Stereocontrol in the synthesis of cyclic amino acids: a new ligand for directed hydrogenation through hydrogen bonding

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General Experimental Protocol

NMR spectra (^{1}H and ^{13}C) were recorded on ECA400 (400 MHz), AV400 (400 MHz), BBFO400 (400MHz) or AV-500 (500 MHz) spectrometer. ^{1}H chemical shifts are referenced to TMS (δ 0.00 ppm for $CDCl_3$ solutions) or H_2O (δ 4.79 ppm for D_2O solutions). ^{13}C chemical shifts are referenced to $CDCl_3$ (δ 77.0 ppm for $CDCl_3$ solutions) or MeOH (internal standard, δ 49.5 ppm for D_2O solutions). When encountered, non-first order multiplets in the ^{1}H NMR spectra are noted as 'nfom', followed by the second order pattern, if possible. The following format is used to report resonances: chemical shift (ppm) [multiplicity, coupling constant(s) (Hz), integral (to the nearest integer)]. In cases of severely overlapping peaks, the integration of individual contributing peaks is assumed to be the expected value. For example, if four individual CH's are overlapped between 1.4 and 1.2 ppm and the integral value over that range equals 4, it is assumed that each resonance corresponds to one ("1H") proton.

Infrared spectra were measured on a Shimadzu IR Prestige-21 FTIR spectrophotometer. Only the more intense and/or diagnostic peaks are reported; spectra were collected on a KBr plate.

High-resolution mass spectrometry (HRMS) measurements were obtained on a Micromass® Q-Tof Premier™ (ESI-TOF) instrument using electrospray ionization mode (ESI). Samples were introduced as methanol solutions.

Specific Optical Rotation was measured on a JASCO P-1030 polarimeter in a 1 mL, 10 mm length polarimeter cell.

Flash chromatography columns were packed with E. Merck silica gel (230-400 mesh). Thin layer chromatography (TLC, silica gel) was performed on glass-backed plates that were visualized by UV detection and/or by dipping into a solution of potassium permanganate or ceric ammonium molybdate (CAM) and heating.

Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware. Anhydrous CH_2Cl_2 was freshly distilled from CaH_2 under nitrogen. Anhydrous THF was freshly distilled from sodium metal and benzophenone under nitrogen. Anhydrous toluene was freshly distilled from sodium metal under nitrogen. Anhydrous ethanol and methanol were distilled from activated magnesium under nitrogen. All other chemicals were obtained commercially and used as received.

General Experimental Procedure for the directed hydrogenation

To a solution of ligand **6** (12% mol) in CH_2Cl_2 in a Fischer – Porter tube was added a solution of bis(norbornadiene)rhodium(I) tetrafluoroborate (10% mol) in CH_2Cl_2. The solution was stirred for 30 min at room temperature under nitrogen. The substrate (1.0 eq) in CH_2Cl_2 was then added dropwise to the solution. The tube was charged with H_2 to 100 psi and stirred for 16-60 h at room temperature. The final concentration of the substrate is ca 0.05 – 0.2 M.[1] The mixture was filtered through a short pad of Celite and concentrated. The residue was purified by flash chromatography, eluting with 20-30% EtOAc/Hexane to give the target hydrogenated product.
Note: (1) The quality of the catalyst is crucial for the reaction. A good source of catalyst will give a clear orange solution upon dissolving the catalyst in CH_2Cl_2, while a bad bottle of catalyst will give a cloudy solution with some dark precipitate.

Good $Rh(nbd)_2BF_4$

Bad $Rh(nbd)_2BF_4$

(2) Before charging hydrogen, the solution is a clear orange or clear dark orange solution. Upon charging hydrogen, the solution will slowly change into dark yellow colour, and eventually dark colour at the end of the reaction. If the reaction did not proceed well, the solution is dark yellow at the end of the reaction.

Before adding the substrate

Before charging hydrogen gas

10 minutes after
charging hydrogen gas

At the end of the reaction

[1] A higher concentration may be used for larger scale reactions

A failed hydrogenation

(3) A new O-ring is used for each hydrogenation. The reaction conditions appeared to be destructive to the O-ring, causing pressure leaking in many cases. Hence, hydrogen pressure must be monitored carefully, and a new O-ring needs to be used to replace the destroyed one immediately.

Detailed Experimental Procedure

Ligand 6[2]

To a solution of aryl ether **5** (744 mg, 3.00 mmol, 1.0 eq), $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol, 0.5% mol), and triethylamine (460 µL, 3.3 mmol, 1.1 eq) in anhydrous toluene (20 mL) was added diphenylphosphine (522 µL, 3.0 mmol, 1.0 eq) under nitrogen. The reaction mixture was heated at reflux for 24 h. The reaction was then cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 0.5% EtOAc/Hexane, to give ligand **6** as a colorless solid, which was further recrystallized from ethanol to afford the pure product as colourless crystals (715 mg, 78%).

m.p: 95-97 °C

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 1H), 7.38 – 7.17 (m, 12H), 6.91 – 6.88 (m, 1H), 4.64 (d, JHP = 1.5 Hz, 2H), 3.26 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.7 (d, J = 23.0 Hz), 136.7 (d, J = 10.5 Hz), 135.5 (d, J = 15.3 Hz), 134.0 (d, J = 20.1 Hz), 133.5, 128.9 (d, J = 21.1 Hz), 128.8, 128.6 (d, J = 7.7 Hz), 127.8 (d, J = 6.7 Hz), 127.8, 72.7 (d, J = 23.0), 58.2

^{31}P-NMR (162 MHz, $CDCl_3$) δ – 15.09 (s)

MS (ESI+) m/z 307 ($[M+1]^+$, 100)

Sulfonamide 9a

To a solution of sulfonamide **7**[3] (483 mg, 2.00 mmol, 1.0 eq) in DMF (8 mL) was added Cs_2CO_3 (1.30 g, 4.00 mmol, 2.0 eq). The mixture was stirred at room temperature for 25 min. Methallyl chloride (0.30 mL, 3.06 mmol, 1.5 eq) was then added dropwise, followed by KI (332mg, 2.00 mmol, 1.0 eq). The solution was stirred at room temperature for 4 h until TLC shown completion. The mixture was diluted with water (60 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography, eluting with 20-30% EtOAc/hexane to give sulfonamide **9a** as a pale yellow oil (528 mg, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 5.49 (ddd, J = 17.6, 10.6 & 7.2 Hz, 1H), 5.14 (d, J = 10.6 Hz, 1H), 4.98 (br s, 1H) 4.97 (d, J = 17.6 Hz, 1H), 4.93 (br s, 1H), 4.28 (br q, J = 7.2 Hz, 1H), 3.90 (d, J = 15.7 Hz, 1H), 3.78 (ddd, J = 11.6, 8.3 & 6.0 Hz, 1H), 3.68 (d, J = 15.7 Hz, 1H), 3.72 – 3.64 (m, 1H), 2.43 (s, 3H), 2.21 (t, J = 6.0 Hz, 1H), 1.78 (s, 3H)

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[2] D. K. Dutta, B. Deb, G. Hua, J. D. Woolins, *J. Mol. Cat. A* **2012**, *353-354*, 7; W. E. McEwen, J. E. Fountaine, D. N. Schulta, W.-I. Shiau, *J. Org. Chem.* **1976**, *41*, 1684.

[3] Prepared by hydrolysis [(a) A. Joosten, A. K. Å. Persson, R. Millet, M. T. Johnson, J.-E. Bäckvall, *Chem. Eur. J.* **2012**, *18*, 15151-15157] of the corresponding cyclic carbamate [(b) A. Lei, G. Liu, X. Lu, *J. Org. Chem.* **2002**, *67*, 974-980.]

^{13}C NMR (100 MHz, $CDCl_3$) δ143.5, 142.2, 137.5, 132.1, 129.6, 127.2, 120.3, 113.9, 63.1, 62.4, 51.5, 21.5, 19.9)

FTIR (neat, cm^{-1}): 3442 (br), 3078, 3028, 2974, 2922, 2733, 1919, 1811, 1651, 1597, 1494, 1454, 1327, 1215, 1157, 1093, 906, 876, 841, 814779, 768, 737, 706, 667.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_3S$: 296.1320; found: 296.1319

Sulfonamide 9b

To a solution of sulfonamide **7** (300 mg, 1.24 mmol, 1.0 eq) in DMF (8 mL) was added Cs_2CO_3 (808 mg, 2.48 mmol, 2.0 eq). The mixture was stirred at room temperature for 25 min. Allylic bromide **8b**[4] (479 mg, 2.48 mmol, 2.0 eq) was then added dropwise, followed by KI (206 mg, 1.24 mmol, 1.0 eq). The solution was let to stir at room temperature for 4 h until TLC shown completion. The mixture was diluted with water (60 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography, eluting with 25-40% EtOAc/hexane to give sulfonamide **9b** as a pale yellow oil (528 mg, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 6.32 (s, 1H), 6.07 (s, 1H), 5.53 (ddd, J = 17.8, 10.7, 6.4 Hz, 1H), 5.18 (dt, J = 10.7 & 1.3 Hz, 1H), 5.12 (dt, J = 17.8 & 1.3 Hz, 1H), 4.56 (qt, J = 6.4 & 1.3 Hz, 1H), 4.12 (nfom, ABX_3 pattern, $J_{AX} = J_{BX} = 7.0$ & $J_{AB} = 20.5$Hz, 2H), 3.99 (nfom, ABXY pattern, $J_{AB} = 16.5$, $J_{AX} = J_{AY} = 1.3$ Hz, $J_{BX} = J_{BY} = 1.5$ Hz, 2H), 3.72 (nfom, ABXY pattern, $J_{AB} = 12$ Hz , $J_{AX} = 5.3$ Hz , $J_{AY} = 8.7$ Hz, $J_{BX} = 7.8$ Hz, $J_{BY} = 5.6$ Hz, 2H), 2.88 (dd, J = 5.3 & 5.6 Hz, 1H), 2.42 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 143.4, 137.6, 136.5, 132.3, 129.5, 128.6, 127.5, 119.9, 62.5, 62.4, 61.1, 45.3, 21.4, 14.0

FTIR (neat, cm^{-1}): 3474 (br), 3090, 2879, 2058, 1699, 1636, 1599, 1492, 1454, 1404, 1375, 1334, 1303, 1267, 1157, 1093, 1047, 1026, 952, 816, 737, 704, 669

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{23}NO_5SNa$: 376.1195; found: 376.1190

Dihydropyrrole 10a

A solution of sulfonamide **9a** (289 mg, 0.978 mmol, 1.0 eq) in toluene (98 mL, 0.01 M) was thoroughly degassed for 20 min by bubbling nitrogen gas and heated to 70 ºC under a continuous nitrogen flow. A solution of Grubbs I catalyst (40 mg, 0.0489 mmol, 5% mol) in toluene (5ml) was added portionwise (1 mL/h). After adding the last portion, the mixture was further stirred overnight (ca 12h) at the same temperature. The solution was then concentrated, and the residue was purified by

[4] Prepared according to: J. Villieras, M. Rambaud, *Org. Syn.* **1993**, Coll. Vol. 8, 265-267.

flash chromatography, eluting with 30-50% EtOAc/hexane to give **10a** as a brownish oil (239 mg, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 5.15 (app sep, J = 1.7 Hz, 1H), 4.41 (m, 1H), 4.10 (br dd, J = 14.4 & 4.9 Hz, 1H), 3.96 (br d, J = 14.4 Hz, 1H), 3.76 (br dd, J = 11.5 & 2.7 Hz, 1H), 3.68 (dd, J = 11.5 & 5.5 Hz, 1H), 3.04 (brs, 1H), 2.43 (s, 3H), 1.66 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 136.2, 133.8, 129.8, 127.4, 120.6, 69.7, 65.9, 59.1, 21.4, 13.8.

FTIR (neat, cm^{-1}): 3506 (br), 3064, 2974, 2918, 2864, 1925, 1732, 1670, 1597, 1492, 1445, 1339, 1246, 1198, 1159, 1096, 1072, 1041, 964, 891, 842, 816, 734, 709, 669.

HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{17}NO_3SNa$: 290.0827; found: 290.0826.

Dihydropyrrole 12

A solution of sulfonamide **9b** (349 mg, 0.988 mmol, 1.0 eq) in toluene (100 mL, 0.01 M) was thoroughly degassed for 20 min by bubbling nitrogen gas and heated to 70 ºC under a continuous nitrogen flow. A solution of Grubbs II catalyst (25 mg, 0.0296 mmol, 3% mol) in toluene (5ml) was added portionwise (1 mL/h). After adding the last portion, the mixture was further stirred overnight (ca 12h) at the same temperature. The solution was then concentrated, and the residue was purified by flash chromatography, eluting with 30-50% EtOAc/hexane to give **12** as a brownish oil (275 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.46 (q, J = 2.1 Hz, 1H), 4.60-4.56 (m, 1H), 4.41 (ddd, J = 14.8, 5.8, 2.1 Hz, 1H), 4.27 (ddd, J = 14.8, 2.9 & 2.1 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.91 (ddd, J = 11.2, 7.4 & 3.6 Hz, 1H), 3.82 (app dt, J = 11.2, 5.7, 1H) 2.66 (dd, J = 7.4 & 5.7 Hz, 1H), 2.44 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 144.2, 137.0, 133.3, 132.3, 130.0, 127.5, 69.9, 65.2, 61.0, 54.9, 21.5, 14.0.

FTIR (neat, cm^{-1}): 3445 (br), 3090, 2981, 2935, 2876, 1933, 1732, 1634, 1597, 1494, 1337, 1242, 1163, 1096, 1016, 920, 885, 860, 816, 741, 708, 652

HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}NO_5S$: 326.1062; found: 326.1074

Dihydropyrrole 10b

To a solution of dihydropyrrole **10a** (71 mg, 0.266 mmol, 1.0 eq) in toluene (5mL) was added tetrabutylammonium iodide (20mg, 0.0531mmol, 20% mol), powdered NaOH (32mg, 0.798 mmol, 3.0 eq), and iodomethane (83 μL, 1.33 mmol, 5.0 eq). The mixture was stirred at 40 °C overnight (ca 14h) until TLC shown completion. Water (10 mL) was added, and the organic layer was separated. The remaining

aqueous layer was further extracted with CH_2Cl_2 (3 x 10mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography, eluting with 20-30% EtOAc/Hexane, to give **10b** as a yellow solid (63mg, 84%)

m.p: 82 – 84 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 5.32 (br s, 1H), 4.47-4.42 (m, 1H), 4.04 (dd, J = 14.2 & 4.7 Hz, 1H), 3.93 (d, J = 14.2 Hz, 1H), 3.77 (dd, J = 9.0 & 3.7 Hz, 1H), 3.44 (dd, J = 9.0 & 7.6 Hz, 1H), 3.37 (s, 3H), 2.42 (s, 3H), 1.65 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 135.3, 134.4, 129.7, 127.4, 122.1, 76.0, 66.6, 59.3, 58.6, 21.5, 13.9.

FTIR (nujol oil, cm^{-1}): 3047, 1930, 1668, 1651, 1595, 1344, 1200, 1159, 1119, 1096, 1080, 1042, 966, 891, 833, 721, 667.

HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{19}NO_3SNa$: 304.0983; found: 304.0986

Dihydropyrrole 10c

To a solution of the alcohol **10a** (100 mg, 0.38 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) at 0 ºC was added triethylamine (0.1 mL, 76 mg, 0.76 mmol, 2.0 eq) dropwise. Acetic anhydride (46 mg, 0.44 mmol, 1.2 eq) was then slowly added to the mixture. The reaction was warmed up to room temperature and stirred for 2h until TLC shown completion. The reaction was quenched with saturated $NaHCO_3$ solution (5 mL) and washed with brine (3 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated. The residues were purified by flash chromatography, eluting with a 20-30% EtOAc/hexane to give acetate **10c** as a colorless solid (112 mg, 95% yield).

m.p: 85 – 88 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 5.19 (app sep, J = 1.7 Hz, 1H), 4.62-4.57 (m, 1H), 4.36 (dd, J = 11.0 & 4.2 Hz, 1H), 4.13 (dd, J = 11.0 & 5.8 Hz, 1H), 4.05 – 4.00 (m, 1H), 3.99 – 3.93 (m, 1H), 2.43 (s, 3H), 2.04 (s, 3H), 1.66 (br s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 143.6, 136.7, 129.8, 127.5, 120.6, 117.2, 66.5, 65.8, 58.5, 21.5, 20.8, 13.9.

FTIR (nujol oil, cm^{-1}): 2723, 2667, 1931, 1732, 1645, 1595, 1301, 1250, 1163, 1040, 970, 893, 820, 721, 667.

HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{19}NO_4SNa$: 332.0932; found: 332.0937

Dihydropyrrole azide 10e

To a solution of **10a** (240mg, 0.898 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) was added triethylamine (0.25 mL, 1.80 mmol, 2.0 eq). The solution was then cooled down to 0 °C in an ice bath. Methanesulfonyl chloride (0.14 mL, 1.80 mmol, 2.0 eq) was then added dropwise. The mixture was left to warm up to room temperature and stirred overnight (ca 14h) until TLC shown completion. The reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the crude mesylate **10d**,[5] which was used in the next step without further purification.

To a solution of unpurified **10d** in DMSO (5 mL) was added sodium azide (292 mg, 4.49 mmol, 5.0 eq). The mixture was heated to 60 ºC and left to stir overnight (ca 14h). After completion of the reaction, the mixture was poured into water (50 mL) and extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography, eluting with a 20-30% EtOAc/hexane to give **10e** as colorless oil (151 mg, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 5.21 (app sep, J = 1.5 Hz, 1H), 4.56 – 4.50 (m, 1H), 4.06 (br dd, J = 14.4 & 4.9 Hz, 1H), 3.95 (br d, J = 14.4 Hz, 1H), 3.65 (dd, J = 12.4 & 5.8 Hz, 1H), 3.50 (dd, J = 12.4 & 3.1 Hz, 1H), 2.43 (s, 3H), 1.66 (app p, J = 1.5, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 137.1, 134.2, 129.9, 127.5, 120.9, 66.7, 58.6, 55.4, 21.6, 14.0.

FTIR (neat, cm^{-1}): 3063, 2916, 2862, 2099, 1923, 1672, 1597, 1492, 1443, 1340, 1266, 1198, 1159, 1096, 891, 814, 734, 661.

HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{16}N_4O_2SNa$: 315.0892; found: 315.0909

Amide 10f

Triphenylphosphine (115 mg, 0.44 mmol), followed by benzoic acid (54 mg, 0.44 mmol) were added to a solution of azide **10e** (65 mg, 0.22 mmol) in toluene (4 mL). The mixture was heated at gentle reflux until TLC showed completion (ca 12h). The mixture was then concentrated, and the residue was purified by flash chromatography, eluting with 50-60% EtOAc/hexane to give amide **10f** as a colourless solid (77 mg, 95% yield).

m.p: 152 °C (dec)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.86 (m, 2H), 7.72 – 7.68 (m, 2H), 7.52-7.42 (m, 3H), 7.41 (br s, 1H) 7.31 (d, J = 8.2 Hz, 2H), 5.20 (app sep, J = 1.70 Hz, 1H), 4.55-4.50 (m, 1H), 4.13-4.07 (m, 1H), 4.01-3.96 (m, 1H), 3.87 (ddd, J = 14.0, 6.5, 2.7 Hz, 1H), 3.43 (dddd, J = 14.0, 7.2, 4.4 Hz, 1H). 2.42 (s. 3H), 1.63 (br s, 3H).

[5] Prepared according to Y. Schramm, M. Takeuchi, K. Semba, Y. Nakao, J. F. Hartwig, *J. Am. Chem. Soc.* **2015**, *137*, 12215-12218.

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 144.0, 136.3, 134.3, 133.7, 131.4, 129.9, 128.5, 127.5, 127.0, 121.5, 67.8, 59.0, 44.5, 21.5, 13.8

FTIR (nujol oil, cm^{-1}): 3308 (br), 2723, 2669, 1695, 1632, 1601, 1577, 1537, 1310, 1229, 1198, 1153, 1090, 972, 939, 887, 851, 812, 801, 775, 721, 690, 663.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{20}H_{23}N_2O_3S$: 371.1429; found: 371.1304

Sulfonamide 10g

To a solution of **10e** (114 mg, 0.340 mmol, 1.0 eq) in THF/H_2O solution (5 mL, 10/1 v/v) was added triphenylphosphine (307 mg, 1.17 mmol, 3.0 eq). The mixture was stirred at room temperature for 12h until TLC shown completion. The solution was acidified by HCl 2M solution (10 mL). The organic layer was separated, and the remaining aqueous layer was further washed with EtOAc (3 x 10 mL). The aqueous solution was then added NaOH 2M solution until pH 14. The solution was then extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the crude amine.
To a solution of crude amine in CH_2Cl_2 (5mL) was added triethylamine (68 μL, 0.488 mmol, 1.4 eq). The solution was then cooled down to 0 °C in an ice bath. Methanesulfonyl chloride (40 μL, 0.488 mmol, 1.4 eq) was then added dropwise. The mixture was left to warm up to room temperature and stirred overnight (ca 14h) until TLC shown completion. The reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography, eluting with 50% EtOAc/Hexane to give sulfonamide **10g** as a white crystalline solid (74 mg, 63% over 2 steps)

m.p: 125 – 127 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 5.16-5.13 (m, 2H), 4.46 – 4.45 (m, 1H), 4.08 (br dd, J = 14.3 & 5.2 Hz, 1H), 3.92 (br d, J = 14.3 Hz, 1H), 3.52 (ddd, *J* = 13.2, 6.6, 3.8 Hz, 1H), 3.30 (ddd, *J* = 13.3, 5.5, 4.6 Hz, 1H), 3.02 (s. 3H), 2.44 (s, 3H), 1.67 (br s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 137.1, 133.3, 130.0, 127.5, 120.8, 67.1, 59.1, 47.5, 40.2, 21.5, 13.9.

FTIR (nujol oil, cm^{-1}): 3287 (br), 2773, 2667, 1925, 1670, 1601, 1304, 1238, 1142, 1092, 976, 895, 826, 772, 721

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{14}H_{21}N_2O_4S_2$: 345.0943; found: 345.0956

Pyrrolidine 11a

To a solution of ligand **6** (10 mg, 0.0322 mmol, 12% mol) in CH_2Cl_2 (1.0 mL) in a Fischer – Porter tube was added a solution of bis(norbornadiene)rhodium(I) tetrafluoroborate (10 mg, 0.0278 mmol, 10% mol) in CH_2Cl_2 (2.0 mL). The solution was stirred for 30 min at room temperature under nitrogen. Dihydropyrrole **10a** (74 mg, 0.278 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) was then added dropwise to the solution. The tube was charged with H_2 to 100 psi and stirred for 16h at room temperature. The mixture was filtered through a short pad of Celite and concentrated. The residue was purified by flash chromatography, eluting with 20-30% EtOAc/Hexane to give pyrrolidine **7a** (68mg, 92%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 3.75-3.65 (m, 3H), 3.61 (dd, J = 9.2 & 6.6 Hz, 1H), 2.76 (brs, 1H), 2.65 (t, *J* = 9.2 Hz, 1H), 2.45 (s, 3H), 2.39-2.26 (m, 1H), 1.86-1.81 (m, 1H), 1.29-1.22 (m, 1H), 0.80 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 133.5, 129.7 (2C), 127.7 (2C), 66.2, 61.6, 56.6, 37.0, 31.8, 21.5, 17.1

FTIR (neat, cm^{-1}): 3500 (br), 3061, 2961, 2928, 2874, 1923, 1643, 1597, 1493, 1454, 1400, 1382, 1339, 1271, 1248, 1213, 1186, 1159, 1093, 1039, 1015, 947, 902, 866, 816, 737, 710, 665

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{20}NO_3S$: 270.1164; found: 270.1157

Pyrrolidine 13

To a solution of ligand **6** (32 mg, 0.101 mmol, 12% mol) in CH_2Cl_2 (1.0 mL) in a Fischer – Porter tube was added a solution of bis(norbornadiene)rhodium(I) tetrafluoroborate (32 mg, 0.0437 mmol, 10% mol) in CH_2Cl_2 (2.0 mL). The solution was stirred for 30 min at room temperature under nitrogen. Dihydropyrrole **12** (275 mg, 0.845 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) was then added dropwise to the solution. The tube was charged with H_2 to 100 psi and stirred for 30 h at room temperature. The mixture was filtered through a short pad of Celite and concentrated. The residue was purified by flash chromatography, eluting with 30-40% EtOAc/Hexane to give pyrrolidine **13** (246, 89%) as yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 3.99 (nfom, ABX_3 pattern, J_{AB} = 10.5 Hz, J_{AX} = J_{BX} = 7.1 Hz), 3.80 – 3.65 (m, 4H), 3.34 (dd, J = 9.9 & 8.5 Hz), 3.13 (m, 1H), 2.69 (br s, 1H), 2.44 (s, 3H), 2.05 (ddd, J = 12.8, 7.2 & 3.5 Hz, 1H), 1.92 (dt, J = 12.8 & 8.7 Hz, 1H), 1.18 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 144.0, 133.3, 129.8, 127.7, 65.5, 61.2, 61.0, 51.7, 41.7, 31.8, 21.5, 14.0.

FTIR (neat, cm^{-1}): 3499 (br), 3061, 2982, 2941, 2878, 2361, 1921, 1732, 1645, 1597, 1495, 1454, 1396, 1379, 1337, 1159, 1092, 1037, 910, 876, 816, 735, 708, 668

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_5S$: 328.1219; found: 328.1222

Sulfonamide 17

To a solution of 3-methylbut-3-en-1-ol (1.0 mL, 9.91 mmol, 1.0 eq) and triethylamine (1.66 mL, 11.9 mmol, 1.2 eq) in CH_2Cl_2 (20 mL) at 0 ºC was added methanesulfonyl chloride (0.92 mL, 11.9 mmol, 1.2 eq) dropwise. The mixture was warmed up to room temperature and stirred overnight (ca 12h) until TLC shown completion. The reaction was quenched with saturated $NaHCO_3$ solution (20 mL). The organic layer was separated, and the remaining aqueous layer was further extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the crude mesylate **16** (1.45 g, 90%), which was used without further purification.

To a solution of sulfonamide **7** (362 mg, 1.50 mmol, 1.0 eq) in DMF (4 mL) was added Cs_2CO_3 (977 mg, 3.00 mmol, 2.0 eq). The mixture was stirred at room temperature for 25 min. Mesylate 10 (369 mg, 2.25 mmol, 1.5 eq) was then added dropwise, followed by KI (249 mg, 1.50 mmol, 1.0 eq). The solution was heated to 60 °C and stirred overnight (ca 14h) until TLC shown completion. The mixture was diluted with water (60 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography, eluting with 25-40% EtOAc/hexane to give sulfonamide **17** as a pale yellow oil (361 mg, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 7.9 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 5.48 (ddd, J = 17.0, 10.7, 6.0 Hz, 1H), 5.15 (d, J = 10.7 Hz, 1H), 5.03 (d, J = 17.0 Hz, 1H), 4.78 (br s, 1H), 4.69 (br s, 1H), 4.40 (app q, J = 7.1 Hz, 1H), 3.76-3.66 (m, 2H), 3.34 (ddd, J = 15.1, 10.1 & 5.5 Hz 1H), 3.14 (ddd, J = 15.1, 10.3 & 5.7 Hz, 1H), 2.47-2.39 (m, 1H), 2.41 (s, 3H), 2.36-2.28 (m, 1H), 2.19 (brs, 1H), 1.73 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 142.7, 137.3, 132.5, 129.6, 127.3, 119.5, 111.9, 62.6, 61.7, 43.8, 39.2, 22.5, 21.5

FTIR (neat, cm^{-1}): 3447, 3074, 3028, 2968, 2937, 2880, 2733, 1919, 1802, 1736, 1674, 1597, 1494, 1454, 1242, 1153, 1096, 997, 891, 843, 814, 752

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{23}NO_3SNa$: 332.1296; found: 332.1300

$[\alpha]_D^{25}$ = -49.03° (c = 0.03, $CHCl_3$, (R)-isomer)

Tetrahydropyridine 18

A solution of sulfonamide **17** (272 mg, 0.879 mmol, 1.0 eq) in toluene (90mL) was thoroughly degassed for 20 min by continuously bubbling nitrogen. The solution was then heated to 70 ºC under a continuous nitrogen flow. A solution of Grubbs I (36 mg, 0.044 mmol, 5% mol) in toluene (5 mL) was added portionwise (1mL/h). After adding the last portion, the mixture was further stirred for overnight (ca 12h) until TLC shown completion. The solution was concentrated, and the residue was purified by flash chromatography, eluting with a gradient of 50% EtOAc/hexane to give **18** as brownish oil (226 mg, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 5.26-5.23 (m, 1H), 4.32 (br s, 1H), 3.92 (dd, J = 14.6 & 6.0 Hz, 1H), 3.63-3.54 (m, 2H), 3.20 (ddd, J = 14.6, 11.8, 4.4 Hz, 1H), 2.41 (s, 3H), 2.32 (br s, 1H), 1.82 – 1.71 (m, 1H), 1.62 (dd, J = 17.3 & 4.4 Hz, 2H), 1.55 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 137.7, 135.6, 129.6, 127.0, 117.2, 64.0, 56.0, 39.0, 27.6, 23.3, 21.5

FTIR (neat, cm^{-1}): 3522 (br), 3509, 3028, 2963, 2932, 2914, 2879, 1923, 1678, 1597, 1494, 1448, 1381, 1334, 1286, 1221, 1153, 1101, 1063, 1040, 1020, 949, 889, 866, 816, 771, 737, 709, 687, 637.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_3S$: 282.1164; found: 282.1168

$[\alpha]_D^{25}$ = +765.7° (c = 0.056, $CHCl_3$, (R)-isomer)

Piperidine 19

To a solution of ligand **6** (26 mg, 0.0853 mmol, 12% mol) in CH_2Cl_2 (1.0 mL) in a Fischer – Porter tube was added a solution of bis(norbornadiene)rhodium(I) tetrafluoroborate (27 mg, 0.0711 mmol, 10% mol) in CH_2Cl_2 (2.0 mL). The solution was stirred for 30 min at room temperature under nitrogen. Tetrahydropyridine **19** (200 mg, 0.711 mmol, 1.0 eq) in CH_2Cl_2 (2 mL) was then added dropwise to the solution. The tube was charged with H_2 to 100 psi and stirred for 60 h at room temperature. The mixture was filtered through a short pad of Celite and concentrated. The residue was purified by flash chromatography, eluting with 30-40% EtOAc/Hexane to give pyrrolidine **7a** (246, 89%) as yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 4.13-4.08 (m, 1H), 3.88 (dddd, J = 14.3, 4.7, 2.4 & 1.1, 1H), 3.83 (dd, J = 11.3 & 9.3 Hz, 1H), 3.52 (dd, J = 11.3 & 5.5 Hz), 3.07 (ddd, J = 14.5, 13.4 & 2.7 Hz), 2.43 (s, 3H), 1.70 – 1.40 (m, 4H), 0.98 (ddd, J = 19.2, 13.4 & 5.5 Hz, 1H), 0.91 – 0.80 (m, 1H), 0.78 (d, J = 6.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.2, 129.7, 126.9, 60.9, 54.8, 41.1, 33.3, 32.7, 25.5, 22.1, 21.4.

FTIR (neat, cm^{-1}): 3418 (br), 3063, 2951, 2926, 2872, 2359, 2342, 1921, 1645, 1597, 1495, 1454, 1337, 1306, 1263, 1201, 1153, 1049, 999, 972, 961, 945, 916, 889, 816, 735, 718, 661, 618.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{21}NO_3SNa$: 306.1140; found: 306.1137

$[\alpha]_D^{25}$ = +36.42° (c =0.072, $CHCl_3$, (*R*, *R*)-isomer)

Diene 9c

To a solution of sulfonamide alcohol (*S*)-**7** (2.47 g, 10.2 mmol, 1.0 eq) in DMF (50 ml) was added cesium carbonate (7.34 g, 22.5 mmol, 2.2 eq). The mixture was stirred at room temperature for 30 minutes. Then, a solution of allylic bromide **8c** (2.67 g, 16.4 mmol, 1.6 eq) in DMF (10 ml) was added dropwise, and the mixture was stirred for 4 hours until TLC showed completion. The reaction was then poured into water (500 ml), and the mixture was extracted with Et_2O (20 ml x 8). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography, eluting with 20-30% EA/Hexane to give diene **9c** as pale yellowish oil (3.12 g, 95%).

^{1}H NMR (400MHz, $CDCl_3$): 7.72 (d, J = 8.2Hz, 2H), 7.30 (d, J = 8.2Hz, 2H), 5.48 (ddd, J = 7.3, 10.5 & 17.4 Hz), 5.14 (d, J = 10.5Hz), 5.04 (s, 1H), 4.96 (d, J = 17.4Hz, 1H), 4.94 (s, 1H), 4.26 (app br q, J = 7.3Hz, 1H), 3.91 (d, J = 16 Hz, 1H), 3.77 (ddd, J = 5.7, 8.3 & 11.7 Hz, 1H), 3.71 – 3.64 (m, 1H), 3.68 (d, J = 16Hz, 1H), 2.43 (s, 3H), 2.14 (dd, J = 5.7 & 7.3Hz, 1H), 2.04 (t, J = 7.8Hz, 2H), 1.46 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100MHz, $CDCl_3$): 146.0, 143.5, 137.5, 132.1, 129.7, 127.3, 120.4, 112.9, 63.1, 62.4, 50.4, 35.2, 21.5, 20.7, 13.8.

FTIR ν_{max}/cm^{-1} 3493, 3082, 2956, 2932, 2872, 1923, 1659, 1599, 1494, 1444, 1337, 1157, 1049, 914, 903, 872, 814, 739, 710.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{25}NO_3SNa$: 346.1453; found: 346.1407

$[\alpha]_D^{25}$ = +27.58° (c = 0.139, $CHCl_3$)

Dihydropyrrole 14

A solution of diene **9c** (975 mg, 3.02 mmol, 1.0 eq) in anhydrous toluene (170 ml) was degassed thoroughly for 15 minutes by bubbling nitrogen gas. Then, the solution was brought to 70°C and a solution of Grubbs II catalyst (128mg, 0.151mmol, 5%mol) in anhydrous toluene (6ml) was added portionwise (1 mL/h) under a continuous nitrogen flow. After adding the last portion, the solution was stirred overnight under nitrogen flow until TLC showed completion. The solution was concentrated, and residue was purified by flash chromatography, eluting with 20-35% EA/Hexane, to give the dihydropyrrole (*S*)-**14** as brownish oil (853 mg, 96%).

^{1}H NMR (400MHz, $CDCl_3$): 7.72 (d, J = 8.2Hz, 2H), 7.33 (d, J = 8.2Hz, 2H), 5.12 (app dd, J = 1.6 & 3.4Hz, 1H), 4.44 – 4.40 (m, 1H), 4.14 – 4.08 (m, 1H), 4.02 – 3.96 (m, 1H), 3.75 (ddd, J = 3.0, 8.5 & 11.7 Hz, 1H), 3.65 (ddd, J = 4.5, 5.9 & 11.5Hz, 1H), 2.90 (dd, J = 4.5 & 8.5 Hz, 1H), 2.43 (s,3H), 1.96 (app br t, J = 7.3), 1.38 (app dh, J = 2.0 & 7.3Hz, 0.80 (t, J = 7.3Hz, 3H).

^{13}C NMR (100MHz, $CDCl_3$): 143.8, 140.8, 133.7, 129.8, 127.4, 119.5, 69.6, 66.0, 57.8, 30.3, 21.4, 20.3, 12.4.

FTIR ν_{max}/cm^{-1} 3451, 3065, 3030, 2957, 2932, 2872, 1931, 1811, 1667, 1597, 1495, 1462, 1290, 1194, 1161, 1094, 1042, 966, 816.

HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_3S$: 296.1320; found: 296.1345

$\mathbf{[\alpha]_D^{25}}$ = - 41.81° (c = 0.120, $CHCl_3$).

Pyrrolidine (*S*,*R*)-15

To a solution of ligand **6** (71 mg, 0.232 mmol, 12 mol%) in anhydrous CH_2Cl_2 (3 mL) in a Fisher – Porter tube was added $Rh(nbd)_2BF_4$ (72 mg, 0.193 mmol, 10 mol%) in anhydrous CH_2Cl_2 (2 ml). The mixture was stirred under nitrogen for 30 minutes, and a solution of cyclic alcohol (570 mg, 1.93 mmol, 1.0 eq) in CH_2Cl_2 (3 ml) was added to the mixture. The tube was then charged with hydrogen (100 psi), and the mixture was stirred at room temperature under hydrogen atmosphere for 24 h. The solution was then filtered through a short path of celite and concentrated. The residue was purified by flash chromatography, eluting with 25%EA/Hexane to give pyrrolidine (*S*,*R*)-**15** as orange oil (554 mg, 97%, dr ≈ 19: 1, inseparable).

^{1}H NMR (400MHz, $CDCl_3$): 7.74 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 3.69 – 3.60 (m, 4H), 2.70 (t, J = 6.0 Hz, 1H), 2.67 (t, J = 9.4 Hz, 1H), 2.45 (s, 3H), 2.25 – 2.17 (m, 1H), 1.83 (ddd, J = 2.5, 6.4, 13 Hz), 1.29 – 1.16 (m, 3H), 1.07 – 1.00 (m, 2H), 0.81 (t, J = 7.3, 3H).

^{13}C NMR (100MHz, $CDCl_3$): 143.8, 133.3, 129.7, 127.7, 66.3, 61.5, 55.2, 37.1, 35.3, 35.0, 21.5, 21.2, 14.0.

FTIR ν_{max}/cm^{-1} 3518, 3063, 3029, 2957, 2928, 2872, 1923, 1736, 1659, 1597, 1495, 1454, 1398, 1373, 1337, 1306, 1290, 1244, 1161, 1096, 1045, 1005, 903, 872, 816, 739, 710.

HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{23}NO_3SNa$: 320.1296; found: 320.1315

$\mathbf{[\alpha]_D^{25}}$ = - 1.33° (c = 0.099, $CHCl_3$)

Hygric acid 1 (isolated as its hydrochloride salt)

To a stirring solution of pyrrolidine (*S*,*R*)-**15** (143 mg, 0.649 mmol, 1.0 eq) in $CHCl_3$ (2 ml) was added CH_3CN (2 ml) and water (3 ml). $NaIO_4$ (833 mg, 3.89 mmol, 6 eq) was then added, followed by $RuCl_3.3H_2O$ (17 mg, 0.065 mmol, 10 mol%). The mixture was stirred at room temperature for 2 hours until TLC shown completion. Water (10 ml) and CH_2Cl_2 (10 ml) was added to facilitate separation. The organic layer was separated, and the remaining aqueous phase was further extracted with CH_2Cl_2 (10ml x 3). The combined organic phase was dried over $MgSO_4$, and Et_2O (20 ml) was added. The mixture was let to stay for 1 hour before filtration through celite and concentrated to give crude acid **19** as a dark tar (128 mg).

The crude acid **19** was dissolved in anhydrous THF (5 ml), and the solution was added to a solution of sodium naphthalenide, prepared by adding sodium (57 mg, 2.47 mmol, 3.8 eq) to a solution of naphthalene (316 mg, 2.47 mmol, 3.8 eq) in THF (20 ml) and stirring for 1 hour, at – 50°C. The mixture was further stirred at – 50°C for 1 hour until TLC shown completion. The reaction was cautiously quenched with water (15 ml) at -40°C, and acidified by HCl 2M solution (20 ml) until pH 0 – 1. The organic phase was separated (if any), and the remaining aqueous layer was washed with CH_2Cl_2 (15 ml x 3). The aqueous phase was then concentrated to give the crude amino acid **20** as its chloride salt with inorganic impurities.

The crude amino acid **20** was dissolved in MeOH (3 ml) and transferred to a Fisher – Porter tube. To the solution was added 37% aqueous formaldehyde (0.20 ml, 2.46 mmol, 3.8 eq), followed by Pd/C 10% w/w (20 mg). The tube was then charged with hydrogen (5 bar), and the mixture was stirred overnight. The solution was then filtered through a short path of celite and concentrated. The residue was purified by ion exchange chromatography, eluting on water-washed Amberlyte CG50 type 1 (8 g) with 1% aqueous ammonia. Combined iodine-stained fraction was concentrated, and HCl 2M (10 ml) was added. The solution was then concentrated to give the amino acid hydrochloride salt **1.HCl** as a yellowish solid (69 mg, 52% over 3 steps).

^{1}H NMR (400MHz, D_2O): 4.26 (dd, J = 4.8 & 10.3 Hz, 1H), 3.80 (dd, J = 6.2 & 11.0 Hz, 1H), 2.95 (s, 3H), 2.86 (t, J = 11.0Hz, 1H), 2.37 – 2.19 (m, 3H), 1.45 – 1.25 (m, 4H), 0.85 (t, J = 7.1Hz, 3H).

^{13}C - NMR (100MHz, D_2O, MeOH standard): 172.7, 69.1, 62.0, 41.4, 36.9, 34.7, 34.4, 21.0, 13.8

HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_9H_{17}NO_2Na$: 194.1157; found: 194.1176

$[\alpha]_D^{25}$ = - 38.4^o (c = 0.0895, MeOH)

Pipecolic acid 3

To a stirring solution of piperidine **19** (141 mg, 0.498 mmol, 1.0 eq) in $CHCl_3$ (2 ml) was added CH_3CN (2 ml) and water (3 ml). $NaIO_4$ (642 mg, 2.99 mmol, 6.0 eq) was then added, followed by $RuCl_3.3H_2O$ (13mg, 0.050 mmol, 10 mol%). The mixture was stirred at room temperature for 2 hours until TLC shown completion. Water (10 ml) and CH_2Cl_2 (10 ml) was added to facilitate separation. The organic layer was separated, and the remaining aqueous phase was further extracted with CH_2Cl_2 (10ml x 3). The combined organic phase was dried over $MgSO_4$, and Et_2O (20 ml) was added. The mixture was let to stay for 1 hour before filtration through celite and concentrated to give crude acid **21** as a dark tar.

The crude acid **21** was dissolved in anhydrous THF (5 ml), and the solution was added to a solution of sodium naphthalenide, prepared by adding sodium (46 mg, 1.99 mmol, 4.0 eq) to a solution of naphthalene (255 mg, 1.99 mmol, 4.0 eq) in THF (5 mL) and stirring for 1 hour, at – 50°C. The mixture was further stirred at – 50°C for 1 hour until TLC shown completion. The reaction was cautiously quenched with water

(5 mL) at -40°C and acidified by addition of HCl 2M solution (5 mL) until pH 0 – 1. The organic phase was separated (if any), and the remaining aqueous layer was washed with CH_2Cl_2 (15 ml x 3). The aqueous phase was then concentrated, and the residue was purified by ion exchange chromatography, eluting on water-washed Amberlyte CG50 type 1 (3 g) with 1% aqueous ammonia. Combined iodine-stained fraction was concentrated, and HCl 2M (2 mL) was added. The solution was then concentrated to give the amino acid hydrochloride salt **3.HCl** as a yellowish solid (61 mg, 68% over 2 steps).

^{1}H NMR (400MHz, D_2O): 4.31 (dd, *J* = 6.0, 4.9 Hz, 1H), 3.36 – 3.33 (m, 2H), 2.26 – 2.20 (m, 1H), 1.98 – 1.78 (m, 3H), 1.56 – 1.43 (m, 1H), 1.07 (d, J = 6.1 Hz).

^{13}C - NMR (100MHz, D_2O, MeOH standard): 172.9, 54.4, 41.4, 32.3, 29.2, 25.5, 19.3.

$[\alpha]_D^{25}$ = - 8.76° (c = 0.015, H_2O)