Enantioselective Formal [3 + 1 + 1] Cycloaddition Reaction by Ru(II)/Iminium Co-catalysis for Construction of Multisubstituted Pyrrolidines

Mingfeng Li, Rui Chu, Jianghui Chen, Xiang Wu, Yun Zhao, Shunying Liu,* and Wenhao Hu*

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1. General Information and Materials

All $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on Brucker spectrometers in CDCl$_3$. Tetramethylsilane (TMS) served as an internal standard ($\delta = 0$) for $^1$H NMR, and CDCl$_3$ was used as internal standard ($\delta = 77.0$) for $^{13}$C NMR. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). High-resolution mass spectrometry (HRMS) was performed on IonSpec FT-ICR or Waters Micromass Q-TOF micro Synapt High Definition Mass Spectrometer. HPLC analysis was performed on Dalian Elite (UV230+ UV/Vis Detector and P230P High Pressure Pump). Chiralpak IC and IA column was purchased from Daicel Chemical Industries, LTD. Single crystal X-ray diffraction data were recorded on Bruker-AXS SMART APEX II single crystal X-ray diffractometer. The racemic standards used in HPLC studies were prepared according to the general procedure by using racemic (S)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine catalysts. Yields for all compounds were isolated yields for major-5 unless otherwise indicated.

All reactions and manipulations were carried out under nitrogen atmosphere in a flame-dried or oven-dried flask containing magnetic stir bar. Dichloromethane (DCM), 1, 2-dichloroethane (DCE), CHCl$_3$ and toluene was distilled over calcium hydride and tetrahydrofuran (THF) were distilled over sodium. Cinnamaldehydes 1 were prepared from palladium-catalyzed synthesis of cinnamaldehydes from acrolein diethyl acetal and aryl iodides according to the literature method.$^1$ Diarylprolinol silyl ethers 4a-b were prepared according to the literature procedure.$^2$ All commercially available reagents were directly used as received from vendors, unless otherwise stated. Solvents for the column chromatography were distilled before use. 4 Å molecular sieves were dried in a Muffle furnace at 250 °C over 5 hrs.
2. General Procedure for Optimization of Reaction Conditions

**General procedure for the preparation of racemic three-component products:**

A mixture of \([\text{Ru(p-cymene)Cl}_2]_2\) (5 mol %), substituted cinnamaldehydes 1 (0.1 mmol), sodium acetate (20 mol%), \(\text{rac-4b}\) (20 mol %), and 4 Å MS (25 mg) in 0.35 mL of DCM under an nitrogen atmosphere was mixed at 35 °C. The mixture of diazo compounds 3 (0.15 mmol) and anilines 2 (0.15 mmol) in 0.35 mL of DCM was then added over 0.35 h via a syringe pump. After completion of the addition, the reaction mixture was stirred for another 24 h at 35 °C. After the completion of the reaction (monitored by LC-MS, minor 5 was totally converted to major 5), the reaction mixture was filtrated and evaporated *in vacuo* to give the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc/light petroleum ether = 1:50 ~ 1:20) to give the pure product as a white solid.

**General procedure for the preparation of enantioselective three-component products:**

A mixture of \([\text{Ru(p-cymene)Cl}_2]_2\) (5 mol %), substituted cinnamaldehydes 1 (0.5 mmol), sodium acetate (20 mol %), \((S)-\text{4b}\) (20 mol %), and 4 Å MS (100 mg) in 1 mL of DCM under an nitrogen atmosphere was mixed at 35 °C. The mixture of diazo compounds 3 (0.75 mmol) and anilines 2 (0.75 mmol) in 1 mL of DCM was then added over 1 h via a syringe pump. After completion of the addition, the reaction mixture was stirred for another 24 h at 35 °C. After the completion of the reaction (monitored by LC-MS, minor 5 was totally converted to major 5), the reaction mixture was filtrated and evaporated *in vacuo* to give the crude product. The crude product was purified by flash chromatography on silica gel (EtOAc/light petroleum ether = 1:50 ~ 1:20) to give the pure product as a white solid.
**Table S1: Screening of solvents for the asymmetric formal [3 + 1 + 1] cycloaddition reaction of 1a, 2a, and 3a**

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>solvents</th>
<th>$t$ (h)</th>
<th>yield (%) $^{[b]}$</th>
<th>dr $^{[c]}$</th>
<th>ee (%) $^{[d]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>48</td>
<td>53</td>
<td>90:10</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>48</td>
<td>40</td>
<td>85:15</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>CHCl$_3$</td>
<td>48</td>
<td>45</td>
<td>90:10</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>CH$_3$CN</td>
<td>48</td>
<td>37</td>
<td>67:33</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>48</td>
<td>50</td>
<td>70:30</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>toluene</td>
<td>48</td>
<td>35</td>
<td>55:45</td>
<td>85</td>
</tr>
</tbody>
</table>

$^{[a]}$ General reaction conditions: [Ru($p$-cymene)Cl$_2$]$_2$: (S)-4b: NaOAc: 1a: 2a: 3a = 0.05:0.2:0.2:1:1.5:1.5. The mixture of 2a and 3a in solvent was added to a suspension of [Ru($p$-cymene)Cl$_2$]$_2$, (S)-4b, NaOAc, 1a and 4 Å M.S. in solvent over 0.35 h by a syringe pump. $^{[b]}$ Isolated yield of 5a. $^{[c]}$ Determined by LC-MS analysis of the crude mixture. $^{[d]}$ Determined by chiral HPLC analysis. M.S. = molecular sieve.

**Procedure for the conversion of pure minor isomer of 5a to pure major isomer of 5a:**

A mixture of [Ru($p$-cymene)Cl$_2$]$_2$ (5 mol %), minor-5a (0.1 mmol), sodium acetate (20 mol %), (S)-4b (20 mol %), and 4 Å MS (25 mg) in 0.35 mL of DCM under an nitrogen atmosphere was mixed at 35 °C. After 2 h, determined by LC-MS analysis of the crude mixture, minor-5a:major-5a = 1:0.56; After 15 h, determined by LC-MS analysis of the crude mixture, minor-5a:major-5a = 1:1; After 24h, determined by LC-MS analysis of the crude mixture, minor-5a:major-5a = 1:20.
Figure S1. Confirmation for the conversion of pure minor isomer of 5a to pure major isomer of 5a.

NOESY spectra provide information about protons that are 5 Å or less apart in space, not bonds. The NOE signal peak is direct evidence that two protons are within 5 Å from each other. For the intramolecular interaction of minor isomer of 5c, the \( H_{C2}(H^a) \) atom shows NOE signals relative to the \( H_{C4}(H^b) \) atom (Figure S2a), which indicates the \( H_{C2} \) and \( H_{C4} \) atoms are cis-configuration in minor isomer of 5c. However, for the intramolecular interaction of major isomer of 5c, the \( H_{C2} \) atom shows no NOE signals relative to the \( H_{C4} \) atom (Figure S2b), which indicates the \( H_{C2} \) and \( H_{C4} \) atoms are trans-configuration in major isomer of 5c. Meanwhile, it was also determined as \((2R, 4S, 5R)\) by comparing to single crystal X-ray crystallography of the major isomer.
of 5a (see below). Therefore, the results of the 2D NOSEY spectrum reveal that absolute configuration of the minor isomer of 5c was (2S, 4S, 5R).

(a). The arrow indicates Hα (H_{C2}) atom shows NOE signals relative to the Hβ (H_{C1}) atom in 2D-NOSEY NMR spectrum of the minor isomer of 5c.
(b). The arrow indicates Hа (HС2) atom shows no NOE signals relative to the Hb (HС4) atom in 2D-NOSEY NMR spectrum of the major isomer of 5c.

Figure S2. The minor isomer of 5c was determined as (2S, 4S, 5R) by 2D-NOSEY NMR spectrum. All the spectra were obtained in CDCl₃.
Figure S3. The energy of all isomers of 5a was calculated by DFT calculation.

Figure S4. A signal of ion fragment D is observed in the HR-MS spectra of 5a.
Figure S5. Confirmed the generation of iminium cation II from 1 and (S)-4b.

Scheme S1: Proposed a competitive stepwise tandem process mechanism.

Scheme S2: The control experiments
3. Characterization Data of Compounds

\((2R,4S,5R)-1-\text{(4-bromophenyl)}-2\text{-hydroxy-4-phenylpyrrolidin-2-yl)}(\text{phenyl})\text{methanone (5a)}\)

Yield: 65% (137 mg); white solid; >95:5 dr; 98% ee. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.79 \) (d, \(J = 7.7 \text{ Hz}, 2\)H), 7.61 (t, \(J = 7.2 \text{ Hz}, 1\)H), 7.49 – 7.38 (m, 3H), 7.36 – 7.29 (m, 3H), 7.24 (s, 1H), 7.22 – 7.18 (m, 2H), 6.59 (d, \(J = 8.6 \text{ Hz}, 2\)H), 5.86 – 5.78 (m, 1H), 5.52 (d, \(J = 4.4 \text{ Hz}, 1\)H), 3.78 (d, \(J = 9.4 \text{ Hz}, 1\)H), 3.60 – 3.52 (m, 1H), 2.62 – 2.41 (m, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 201.53, 142.63, 142.56, 134.44, 134.38, 132.12, 129.19, 129.01, 128.70, 127.56, 127.06, 115.22, 110.67, 83.49, 70.58, 48.24, 44.61.

HRMS(ESI): Calcd. for C\(_{23}\)H\(_{20}\)NO\(_2\)NaBr [M+Na\(^+\): 444.0575, Found: 444.0571.

HPLC (Chiral IA, \(\lambda = 254 \text{ nm}, \) hexane/2-propanol = 9/1, Flow rate =1 mL/min), \(t_{\text{major}}\) = 23.31 min, \(t_{\text{minor}}\) = 19.83 min.

\((2R,4S,5R)-1-\text{(4-bromophenyl)}-2\text{-hydroxy-4-(4-methoxyphenyl)pyrrolidin-2-yl)(phenyl)methanone (5b)}\)

Yield: 48% (108 mg); white solid; >95:5 dr; 91% ee. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.79 \) (d, \(J = 7.6 \text{ Hz}, 2\)H), 7.61 (t, \(J = 7.4 \text{ Hz}, 1\)H), 7.43 (t, \(J = 7.7 \text{ Hz}, 2\)H), 7.24 (s, 1H), 7.12 (d, \(J = 8.6 \text{ Hz}, 2\)H), 6.86 (d, \(J = 8.6 \text{ Hz}, 2\)H), 6.58 (d, \(J = 8.9 \text{ Hz}, 2\)H), 5.78 (s, 1H), 5.47 (d, \(J = 4.6 \text{ Hz}, 1\)H), 3.81 (s, 3H), 3.79 – 3.72 (m, 1H), 3.59 – 3.48 (m, 1H), 2.58 – 2.40 (m, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 201.67, 158.93, 142.61, 134.58, 134.42, 132.11, 129.02, 128.72, 128.13, 115.19, 114.49, 110.61, 83.42, 70.77, 55.35, 47.57, 44.76.

HRMS(ESI): Calcd. for C\(_{24}\)H\(_{22}\)NO\(_3\)NaBr [M+Na\(^+\): 474.0681, Found: 474.0681.

HPLC (Chiral IA, \(\lambda = 220 \text{ nm}, \) hexane/2-propanol = 10/1, Flow rate =1 mL/min), \(t_{\text{major}}\) = 14.08 min, \(t_{\text{minor}}\) = 11.97 min.

\((2R,4S,5R)-1-\text{(4-bromophenyl)}-4\text{-}(4\text{-chlorophenyl)}-2\text{-hydroxypyrrolidin-2-yl)(phenyl)methanone}\)
enyl)methanone (5c)

Yield: 55% (125 mg); white solid; >95:5 dr; 94% ee. \[^1^H\text{NMR}\] (400 MHz, CDCl\(_3\)) \(\delta\) 7.79 (d, \(J = 7.6\) Hz, 2H), 7.63 (t, \(J = 7.3\) Hz, 1H), 7.52 – 7.34 (m, 3H), 7.31 (d, \(J = 8.3\) Hz, 2H), 7.24 (s, 1H), 7.14 (d, \(J = 8.3\) Hz, 2H), 6.58 (d, \(J = 8.7\) Hz, 2H), 5.79 (s, 1H), 5.48 (d, \(J = 4.4\) Hz, 1H), 3.81 (br, \(J = 6.8\) Hz, 1H), 3.60 – 3.43 (m, 1H), 2.54 – 2.38 (m, 2H).

\[^{13}\text{C\ NMR}\] (100 MHz, CDCl\(_3\)) \(\delta\) 201.26, 142.43, 141.16, 134.62, 134.29, 133.38, 132.16, 129.35, 129.14, 128.64, 128.42, 115.25, 110.87, 83.36, 70.36, 47.60, 44.57.


HPLC (Chiral IA, \(\lambda = 220\) nm, hexane/2-propanol = 10/1, Flow rate = 1 mL/min), t\(_{\text{major}} = 33.23\) min, t\(_{\text{minor}} = 27.42\) min.

\((2R,4S,5R)\)-1-(4-bromophenyl)-2-hydroxy-4-(4-nitrophenyl)pyrrolidin-2-yl)(phenyl)methanone (5d)

Yield: 58% (135 mg); white solid; >95:5 dr; 95% ee. \[^1^H\text{NMR}\] (400 MHz, CDCl\(_3\)) \(\delta\) 8.20 (d, \(J = 8.5\) Hz, 2H), 7.80 (d, \(J = 7.5\) Hz, 2H), 7.65 (t, \(J = 7.4\) Hz, 1H), 7.45 (t, \(J = 7.8\) Hz, 2H), 7.38 (d, \(J = 8.6\) Hz, 2H), 7.30 – 7.24 (m, 2H), 6.61 (d, \(J = 8.8\) Hz, 2H), 5.84 (s, 1H), 5.54 (d, \(J = 4.3\) Hz, 1H), 3.90 (s, 1H), 3.75 – 3.57 (m, 1H), 2.64 – 2.39 (m, 2H).

\[^{13}\text{C\ NMR}\] (100 MHz, CDCl\(_3\)) \(\delta\) 200.74, 150.08, 147.34, 142.17, 134.91, 134.07, 132.25, 129.29, 128.56, 128.03, 124.50, 115.33, 111.20, 83.26, 69.83, 47.80, 44.35.

HRMS(ESI): Calcd. for C\(_{23}\)H\(_{19}\)NO\(_2\)NaBr [M+Na]\(^+\): 489.0426, Found: 489.0417.

HPLC (Chiral IA, \(\lambda = 220\) nm, hexane/2-propanol = 10/1, Flow rate = 1 mL/min), t\(_{\text{major}} = 24.82\) min, t\(_{\text{minor}} = 41.71\) min.

\((2R,4S,5R)\)-1-(4-bromophenyl)-2-hydroxy-4-(2-nitrophenyl)pyrrolidin-2-yl)(phenyl)methanone (5e)

Yield: 60% (140 mg); yellow oil; >95:5 dr; 89% ee. \[^1^H\text{NMR}\] (400 MHz, CDCl\(_3\)) \(\delta\) 7.82 – 7.79 (m, 2H), 7.64 (dd, \(J = 13.6, 7.4\) Hz, 2H), 7.43 – 7.30 (m, 3H), 7.30 – 7.12 (m, 2H), 7.07 – 7.01 (m, 3H), 6.90 (d, \(J = 8.5\) Hz, 2H), 5.82 (s, 1H), 5.54 (d, \(J = 4.3\) Hz, 1H), 3.94 (s, 1H), 3.76 – 3.57 (m, 1H), 2.61 – 2.33 (m, 2H).
Hz, 2H), 7.54 (d, J = 7.3 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.31 – 7.25 (m, 3H), 6.64 (d, J = 8.9 Hz, 2H), 5.82 (s, 1H), 5.59 (d, J = 3.4 Hz, 1H), 4.17 – 4.08 (m, 1H), 3.94 (brs, 1H), 2.70 – 2.45 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.53, 149.33, 142.15, 137.58, 134.77, 134.03, 133.91, 132.22, 129.19, 128.51, 128.38, 127.81, 124.50, 115.44, 111.10, 83.09, 69.42, 44.56, 41.80.


HPLC (Chiral IA, $\lambda$= 254 nm, hexane/2-propanol = 10/1, Flow rate =1 mL/min), $t_{\text{major}}$ = 39.51 min, $t_{\text{minor}}$ = 25.04 min.

((2R,4R,5R)-1-(4-bromophenyl)-4-(furan-2-yl)-2-hydroxyprrolidin-2-yl)(phenyl)methanone (5f)

Yield: 59% (121 mg); yellow oil; 86:14 dr; 82% ee. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.15 – 7.91 (m, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.59 – 7.39 (m, 3H), 7.25 – 7.19 (m, 2H), 6.61 – 6.51 (m, 2H), 6.41 – 6.29 (m, 1H), 6.07 (d, J = 3.2 Hz, 1H), 5.75 – 5.59 (m, 2H), 3.79 – 3.67 (m, 1H), 3.64 – 3.52 (m, 1H), 2.78 – 2.57 (m, 1H), 2.44 – 2.24 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 201.17, 153.82, 142.62, 142.23, 134.54, 132.05, 131.92, 129.07, 128.71, 128.51, 115.02, 110.53, 106.70, 83.12, 67.44, 41.43, 40.75.


HPLC (Chiral IA, $\lambda$= 254 nm, hexane/2-propanol = 5/1, Flow rate =1 mL/min), $t_{\text{major}}$ = 21.83 min, $t_{\text{minor}}$ = 17.39 min.

((2R,4S,5R)-2-hydroxy-1,4-diphenylpyrrolidin-2-yl)(phenyl)methanone (5g)

Yield: 65% (111 mg); yellow oil; >95:5 dr; 96% ee. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 – 7.76 (m, 2H), 7.59 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.8 Hz, 2H), 7.33 – 7.30 (m, 2H), 7.19 – 7.14 (m, 3H), 6.81 – 6.67 (m, 4H), 5.88 (s, 1H), 5.57 (d, J = 4.7 Hz, 1H), 3.88 – 3.76 (m, 1H), 3.62 – 3.51 (m, 1H), 2.63 – 2.60 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 201.96, 143.43, 142.83, 134.55, 134.27, 129.41, 129.14, 128.95, 128.71, 127.46, 127.16, 118.57, 113.49, 83.37, 70.51, 48.23, 44.73.
HRMS(ESI): Calcd. for C\textsubscript{23} H\textsubscript{21} NO\textsubscript{2}Na [M+Na]\textsuperscript{+}: 366.1470, Found: 366.1458.

HPLC (Chiral IA, λ = 254 nm, hexane/2-propanol = 10/1, Flow rate =1 mL/min), t\textsubscript{major} = 17.25 min, t\textsubscript{minor} = 14.75 min.

\((2R,4S,5R)-1-(3,5\text{-dichlorophenyl})-2\text{-hydroxy}-4\text{-phenylpyrrolidin}-2\text{-yl})(\text{phenyl})\text{meth}anone (5h)

Yield: 53% (109 mg); yellow oil; 86:14 dr; 80% ee. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.82 (d, \(J = 7.6\) Hz, 2H), 7.63 (t, \(J = 7.3\) Hz, 1H), 7.44 (t, \(J = 7.6\) Hz, 2H), 7.38 – 7.29 (m, 3H), 7.18 (d, \(J = 6.8\) Hz, 2H), 6.75 (s, 1H), 6.60 (s, 2H), 5.83 – 5.69 (m, 1H), 5.48 (d, \(J = 4.0\) Hz, 1H), 3.76 (d, \(J = 9.5\) Hz, 1H), 3.61 – 3.49 (m, 1H), 2.61 – 2.34 (m, 2H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 200.74, 145.36, 142.45, 135.65, 134.67, 134.07, 129.28, 129.11, 128.79, 127.69, 126.93, 118.52, 112.05, 83.54, 70.56, 48.07, 44.15.

HRMS(ESI): Calcd. for C\textsubscript{23} H\textsubscript{19} NO\textsubscript{2}NaCl \[M+Na\] \(+\): 434. 0691, Found: 434.0700.

HPLC (Chiral IA, λ = 220 nm, hexane/2-propanol = 5/1, Flow rate =1 mL/min), t\textsubscript{major} = 11.32 min, t\textsubscript{minor} = 13.29 min.

\((2R,4S,5R)-1-(4\text{-chlorophenyl})-2\text{-hydroxy}-4\text{-phenylpyrrolidin-2-yl})(\text{phenyl})\text{meth}\anone (5i)

Yield: 42% (79 mg); yellow oil; >95:5 dr; 96% ee. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.83 – 7.76 (m, 2H), 7.61 (t, \(J = 7.4\) Hz, 1H), 7.53 – 7.48 (m, 1H), 7.42 (t, \(J = 7.8\) Hz, 2H), 7.35 – 7.30 (m, 2H), 7.23 – 7.19 (m, 2H), 7.12 (d, \(J = 9.0\) Hz, 2H), 6.69 – 6.58 (m, 2H), 5.88 – 5.78 (m, 1H), 5.53 (d, \(J = 4.6\) Hz, 1H), 3.80 (d, \(J = 9.2\) Hz, 1H), 3.60 – 3.53 (m, 1H), 2.59 – 2.43 (m, 2H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 201.61, 142.63, 142.13, 134.45, 134.38, 129.24, 129.19, 129.02, 128.71, 127.57, 127.08, 123.45, 114.71, 83.54, 70.64, 48.25, 44.63.

HRMS(ESI): Calcd. for C\textsubscript{23} H\textsubscript{20} NO\textsubscript{2}NaCl \[M+Na\] \(+\): 400.1080, Found: 400.1061.

HPLC (Chiral IA, λ = 220 nm, hexane/2-propanol = 5/1, Flow rate =1 mL/min), t\textsubscript{major} = 13.03 min, t\textsubscript{minor} = 10.94 min.

\((2R,4S,5R)-1-(3\text{-chlorophenyl})-2\text{-hydroxy}-4\text{-phenylpyrrolidin-2-yl})(\text{phenyl})\text{meth}\anone
anone (5j)

Yield: 60% (113 mg); yellow oil; >95:5 dr; 93% ee. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.81 (dd, \(J = 8.4, 1.2\) Hz, 2H), 7.64 – 7.59 (m, 1H), 7.45 – 7.39 (m, 2H), 7.36 – 7.29 (m, 3H), 7.22 – 7.17 (m, 2H), 7.06 (t, \(J = 8.1\) Hz, 1H), 6.79 – 6.70 (m, 2H), 6.54 (dd, \(J = 8.3, 1.7\) Hz, 1H), 5.82 (s, 1H), 5.53 (d, \(J = 4.4\) Hz, 1H), 3.78 (brs, 1H), 3.62 – 3.51 (m, 1H), 2.62 – 2.43 (m, 2H).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.76 (d, \(J = 8.8\) Hz, 2H), 7.32 (d, \(J = 7.3\) Hz, 3H), 7.22 (dd, \(J = 10.9, 8.5\) Hz, 4H), 6.86 (d, \(J = 8.8\) Hz, 2H), 6.58 (d, \(J = 8.8\) Hz, 2H), 5.85 – 5.74 (m, 1H), 5.47 (d, \(J = 4.7\) Hz, 1H), 3.85 (s, 3H), 3.82 – 3.76 (m, 1H), 3.61 – 3.49 (m, 1H), 2.56 – 2.43 (m, 2H).

\(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 199.84, 164.62, 142.72, 132.07, 131.21, 129.16, 127.51, 127.43, 127.13, 115.23, 114.22, 110.54, 83.46, 70.35, 55.60, 48.41, 44.66.

HRMS(ESI): Calcd. for C\(_{23}\) H\(_{20}\) NO\(_2\)Cl [M+Na]\(^+\): 400.1080, Found: 400.1060.

HPLC (Chiral IA, \(\lambda = 220\) nm, hexane/2-propanol = 20/1, Flow rate =1 mL/min), \(t_{\text{major}} = 21.80\) min, \(t_{\text{minor}} = 20.33\) min.

\((2R,4S,5R)-1-(4-bromophenyl)-2-hydroxy-4-phenylpyrrolidin-2-yl)(4-methoxyp henyl)methanone (5k)

Yield: 65% (147 mg); white solid; 89:11 dr; 91% ee. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.76 (d, \(J = 8.8\) Hz, 2H), 7.32 (d, \(J = 7.3\) Hz, 3H), 7.22 (dd, \(J = 10.9, 8.5\) Hz, 4H), 6.86 (d, \(J = 8.8\) Hz, 2H), 6.58 (d, \(J = 8.8\) Hz, 2H), 5.85 – 5.74 (m, 1H), 5.47 (d, \(J = 4.7\) Hz, 1H), 3.85 (s, 3H), 3.82 – 3.76 (m, 1H), 3.61 – 3.49 (m, 1H), 2.56 – 2.43 (m, 2H).

\(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 199.84, 164.62, 142.72, 132.07, 131.21, 129.16, 127.51, 127.43, 127.13, 115.23, 114.22, 110.54, 83.46, 70.35, 55.60, 48.41, 44.66.

HRMS(ESI): Calcd. for C\(_{24}\) H\(_{22}\) NO\(_3\)NaBr [M+Na]\(^+\): 474.0681, Found: 474.0685.

HPLC (Chiral IA, \(\lambda = 220\) nm, hexane/2-propanol = 20/1, Flow rate =1 mL/min), \(t_{\text{major}} = 28.13\) min, \(t_{\text{minor}} = 14.56\) min.

\((2R,4S,5R)-1-(4-bromophenyl)-2-hydroxy-4-phenylpyrrolidin-2-yl)(3,4-dichloro phenyl)methanone (5l)

Yield: 45% (110 mg); yellow oil; >95:5 dr; 84% ee. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.87 (d, \(J = 1.8\) Hz, 1H), 7.68 – 7.60 (m, 2H), 7.55 (d, \(J = 8.4\) Hz, 1H), 7.47 – 7.42 (m, 1H), 7.44 – 7.38 (m, 1H), 7.29 – 7.19 (m, 9H), 6.52 (d, \(J = 1.8\) Hz, 1H), 6.49 (d, \(J = 8.4\) Hz, 1H), 4.70 – 4.55 (m, 1H), 3.85 – 3.70 (m, 2H), 3.51 – 3.35 (m, 2H), 2.72 – 2.58 (m, 2H).

\(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 198.78, 142.62, 131.21, 129.16, 127.51, 127.43, 127.13, 115.23, 114.22, 110.54, 83.46, 70.35, 55.60, 48.41, 44.66.
3H), 7.34 (s, 1H), 7.32 – 7.28 (m, 2H), 6.63 (d, \(J = 8.9\) Hz, 2H), 5.89 – 5.82 (m, 1H), 5.47 (d, \(J = 5.6\) Hz, 1H), 3.69 – 3.59 (m, 1H), 2.66 – 2.54 (m, 2H), 2.34 – 2.21 (m, 1H).\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 199.47, 142.45, 141.46, 139.19, 133.85, 133.80, 132.21, 131.05, 130.77, 129.37, 127.96, 127.54, 127.18, 115.07, 110.97, 83.84, 71.05, 48.41, 44.51.

HRMS(ESI): Calcd. for C\(_{23}\)H\(_{29}\)NO\(_2\)Cl\(_2\)Br \([\text{M}+\text{Na}]^+\): 489.9976, Found: 489.9958.

HPLC (Chiral IA, \(\lambda = 254\) nm, hexane/2-propanol = 10/1, Flow rate =1 mL/min), \(t_{\text{major}} = 14.96\) min, \(t_{\text{minor}} = 19.34\) min.

(3-bromophenyl)((2\(R\),4\(S\),5\(R\))-1-(4-bromophenyl)-2-hydroxy-4-phenylpyrrolidin-2-yl)methanone (5m)

Yield: 51\% (127 mg); white solid; \(>95:5\) dr; 91\% ee.\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.87 – 7.83 (m, 1H), 7.72 (d, \(J = 7.9\) Hz, 1H), 7.66 (d, \(J = 7.9\) Hz, 1H), 7.37 – 7.31 (m, 3H), 7.29 – 7.27 (m, 2H), 7.25 (s, 1H), 7.23 – 7.19 (m, 2H), 6.56 (d, \(J = 9.0\) Hz, 2H), 5.87 – 5.71 (m, 1H), 5.42 (d, \(J = 5.2\) Hz, 1H), 3.59 – 3.51 (m, 1H), 2.65 – 2.38 (m, 2H), 2.27 – 2.15 (m, 1H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 200.28, 142.44, 141.90, 137.20, 136.04, 132.18, 131.85, 130.49, 129.31, 127.83, 127.14, 127.09, 123.35, 115.14, 110.87, 83.68, 70.95, 48.33, 44.54.

HRMS(ESI): Calcd. for C\(_{23}\)H\(_{19}\)NO\(_2\)NaBr\(_2\) \([\text{M}+\text{Na}]^+\): 521.9680, Found: 521.9701.

HPLC (Chiral IC, \(\lambda = 220\) nm, hexane/2-propanol = 10/1, Flow rate =0.8 mL/min), \(t_{\text{major}} = 14.58\) min, \(t_{\text{minor}} = 13.60\) min.

(2-bromophenyl)((2\(R\),4\(S\),5\(R\))-1-(4-bromophenyl)-2-hydroxy-4-phenylpyrrolidin-2-yl)methanone (5n)

Yield: 40\% (100 mg); \(>95:5\) dr; white solid; 95\% ee.\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.63 (dd, \(J = 7.6, 1.5\) Hz, 1H), 7.36 – 7.33 (m, 2H), 7.32 – 7.28 (m, 3H), 7.24 – 7.19 (m, 3H), 7.12 – 7.07 (m, 2H), 6.77 – 6.68 (m, 2H), 5.71 (s, 1H), 5.38 (d, \(J = 5.1\) Hz, 1H), 3.72 – 3.62 (m, 1H), 3.21 (s, 1H), 2.55 – 2.40 (m, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 202.97, 142.79, 141.84, 137.93, 134.68, 132.88, 132.16, 129.61, 128.94, 127.37, 126.88, 120.39, 115.22, 110.93, 110.93, 110.93.

---

s15
HRMS(ESI): Calcd. for C_{23}H_{19}NO_{2}Br_{2} [M+Na]$^{+}$: 521.9680, Found: 521.9680.
HPLC (Chiral IA, $\lambda$ = 254 nm, hexane/2-propanol = 10/1, Flow rate =1 mL/min), $t_{\text{major}}$ = 15.26 min, $t_{\text{minor}}$ = 21.51 min.

(2'R/S,4'S,5'S)-1-benzyl-1'-(4-bromophenyl)-2'-hydroxy-4'-phenylspiro[indoline-3,2'-pyrrolidin]-2-one (5o)

Yield: 58% (152 mg); yellow oil;
67:33 dr; 94%/94% ee. The mixture of 5o. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57
- 7.54 (m, 0.5H), 7.42 – 7.34 (m, 2.5H),
7.30 – 7.27 (m, 2H), 7.19 – 7.15 (m, 4H),
7.15 – 7.12 (m, 2H), 7.09 – 7.06 (m, 2.5H), 7.04 – 7.01 (m, 2.5H), 6.98 – 6.91 (m, 2H), 6.85 – 6.82 (m, 2.5H), 6.77 – 6.74 (m, 0.5H), 6.73 – 6.68 (m, 2H), 6.56 – 6.53 (m, 0.5H), 6.49 (d, $J$ = 7.8 Hz, 1H),
6.32 – 6.26 (m, 2.5H), 5.88 (major, d, $J$ = 5.2 Hz, 1H), 5.79 (minor, s, 0.5H), 5.06 (minor, d, $J$ = 15.3 Hz, 0.5H), 5.00 (minor, s, 0.5H), 4.85 – 4.60 (major, m, 1H), 4.48 (major, s, 2H), 4.38 – 4.31 (minor, m, 0.5H), 4.28 (minor, dd, $J$ = 13.8, 5.8 Hz, 0.5H),
4.17 (major, dd, $J$ = 14.3, 5.6 Hz, 1H), 3.41 – 3.27 (major, m, 1H), 2.95 – 2.85 (minor, m, 0.5H), 2.44 (minor, dd, $J$ = 12.8, 5.9 Hz, 0.5H), 2.15 (major, dd, $J$ = 12.6, 5.6 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.27 (minor), 174.98 (major), 142.72, 142.31,
142.15, 140.96, 135.23, 134.42, 133.92, 132.59, 131.87, 131.84, 129.37, 128.97,
128.84, 128.67, 128.35, 128.32, 128.20, 127.97, 127.87, 127.73, 127.47, 127.44,
127.12, 124.38, 123.40, 123.13, 122.87, 122.84, 119.77, 115.76, 115.37, 111.28,
111.08, 110.51, 109.73, 109.64, 85.27 (major), 84.28 (minor), 74.72 (minor), 74.64 (major), 54.63 (major), 53.95 (minor), 44.53 (minor), 43.88 (major), 38.61 (minor),
36.22 (major).

HPLC (Chiral IA, $\lambda$ = 254 nm, hexane/2-propanol = 10/1, Flow rate =1 mL/min), $t_{\text{major}}$ = 15.26 min, $t_{\text{minor}}$ = 21.51 min.

2-((4-bromophenyl)amino)-1-phenylethan-1-one (6)
White solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (d, $J = 7.7$ Hz, 2H), 7.76 – 7.60 (m, 1H), 7.59 – 7.40 (m, 2H), 7.39 – 7.12 (m, 2H), 6.58 (d, $J = 8.1$ Hz, 2H), 4.96 (brs, 1H), 4.56 (d, $J = 3.6$ Hz, 2H).

References


4. X-ray Diffraction Parameters and Data

Single Crystal X-ray Diffraction Data of the major isomer of 5a (CCDC NO.: 1478560)

![Chemical structure of 5a]

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S18
5. NMR Spectra of Compounds

(2R,4S,5R)-5a

(2R,4S,5R)-5a
(2R,4S,5R)-5m

(2R,4S,5R)-5m
6. HPLC spectra of compounds

**Condition:** hexane/2-propanol = 9/1  
Flow rate = 1.0 mL/min  
\( \lambda = 254 \text{ nm} \)

Chiral IA
**Condition**: hexane/2-propanol = 10/1
Flow rate = 1.0 mL/min
$\lambda = 220$nm
Chiral IA
**Condition:** hexane/2-propanol = 10/1
Flow rate = 1.0 mL/min
λ = 220nm
Chiral IA
**Condition:** hexane/2-propanol = 10/1
Flow rate = 1.0 mL/min
$\lambda = 220$nm
Chiral IA
**Condition:** hexane/2-propanol = 10/1
Flow rate = 1.0 mL/min
\( \lambda = 254 \text{nm} \)
Chiral IA

![Graph of racemic 5e](image1)

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![Graph of (2R,4S,5R)-5e](image2)

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S39
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Chiral IA

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Chiral IA

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### Table 1

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### Table 2

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**Sum**  
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*5g*
**Condition:** hexane/2-propanol = 15/1
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\( \lambda = 220 \) nm
Chiral IA
**Condition:** hexane/2-propanol = 5/1

Flow rate = 1.0 mL/min

$\lambda = 220$ nm

Chiral IA
**Condition:** hexane/2-propanol = 20/1

Flow rate = 1.0 mL/min

$\lambda = 220\text{nm}$

Chiral IA
**Condition:** hexane/2-propanol = 20/1
Flow rate = 1.0 mL/min
\( \lambda = 220 \text{nm} \)
Chiral IA
**Condition:** hexane/2-propanol = 10/1  
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Chiral IA
**Condition**: hexane/2-propanol = 10/1
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Chiral IC
Condition: hexane/2-propanol = 10/1
Flow rate = 1.0 mL/min
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Chiral IA
**Condition:** hexane/2-propanol = 10/1  
Flow rate = 1.0 mL/min  
\( \lambda = 254\text{nm} \)  
Chiral IA
**Condition:** hexane/2-propanol = 10/1
Flow rate = 1.0 mL/min
\( \lambda = 254 \text{nm} \)
Chiral IA

![Diagram](image1)

**Peak Name** | **Ret. Time (min)** | **Area (mV sec)** | **Rel. Area (%)**
--- | --- | --- | ---
1 Unknown | 26.16250 | 3784.94 | 49.7515
2 Unknown | 35.33683 | 3616.83 | 50.2084

**Total Area:** 7601.57

![Diagram](image2)

**Peak Name** | **Ret. Time (min)** | **Area (mV sec)** | **Rel. Area (%)**
--- | --- | --- | ---
1 Unknown | 26.30200 | 335.79 | 2.8624
2 Unknown | 35.33683 | 10685.84 | 97.0076

**Total Area:** 11221.83

S50
7. Computation Data

Computational methods
The density functional theory (DFT) calculations were carried out by us using the Gaussian 09 program package.\[1] The geometrical structures of intermediates were optimized using the M06 functional combined with the 6-31+G* basis. \[2-3] The solvent effect of CH₂Cl₂ was considered by performing the single point calculations based on the gaseous structures using the polarizable continuum model (PCM). \[4]

References
major-5a
$(2R,4S,5R)$

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