N-methoxycarbonyl-5-(2,4,6-trimethylphenyl)-L-prolinate (3b)

Colorless crystal; mp 48-50\(^0\)C; \([\alpha]\)\(_{D}\) \(-49.1\) (c=1.0, CHCl\(_3\)); IR (neat) \(\nu\) = 2953, 1754, 1701, 1612, 1447, 1348, 1198, 1123, 1078, 851, 781 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.80 (s, 2H), 5.10 (t, \(J = 9.0\) Hz, 1H), 4.59-4.51 (m, 1H), 3.78 (s, 3H), 3.55 (s, 3H), 2.44-2.07 (m, 13H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.5, 157.1, 135.8, 135.6, 133.1, 130.0, 60.4, 52.6, 51.9, 30.2, 27.9, 20.5; HR-EI(+) \(m/z\) calcd for C\(_{17}\)H\(_{23}\)NO\(_4\) [M]\(^+\) 305.1627, found 305.1623.

4.3.4. Methyl N-benzyloxycarbonyl-5-(2,4,6-trimethylphenyl)-L-prolinate (3c)

Colorless oil; \([\alpha]\)\(_{D}\) \(-49.6\) (c=1.0, CHCl\(_3\)); IR (neat) \(\nu\) = 2960, 1753, 1701, 1456, 1338, 1197, 1174, 1120, 851, 735 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35-7.10 (m, 5H), 6.79 (s, 2H), 5.15-4.90 (m, 3H), 4.63-4.55 (m, 1H), 3.74 (s, 3H), 2.45-2.05 (m, 13H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 172.5, 156.4, 135.8, 135.7, 135.3, 131.3, 130.1, 129.3, 128.2, 127.9, 127.8, 127.4, 127.2, 67.0, 60.4, 52.0, 30.4, 27.8, 20.6, 20.5; HR-EI(+) \(m/z\) calcd for C\(_{23}\)H\(_{27}\)NO\(_4\) [M]\(^+\) 381.1940, found 381.1938.
4.3.5. **Methyl trans-N-benzoyl-5-(2,4,6-trimethylphenyl)-L-prolinate (3d)**

Colorless crystal; mp 112-114 °C; \([\alpha]_D^{18} = 133.5\) \((c=1.0, \text{CHCl}_3)\); IR (neat) \(\nu = 2953, 1755, 1745, 1659, 1641, 1632, 1580, 1444, 1414, 1279, 1202, 1175, 1127, 1028, 853\) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \((cis/trans = 11/89)\) \(\delta = 7.50-7.00\) \((m, 5H)\), 6.80 \((br s, 0.11H)\), 6.64 \((s, 0.89H)\), 6.60 \((br s, 0.11H)\), 6.39 \((s, 0.89H)\), 5.64 \((t, J= 8.7\) Hz, 0.11H), 5.40 \((t, J= 8.7\) Hz, 0.89H), 4.77 \((t, J= 9.0\) Hz, 1H), 3.83-3.76 \((m, 3H)\), 2.58-1.95 \((m, 13H)\); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 170.8, 169.5, 134.3, 133.3, 132.1, 129.6, 127.2, 127.0, 125.4, 123.5, 59.3, 58.0, 50.3, 30.4, 26.8, 18.4, 18.3\); HR-EI(+) m/z calec for C\(_{22}\)H\(_{25}\)NO\(_3\) \([M]^+\) 351.1834, found 351.1832. HPLC: Daicel Chiralcel OJ-H column, \(n\)-hexane : isopropanol = 20 : 1, wavelength: 254 nm, flow rate: 1.0 ml/min, retention time: 19.1 min \((cis-3d)\), 23.3 min \((trans-3d)\).

4.3.6. **Methyl cis-N-formyl-5-(2,4,6-triethylphenyl)-L-prolinate (cis-6a)**

Colorless oil; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.87\) \((s, 1H)\), 7.10-6.82 \((br s, 2H)\), 5.03 and 5.01 \((d, J= 12.0\) Hz, 1H), 4.58-4.50 \((m, 1H)\), 3.80 \((s, 3H)\), 2.95-2.05 \((m, 10H)\), 1.30-1.10 \((m, 9H)\).

4.3.7. **Methyl trans-N-formyl-5-(2,4,6-triethylphenyl)-L-prolinate (trans-6a)**

Colorless oil; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.79\) \((s, 1H)\), 6.99 \((s, 1H)\), 6.88 \((s, 1H)\), 5.34 and 5.33 \((d, J= 9.9\) Hz, 1H), 4.62 \((t, J= 7.8\) Hz, 1H), 3.80 \((s, 3H)\), 2.74 \((q, J= 7.8\) Hz, 2H), 2.65-2.40 \((m, 5H)\), 2.38-2.01 \((m, 3H)\), 1.30-1.10 \((m, 9H)\).

4.3.8. **Methyl trans-N-methoxycarbonyl-5-(2,4,6-triethylphenyl)-L-prolinate (6b)**

Colorless oil; \([\alpha]_D^{28} = -41.3\) \((c=1.1, \text{CHCl}_3)\); IR (neat) \(\nu = 2963, 1755, 1709, 1445, 1348, 1198, 1150, 1125, 1080, 874, 781\) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 6.86\) \((m,
2H), 5.10 (t, J= 8.7 Hz, 1H), 4.60-4.50 (m, 1H), 3.80-3.50 (m, 6H), 2.80-2.11 (m, 10H), 1.30-1.10 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) (a mixture of rotamers) $\delta$ 172.8, 157.1, 142.5, 142.1, 141.9, 141.7, 132.0, 127.0, 125.5, 60.5, 59.8, 52.1, 51.8, 32.6, 28.2, 28.0, 26.5, 25.6, 24.9, 24.7, 15.9, 15.5, 15.4, 14.8; HR-EI(+) m/z calcd for C$_{26}$H$_{29}$NO$_4$ [M]$^+$ 347.2097, found 347.2081.

4.3.9. Methyl trans-N-benzyloxycarbonyl-5-(2,4,6-triethylphenyl)-L-prolinate (6c)

Colorless oil; [\(\alpha\)]$_D^{28}$ -42.3 (c=1.0, CHCl$_3$); IR (neat) $\nu$ = 2965, 1755, 1705, 1408, 1339, 1198, 1175, 1080, 696 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40-6.80 (m, 7H), 5.20-4.80 (m, 3H), 4.60-4.50 (m, 1H), 3.77 (s, 3H), 3.10-1.95 (m, 10H), 1.32-0.86 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) (a mixture of rotamers) $\delta$ 172.6, 156.7, 142.4, 142.3, 142.1, 135.7, 132.3, 128.1, 127.9, 127.7, 127.4, 126.5, 67.0, 61.0, 60.8, 59.9, 57.7, 52.2, 52.1, 33.3, 32.7, 28.9, 28.2, 27.8, 27.5, 27.1, 26.3, 25.1, 25.0, 24.8, 15.9, 15.7, 15.4, 15.3, 15.2; HR-EI(+) m/z calcd for C$_{26}$H$_{33}$NO$_4$ [M]$^+$ 423.2410, found 423.2394.

4.3.10. Methyl N-methoxycarbonyl-5-allyl-L-prolinate (7b)$^{7c}$

$^1$H NMR (400 MHz, CDCl$_3$) (cis/trans = 73/27) $\delta$ 5.83-5.65 (m, 1H), 5.12-5.03 (m, 2H), 4.40-4.27 (m, 1H), 4.15-3.91 (m, 1H), 3.77-3.63 (m, 6H), 2.80-2.42 (m, 1H), 2.25-1.72 (m, 5H).

4.3.11. Methyl N-benzoyl-5-allyl-L-prolinate (7d)

Colorless oil; [\(\alpha\)]$_D^{20}$ -26.9 (c=1.0 CHCl$_3$); IR (neat) $\nu$ = 2977, 2953, 1750, 1644, 1603, 1446, 1410, 1277, 1203, 1174, 1076 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) (cis/trans = 13/87) $\delta$ 7.53-7.28 (m, 5H), 5.97-5.80 (m, 0.5H), 5.55-5.38 (m, 0.5H), 5.16-4.72 (m,
2H), 4.44-4.17 (m, 1H), 3.96 (br s, 0.5H), 3.77-3.60 (m, 3H), 3.06 (br s, 0.5H), 2.23-1.18 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(^{(cis/trans \, = 13/87, \text{a mixture of rotamers})}\) \(\delta\) 173.0, 171.5, 134.7, 133.5, 129.7, 128.3, 128.2, 126.7, 126.5, 118.1, 117.6, 62.1, 59.6, 59.3, 58.9, 52.2, 39.1, 38.4, 37.7, 28.9, 28.5, 26.8; HR-FAB(+) \(m/z\) calcd for C\(_{16}\)H\(_{20}\)NO\(_3\) [M+H]\(^+\) 274.1443 found 274.1444.

4.4. Synthesis of cis-N-formyl-5-(2,4,6-triethylphenyl)-L-proline (4)

5% Pd-C (30 mg) was added to the solution of \(6c\) (2.0 mmol, 847 mg) and triethylamine (279 \(\mu\)L, 2.0 mmol) in MeOH (5.0 mL). The mixture was then stirred under 1 atm of H\(_2\) for 12 h. Upon completion of reaction the mixture was then filtered through celite and solvent removed in vacuo to obtain methyl cis-5-(2,4,6-triethylphenyl)-L-prolinate which was used for next reaction without further purification. Colorless oil; \([\alpha]\)^{28}_D +13.4 (\(c=1.1, \text{CHCl}_3\)); IR (neat) \(\nu\) = 3350, 2963, 1734, 1458, 1210, 874, 669 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.89 (s, 2H), 4.57 (t, \(J= 8.7\) Hz, 1H), 3.87 (t, \(J= 7.8\) Hz, 1H), 3.76 (s, 3H), 2.90-2.50 (m, 6H), 2.35-2.00 (m, 4H), 1.78 (br s, 1H), 1.23 (t, \(J= 7.5\) Hz, 9H); HR-EI(+) \(m/z\) calcd for C\(_{18}\)H\(_{27}\)NO\(_2\) [M]\(^+\) 289.2042, found 289.2027.

Under an argon atmosphere, acetic anhydride (2.0 mL) was added dropwise to a solution of methyl cis-5-(2,4,6-triethylphenyl)-L-prolinate in formic acid (6.0 mL) and stirred at room temperature for 9 h. Upon completion of reaction the solvent was removed under reduced pressure, then the residue was purified by silica gel column chromatography (\(n\)-hexane : AcOEt = 3 : 1) to afford methyl cis-N-formyl-5-(2,4,6-triethylphenyl)-L-prolinate\(^4\) as a colorless crystal (372 mg, 58 % for 2 steps). Then, aqueous 1M NaOH (2.0 mL) was added to the stirred solution of
methyl cis-N-formyl-5-(2,4,6-triethylphenyl)-L-proline (1.0 mmol, 317 mg) in MeOH (4.0 mL), and the solution was stirred at room temperature for 12 h. The solution was neutralized with 3% aqueous HCl, and then MeOH was evaporated. The residue was diluted with brine, extracted with AcOEt, and dried over MgSO₄. Removal of the solvent afforded compound 4 (303 mg, quant.) as colorless crystals. Mp 132-133 °C; [α]D²⁵ -135.5 (c=0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.96 (s, 1H), 6.98 (s, 1H), 6.89 (s, 1H), 5.21 and 5.19 (d, J = 11.0 Hz, 1H), 4.75 (q, J = 9.3 Hz, 1H), 2.90 and 2.88 (d, J = 10 Hz, 1H), 2.85-2.05 (m, 9H), 1.30-1.10 (m, 9H).

4.5. Synthesis of N-picolinoyl (2S,5S)-[2,5-bis-(2,4,6-trimethylphenyl)pyrrolidine (5)

4.5.1. trans-N-Benzoyl-5-(2,4,6-trimethylphenyl)-L-proline (8)

NaOH (12.9 mmol, 516 mg) was added to the stirred solution of 3d (6.5 mmol, 2.27 g) in THF/H₂O = 1 : 1 (60 mL), and the solution was stirred at room temperature for 4 h. The solution was then neutralized with 10% aqueous HCl, and extracted with AcOEt (150 mL x 3), and dried over MgSO₄. After removal of the solvent and recrystallization from CHCl₃/hexane, compound 8 was obtained as colorless crystals (1.27 g, 58%). Mp 204-207°C; [α]D¹⁰ -82.3 (c=0.3, CHCl₃), IR (neat) ν = 3640, 1727, 1642, 1620, 1445, 1354, 1123 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.20-7.00 (m, 5H), 6.66 (s, 1H), 6.41 (s, 1H), 5.38 (t, J = 8.4 Hz, 1H), 4.83 (t, J = 7.8 Hz, 1H), 4.20 (br s, 1H), 2.58-1.90 (m, 13H); ¹³C NMR (100MHz, CDCl₃) (a mixture of rotamers) δ 176.1, 171.4, 136.2, 136.0, 135.7, 135.1, 134.5, 134.1, 134.0, 131.2, 130.2, 129.2, 128.9, 128.1, 127.6, 127.4, 125.6, 63.1, 61.4, 60.3, 59.4, 32.3, 31.0, 29.9, 28.6, 20.6, 20.4, 20.3; EA calcd for C₂₁H₂₃NO₃: C 74.75, H 6.87, N 4.15: found C 74.41, H 6.92, N 3.93; HR-El(+) m/z calced for C₂₁H₂₃NO₃ [M]⁺ 337.1678, found 337.1674.
4.5.2. *N*-Benzoyl-2-methoxy-(5S)-(2,4,6-trimethylphenyl)pyrrolidine (9)

Anodic oxidation of 8 was carried out using graphite cathode (10 cm x 5 cm) and platinum anode (12 cm x 5 cm) in an undivided beaker-type cell. 8 (29.4 mmol, 9.9 g), and 2,6-lutidine (38.2 mmol, 4.5 mL) were added into MeOH (200 mL). After passing through 2.0 $F$/mol of electricity at constant voltage (18 V) at 0°C, MeOH was evaporated, then the residue was poured in water and extracted with AcOEt (200 mL x 3). The combined organic layer was dried over MgSO₄ and solvent removed under reduced pressure. The residue was purified by silica gel column chromatography ($n$-hexane : AcOEt = 3 : 1) to afford 9 (6.9 g, 73% yield) as colorless oil. [α]$_D^{24}$ +17.8 (c=1.0, CHCl₃); IR (neat) ν = 2732, 1765, 1727, 1692, 1642, 1613, 1582, 1547, 1503, 1468 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl₃) δ 7.83 (br s, 2H), 7.37 (br s, 3H), 6.77 (s, 2H), 5.23 (br s, 1H), 4.72 (br s, 1H), 3.14 (s, 3H), 2.60-2.03 (m, 13H); $^{13}$C NMR (100 MHz, CDCl₃) (a mixture of diastereomers and rotamers) δ 171.3, 169.2, 135.8, 133.8, 133.4, 132.6, 132.0, 130.7, 129.7, 129.5, 127.8, 126.5, 125.9, 125.6, 125.2, 123.2, 92.7, 90.0, 60.2, 58.1, 54.5, 31.5, 31.1, 30.6, 28.6, 20.6, 20.5; HR-EI(+) m/z calcd for C$_{21}$H$_{25}$NO$_2$ [M]$^+$ 323.1885, found 323.1866.

4.5.3. *N*-Benzoyl-(2S,5S)-[2,5-bis-(2,4,6-trimethylphenyl)]pyrrolidine (10)

Under an argon atmosphere, TiCl$_4$ (140 μL, 1.0 mmol) was added dropwise to the solution of 9 (313 mg, 0.97 mmol) and 1,3,5-trimethylbenzene (400 μL, 2.9 mmol) in CH$_2$Cl$_2$ (10 mL) at -78°C. The resulting mixture was stirred for 24 h and allowed to stand until it warmed to room temperature. The solution was poured in ice water (10 mL) and extracted with CHCl₃ (10 mL x 3). The combined organic layer was dried over
MgSO₄ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : AcOEt = 10 : 1) to afford 10 (351 mg, 88%) as colorless crystals. Mp 184-187 °C; [α]D²² +24.9 (c=0.5, CHCl₃); IR (neat) ν = 2963, 1738, 1632, 1580, 1483, 1408, 1348, 1240, 1102, 849, 795 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.20-7.00 (m, 5H), 6.85 (s, 1H), 6.81 (s, 1H), 6.60 (s, 1H), 6.35 (s, 1H), 5.65-5.59 (m, 2H), 2.61-2.20 (m, 22H); ¹³C NMR (100 MHz, CDCl₃) (a mixture of rotamers) δ 169.7, 137.3, 136.8, 136.0, 135.8, 134.9, 134.6, 134.5, 133.6, 131.2, 131.0, 129.3, 129.2, 128.8, 127.1, 126.2, 60.3, 60.0, 32.4, 30.2, 21.2, 20.7, 20.6, 20.4, 20.1; EA calcd for C₂₉H₃₃NO: C 84.63, H 8.08, N 3.40; found C 84.43, H 8.15, N 3.02; HR-EI(+) m/z calcd for C₂₉H₃₃NO [M]+ 411.2562, found 411.2560. HPLC: Daicel Chiralcel OD-H column, n-hexane : ethanol = 30 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 8.9 min for (2R,5R)-10, 11.9 min for (2S,5S)-10.

4.5.4. N-Benzyl-(2S,5S)-[2,5-bis-(2,4,6-trimethylphenyl)pyrrolidine (11)

1.03 M BH₃-THF (17.4 mL, 18.0 mmol) was added to the solution of 10 (3.6 g, 8.7 mmol) in THF (70 mL), and refluxed at 80 °C for 17 h. The solution was poured in water (100 mL) and extracted with AcOEt (100 mL x 3). The combined organic layer was dried over MgSO₄ and solvent removed in vacuo to obtain 11 (3.45 g, quant.), which was used for next reaction without further purification. Colorless crystal; mp 109-110 °C; [α]D²³ -124.5 (c=1.0, CHCl₃); IR (neat) ν = 2947, 1611, 1480, 1372, 1312, 1213, 1188, 1165, 1105, 1075, 1028, 851, 741, 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.00-6.89 (m, 3H), 6.78 (s, 2H), 6.63 (s, 2H), 6.38 (dd, J= 2.1, 7.8 Hz, 2H), 4.95 (t, J= 7.2 Hz, 2H), 3.37 (q, J= 12.9 Hz, 2H), 2.41-2.11 (m, 22H); ¹³C NMR (100 MHz, CDCl₃) δ 140.9, 138.8, 136.9, 136.3, 135.8, 131.2, 129.5, 129.2, 127.3, 125.9, 60.9,
51.7, 31.0, 21.5, 20.9; HR-EI(+) m/z calcd for C\textsubscript{29}H\textsubscript{35}N [M]+ 397.2769, found 397.2766.

4.5.5. (2S,5S)-[2,5-Bis-(2,4,6-trimethylphenyl)]pyrrolidine (12)

20% Pd(OH)\textsubscript{2} (80 mg, 0.12 mmol) was added to the solution of 11 (228 mg, 0.57 mmol) and 3 drops of concentrated aqueous HCl in MeOH (5.0 mL). The mixture was then stirred under 1 atm of H\textsubscript{2} for 3 h. Upon completion of reaction the mixture was then filtered through celite and solvent removed in vacuo. The residue was poured into saturated aqueous NaHCO\textsubscript{3} (10 mL) and extracted with CHCl\textsubscript{3} (20 mL x 3). The combined organic layer was dried over MgSO\textsubscript{4} and solvent removed in vacuo to afford 12 (142 mg, 81% from 10), which was used for next reaction without further purification. Colorless oil; [α]\textsubscript{D}\textsuperscript{22} -107.1 (c=0.5, CHCl\textsubscript{3}); IR (neat) \nu = 2951, 1611, 1462, 1084, 849 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 6.81 (s, 4H), 5.04 (t, J= 7.2 Hz, 2H), 2.46 (s, 12H), 2.23 (s, 6H), 2.13-2.08 (m, 4H), 1.68 (br s, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 134.8, 134.2, 133.5, 128.2, 56.4, 31.0, 18.7, 18.6; HR-EI(+) m/z calcd for C\textsubscript{22}H\textsubscript{29}N [M]+ 307.2300, found 307.2281.

4.5.6. N-Picolinoyl-(2S,5S)-[2,5-bis-(2,4,6-trimethylphenyl)]pyrrolidine (5)

A solution of picolinic acid (68.9 mg, 0.55 mmol) and CDI (122 mg, 0.75 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (2.5 mL) was stirred at 0°C for 30 min. Then, a solution of 12 (153 mg, 0.50 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (2.5 mL) was added at 0°C, and the mixture was stirred at room temperature for 24 h. The solution was poured into saturated aqueous NaHCO\textsubscript{3} (10 mL) and extracted with AcOEt (20 mL x 3). The combined organic layer was dried over MgSO\textsubscript{4} and solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : AcOEt = 5 : 1) to afford 5 (192 mg, 93% yield)
as colorless crystals. Mp 73-74 °C; [α]D20 +6.8 (c=0.3, CHCl3), IR (neat) 2963, 1738, 1639, 1503, 1443, 1408, 1356, 1287, 1242, 1183, 1107, 851 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 8.30 (d, J= 4.2 Hz, 1H), 7.32-7.26 (m, 2H) 6.91 (t, J= 4.8 Hz, 1H), 6.85 (s, 1H), 6.79 (s, 1H), 6.53 (s, 1H), 6.40 (s, 1H), 6.03 (t, J= 7.2 Hz, 1H), 5.67 (t, J= 7.2 Hz, 1H), 2.63-2.02 (m, 22H); ¹³C NMR (100 MHz, CDCl3) (a mixture of rotamers) δ 167.1, 154.4, 146.7, 136.1, 135.9, 135.7, 135.5, 135.4, 134.6, 134.5, 133.9, 131.1, 130.7, 129.0, 128.6, 123.7, 122.5, 60.0, 59.8, 32.2, 29.9, 21.0, 20.6, 20.5, 20.3, 19.9; EA calcd for C28H32N2O: C 81.51, H 7.82, N 6.79: found C 81.21, H 7.84, N 6.54; HR-EI(+) m/z calcd for C28H32N2O [M]+ 412.2515, found 412.2506.

4.6. General procedure for asymmetric reduction of imines 13a-f

Cl₃SiH (0.45 mmol) was added into a solution of imines 13a (0.3 mmol) and compound 5 (0.03 mmol) in CH₂Cl₂ (1.5 mL), and the mixture was stirred at room temperature for 4 h. The mixture was then poured into saturated aqueous NaHCO₃ (10 mL) and extracted with CHCl₃ (10 mL x 3). The combined organic layer was dried over MgSO₄ and solvent removed under reduced pressure. The residue was purified by silica gel column chromatography to afford amine 14a (159 mg, 77% yield).

4.6.1. (S)-N-Phenyl-N-(1-phenylethyl)amine (14a)⁶b

HPLC: Daicel Chiralcel OD-H column, n-hexane : isopropanol : diethylamine = 10 : 1 : 0.01, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 7.2 min for (S)-14a, 8.6 min for (R)-14a.

4.6.2. (S)-N-[1-(4-Methoxylphenyl)ethyl]-N-phenylamine (14b)⁶b
HPLC: Daicel Chiralcel OD-H column, n-hexane : isopropanol = 99 : 1, wavelength: 254 nm, flow rate: 0.7 mL/min, retention time: 13.1 min for (S)-14b, 14.4 min for (R)-14b.

4.6.3. (14c) (S)-N-(4-Methoxylphenyl)-N-(1-phenylethyl)amine (14c)

HPLC: Daicel Chiralcel OD-H column, n-hexane : isopropanol = 99 : 1, wavelength: 254 nm, flow rate: 0.7 mL/min, retention time: 17.5 min for (S)-14c, 19.3 min for (R)-14c.

4.6.4. (S)-N-[1-(4-Chlorophenyl)ethyl]-N-phenylamine (14d)

HPLC: Daicel Chiralcel OD-H column, n-hexane : isopropanol = 95 : 5, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 9.0 min for (S)-14d, 10.8 min for (R)-14d.

4.6.5. (S)-N-[1-(4-Acetylphenyl)ethyl]-N-phenylamine (14e)

Pale yellow oil; [α]D27 -18.8 (c=0.7, CHCl3), IR (neat) 3390, 3054, 2980, 2926, 2869, 1678, 1603, 1506, 1429, 1360, 1320, 1269, 1210, 1181, 1144, 1015, 1015, 959 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.92 (d, J= 8.7 Hz, 2H), 7.47 (d, J= 8.7 Hz, 2H), 7.08 (t, J= 6.9 Hz, 2H), 6.65 (t, J= 6.3 Hz, 1H), 6.47 (d, J= 7.8 Hz, 2H), 4.53 (q, J= 8.2 Hz, 1H), 4.08 (br s, 1H), 2.58 (s, 3H), 1.53 (d, J= 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 197.7, 151.0, 146.8, 136.0, 129.2, 129.1, 128.9, 126.0, 113.2, 53.4, 26.6, 24.9; HR-EI(+) m/z calcd for C₁₆H₁₇NO [M]+ 239.1310, found 239.1287. HPLC: Daicel Chiralcel OD-H column, n-hexane : isopropanol = 5 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 11.1 min for (S)-14e, 13.2 min for (R)-14e.
4.6.6. (S)-N-[1-(4-Nitrophenyl)ethyl]-N-phenylamine (14f)\textsuperscript{6b}

HPLC: Daicel Chiralcel OD-H column, \textit{n}-hexane : isopropanol = 95 : 5, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 33.5 min for (S)-14f, 38.0 min for (R)-14f.

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References and notes


8. Stereoconfiguration of trans-3d was determined by the X-ray analysis. Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 686483.
Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

9. After hydrogenation of 7d, its stereoconfiguration was determined by comparison with authentic sample, see: Cossy, J.; Cécile, D.; Pardo, D. G.; *Synlett* 1997, 905-906.

10. Deprotection of 6b with Me₃SiI led to epimerization at the 5-position.