Catalytic Asymmetric [3+2] Cycloaddition of Azomethine Ylides. Development of a Versatile Stepwise, Three-Component Reaction for Diversity-Oriented Synthesis

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Supporting Information

Table 1S. Exploration of the reaction conditions for the silver(I)-catalyzed azomethine ylide cycloaddition.^a

entry	ligand	solvent	temp	yield ^b	endo:exo ^c	ee ^d
1 ^e	1	toluene	4 °C	<10% ^c	— ^f	— ^f
2	2	toluene	4 °C	<10% ^c	— ^f	— ^f
3	3	toluene	4 °C	76%	6.5:1	99%
4	4	toluene	4 °C	87%	>20:1	72%
5	4	toluene	−20 °C	92%	>20:1	82%
6	4	THF	−20 °C	91%	>20:1	85%
7	4	THF	−45 °C	88%	>20:1	92%
8	5	toluene	4 °C	85%	>20:1	−15%
9	6	toluene	4 °C	85%	>20:1	16%

^a Conditions: iminoester: 1.0 equiv, *tert*-butyl acrylate: 1.5 equiv, Hünig's base: 0.10 equiv, catalyst loading: 3 mol%, concentration: 0.1 M, reaction time: 20 h. ^b Isolated yield. ^c Determined by integration of the crude ¹H NMR spectra. ^d Determined by HPLC with chiral stationary phase. ^e The Trost ligand (**1**) was reported by Zhang and co-workers to give 59% ee at rt in the reaction of iminoester **7** with dimethyl maleate. ^f Not determined.

Table 2S. Exploration of the reaction conditions for iminoester **28**.^a

entry	solvent	yield ^b (conversions) ^c	ee ^d
1	CH ₂ Cl ₂	(36-63%)	62%
2	toluene	(66%)	72%
3	THF	93%	77%

^a Conditions: iminoester: 1.0 equiv, *tert*-butyl acrylate: 1.5 equiv, Hünig's base: 0.20 equiv, catalyst loading: 10 mol%, concentration: 0.08 M, reaction time: 48 h. ^b Isolated yield. ^c Determined by integration of the crude ¹H NMR spectra. ^d Determined by HPLC with chiral stationary phase.

Figure 1S. Proposed transition state for the silver(I)/(S)-QUINAP catalyzed azomethine ylide cycloaddition.

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of argon. Air and moisture-sensitive liquids and solutions were transferred via syringe. Organic solutions were concentrated by rotary evaporator at ca. 30 mmHg. Flash column chromatography was performed as described by Still et al.¹ employing E. Merck silica gel 60 (230–400 mesh ASTM). TLC analyses were performed on triethylamine deactivated 250 μ m Silica Gel 60 F₂₅₄ plates purchased from EM Science and visualized by quenching of UV fluorescence (λ_{max} =254 nm) or by staining with ceric ammonium molybdate. Conversions and diastereoselectivities were determined by integration of the crude ¹H NMR spectra recorded with 10 s recycle delay. Enantioselectivities were determined by HPLC using chiral stationary phase (Daicel Chiralcel OD, Chiralpak AD or Chiralpak AS) with 1 mL/min flow rate and monitored by UV fluorescence at 230 nm or 205 nm. Racemic compounds were prepared by using 3 mol% of silver(I) acetate/triphenylphosphine (1:2.4) as catalyst and used to calibrate the retention times of the enantiomers. The absolute configuration for pyrrolidine **11** was determined by single crystal X-ray analysis and others were assigned by analogy. These assignments are consistent with the literature^{2,3} while comparing the optical rotation values of pyrrolidine **9**.

Materials. Commercial solvents and reagents were used as received with the following exceptions. Anhydrous solvents were dispensed from a delivery system which passes the solvents through packed columns (tetrahydrofuran, methylene chloride: dry neutral alumina; toluene: dry neutral alumina and Q5 reactant). Hünig's base, triethylamine and 2,6-lutidine were distilled under nitrogen from calcium hydride. *tert*-Butyl acrylate and dimethyl maleate were distilled under vacuum (ca. 30 mmHg) from calcium hydride.

Instrumentation. Optical rotations were measured on a JASCO DIP-370 digital polarimeter with an average of 10 measurements, each with an integration time of 15 s. Infrared spectra were recorded on a Nicolet 5PC FT-IR spectrometer. ¹H and ¹³C NMR spectra were recorded on a Varian INOVA500 spectrometer. Chemical shifts for ¹H and ¹³C NMR spectra are reported in ppm (δ) relative to residue protium in the solvent (CHCl₃: δ 7.26, 77.07; respectively) and the multiplicities are presented as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. X-ray data were collected using a Bruker SMART CCD (charge coupled device) based diffractometer equipped with an LT-3 low-temperature apparatus operating at 213 K. A suitable crystal was chosen and mounted on a glass fiber using grease. Data were measured using omega scans of 0.3° per frame for 30 s, such that a

(1) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(2) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401.

(3) Willams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527–6532.

hemisphere was collected. A total of 1271 frames were collected with a maximum resolution of 0.75 Å. The first 50 frames were recollected at the end of data collection to monitor for decay. Cell parameters were retrieved using SMART software and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software which corrects for Lp and decay. The structures were solved by the direct method using the SHELXS-97 program and refined by least squares method on F^2 , SHELXL-97, incorporated in SHELXTL V5.10. The structure was solved in the space group $P2_1$ (#4) by analysis of systematic absences. All non-hydrogen atoms are refined anisotropically. Hydrogens were calculated by geometrical methods and refined as a riding model. The crystal used for the diffraction study showed no decomposition during data collection. The drawing was done at 50% ellipsoids.

General procedure for the synthesis of α -iminoesters. The α -iminoesters were prepared according to the procedure reported by Longmire et al.² To a suspension of the amino acid (glycine, alanine, leucine, phenylalanine or tryptophan) methyl ester hydrochloride (1.1 equiv) and magnesium sulfate (2.0 equiv) in methylene chloride was added triethylamine (1.1 equiv). This solution was stirred at room temperature for 1 h before the aldehyde (1.0 equiv) (benzaldehyde, 4-anisaldehyde, 4-bromobenzaldehyde, 4-cyanobenzaldehyde, 2-naphthaldehyde or 2-tolualdehyde) was added. After stirred at room temperature overnight, magnesium sulfate was filtered off and washed with methylene chloride. The filtrate was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate and concentrated to afford the α -iminoesters. The crude iminoesters could be used directly for the cycloaddition reactions except for the followings. Iminoester **12** was recrystallized from diethyl ether and iminoester **29** was passed through a plug of neutral alumina followed by washing with diethyl ether to remove the pale yellow color. The reactions reported above were performed on the scale of 1.0–4.0 g of aldehydes at 0.5 M concentration.

General procedure for the [3+2] cycloaddition reactions. The silver(I) acetate (1.0 equiv) and (*S*)-QUINAP (1.2 equiv) was weighted out in a glove box and added to a round-bottomed flask equipped with a side arm. Tetrahydrofuran was then introduced and this solution was stirred at room temperature for 1 h to make a stock solution of 0.01 M silver(I)/(*S*)-QUINAP catalyst. This solution of catalyst could be stored at –20 °C for at least one month without noticeable reduction of activities. To a solution of the α -iminoester (1.0 equiv) (**7**, **10–14**, **26–29**, dried over 4Å molecular sieve or azeotroped with toluene) in tetrahydrofuran at the indicated temperature was added the silver(I) acetate/(*S*)-QUINAP catalyst solution (0.03 equiv) prepared above followed by the dipolarophile (1.5 equiv) (*tert*-butyl acrylate, *tert*-butyl crotonate, *tert*-butyl cinnamate or dimethyl maleate) and Hünig's base (0.1 equiv).

The final concentration of the α -iminoesters was 0.1 M. After stirring for 20 hr, the reaction was either quenched with a tetrahydrofuran solution of acetic acid (1.1 equiv) or concentrated directly. The reactions reported above were performed on the scale of 20–80 mg of iminoesters.

***tert*-Butyl**

(2*R*,4*R*,5*S*)-2-methoxycarbonyl-5-phenylpyrrolidin-4-

carboxylate (9).² According to the general procedure using methyl *N*-benzylideneglycinate (7), *tert*-butyl acrylate (8), and 1 mol% silver(I)

acetate/(*S*)-QUINAP catalyst at $-45\text{ }^{\circ}\text{C}$ for 40 h, pyrrolidine **9** was obtained as a white solid after silica gel column chromatography (30→50% ethyl acetate-hexanes with 1% triethylamine) in 84% yield and 91% ee (Chiralpak AS column, 10% *iso*-propanol-hexanes; $t_{\text{R(minor)}}$ = 5.9 min, $t_{\text{R(major)}}$ = 8.6 min). $[\alpha]_{\text{D}}^{28}$ -30.8° (c = 1.15, CH_2Cl_2); R_f = 0.23 (40% ethyl acetate-hexanes); ^1H NMR (500 MHz, CDCl_3) δ 7.35 (d, J = 7.5 Hz; 2H), 7.30 (t, J = 7.5 Hz; 2H), 7.24 (dd, J = 15.0, 8.0 Hz; 1H), 4.47 (d, J = 8.0 Hz; 1H), 3.94 (t, J = 8.3 Hz; 1H), 3.80 (s, 3H), 3.25 (td, J = 7.9, 6.3 Hz; 1H), 2.73 (br, 1H), 2.46-2.40 (m, 1H), 2.33-2.28 (m, 1H), 1.01 (s, 9H).

***tert*-Butyl**

(2*R*,4*R*,5*S*)-2-methoxycarbonyl-5-(4-

methoxyphenyl)pyrrolidin-4-carboxylate (15). According to the

general procedure using iminoester **10**, *tert*-butyl acrylate (8), and 3 mol% silver(I) acetate/(*S*)-QUINAP catalyst at $-45\text{ }^{\circ}\text{C}$ for 20 h, pyrrolidine **15** was obtained as a white solid after silica gel column chromatography (30→50% ethyl acetate-hexanes with 1% triethylamine) in 93% yield and 95% ee (Chiralpak AS column, 10% *iso*-propanol-hexanes; $t_{\text{R(minor)}}$ = 7.8 min, $t_{\text{R(major)}}$ = 11.3 min). $[\alpha]_{\text{D}}^{25}$ -29.2° (c = 1.23, CH_2Cl_2); R_f = 0.12 (40% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 3734, 2976, 2950, 1736, 1513, 1244, 1149; ^1H NMR (500 MHz, CDCl_3) δ 7.22 (d, J = 8.8 Hz; 2H), 6.79 (d, J = 8.8 Hz; 2H), 4.37 (d, J = 8.0 Hz; 1H), 3.86 (t, J = 8.5 Hz; 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.16 (dd, J = 14.3, 7.8 Hz; 1H), 2.72 (br, 1H), 2.38-2.32 (m, 1H), 2.27-2.21 (m, 1H), 1.00 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.7, 171.8, 158.8, 131.5, 128.2, 113.4, 80.4, 64.9, 59.7, 55.2, 52.1, 50.2, 33.9, 27.4; HRMS(ES^+) calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_5$ ($\text{M}+\text{H}$) 336.1811, found 336.1811.

***tert*-Butyl**

(2*R*,4*R*,5*S*)-2-methoxycarbonyl-5-(4-

bromophenyl)pyrrolidin-4-carboxylate (16). According to the general

procedure using iminoester **11**, *tert*-butyl acrylate (8), and 3 mol% silver(I) acetate/(*S*)-QUINAP catalyst at $-45\text{ }^{\circ}\text{C}$ for 20 h, pyrrolidine **16** was obtained as a white solid after silica gel column chromatography (30→50% ethyl acetate-hexanes with 1% triethylamine) in 89% yield and 95% ee (Chiralpak AS column, 10% *iso*-propanol-hexanes; $t_{\text{R(minor)}}$ = 6.4 min, $t_{\text{R(major)}}$ = 10.2

min). Recrystallization from diethyl ether-hexanes at room temperature or methylene chloride-hexanes at $-20\text{ }^{\circ}\text{C}$ provided crystals (needles) suitable for X-ray analysis. $[\alpha]_{\text{D}}^{27} -23.2^{\circ}$ ($c = 0.50$, CH_2Cl_2); $R_f = 0.14$ (40% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 3735, 3223, 2979, 2945, 1738, 1720, 1700, 1436, 1365, 1206, 1151; ^1H NMR (500 MHz, CDCl_3) δ 7.42 (d, $J = 8.3$ Hz; 2H), 7.24 (d, $J = 8.3$ Hz; 2H), 4.40 (d, $J = 8.0$ Hz; 1H), 3.91 (t, $J = 8.5$ Hz; 1H), 3.78 (s, 3H), 3.21 (dd, $J = 14.3, 8.0$ Hz; 1H), 2.77 (br, 1H), 2.43-2.37 (m, 1H), 2.29 (ddd, $J = 13.9, 7.9, 5.6$ Hz; 1H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.6, 171.6, 138.6, 131.1, 129.1, 121.2, 80.9, 64.9, 59.8, 52.3, 50.0, 33.9, 27.5; HRMS(ES^+) calcd for $\text{C}_{17}\text{H}_{23}\text{BrNO}_4$ ($\text{M}+\text{H}$) $^+$ 384.0810, found 384.0815.

***tert*-Butyl**

(2*R*,4*R*,5*S*)-2-methoxycarbonyl-5-(4-

cyanophenyl)pyrrolidin-4-carboxylate (17). According to the general procedure using iminoester **12**, *tert*-butyl acrylate (**8**), and 3 mol%

silver(I) acetate/(*S*)-QUINAP catalyst at $-45\text{ }^{\circ}\text{C}$ for 20 h, pyrrolidine **17** was obtained as a white solid after silica gel column chromatography (30 $\rightarrow$ 50% ethyl acetate-hexanes with 1% triethylamine) in 92% yield and 96% ee (Chiralpak AS column, 10% *iso*-propanol-hexanes; $t_{\text{R(minor)}}$ = 17.7 min, $t_{\text{R(major)}}$ = 22.8 min). $[\alpha]_{\text{D}}^{26} -31.6^{\circ}$ ($c = 0.96$, CH_2Cl_2); $R_f = 0.10$ (40% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 3363, 2979, 2956, 2228, 1731, 1367, 1210, 1149; ^1H NMR (500 MHz, CDCl_3) δ 7.61 (d, $J = 8.0$ Hz; 2H), 7.51 (d, $J = 8.0$ Hz; 2H), 4.51 (d, $J = 7.5$ Hz; 1H), 3.95 (t, $J = 8.5$ Hz; 1H), 3.80 (s, 3H), 3.27 (dd, $J = 14.5, 6.5$ Hz; 1H), 2.79 (br, 1H), 2.47-2.41 (m, 1H), 2.35-2.29 (m, 1H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.7, 171.4, 145.6, 132.1, 128.5, 119.0, 111.3, 81.4, 65.0, 59.9, 52.6, 50.1, 33.8, 27.8; HRMS(ES^+) calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 331.1658, found 331.1662.

***tert*-Butyl (2*R*,4*R*,5*S*)-2-methoxycarbonyl-5-(2-naphthyl)pyrrolidin-4-**

carboxylate (18). According to the general procedure using iminoester **13**, *tert*-butyl acrylate (**8**), and 3 mol%

silver(I) acetate/(*S*)-QUINAP catalyst at $-45\text{ }^{\circ}\text{C}$ for 20 h, pyrrolidine **18** was obtained as a white solid after silica gel column chromatography (30 $\rightarrow$ 50% ethyl acetate-hexanes with 1% triethylamine) in 89% yield and 94% ee (Chiralpak AS column, 10% *iso*-propanol-hexanes; $t_{\text{R(minor)}}$ = 7.2 min, $t_{\text{R(major)}}$ = 12.1 min). $[\alpha]_{\text{D}}^{26} -26.8^{\circ}$ ($c = 1.29$, CH_2Cl_2); $R_f = 0.13$ (40% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 2973, 2945, 1741, 1697, 1429, 1360, 1303, 1153, 1108; ^1H NMR (500 MHz, CDCl_3) δ 7.83-7.78 (m, 4H), 7.48-7.44 (m, 3H), 4.62 (d, $J = 7.5$ Hz; 1H), 4.01 (t, $J = 8.3$ Hz; 1H), 3.83 (s, 3H), 3.34 (dd, $J = 13.5, 7.5$ Hz; 1H), 3.00 (br, 1H), 2.52-2.46 (m, 1H), 2.41-2.36 (m, 1H), 0.89 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.7, 171.9, 136.6, 133.1, 132.7, 127.9, 127.6, 127.5, 126.1, 125.7, 125.5, 80.6, 65.8, 59.9, 52.3, 50.1, 34.2, 27.4; HRMS(ES^+) calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_4$ ($\text{M}+\text{H}$) $^+$ 356.1862, found 356.1864.

tert-Butyl (2R,4R,5S)-2-methoxycarbonyl-5-(2-tolyl)pyrrolidin-4-carboxylate (19). According to the general procedure using iminoester **14**, *tert*-butyl acrylate (**8**), and 3 mol% silver(I) acetate/(*S*)-QUINAP catalyst at

−45 °C for 20 h, pyrrolidine **19** was obtained as a white solid after silica gel column chromatography (30→50% ethyl acetate-hexanes with 1% triethylamine) in 95% yield and 89% ee (Chiralpak AS column, 10% *iso*-propanol-hexanes; $t_{R(\text{minor})}$ = 4.7 min, $t_{R(\text{major})}$ = 11.2 min). $[\alpha]_D^{26}$ −80.4° (c = 1.13, CH₂Cl₂); R_f = 0.20 (40% ethyl acetate-hexanes); FTIR (neat, cm^{−1}) 3343, 2979, 1727, 1458, 1433, 1365, 1213, 1137; ¹H NMR (500 MHz, CDCl₃) δ 7.40-7.38 (m, 1H), 7.12-7.08 (m, 3H), 4.50 (d, J = 7.5 Hz; 1H), 3.84 (t, J = 8.5 Hz; 1H), 3.76 (s, 3H), 3.27 (dt, J = 8.0, 5.5 Hz; 1H), 2.80 (br, 1H), 2.41-2.30 (m, 2H), 2.33 (s, 3H), 0.91 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 173.3, 171.8, 136.8, 135.9, 129.8, 127.1, 125.78, 125.76, 80.2, 62.5, 59.5, 52.0, 47.5, 33.9, 27.2, 19.6; HRMS(ES⁺) calcd for C₁₈H₂₆NO₄ (M+H)⁺ 320.1862, found 320.1866.

(2R,3S,4R,5S)-2,3,4-Trimethoxycarbonyl-5-phenylpyrrolidine (23).²

According to the general procedure using iminoester **7**, dimethyl maleate (**20**), and 3 mol% silver(I) acetate/(*S*)-QUINAP catalyst in toluene at −60 °C for 48 h in toluene, pyrrolidine **23** was obtained as a white solid after silica gel column chromatography (30→50% ethyl acetate-hexanes with 1% triethylamine) in 88% yield and 60% ee (Chiralpak AS column, 50% *iso*-propanol-hexanes; $t_{R(\text{minor})}$ = 5.4 min, $t_{R(\text{major})}$ = 10.0 min). ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.26 (m, 4H), 7.23-7.20 (m, 1H), 4.44 (d, J = 6.5 Hz; 1H), 4.12 (d, J = 9.5 Hz; 1H), 3.76 (s, 3H), 3.69 (t, J = 8.8 Hz; 1H), 3.64 (s, 3H), 3.54 (t, J = 7.5 Hz; 1H), 3.34 (br, 1H), 3.18 (s, 3H).

tert-Butyl (2R,3R,4R,5S)-2-methoxycarbonyl-3-methyl-5-phenylpyrrolidin-4-carboxylate (24). According to the general procedure using iminoester **7**, *tert*-butyl crotonate (**21**), and 10 mol% silver(I) acetate/(*S*)-

QUINAP catalyst at −20 °C for 85 h, pyrrolidine **24** was obtained as a white solid after silica gel column chromatography (30→50% ethyl acetate-hexanes with 1% triethylamine) in 97% yield (ca. 95% purity) and 84% ee (Chiralcel OD column, 4% *iso*-propanol-hexanes; $t_{R(\text{minor})}$ = 11.9 min, $t_{R(\text{major})}$ = 25.3 min). $[\alpha]_D^{25}$ −15.1° (c = 0.48, CH₂Cl₂); R_f = 0.25 (40% ethyl acetate-hexanes); FTIR (neat, cm^{−1}) 3365, 2976, 1729, 1454, 1433, 1367, 1151; ¹H NMR (500 MHz, CDCl₃) δ 7.30 (d, J = 7.5 Hz; 2H), 7.25 (t, J = 7.8 Hz; 2H), 7.18 (t, J = 7.3 Hz; 1H), 4.51 (d, J = 8.5 Hz; 1H), 3.76 (s, 3H), 3.44 (d, J = 9.0 Hz; 1H), 2.86 (t, J = 8.0 Hz; 1H), 2.80 (br, 1H), 2.61 (dq, J = 15.0, 7.5 Hz; 1H), 1.21 (d, J = 7.0 Hz; 3H), 0.98 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 173.5, 170.9, 140.2, 128.0, 127.3, 127.25, 80.4, 67.2, 64.1, 58.8, 52.1, 42.3, 27.4, 18.0; HRMS(ES⁺) calcd for C₁₈H₂₆NO₄ (M+H)⁺ 320.1862, found 320.1854.

tert-Butyl (2*R*,3*R*,4*R*,5*S*)-2-methoxycarbonyl-3-phenyl-5-phenylpyrrolidin-4-carboxylate (25a**).** According to the general procedure using iminoester **7**, *tert*-butyl cinnamate (**22**), and 10 mol% silver(I) acetate/(*S*)-QUINAP catalyst at $-20\text{ }^{\circ}\text{C}$ for 85 h, an inseparable mixture of pyrrolidine **25a** in 81% ee (Chiralpak AS column, 5% *iso*-propanol-hexanes; $t_{R(\text{minor})} = 6.7\text{ min}$, $t_{R(\text{major})} = 11.3\text{ min}$) and **25b** in 50% ee ($t_{R(\text{minor})} = 6.1\text{ min}$, $t_{R(\text{major})} = 8.2\text{ min}$) was obtained in a combined yield of 62% after silica gel column chromatography (30 $\rightarrow$ 50% ethyl acetate-hexanes with 1% triethylamine). A portion of this mixture was separated by preparative HPLC (Zorbax CN 21.2 mm $\times$ 25 cm column, 0 $\rightarrow$ 10% ethanol-hexanes, 20 mL/min) to provided pure pyrrolidine **25a** as white solid and pyrrolidine **25b** as colorless oil.

Pyrrolidine **25a**: $[\alpha]_{\text{D}}^{24} +11.3^{\circ}$ ($c = 0.46$, CH_2Cl_2); $R_f = 0.29$ (40% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 2971, 1731, 1454, 1365, 1258, 1208, 1151; ^1H NMR (500 MHz, CDCl_3) δ 7.43 (d, $J = 7.0\text{ Hz}$; 2H), 7.35-7.30 (m, 6H), 7.27-7.24 (m, 2H), 4.81 (d, $J = 8.0\text{ Hz}$; 1H), 4.01 (d, $J = 9.0\text{ Hz}$; 1H), 3.82 (t, $J = 8.5\text{ Hz}$; 1H), 3.69 (s, 3H), 3.45 (t, $J = 8.3\text{ Hz}$; 1H), 3.00 (br, 1H), 0.96 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.0, 170.6, 140.6, 139.6, 128.6, 128.1, 127.6, 127.5, 127.0, 80.7, 67.9, 65.3, 59.4, 53.2, 52.1, 27.3; HRMS(ES^+) calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_4$ ($\text{M}+\text{H}^+$) 382.2018, found 382.2017.

tert-Butyl (2*R*,3*S*,4*S*,5*S*)-2-methoxycarbonyl-3-phenyl-5-phenylpyrrolidin-4-carboxylate (25b**):** $R_f = 0.29$ (40% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 3375, 2971, 2919, 1722, 1454, 1365, 1206, 1151; ^1H NMR (500 MHz, CDCl_3) δ 7.61 (d, $J = 7.0\text{ Hz}$; 2H), 7.39 (t, $J = 7.5\text{ Hz}$; 2H), 7.34-7.23 (m, 6H), 4.49 (d, $J = 10.0\text{ Hz}$; 1H), 4.33 (d, $J = 9.7\text{ Hz}$; 1H), 4.03 (t, $J = 9.7\text{ Hz}$; 1H), 3.27 (t, $J = 10.0\text{ Hz}$; 1H), 3.24 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.0, 171.1, 139.5, 137.5, 128.8, 128.4, 128.3, 128.1, 127.5, 127.4, 81.3, 66.5, 64.8, 57.4, 53.3, 51.8, 27.9; HRMS(ES^+) calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_4$ ($\text{M}+\text{H}^+$) 382.2018, found 382.2018.

Selected NOE data of pyrrolidine **25a** and **25b**.

tert-Butyl (2*R*,4*R*,5*S*)-2-methyl-2-methoxycarbonyl-5-phenylpyrrolidin-4-carboxylate (30**).** According to the general procedure using iminoester **26**, *tert*-butyl acrylate (**8**), and 10 mol% silver(I) acetate/(*S*)-QUINAP catalyst at

0.08 M at $-20\text{ }^{\circ}\text{C}$ for 48 h, pyrrolidine **30** was obtained as a white solid after silica gel column chromatography (10 $\rightarrow$ 20% ethyl acetate-hexanes with 1% triethylamine) in 98% yield and 80% ee (Chiralcel OD column, 2% *iso*-propanol-hexanes; $t_{\text{R(minor)}}$ = 11.4 min, $t_{\text{R(major)}}$ = 21.5 min). $[\alpha]_{\text{D}}^{28} -22.3^{\circ}$ (c = 1.22, CH_2Cl_2); R_f = 0.27 (40% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 3360, 2979, 1729, 1456, 1433, 1390, 1365, 1253, 1153; ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.26 (m, 4H), 7.22-7.19(m, 1H), 4.59 (d, J = 8.0 Hz; 1H), 3.79 (s, 3H), 3.30 (dd, J = 13.5, 8.0, Hz; 1H), 3.15 (br, 1H), 2.61 (dd, J = 13.5, 6.0 Hz; 1H), 2.05 (dd, J = 13.5, 7.8 Hz; 1H), 1.47 (s, 3H), 0.99 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.3, 171.6, 139.4, 128.0, 127.2, 127.1, 80.3, 65.4, 64.3, 52.4, 50.7, 40.8, 27.4, 27.0; HRMS(ES^+) calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_4$ ($\text{M}+\text{H}$) $^+$ 320.1826, found 320.1822.

***tert*-Butyl (2*S*,4*R*,5*S*)-2-*iso*-butyl-2-methoxycarbonyl-5-phenylpyrrolidin-4-carboxylate (**31**).** According to the general procedure using iminoester **27**, *tert*-butyl acrylate (**8**), and 10 mol% silver(I) acetate/(*S*)-QUINAP catalyst at

0.08 M at $-20\text{ }^{\circ}\text{C}$ for 72 h, pyrrolidine **31** was obtained as a white solid after silica gel column chromatography (6% ethyl acetate-hexanes with 1% triethylamine) in 77% yield and 80% ee (Chiralcel OD column, 0.2% *iso*-propanol-hexanes; $t_{\text{R(major)}}$ = 13.4 min, $t_{\text{R(minor)}}$ = 16.2 min). $[\alpha]_{\text{D}}^{29} +40.8^{\circ}$ (c = 0.48, CH_2Cl_2); R_f = 0.56 (40% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 3363, 3314, 2950, 2868, 1725, 1454, 1392, 1365, 1256, 1222, 1148; ^1H NMR (500 MHz, CDCl_3) δ 7.32 (d, J = 7.5 Hz; 2H), 7.27 (t, J = 7.5 Hz; 2H), 7.20 (t, J = 7.0 Hz; 1H), 4.51 (d, J = 8.0 Hz; 1H), 3.77 (s, 3H), 3.25 (dt, J = 7.9, 5.8 Hz; 1H), 3.06 (br, 1H), 2.52 (dd, J = 13.5, 6.0 Hz; 1H), 2.03 (dd, J = 13.5, 8.0 Hz; 1H), 1.80-1.75 (m, 2H), 1.62-1.58 (m, 1H), 0.99 (s, 9H), 0.93 (d, J = 6.0 Hz; 3H), 0.82 (d, J = 6.0 Hz; 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.5, 171.9, 139.8, 128.1, 127.3, 127.2, 80.3, 68.7, 64.6, 52.1, 50.5, 48.2, 41.7, 27.5, 25.2, 24.3, 22.7; HRMS(ES^+) calcd for $\text{C}_{21}\text{H}_{32}\text{NO}_4$ ($\text{M}+\text{H}$) $^+$ 362.2331, found 362.2334.

***tert*-Butyl (2*S*,4*R*,5*S*)-2-benzyl-2-methoxycarbonyl-5-phenylpyrrolidin-4-carboxylate (**32**).** According to the general procedure using iminoester **28**, *tert*-butyl acrylate (**8**), and 10 mol% silver(I) acetate/(*S*)-QUINAP catalyst at 0.08M at $-20\text{ }^{\circ}\text{C}$ for 48 h, pyrrolidine **32** was obtained as colorless oil after

silica gel column chromatography (10% ethyl acetate-hexanes with 1% triethylamine) in 93% yield and 77% ee (Chiralcel OD column, 1% *iso*-propanol-hexanes; $t_{\text{R(minor)}}$ = 11.0 min, $t_{\text{R(major)}}$ = 17.0 min). $[\alpha]_{\text{D}}^{29} +30.9^{\circ}$ (c = 0.81, CH_2Cl_2); R_f = 0.59 (40% ethyl acetate-hexanes); FTIR (neat, cm^{-1}) 3363, 3027, 2976, 2953, 1727, 1602, 1492, 1456, 1390, 1367, 1258, 1206, 1153; ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.21 (m, 10H), 4.55 (d, J = 8.0 Hz; 1H), 3.73 (s, 3H), 3.23 (dd, J = 13.5, 8.0 Hz; 1H), 3.12 (d, J = 13.5 Hz; 1H), 2.98 (br, 1H), 2.97 (d, J = 13.5 Hz), 2.72 (dd, J = 13.8, 5.8 Hz; 1H), 2.23 (dd, J = 13.8, 7.8 Hz;

1H), 1.02 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 175.4, 171.6, 140.1, 137.1, 130.1, 128.1, 127.4, 127.3, 126.8, 80.5, 70.2, 64.4, 52.2, 50.4, 45.4, 39.2, 27.5; HRMS(ES⁺) calcd for C₂₄H₃₀NO₄ (M+H)⁺ 396.2175, found 396.2178.

***tert*-Butyl (2*S*,4*R*,5*S*)-2-(3-indonylmethyl)-2-methoxycarbonyl-5-phenylpyrrolidin-4-carboxylate (33).** According to the general procedure using iminoester **29**, *tert*-butyl acrylate (**8**), and 10 mol% silver(I) acetate/(*S*)-QUINAP catalyst at 0.08 M at −20 °C for 96 h, pyrrolidine **33** was obtained as

a white solid after silica gel column chromatography (30→40% ethyl acetate-hexanes with 1% triethylamine) in 47% yield and 81% ee (Chiralpak AD column, 5% *iso*-propanol-hexanes; *t*_{R(minor)} = 27.9 min, *t*_{R(major)} = 44.8 min). [*a*]_D²⁹ +72.9° (*c* = 0.38, CH₂Cl₂); *R*_f = 0.19 (40% ethyl acetate-hexanes); FTIR (neat, cm^{−1}) 3400, 2979, 1725, 1454, 1365, 1251, 1206, 1153; ¹H NMR (500 MHz, CDCl₃) δ 8.29 (s, 1H), 7.66 (d, *J* = 7.5 Hz; 1H), 7.36 (d, *J* = 7.0 Hz; 2H), 7.31-7.22 (m, 4H), 7.15-7.09 (m, 3H), 4.62 (d, *J* = 7.5 Hz; 1H), 3.64 (s, 3H), 3.34 (d, *J* = 14.3 Hz; 1H), 3.29 (dd, *J* = 17.0, 11.0 Hz; 1H), 3.16 (d, *J* = 14.3 Hz; 1H), 3.12 (br, 1H), 2.75 (dd, *J* = 13.8, 5.8 Hz; 1H), 2.31 (dd, *J* = 13.8, 7.8 Hz; 1H), 1.04 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 176.1, 171.8, 140.2, 135.8, 128.1, 128.06, 127.4, 127.2, 123.6, 121.6, 119.2, 118.8, 111.1, 111.0, 80.5, 70.1, 64.4, 52.3, 39.0, 35.3, 27.5; HRMS(ES⁺) calcd for C₂₆H₃₁N₂O₄ (M+H)⁺ 435.2284, found 435.2293.

Polystyrene-bound 4-siloxybenzaldehyde (34). To a suspension of [(4-methoxyphenyl)di-*iso*-propylsilyl]propyl functionalized 500-600 μm polystyrene beads (ca. 1.4 mmol/g, incubated with 2.5% v/v

trimethylsilyl chloride in methylene chloride for 1 h and then washed with dry methylene chloride (3×) before use) in methylene chloride was added a solution of trifluoromethanesulfonic acid (3% v/v in methylene chloride, 6.0 equiv). After 30 min, the resulting orange [di-*iso*-propyl(trifluoromethanesulfonyl)silyl]propyl polystyrene were washed with dry methylene chloride (3×). A solution of 4-hydroxybenzaldehyde (3.0 equiv) in methylene chloride was then introduced and the suspension was tumbled at room temperature overnight to give the polystyrene-bound 4-siloxybenzaldehyde **34** after washed with methylene chloride (3×), tetrahydrofuran (3×) and again methylene chloride (3×) and then dried. The loading level of **34** was determined to be 166 nmol/bead (ca. 1.0 mmol/g) by treating **34** with a solution of hydrogen fluoride-pyridine/pyridine/tetrahydrofuran (0.01 mL/bead) (5%-5% v-v/v) for 2 h followed by quenching with methoxytrimethylsilane (0.02 mL/bead) and measure the weight of the recovered 4-hydroxybenzaldehyde.

Polystyrene-bound methyl *N*-(4-hydroxybenzylidene)glycinate.

To the polystyrene-bound 4-siloxybenzaldehyde **34** (1.0 equiv) was added a solution of methyl glycinate (10 equiv) (washing glycine methyl ester hydrochloride methylene chloride solution with a mixture of 1 N sodium hydroxide aqueous solution and brine (1:1) followed by drying over sodium sulfate, filtration and concentration) in methylene chloride (50 mg/mL) followed by an equal volume of trimethyl orthoformate. This suspension was tumbled overnight. The clear solution was filtered off and the beads were washed sequentially with methylene chloride, tetrahydrofuran and methylene chloride again, dried to afford the desired iminoester as pale yellow beads (ca. 85% conversion as judged by MAS ^1H NMR spectra). The beads were subjected to the reaction conditions again to consume all the aldehyde.

[3+2] azomethine ylide cycloaddition on the solid support.

According to the general procedure, to a suspension of the polystyrene-bound iminoester obtained above (1.0 equiv) in tetrahydrofuran was added the silver(I) acetate/(*S*)-QUINAP catalyst solution (0.1 equiv). This solution was cooled to $-45\text{ }^\circ\text{C}$ followed by addition of *tert*-butyl acrylate (10 equiv) and Hünig's base (0.2 equiv). After stirred for 40 h, the colorless solution was filtered off and the pale orange beads were washed sequentially with methylene chloride, tetrahydrofuran, acetonitrile, *iso*-propanol, *N,N*-dimethyl formamide, water-*N,N*-dimethyl formamide (1:1), *N,N*-dimethyl formamide, acetonitrile, tetrahydrofuran and finally methylene chloride, dried to afford the polystyrene-bound pyrrolidine as pale yellow beads.

tert-butyl

(2*R*,4*R*,5*S*)-2-methoxycarbonyl-5-(4-

hydroxyphenyl)pyrrolidin-4-carboxylate (**35**)

The polystyrene-bound pyrrolidine obtained above was treated with a solution of hydrogen fluoride-pyridine/pyridine/tetrahydrofuran (0.01 mL/bead) (5%-5% v-v/v) for 2 h followed by quenched with methoxytrimethylsilane (0.02 mL/bead). The polystyrene beads were filtered off and washed with methylene chloride (3 $\times$). The filtrate was collected, concentrated and purified by silica gel column chromatography (80% ethyl acetate-hexanes with 1% triethylamine) to give pyrrolidine **35** in 79% yield and 90% ee (Chiralpak AS column, 10% *iso*-propanol-hexanes; $t_{\text{R(minor)}}$ = 16.7 min, $t_{\text{R(major)}}$ = 20.4 min). $[\alpha]_{\text{D}}^{26} -36.6^\circ$ (c = 0.14, CH_2Cl_2); R_f = 0.30 (ethyl acetate); FTIR (neat, cm^{-1}) 2967, 1739, 1706, 1518, 1379, 1217, 1210, 1153; ^1H NMR (500 MHz, CDCl_3) δ 7.18 (d, J = 8.8 Hz; 2H), 6.74 (d, J = 8.8 Hz; 2H), 4.42 (d, J = 8.0 Hz; 1H), 3.93 (t, J = 8.5 Hz; 1H), 3.81 (s, 3H), 3.22 (td, J = 7.9, 6.3 Hz; 1H), 2.46-2.40 (m, 1H), 2.34-2.28 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.4, 172.0, 155.8,

129.9, 128.4, 115.3, 81.2, 65.1, 59.6, 52.6, 50.2, 33.9, 27.7; HRMS(ES^+) calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_5$ ($\text{M}+\text{H}$) 322.1654, found 322.1656.

Table 3. Crystal data and structure refinement for pyrrolidine **16**.

Empirical formula	C17 H22 Br N O4	
Formula weight	384.27	
Temperature	213(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 12.1641(13) Å	$\alpha = 90^\circ$
	b = 5.7004(6) Å	$\beta = 108.086(2)^\circ$
	c = 13.6078(15) Å	$\gamma = 90^\circ$
Volume	896.95(17) Å ³	
Z	2	
Density (calculated)	1.423 Mg/m ³	
Absorption coefficient	2.310 mm ⁻¹	
F(000)	396	
Crystal size	0.16 x 0.10 x 0.10 mm ³	
Theta range for data collection	1.57 to 27.86°.	
Index ranges	-15 ≤ h ≤ 15, -7 ≤ k ≤ 7, -17 ≤ l ≤ 13	
Reflections collected	5783	
Independent reflections	3947 [R(int) = 0.0454]	
Completeness to theta = 27.86°	98.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3947 / 1 / 212	
Goodness-of-fit on F ²	1.004	
Final R indices [I > 2sigma(I)]	R1 = 0.0361, wR2 = 0.0924	
R indices (all data)	R1 = 0.0423, wR2 = 0.0956	
Absolute structure parameter	-0.008(9)	
Largest diff. peak and hole	0.600 and -0.452 e.Å ⁻³	

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for pyrrolidine **16**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	5461(1)	4848(1)	7513(1)	57(1)
O(1)	1217(2)	5006(4)	9022(1)	38(1)
O(2)	384(2)	1932(4)	8044(2)	50(1)
O(3)	-3446(2)	2217(4)	5579(2)	43(1)
O(4)	-1850(2)	35(4)	5890(2)	44(1)
N(1)	-553(2)	3992(4)	5783(2)	32(1)
C(1)	151(2)	5805(4)	6441(2)	28(1)
C(2)	-222(2)	5833(4)	7451(2)	28(1)
C(3)	-1508(2)	5158(5)	7046(2)	31(1)
C(4)	-1694(2)	4220(4)	5920(2)	28(1)
C(5)	1442(2)	5509(4)	6645(2)	28(1)
C(6)	1930(2)	3527(5)	6376(2)	33(1)
C(7)	3137(2)	3330(5)	6636(2)	36(1)
C(8)	3824(2)	5150(6)	7160(2)	36(1)
C(9)	3359(2)	7128(5)	7429(2)	42(1)
C(10)	2161(2)	7321(5)	7173(2)	38(1)
C(11)	475(2)	3998(5)	8203(2)	32(1)
C(12)	2028(3)	3590(6)	9847(2)	44(1)
C(13)	2632(5)	5446(8)	10605(4)	121(3)
C(14)	1367(4)	1942(10)	10315(3)	80(1)
C(15)	2853(4)	2294(9)	9414(3)	69(1)
C(16)	-2310(2)	1901(5)	5779(2)	31(1)
C(17)	-4118(3)	128(7)	5573(3)	55(1)

Table 5. Bond lengths [Å] and angles [°] for pyrrolidine **16**.

Br(1)-C(8)	1.905(2)
O(1)-C(11)	1.327(3)
O(1)-C(12)	1.482(3)
O(2)-C(11)	1.196(3)
O(3)-C(16)	1.336(3)
O(3)-C(17)	1.443(4)
O(4)-C(16)	1.189(4)
N(1)-C(1)	1.459(3)
N(1)-C(4)	1.463(3)
N(1)-H(1)	0.8700
C(1)-C(5)	1.516(3)
C(1)-C(2)	1.576(3)
C(1)-H(1A)	0.9900
C(2)-C(11)	1.524(4)
C(2)-C(3)	1.537(3)
C(2)-H(2)	0.9900
C(3)-C(4)	1.572(3)
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(4)-C(16)	1.502(4)
C(4)-H(4)	0.9900
C(5)-C(6)	1.378(3)
C(5)-C(10)	1.399(4)
C(6)-C(7)	1.403(4)
C(6)-H(6)	0.9400
C(7)-C(8)	1.383(4)
C(7)-H(7)	0.9400
C(8)-C(9)	1.362(5)
C(9)-C(10)	1.393(4)
C(9)-H(9)	0.9400
C(10)-H(10)	0.9400
C(12)-C(14)	1.501(6)
C(12)-C(13)	1.501(5)
C(12)-C(15)	1.505(5)
C(13)-H(13A)	0.9700
C(13)-H(13B)	0.9700
C(13)-H(13C)	0.9700

C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700
C(14)-H(14C)	0.9700
C(15)-H(15A)	0.9700
C(15)-H(15B)	0.9700
C(15)-H(15C)	0.9700
C(17)-H(17A)	0.9700
C(17)-H(17B)	0.9700
C(17)-H(17C)	0.9700

C(11)-O(1)-C(12)	121.3(2)
C(16)-O(3)-C(17)	116.0(2)
C(1)-N(1)-C(4)	104.96(18)
C(1)-N(1)-H(1)	127.5
C(4)-N(1)-H(1)	127.5
N(1)-C(1)-C(5)	114.25(19)
N(1)-C(1)-C(2)	105.63(19)
C(5)-C(1)-C(2)	113.8(2)
N(1)-C(1)-H(1A)	107.6
C(5)-C(1)-H(1A)	107.6
C(2)-C(1)-H(1A)	107.6
C(11)-C(2)-C(3)	111.2(2)
C(11)-C(2)-C(1)	109.2(2)
C(3)-C(2)-C(1)	102.82(18)
C(11)-C(2)-H(2)	111.1
C(3)-C(2)-H(2)	111.1
C(1)-C(2)-H(2)	111.1
C(2)-C(3)-C(4)	104.88(17)
C(2)-C(3)-H(3A)	110.8
C(4)-C(3)-H(3A)	110.8
C(2)-C(3)-H(3B)	110.8
C(4)-C(3)-H(3B)	110.8
H(3A)-C(3)-H(3B)	108.8
N(1)-C(4)-C(16)	111.2(2)
N(1)-C(4)-C(3)	107.45(19)
C(16)-C(4)-C(3)	109.8(2)
N(1)-C(4)-H(4)	109.5
C(16)-C(4)-H(4)	109.5
C(3)-C(4)-H(4)	109.5

C(6)-C(5)-C(10)	119.3(2)
C(6)-C(5)-C(1)	123.4(2)
C(10)-C(5)-C(1)	117.3(2)
C(5)-C(6)-C(7)	120.1(2)
C(5)-C(6)-H(6)	119.9
C(7)-C(6)-H(6)	119.9
C(8)-C(7)-C(6)	119.2(3)
C(8)-C(7)-H(7)	120.4
C(6)-C(7)-H(7)	120.4
C(9)-C(8)-C(7)	121.6(2)
C(9)-C(8)-Br(1)	119.7(2)
C(7)-C(8)-Br(1)	118.6(2)
C(8)-C(9)-C(10)	119.2(3)
C(8)-C(9)-H(9)	120.4
C(10)-C(9)-H(9)	120.4
C(9)-C(10)-C(5)	120.6(3)
C(9)-C(10)-H(10)	119.7
C(5)-C(10)-H(10)	119.7
O(2)-C(11)-O(1)	125.4(3)
O(2)-C(11)-C(2)	123.6(3)
O(1)-C(11)-C(2)	111.0(2)
O(1)-C(12)-C(14)	110.1(3)
O(1)-C(12)-C(13)	101.8(3)
C(14)-C(12)-C(13)	111.2(4)
O(1)-C(12)-C(15)	109.8(2)
C(14)-C(12)-C(15)	111.7(3)
C(13)-C(12)-C(15)	111.8(4)
C(12)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(12)-C(14)-H(14A)	109.5
C(12)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(12)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5

C(12)-C(15)-H(15A)	109.5
C(12)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(12)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
O(4)-C(16)-O(3)	124.2(2)
O(4)-C(16)-C(4)	125.1(2)
O(3)-C(16)-C(4)	110.6(2)
O(3)-C(17)-H(17A)	109.5
O(3)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
O(3)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5

Table 6. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for pyrrolidine **16**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
Br(1)	28(1)	71(1)	66(1)	-7(1)	6(1)	1(1)
O(1)	47(1)	30(1)	28(1)	0(1)	-1(1)	3(1)
O(2)	65(1)	27(1)	43(1)	3(1)	-6(1)	0(1)
O(3)	27(1)	36(1)	63(1)	-1(1)	11(1)	0(1)
O(4)	36(1)	28(1)	63(1)	-2(1)	11(1)	3(1)
N(1)	29(1)	39(1)	27(1)	-8(1)	9(1)	-1(1)
C(1)	30(1)	26(1)	27(1)	4(1)	9(1)	3(1)
C(2)	33(1)	26(1)	24(1)	-2(1)	7(1)	3(1)
C(3)	32(1)	31(1)	31(1)	-1(1)	13(1)	0(1)
C(4)	28(1)	30(1)	25(1)	3(1)	5(1)	3(1)
C(5)	31(1)	28(1)	25(1)	3(1)	7(1)	0(1)
C(6)	32(1)	34(1)	33(1)	-4(1)	10(1)	-3(1)
C(7)	32(1)	37(2)	38(1)	-2(1)	11(1)	2(1)
C(8)	26(1)	44(2)	34(1)	5(1)	6(1)	2(1)
C(9)	36(1)	37(2)	49(2)	-4(1)	8(1)	-9(1)
C(10)	35(1)	29(1)	49(2)	-2(1)	9(1)	1(1)
C(11)	38(1)	31(1)	28(1)	0(1)	10(1)	0(1)
C(12)	52(2)	40(2)	29(1)	4(1)	-3(1)	11(1)
C(13)	149(5)	64(3)	77(3)	-12(2)	-69(3)	17(3)
C(14)	73(3)	115(4)	60(2)	51(3)	29(2)	30(3)
C(15)	61(2)	91(3)	54(2)	27(2)	17(2)	31(2)
C(16)	29(1)	33(1)	29(1)	-2(1)	7(1)	2(1)
C(17)	38(1)	43(2)	86(2)	-9(2)	22(1)	-10(2)

Table 7. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for pyrrolidine **16**.

	x	y	z	U(eq)
H(1)	-340	2993	5393	38
H(1A)	-75	7330	6088	33
H(2)	-119	7411	7770	34
H(3A)	-1999	6525	7036	37
H(3B)	-1688	3938	7480	37
H(4)	-2162	5362	5413	34
H(6)	1454	2304	6017	39
H(7)	3474	1978	6457	43
H(9)	3840	8349	7783	50
H(10)	1833	8680	7357	46
H(13A)	2986	6575	10263	181
H(13B)	3225	4724	11173	181
H(13C)	2076	6237	10869	181
H(14A)	746	2788	10465	121
H(14B)	1883	1293	10950	121
H(14C)	1045	681	9833	121
H(15A)	2429	1150	8911	103
H(15B)	3430	1498	9970	103
H(15C)	3231	3399	9083	103
H(17A)	-3852	-1122	5220	83
H(17B)	-4927	447	5217	83
H(17C)	-4027	-344	6279	83

Table 8. Torsion angles [$^{\circ}$] for pyrrolidine **16**.

C(4)-N(1)-C(1)-C(5)	164.77(19)
C(4)-N(1)-C(1)-C(2)	38.9(2)
N(1)-C(1)-C(2)-C(11)	86.0(2)
C(5)-C(1)-C(2)-C(11)	-40.2(3)
N(1)-C(1)-C(2)-C(3)	-32.1(2)
C(5)-C(1)-C(2)-C(3)	-158.3(2)
C(11)-C(2)-C(3)-C(4)	-103.5(2)
C(1)-C(2)-C(3)-C(4)	13.2(2)
C(1)-N(1)-C(4)-C(16)	-150.4(2)
C(1)-N(1)-C(4)-C(3)	-30.2(2)
C(2)-C(3)-C(4)-N(1)	9.5(3)
C(2)-C(3)-C(4)-C(16)	130.5(2)
N(1)-C(1)-C(5)-C(6)	-9.7(3)
C(2)-C(1)-C(5)-C(6)	111.7(3)
N(1)-C(1)-C(5)-C(10)	173.0(2)
C(2)-C(1)-C(5)-C(10)	-65.5(3)
C(10)-C(5)-C(6)-C(7)	0.4(4)
C(1)-C(5)-C(6)-C(7)	-176.8(2)
C(5)-C(6)-C(7)-C(8)	-0.3(4)
C(6)-C(7)-C(8)-C(9)	0.0(4)
C(6)-C(7)-C(8)-Br(1)	179.7(2)
C(7)-C(8)-C(9)-C(10)	0.2(4)
Br(1)-C(8)-C(9)-C(10)	-179.5(2)
C(8)-C(9)-C(10)-C(5)	-0.1(4)
C(6)-C(5)-C(10)-C(9)	-0.2(4)
C(1)-C(5)-C(10)-C(9)	177.1(3)
C(12)-O(1)-C(11)-O(2)	-0.3(4)
C(12)-O(1)-C(11)-C(2)	-177.6(2)
C(3)-C(2)-C(11)-O(2)	46.2(3)
C(1)-C(2)-C(11)-O(2)	-66.5(3)
C(3)-C(2)-C(11)-O(1)	-136.4(2)
C(1)-C(2)-C(11)-O(1)	110.8(2)
C(11)-O(1)-C(12)-C(14)	-59.5(4)
C(11)-O(1)-C(12)-C(13)	-177.5(4)
C(11)-O(1)-C(12)-C(15)	63.8(4)
C(17)-O(3)-C(16)-O(4)	4.4(4)
C(17)-O(3)-C(16)-C(4)	-171.5(2)

N(1)-C(4)-C(16)-O(4)	23.9(3)
C(3)-C(4)-C(16)-O(4)	-94.9(3)
N(1)-C(4)-C(16)-O(3)	-160.3(2)
C(3)-C(4)-C(16)-O(3)	80.9(2)

500 anisidy1
Pulse Sequence: s2pu1

500 pBrPh
Pulse Sequence: s2pu1

500 cyano
Pulse Sequence: s2pu1

500 naphibu
Pulse Sequence: s2pu1

500 tolyl
Pulse Sequence: s2pu1

500 crotonate
Pulse Sequence: s2pu1

500 cinnendo
Pulse Sequence: s2pu1

500 cinnaxeo
Pulse Sequence: s2pu1

500 alaacr1
Pulse Sequence: s2pu1

500 1eu
Pulse Sequence: s2pu1

500 phala
Pulse Sequence: s2pul

500 phindme
Pulse Sequence: s2pul

500 solid
Pulse Sequence: s2pu1