Proline Sulphonamide-Catalysed Yamada-Otani Condensation: Reaction Development, Substrate Scope and Scaffold Reactivity

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General. Infrared spectra were recorded neat unless otherwise indicated and are reported in cm⁻¹. ¹H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ¹³C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. Chiral HPLC was performed with chiral columns (chirapak AD, OD, OJ, AS-H columns, (Daicel Chemical Ind., Ltd.)).

Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230-400 mesh silica gel.

Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120°C or by flame, then cooled under argon. Dry THF and DCM were obtained via a solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without further purification.

2-(4-Methylphenyl)-propanal **40a**, ^{1b} 2-(4-bromophenl)-propanal **33**,² 2-(4-chlorophenl)-propanal **40c**,² 7-iodo-3-hepten-2-one **42i**,³ 3-octen-8-[[(4-methylphenyl)sulfonyl]oxy]-2-one **42q**,⁴ 8-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-3-octen-2-one **42m**,⁵ [(5-hexen-1-yloxy)methyl]-benzene **51**,⁶ 6-azido-1-hexene **53**⁷ and 8- bromo-3-octen-2-one **59**³ were prepared according to the reported procedure.



7-Iodo-3-hepten-2-one (42i)⁸: To a solution of bromide **42h** (0.397 g, 2.08 mmol) in acetone (6.0 mL) was added Nal (0.934 g, 6.23 mmol). The reaction mixture was heated to reflux. After 36 h, the reaction was cooled to rt and the solvent was removed *in vacuo*. The reaction mixture was loaded directly onto silica gel and was purified by chromatography, eluting with 2-10% Ether / hexanes, to give the iodide **42i** (0.423 g, 1.78 mmol, 85%) as colorless liquid: ¹H NMR (400 MHz, CDCl₃) δ 6.77 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.16 (dd, *J* = 16.0, 1.2 Hz, 1H), 3.22 (t, *J* = 6.8 Hz, 2H), 2.36-2.42 (m, 2H), 2.27 (s, 3H), 2.02 (p, *J* = 6.8 Hz, 2H); ¹³C NMR (400 MHz, CDCl₃) δ 198.2, 145.4, 132.1, 33.0, 31.5, 27.1, 5.3.

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3, 8-Nonadien-2-one (42k)⁹: To a solution of 5-hexen-1-ol **50** (0.5 g, 5.0 mmol) and 4 Å MS (1.0 g) in CH₂Cl₂ (10 mL) was added *N*-methylmorpholine-*N*-oxide (1.17 g, 10 mmol) and TPAP (87.8 mg, 0.25 mmol). After 6 h, the suspension was diluted with hexanes (5 mL), filtered through silica gel pad, washed with 20% EtOAc in hexanes, and then concentrated *in vacuo* to give crude aldehyde. The crude aldehyde was immediately redissovled in THF (25 mL), and 1-(triphenylphosphoranylidene)-2-propanone (1.91 g, 6.0 mmol) was added to the solution. The resulting mixture was heated to reflux. After 16 h, the reaction was concentrated *in vacuo* and loaded directly onto silica gel. It was purified by chromatography, eluting with 2-15% Ether / hexanes, to give **42k** (0.491 g, 3.55 mmol, 71%) as colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 6.79 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.06 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.74-5.81 (m, 1H), 4.96 (m, 2H), 2.20-2.26 (m, 5H), 2.05-2.11 (m, 2H), 1.57 (p, *J* = 7.6 Hz, 2H); ¹³C NMR (400 MHz, CDCl₃) δ 198.6, 148.0, 137.9, 131.5, 115.2, 33.1, 31.7, 27.2, 26.8.



8-(PhenyImethoxy)-3-octen-2-one (42I): To a solution of alkene **51** (0.760 g, 4.0 mmol) in CH₂Cl₂ (4.0 mL) was added 2nd Gen. Grubbs catalyst (84.9 mg, 0.1 mmol) and 3-penten-2-one (1.01 g, 1.8 mL, 12.0 mmol, 65% pure). After stirring at 40°C for 24 h, the reaction was concentrated *in vacuo* and loaded directly onto silica gel. It was purified by chromatography, eluting with 1-20% EtOAc / hexanes, to give **42I** (0.824 g, 3.54 mmol, 89%) as colorless oil: IR (neat) 2938, 2856, 1696, 1673, 1621, 1455, 1361, 1252, 1101, 984, 739, 696, 610 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.38 (m, 5H), 6.81 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.09 (dt, *J* = 16.0, 1.2 Hz, 1H), 4.52 (s, 2H), 3.50 (t, *J* = 6.0 Hz, 2H), 2.24-2.30 (m, 5H), 1.58-1.69 (m, 4H); ¹³C NMR (400 MHz, CDCl₃) δ 198.8, 148.1, 138.5, 131.5, 128.4, 127.63, 127.58, 73.0, 69.9, 32.2, 29.3, 26.9, 24.8; HRMS (EI+) calcd. for C₁₅H₂₀O₂ (M+), 232.1463 found 232.1467.



8-Azido-3-octen-2-one 42n: To a solution of alkene **53** (0.292 g, 2.33 mmol) in CH_2Cl_2 (2.3 mL) was added 2nd Gen. Hoveyda-Grubbs catalyst (36.5 mg, 0.058 mmol) and 3-penten-2-one (0.587 g, 1.05 mL, 6.99 mmol, 65% pure). After stirring in the dark at rt for 6 h, the reaction was concentrated *in vacuo* and

loaded directly onto silica gel. It was purified by chromatography, eluting with 2-10% Ether / hexanes, to give **42n** (0.167 g, 1.0 mmol, 43%) as colorless oil: IR (neat) 2941, 2864, 2093, 1673, 1622, 1365, 1252, 976 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.79 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.10 (dt, *J* = 16.0, 1.6 Hz, 1H), 3.31 (t, *J* = 6.4 Hz, 2H), 2.26-2.31 (m, 5H), 1.58-1.67 (m, 4H); ¹³C NMR (400 MHz, CDCl₃) δ 198.4, 147.1, 131.7, 51.1, 31.8, 28.4, 26.9, 25.2.



8-lodo-3-octen-2-one (420)¹⁰: To a solution of bromide **54**(0.282 g, 1.38 mmol) in acetone (4.2 mL) was added Nal (0.620 g, 4.13 mmol). The reaction mixture was heated to reflux. After 36 h, the reaction was cooled to rt and the solvent was removed *in vacuo*. The reaction mixture was loaded directly onto silica gel and was purified by chromatography, eluting with 2-6% Ether / hexanes, to give the iodide **42o** (0.318 g, 1.26 mmol, 91%) as colorless liquid: ¹H NMR (400 MHz, CDCl₃) δ 6.79 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.10 (dd, *J* = 16.0, 1.2 Hz, 1H), 3.21 (t, *J* = 6.8 Hz, 2H), 1.86 (p, *J* = 7.2 Hz, 2H), 1.61 (p, *J* = 7.6 Hz, 2H); ¹³C NMR (400 MHz, CDCl₃) δ 198.3, 147.2, 131.7, 32.8, 31.3, 28.9, 27.0, 6.15.



(5-Hexen-1-ylsulfonyl)-benzene (56)¹¹: To a solution of 6-bromo-hexene 55 (1.63 g, 10.0 mmol) in DMF (10 mL) was added NaSO₂Ph (1.97 g, 12.0 mmol). After 6 h, diethyl ether (30 mL) was added to the reaction mixture. The resulting solution was washed with brine (3 x 30 mL). The dried (Na₂SO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 2-10% EtOAc / hexanes, to give sulphone 56 (1.51 g, 6.73 mmol, 67%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 2H), 5.65-5.74 (m, 1H), 4.91-4.98 (m, 2H), 3.07-3.11 (m, 2H), 2.02 (q, *J* = 7.2 Hz, 2H), 1.68-1.76 (m, 2H), 1.45 (p, *J* = 7.6 Hz, 2H); ¹³C NMR (400 MHz, CDCl₃) δ 139.2, 137.5, 133.7, 129.3, 128.0, 115.3, 56.1, 33.0, 27.4, 22.1.



8-(Phenylsulfonyl)-3-octen-2-one (42q): To a solution of alkene **56** (0.448 g, 2.0 mmol) in CH_2Cl_2 (2.0 mL) was added 2nd Gen. Grubbs catalyst (42.5 mg, 0.05 mmol) and 3-penten-2-one (0.504 g, 0.899 mL, 6.0 mmol, 65% pure). After stirring at rt for 13 h, the reaction was concentrated *in vacuo* and loaded directly onto silica gel. It was purified by chromatography, eluting with 10-

30% EtOAc / hexanes, to give enone **42q** (0.498 g, 1.87 mmol, 93%) as colorless oil: IR (neat) 2941, 2871, 1696, 1673, 1626, 1447, 1365, 1303, 1147, 1089, 980, 750, 692, 563 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.91-7.93 (m, 1H), 7.68 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.29-7.61 (m, 2H), 6.72 (dt, *J* = 16.0, 1.2 Hz, 1H), 6.05 (dt, *J* = 16.0, 1.2 Hz, 1H), 3.09-3.03 (m, 2H), 2.20-2.26 (m, 5H), 1.57-1.82 (m, 4H); ¹³C NMR (400 MHz, CDCl₃) δ 198.3, 146.4, 139.1, 133.8, 131.8, 129.4, 128.0, 55.9, 31.8, 27.0, 26.7, 22.3; HRMS (EI+) calcd. for C₁₄H₁₈O₃S (M+), 266.0977 found 266.0972.



2-(6-Hepten-1-yl)-1H-isoindole-1,3(2H)-dione (58): To a solution of TBAI (36.9 mg, 0.1 mmol) and potassium phthalimide (1.85 g, 10 mmol) in benzene (40 mL) was added 7-bromo-1-heptene **57** (0.886 g, 5.0 mmol) dropwise. The resulting mixture was heated at 95°C for 24 h. The suspension was cooled to rt, diluted with ether (50 mL), filtered through celite, then concentrated *in vacuo*. It was purified by chromatography, eluting with 5-15% Ether / hexanes, to give **58** (1.18 g, 4.85 mmol, 97%) as colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.72-7.87 (m, 4H), 5.76-5.86 (m, 1H), 4.93-5.03 (m, 2H), 3.70 (t, *J* = 7.2 Hz, 2H), 2.04-2.10 (m, 2H), 1.71 (p, *J* = 7.6 Hz, 2H), 1.34-1.50 (m, 4H); ¹³C NMR (400 MHz, CDCl₃) δ 168.4, 138.7, 133.8, 132.2, 123.1, 114.5, 38.0, 33.5, 28.4, 26.3.



2-(8-Oxo-6-nonen-1-yl)-1H-isoindole-1,3(2H)-dione (42r): To a solution of alkene **58** (0.365 g, 1.5 mmol) in CH₂Cl₂ (1.5 mL) was added 2nd Gen. Grubbs catalyst (31.8 mg, 0.0375 mmol) and 3-penten-2-one (0.375 g, 0.675 mL, 4.5 mmol, 65% pure). After stirring at 45°C for 36 h, the reaction was concentrated *in vacuo* and loaded directly onto silica gel. It was purified by chromatography, eluting with 5-30% Ether / hexanes, to give enone **42r** (0.293 g, 1.03 mmol, 68%) as colorless oil: IR (neat) 2938, 2860, 1770, 1712, 1669, 1618, 1439, 1361, 1252, 1047, 980, 875, 797, 723 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.71-7.86 (m, 4H), 6.78 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.06 (t, *J* = 16.0 Hz, 1H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.21-2.26 (m, 5H), 1.71 (p, *J* = 7.6 Hz, 2H), 1.54 (p, *J* = 8.0 Hz, 2H), 1.35-1.43 (m, 2H); ¹³C NMR (400 MHz, CDCl₃) δ 198.6, 168.4, 148.0, 133.9, 132.1, 131.5, 123.2, 37.7, 32.2, 28.3, 27.6, 26.9, 26.3; HRMS (EI+) calcd. for C₁₇H₁₉NO₃ (M+), 285.1365 found 285.1376.



9-Bromo-3-nonen-2-one (59): To a solution of alkene **57** (1.24 g, 7.0 mmol) in CH₂Cl₂ (35 mL) was added 2nd Gen. Grubbs catalyst (297 mg, 0.35 mmol) and 3-penten-2-one (0.588 g, 1.05 mL, 7.0 mmol, 65% pure). After 48 h, the reaction was concentrated *in vacuo* and loaded directly onto silica gel. It was purified by chromatography, eluting with 1-20% Ether / hexanes, to give enone **59** (792 mg, 3.6 mmol, 52%) as colorless oil: IR (neat) 2938, 2856, 1677, 1626, 1431, 1361, 1256, 980, 731, 645 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.80 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.09 (dt, *J* = 16.0, 1.2 Hz, 1H), 3.42 (t, *J* = 6.8 Hz, 2H), 2.21-2.26 (m, 5H), 1.85-1.94 (m, 2H), 1.47-1.55 (m, 2H); ¹³C NMR (400 MHz, CDCl₃) δ 198.6, 147.8, 131.5, 33.6, 32.5, 32.2, 27.7, 27.2, 27.0; HRMS (EI+) calcd. for C₉H₁₅OBr (M+), 218.0306 found 218.0302.



9-lodo-3-nonen-2-one (42p): To a solution of bromide **59** (0.371 g, 1.69 mmol) in acetone (5.1 mL) was added Nal (0.760 g, 5.07 mmol). The reaction mixture was heated to reflux. After 36 h, the reaction was cooled to rt and the solvent was removed *in vacuo*. The reaction mixture was loaded directly onto silica gel and was purified by chromatography, eluting with 2-10% Ether / hexanes, to give iodide **42p** (0.413 g, 1.55 mmol, 92%) as colorless liquid: IR (neat) 2933, 2856, 1677, 1626, 1427, 1361, 1256, 1198, 980, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.81 (dt, *J* = 16.0, 6.8 Hz, 1H), 6.10 (dt, *J* = 16.0, 1.6 Hz, 1H), 3.21 (t, *J* = 6.8 Hz, 2H), 2.24-2.30 (m, 5H), 1.86 (p, *J* = 6.8 Hz, 2H), 1.45-1.57 (m, 4H); ¹³C NMR (400 MHz, CDCl₃) δ 198.5, 147.7, 131.5, 33.1, 32.2, 30.0, 27.0, 26.9, 6.53; HRMS (EI+) calcd. for C₉H₁₅OI (M+), 266.0168 found 266.0176.)

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