Rh-Catalyzed reductive Mannich-type reaction and its application towards the synthesis of (±)-ezetimibe

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Experimental details, characterization of the compounds, X-ray crystallographic analysis of anti-3Ai, and ¹H, ¹³C NMR spectra
General information:

$^1$H NMR and $^{13}$C NMR spectra were recorded on JNM-GX400 spectrometers and ECZS-400 spectrometers. $^{19}$F NMR spectra were recorded on Hitachi FT-NMR R-90H spectrometers. Chemical shifts of $^1$H NMR and $^{13}$C NMR are reported in ppm from tetramethylsilane (TMS) as an internal standard. Chemical shifts of $^{19}$F NMR are reported in ppm from benzotrifluoride (BTF) as an internal standard. All data are reported with the chemical shift(s), relative integration value, multiplicity ($s$ = singlet, $d$ = doublet, $t$ = triplet, $q$ = quartet, $br$ = broad, $m$ = multiplet), and coupling constants (Hz). Mass spectra were obtained on JEOL JMS-700T spectrometers. IR spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. Melting points were measured on a Yanagimoto micro melting point apparatus MP-S3. Analytical gas–liquid chromatography (GLC) was carried out on a Hitachi G-3500 gas chromatograph (column; TC-5 0.25 mm × 15 m, carrier; He). Peak areas were calculated on a Hitachi D-2500 Chromato-Integrator. $^1$H and $^{13}$C NMR spectra and characterization data for the compounds syn-anti-3Aa, syn-3Ad and anti-3Ah are found in reference [1].

Experimental section:

Materials

Tetrahydrofuran (THF) was purchased from Kanto Chemical Co. Inc. (Tokyo, Japan) in the dehydrated form. $N,N$-Dimethylformamide (DMF) and dichloromethane (CH$_2$Cl$_2$) were distilled over CaH$_2$ and phosphorus pentoxide just before use, respectively. All imines were prepared from corresponding aldehydes and amines. Methyl acrylate was distilled just before use. Other commercially available reagents were used without further purification. All experiments were carried out under an argon atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted.

Typical procedure for the synthesis of syn-1-(p-methoxyphenyl)-3-methyl-4-phenylazetidin-2-one (syn-3Aa)

In a manner closely related to a procedure in reference [1]; (E)-N-benzylidene-4-methoxybenzenamine (1A, 0.5 mmol) and methyl acrylate (2a, 1 mmol) was added to a solution of [RhCl(cod)$_2$] (2 mol %) in DMF (1.25 mL) at 0 °C. Then, 1.0 M Et$_2$Zn in hexane (1.5 mmol, 1.5 mL) was gradually added to the mixture at room temperature, and the mixture was stirred
at same temperature for 24 h. The mixture was quenched with sat. NH₄Cl and extracted with AcOEt. The AcOEt layer was washed with sat. NaCl and dried over MgSO₄. The solvent was removed in vacuo, and the residue was purified by column chromatography (AcOEt/hexane = 2:8) and the diastereomers were obtained in 69% (92.4 mg; syn form) and 9% yield (11.5 mg; anti form), respectively. The stereochemistry of products were determined by NOE between the CH₃ and C₆H₅ groups on azetidin-2-one ring and coupling constant between each protons of C3 and C4 (syn form: J = 5.0–6.0 Hz, anti form: J = 2.0–3.0 Hz) [2].

### Typical procedure for the synthesis of anti-3-(3-hydroxypropyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (anti-3Bh)

To a solution of [RhCl(cod)]₂ (2 mol %) and N-((4-(benzyloxy)benzylidene)-4-fluoroaniline (1B, 0.5 mmol) in THF (1.25 mL) at room temperature was added BF₃·Et₂O (0.6 mmol), and then it stirred for 30 min at the same temperature. Subsequently, 5,6-dihydro-2H-pyran-2-one (2h, 0.6 mmol) was added to the suspension mixture, and then 1.0 M Et₂Zn in hexane (1.5 mmol, 1.5 mL) was gradually added to the mixture and stirred for 24 h. The mixture was quenched with sat. NH₄Cl and extracted with AcOEt. The AcOEt layer was washed with sat. NaCl and dried over MgSO₄. The solvent was removed in vacuo, and the residue was purified by column chromatography (AcOEt/hexane = 4:6) and the diastereomer was obtained in 46% (93.3 mg) [2].

### Synthesis of 4-(4-(benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-hydroxypropyl)azetidin-2-one (3Bj)

To a solution of [RhCl(cod)]₂ (2 mol %) and N-((4-(benzyloxy)benzylidene)-4-fluoroaniline (1B, 0.5 mmol) in THF (1.25 mL) at room temperature was added BF₃·Et₂O (0.6 mmol) was added to the mixture, and then it stirred for 30 min at the same temperature. Subsequently, 6-(4-fluorophenyl)-5,6-dihydro-2H-pyran-2-one (2j, 0.6 mmol) was added to the suspension
mixture, and then 1.0 M Et₂Zn in hexane (1.5 mmol, 1.5 mL) was gradually added to the mixture and stirred for 24 h. The mixture was quenched with sat. NH₄Cl and extracted with AcOEt. The AcOEt layer was washed with sat. NaCl and dried over MgSO₄. The solvent was removed in vacuo, and the residue was purified by column chromatography (AcOEt/hexane = 5:5) to give 3Bj in 58% (144.9 mg).

**Synthesis of (±)-ezetimibe**

To a suspension of 10% Pd/C (5.5 mol %) in 1:1 AcOEt/CH₃OH (10 mL) was added 3Bj (0.2 mmol), and then it was placed under H₂ (1 atm) for 24 h. Then the mixture was filtered, and the solvent was removed in vacuo. The residue was purified by column chromatography (AcOEt/hexane = 5:5) to give (±)-ezetimibe in 80% (65.5 mg).

**Spectroscopic Data:**

**3-Benzyl-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (3Ab)**

The title product (3Ab) was purified by column chromatography (AcOEt/hexane = 2:8) and only the syn diastereomer was obtained in 66% yield (113.5 mg).

*syn-3Ab:* A colorless solid; M.p. 140.0–140.5 °C; ¹H NMR (CDCl₃) δ: 2.46 (1H, dd, J = 15.2, 10.0 Hz), 2.98 (1H, dd, J = 15.2, 5.2 Hz), 3.73 (3H, s), 3.90 (1H, dt, J = 15.2, 5.2 Hz), 5.15 (1H, d, J = 5.2 Hz), 6.74–6.80 (4H, m), 7.10–7.18 (4H, m), 7.22–7.26 (3H, m), 7.30–7.35 (3H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 31.1, 55.5, 55.7, 58.7, 114.4, 118.5, 126.2, 127.6, 128.3, 128.5, 128.6, 128.7, 131.2, 134.8, 138.4, 156.0, 166.7; MS m/z: 343 (M⁺); HRMS Calcd. for C₂₃H₂₁NO₂: 343.157 (M⁺), Found: 343.157; IR (KBr) cm⁻¹: 1722.

**1-(4-Methoxyphenyl)-3,3-dimethyl-4-phenylazetidin-2-one (3Ae)**

The title product (3Ae) was purified by column chromatography (AcOEt/hexane = 2:8) and was obtained in 98% yield (137.2 mg).

*3Ae:* A colorless solid; M.p. 146.5–147.0 °C; ¹H NMR (CDCl₃) δ: 0.83 (3H, s), 1.51 (3H, s), 3.14 (3H, s), 4.76 (1H, s), 6.77–6.81 (2H, m), 7.17–7.20 (2H, m), 7.23–7.36 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 18.1, 22.9, 55.5, 55.6,
66.7, 114.4, 118.6, 126.7, 128.1, 128.7, 131.6, 135.8, 155.9, 171.0; MS m/z: 281 (M'); HRMS Calcd. for C_{18}H_{19}NO_{2}: 281.142 (M'), Found: 281.142; IR (KBr) cm\(^{-1}\): 1731.

3-(But-1-enyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (3Ag)

The title product (3Ag) was purified by column chromatography (AcOEt/hexane = 2:8) and was obtained in 59% yield (90.0 mg) as anti product of (E/Z)-mixture.

(E/Z)-anti-3Ag: A colorless viscous oil; \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 0.93 (0.3H, t, \(J = 7.2\) Hz), 1.01 (3H, t, \(J = 7.2\) Hz), 1.92–2.04 (0.2H, m), 2.06–2.13 (2H, m), 3.64–3.67 (1H, m), 3.73 (1.1H, m), 3.93–3.96 (0.1H, m), 4.67 (0.1H, d, \(J = 2.8\) Hz), 4.70 (1H, d, \(J = 2.4\) Hz), 5.57–5.66 (1.1H, m), 5.70–5.84 (1.1H, m), 6.75–6.79 (2.2H, m), 7.20–7.25 (2.2H, m), 7.29–7.38 (5.5H, m); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 13.3, 14.3, 21.5, 22.7, 25.7, 55.1, 59.3, 62.0, 62.2, 63.6, 114.4, 118.38, 118.43, 121.3, 121.4, 125.9, 126.0, 128.5, 129.2, 131.4, 137.8, 138.1, 138.2, 156.1, 165.8; MS m/z: 307 (M'); HRMS Calcd. for C_{20}H_{21}NO_{2}: 307.157 (M'), Found: 307.157.

3-(4-Methoxyphenylamino)-N,N,2-trimethyl-3-phenylpropanamide (4Ai)

The title product (4Ai) was purified by column chromatography (AcOEt/hexane = 4:6) and each diastereomers were obtained in 5% (7.8 mg; syn form) and 22% yield (34.9 mg; anti form), respectively.

syn-4Ai: A colorless solid; M.p. 180.0–182.0; \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 1.34 (3H, d, \(J = 6.8\) Hz), 2.37 (3H, s), 2.78 (3H, s), 3.20–3.26 (1H, m), 3.66 (3H, s). 4.42 (1H, d, \(J = 4.0\) Hz), 5.65 (1H, br), 6.41–6.45 (2H, m), 6.62–7.66 (2H, m), 7.17–7.22 (1H, m), 7.24–7.30 (4H, m); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 16.9, 35.5, 37.1, 41.1, 55.9, 61.9, 113.9, 114.9, 126.5, 127.3, 128.6, 141.8, 143.2, 151.3, 174.6; MS m/z: 312 (M'); HRMS Calcd. for C_{19}H_{24}N_{2}O_{2}: 312.184 (M'), Found: 312.184; IR (KBr) cm\(^{-1}\): 3357, 1633.

anti-4Ai: A colorless solid; M.p. 119.5–120.5 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 1.14 (3H, d, \(J = 6.8\) Hz), 1.56 (1H, s), 2.86 (3H, s), 2.95 (3H, s), 3.07–3.13 (1H, m), 3.66 (3H, s), 4.40 (1H, d, \(J = 5.2\) Hz), 4.64 (1H, br), 6.41–6.45 (2H, m), 6.62–6.66 (2H, m), 7.20–7.40 (5H, m); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 12.4, 35.8, 37.4, 42.1, 55.8, 60.6, 114.7, 115.2, 126.9, 127.3, 128.6, 142.1, 142.1, 152.1, 174.7; MS m/z: 312 (M'); HRMS Calcd. for C_{19}H_{24}N_{2}O_{2}: 312.184 (M'), Found 312.184; IR (KBr) cm\(^{-1}\): 3350, 1633.
3-(3-Hydroxypropyl)-1-(p-methoxyphenyl)-4-phenylazetidin-2-one (3Bh)

The title product (3Bh) was purified by column chromatography (AcOEt/hexane = 4:6) and only the anti diastereomer was obtained in 46% (93.3 mg).

\( \text{anti-3Bh}: \) A colorless solid; M.p. 75.5–76.0 °C; \(^1\)H NMR (CDCl\(_3\)) \( \delta: 1.70-2.05 \) (5H, m), 3.10 (1H, td, \( J = 8.0, 2.4 \) Hz), 3.68 (2H, t, \( J = 6.4 \) Hz), 4.56 (1H, d, \( J = 2.4 \) Hz), 5.04 (2H, s), 6.89–6.98 (4H, m), 7.21–7.27 (4H, m), 7.30–7.42 (5H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta: 25.3, 30.4, 60.5, 61.3, 62.2, 70.2, 115.6, 115.9 \) (d, \( J = 8.0, 2.4 \) Hz), 115.5 (d, \( J = 22 \) Hz), 127.3, 127.6, 128.2, 128.7, 129.7, 134.0, 136.7, 159.1 (d, \( J = 243 \) Hz), 159.2, 168.0; \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta: -55.4 \) (1F, m); MS \( m/z: \) 405 (M\(^+\)); HRMS Calcd. for \( C_{25}H_{32}FNO_3: \) 405.174 (M\(^+\)), Found: 405.174; IR (KBr) \( \text{cm}^{-1}: \) 3392, 1732.

4-(4-(Benzyloxy)phenyl)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-3-hydroxypropyl)azetidin-2-one (3Bj)

The title product (3Bj) was purified by column chromatography (AcOEt/hexane = 5:5) to give anti-3Bj in 58% (144.9 mg) as a diastereomeric mixture.

\( \text{anti-3Bj}: \) A colorless oil; \(^1\)H NMR (CDCl\(_3\)) \( \delta: 1.79-2.06 \) (4H, m), 2.31 (1H, br), 3.04–3.13 (1H, m), 4.51–4.57 (1H, m), 4.70 (1H, m), 5.04 (2H, s), 6.88–7.04 (6H, m), 7.19–7.42 (11H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta: 25.1, 36.6, 36.7, 60.4, 60.4, 61.2, 70.2, 73.2, 73.4, 115.4 \) (d, \( J = 22.1 \) Hz), 115.5 (d, \( J = 21.1 \) Hz), 115.6, 115.9 (d, \( J = 23.0 \) Hz), 118.5 (d, \( J = 8.5 \) Hz), 127.3, 127.4 (d, \( J = 22.0 \) Hz), 127.5 (d, \( J = 7.7 \) Hz), 127.6, 128.2, 128.7, 129.7, 134.0, 136.7, 140.0 (d, \( J = 2.9 \) Hz), 140.1 (d, \( J = 2.9 \) Hz), 159.0 (d, \( J = 242.4 \) Hz), 159.1, 162.3 (d, \( J = 244.4 \) Hz), 167.7, 167.8; \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta: -51.7-51.8 \) (1F, m), -54.9–55.0 (1F, m); MS \( m/z: \) 499 (M\(^+\)); HRMS Calcd. for \( C_{31}H_{27}F_2NO_3: \) 499.196 (M\(^+\)), Found: 499.196.

\( \text{anti-1-(4-Fluorophenyl)-3-(3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)azetidin-2-one [(±)-Ezetimibe]} \)

The title product ((±)-ezetimibe) was purified by column chromatography (AcOEt/hexane = 5:5) to give (±)-ezetimibe in 80% (65.5 mg) as a diastereomeric mixture.

(±)-ezetimibe: A colorless solid; \(^1\)H NMR (DMSO-d6) \( \delta: 1.59-1.86 \) (4H, m), 3.00–3.06 (1H, m), 4.42–4.53 (1H, m), 4.75–4.77 (1H, m), 5.23–5.24 (1H, m), 6.69–6.72 (2H, m),
7.05–7.13 (4H, m), 7.14–7.20 (4H, m), 7.23–7.31 (2H, m), 9.48 (1H, br); $^{13}$C NMR (100 MHz, DMSO-d6) $\delta$: 25.1, 36.9, 59.9, 60.0, 60.1, 71.6, 71.7, 115.2 (d, $J = 20.2$ Hz), 116.2, 116.5, 118.8 (d, $J = 7.5$ Hz), 128.1 (d, $J = 13.4$ Hz), 128.1, 128.4 (d, $J = 4.8$ Hz), 134.5, 142.6 (d, $J = 4.8$ Hz), 142.7 (d, $J = 5.7$ Hz), 158.0, 158.5 (d, $J = 238.6$ Hz), 161.6 (d, $J = 240.6$ Hz), 167.8, 167.9; $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$: -55.4—55.5 (1F, m), -57.7—57.8 (1F, m); MS $m/z$: 409 (M$^+$); HRMS Calcd. for C$_{24}$H$_{21}$FNO$_3$: 409.149 (M$^+$), Found: 409.149.
X-ray crystallographic analysis of anti-4Ai:

The product was recrystallized from ethyl acetate/hexane. The single crystal was mounted on a glass fiber. All measurements were made on a Rigaku R-AXIS RAPID diffractometer using graphite monochromated CuKα (λ = 1.54187 Å) radiation. The 2θ (max) value cut of 136.5°. The crystal structure was solved by the SIR2008 [3] direct methods and refined by the full-matrix least squares using the program CRYSTALS [4]. The crystallographic data were summarized in the following table.

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The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1431128). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html.
References:
**syn-3Ab**

**$^1$H NMR**

![1H NMR spectrum](image1)

**$^{13}$C NMR**

![$^{13}$C NMR spectrum](image2)
**syn-3Ae**

**<sup>1</sup>H NMR**

![<sup>1</sup>H NMR spectrum of syn-3Ae](image1)

**<sup>13</sup>C NMR**

![<sup>13</sup>C NMR spectrum of syn-3Ae](image2)
anti-3Ag

$^{1}H$ NMR

$^{13}C$ NMR
syn-4Ai

$^1$H NMR

$^{13}$C NMR

S14
anti-4Ai

$^1$H NMR

$^{13}$C NMR
anti-3Bh

$^1$H NMR

$^{13}$C NMR

S16
anti-3Bj

$^1$H NMR

$^{13}$C NMR
(±)-Ezetimibe

$^1$H NMR

$^{13}$C NMR