Appendix

On the Synthesis of Z-γ-Amino-α,β-Unsaturated Amino Esters Via Ru Catalyzed Coupling

Barry M. Trost and Gerald J. Roth
Department of Chemistry
Stanford University
Stanford, CA 94305-5080, USA

CpRu(cod)Cl-catalyzed Coupling

General procedure:

CpRu(cod)Cl (0.005 mmol or *0.0125 mmol*, 5%) was placed into an oven-dried reaction tube that had been flushed with argon for 30 min. After flushing for another 30 min with argon, anhydrous degassed methanol (0.20 mL or *0.50 mL*), followed by alkyne (0.10 mmol or *0.25 mmol*) dissolved in dry degassed methanol (0.57 mL or *1.50 mL*) and finally alkene (0.10 mmol or *0.25 mmol*) were added with a syringe. The resulting solution is 0.13 M with respect to alkyne or alkene. The mixture was heated to 65°C (oil-bath temperature) for 10 hrs. After cooling to room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography. Flash chromatography was performed on columns that were packed with dry silica gel first and then flushed with the eluent indicated. The separation of the products is not always achieved easily. After a fraction containing the recovered alkene, the β-substituted adduct usually elutes first. After some fractions containing mixtures of α- and β-substituted adducts the pure α-adduct comes off the column. Possible lactams elute last. Yields always refer to the total amount of products formed. Since mixtures of the two isomers are usually hard to distinguish in the NMR all yields (and therefore ratios) are isolated yields.

Entry 3:($R^1 = R^2 = R^3 = CH_3$)

The residue was purified by flash chromatography with hexanes/EtOAc 3/1 to give partially separated products. Total yield: 26 mg (68%, 79% brsm). α-isomer **13**: 21 mg (58%, 67% brsm) of a colorless oil, $[a]^D$ n. d. since educt was not enantiopure, R_f = 0.22 (hex/EtOAc 3/1). IR (neat): 3356, 2928, 2855, 1720, 1526, 1437, 1437, 1224, 1058 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.69 (d, *J* = 8 Hz, 1H), 5.47-5.28 (m, 2H), 4.97-4.89 (m,

1H), 4.80 (br, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 3.63 (s, 3H), 3.00-2.84 (m, 4H), 2.30 (t, *J* = 7 Hz, 2H), 1.96 (m, 2H), 1.60 (m, 2H), 1.28 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 167.7, 156.1, 142.4, 133.2, 131.4, 126.4, 52.0, 51.6, 51.4, 46.2, 36.7, 34.1, 32.4, 29.3, 29.1, 29.0, 28.8, 24.9, 21.0. HRMS: Calcd for $C_{20}H_{33}NO_6$: 383.2308. Found: 383.2322.

β-isomer **14:** 5 mg (14%, 16% brsm) of a colorless oil, R_f = 0.36 (hex/EtOAc 3/1). IR (neat): 3359, 2927, 2854, 1722, 1529, 1438, 1228 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.82 (s, 1H), 5.58-5.33 (m, 2H), 4.73 (m, 1H), 4.32 (m, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.65 (s, 3H), 3.40-3.33 (m, 2H), 2.29 (t, *J* = 7 Hz, 2H), 2.00-1.96 (m, 2H), 1.58 (m, 2H), 1.28-1.19 (m, 11H).

Table. Experimental data for the CpRu(cod)Cl-catalyzed reactions

entry	alkene	alkyne	catalyst	solvent	rec. alkene	yield [%]	ratio (α:β)
1	50 mg **70**	43 mg **6** (R=H)	3.9 m*g*	0.50 mL	20 mg (40%)	36 (59)[a]	2.0:1
2	20 mg **70**	26 mg **6c**	1.6 mg	0.20 mL	4 mg (20%)	76 (94)	3.8:1
3	20 mg **70**	19 mg **6a**	1.6 mg	0.20 mL	3 mg (15%)	72 (83)	4.2:1
4	50 mg **70**	53 m*g* **6b**	3.9 m*g*	0.50 mL	7 mg (14%)	77 (90)	3.4:1
5	20 mg **9**	24 mg **17**	1.6 mg	0.20 mL	2 mg (10%)	81 (90)	10:1
6	20 mg **9**	32 mg **8b**	1.6 mg	0.20 mL	3 mg (15%)	61 (72)	3.5:1
7	20 mg **9**	26 mg **8a**	1.6 mg	0.20 mL	6 mg (30%)	71 (Q)	4.3:1
8	21 mg **15**	26 mg **6c**	1.6 mg	0.20 mL	8 mg (38%)	59 (94)	4.2:1
9[b]	29 mg[b]	24 mg **17**	1.6 mg	1.0 mL	-	58	4.1:1

[a] Based on recovered alkene

[b] Reaction was run in DMF/H_2O (1:1) at 95°C, 4 equiv. of 3-buten-2-ol as alkene (0.40 mmole) were used

entry 4: (R^1 = i-C_3H_7, R^2 = R^3 = CH_3)

The residue was purified by flash chromatography with hexanes/EtOAc 3/1 to give clearly separated products. Total yield: 75 mg (73%, 85% brsm). α-isomer **13**: 58 mg (59%, 70% brsm) of a colorless oil, R_f = 0.21 (hex/EtOAc 3/1). IR (neat): 3363, 2929,

1724, 1527, 1437, 1223 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.64 (m, 1H), 5.44-5.30 (m, 2H), 4.81 (m, 1H), 4.68 (m, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.62 (s, 3H), 3.02-2.82 (m, 2H), 2.28 (t, *J* = 7 Hz, 2H), 1.96 (m, 2H), 1.81 (m, 1H), 1.59 (m, 2H), 1.26 (m, 8H), 0.90 (d, *J* = 7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 168.0, 156.6, 139.6, 133.3, 132.8, 126.5, 54.8, 51.9, 51.5, 51.4, 36.9, 34.0, 32.6, 32.3, 29.2, 29.0, 28.7, 24.8, 18.9, 18.0. MS (m/z, %): 411 (1), 380 (11), 368 (42), 348 (24), 347 (128), 336 (71), 304 (100), 261 (91), 130 (95). Anal. Calc'd for $C_{22}H_{37}NO_6$: C, 64.19; H, 9.08; N, 3.40. MW, 411.2621. Found: C, 64.02; H, 8.77; N, 3.18; MW, 411.2620.

β-isomer **14**: 17 mg (18%, 20% brsm) of a colorless oil, R_f = 0.24 (hex/EtOAc 3/1). IR (neat): 3357, 2930, 2856, 1722, 1527, 1436, 1239, 1169 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.76 (s, 1H), 5.60-5.35 (m, 2H), 4.78 (d, *J* = 9 Hz, 1H), 3.99 (dd, *J* = 8 Hz, 8 Hz, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 3.31 (d, *J* = 6 Hz, 2H), 2.29 (t, *J* = 7 Hz, 2H), 2.00-1.90 (m, 3H), 1.60 (m, 2H), 1.27 (m, 8H), 0.91 (d, *J* = 7 Hz, 3H), 0.84 (d, *J* = 6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 166.6, 159.6(?), 133.0, 126.5, 116.3, 62.5, 52.1, 51.4, 51.0, 34.8(?), 34.0, 33.3, 32.3, 29.5, 29.2, 29.0, 28.9(?), 24.8, 20.2, 17.3. Anal. Calc'd for $C_{22}H_{37}NO_6$: C, 64.19; H, 9.08; N, 3.40. Found: C, 63.94; H, 8.91; N, 3.58.

entry 5 ($R^1 = t\text{-}C_4H_9$, $R^2 = C_2H_5$, $R^3 = CH_3$):

The residue was purified by flash chromatography with hexanes/EtOAc 1/1 to give partially separated products. Total yield: 34 mg. α-isomer **71f** (GR-III-43B): 31 mg (74%, 81% brsm) of a colorless oil, R_f = 0.45 (hex/EtOAc 1/1). IR (neat): 3373, 2929, 2856, 1724, 1528, 1463, 1367, 1225, 1193 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.56 (d, *J* = 10 Hz, 1H), 5.49-5.29 (m, 2H), 4.87-4.69 (m, 2H), 4.23 (q, *J* = 7 Hz, 2H), 3.66 (s,

3H), 3.64 (s, 3H), 3.04-2.86 (m, 2H), 2.29 (t, *J* = 7 Hz, 2H), 1.96 (m, 2H), 1.60 (m, 2H), 1.32 (t, *J* = 7Hz, 3H), 1.27 (m, 8H), 0.91 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 167.6, 156.9, 135.4, 134.0, 133.3, 126.4, 60.6, 56.8, 52.1, 51.4, 37.4, 34.1, 32.4, 29.3, 29.1, 29.0, 26.1, 24.9, 14.2. Anal. Calc'd for $C_{27}H_{47}NO_6$: C, 65.58; H, 9.40; N, 3.19. Found: C, 65.38; H, 9.16; N, 3.23.

β-isomer **14**: 3 mg (7%, 9% brsm) of a colorless oil, R_f = 0.60 (hex/EtOAc 1/1). IR (neat): 3374, 2930, 2361, 1715, 1529, 1446, 1368, 1240, 1175 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.71 (s, 1H), 5.53-5.37 (m, 2H), 5.02-4.95 (m, 1H), 4.14 (q, *J* = 7 Hz, 2H), 4.04 (m, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.31 (m, 2H), 2.29 (t, *J* = 7 Hz, 2H), 1.97 (m, 2H), 1.60 (m, 2H), 1.33 (t, *J* = 7 Hz, 3H), 1.28-1.25 (m, 8H), 0.95 (s, 9H).

entry 6: ($R^1 = CH_2Ph$, $R^2 = C_2H_5$, $R^3 = t\text{-}C_4H_9$)

The residue was purified by flash chromatography with hexanes/EtOAc 9/1 to give a mixture of products. α-isomer **13** and β-isomer **14**: 30 mg (58%, 68% brsm) of a colorless oil, R_f = 0.41 (hex/EtOAc 9/1). IR (neat): 3377, 2929, 2855, 1715, 1366, 1171 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33-7.12 (m, 5H), 5.73 (m, 1H), 5.54-5.29 (m, 2H), 5.14-5.07 (m, 1H), 4.56 (br, 1H), 4.20 (q, *J* = 7 Hz, 2H), 4.15 (q, J = 7 Hz, 2H), 3.66 (s, 3H), 3.02-2.90 (m, 2H), 2.30 (t, *J* = 7 Hz, 2H), 2.29 (t, J = 7 Hz, 2H), 2.01-1.96 (m, 2H), 1.58 (m, 2H), 1.36 (s, 9H), 1.40-1.23 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 167.0, 155.1, 137.0, 133.1, 131.6, 129.6, 129.2, 128.5, 128.3, 126.5, 60.5, 51.5, 50.6, 40.9, 36.8, 34.1, 32.5, 29.3, 29.1, 28.9, 28.3, 24.9, 14.2 (only the α-isomer can be seen). Anal. Calc'd for $C_{30}H_{45}NO_6$: C, 69.87; H, 8.80; N, 2.72. Found: C, 69.25; H, 8.61; N, 2.66.

entry 7: (R^1 = i-C_3H_7, R^2 = CH_3, R^3 = t-C_4H_9)

The residue was purified by flash chromatography with hexanes/EtOAc 5/1 to give partially separated products. Total yield: 31 mg (67%, 97% brsm). α-isomer **13**: 25 mg (57%, 82% brsm) of a colorless oil, R_f = 0.45 (hex/EtOAc 5/1). IR (neat): 3377, 2929, 2856, 1719, 1513, 1366, 1223, 1173 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.66 (d, *J* = 9 Hz, 1H), 5.46-5.32 (m, 2H), 4.69-4.64 (m, 2H), 3.74 (s, 3H), 3.66 (s, 3H), 3.07-2.92 (m, 2H), 2.30 (t, *J* = 7 Hz, 2H), 1.96 (m, 2H), 1.87-1.83 (m, 1H), 1.62 (m, 2H), 1.42 (s, 9H), 1.28 (m, 8H), 0.91 (d, *J* = 7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 167.8, 155.3, 140.4, 133.1, 132.3, 126.6, 79.1, 54.3, 51.5, 37.0, 34.1, 32.4, 29.3, 29.1, 28.9, 28.4, 24.9, 19.1, 18.0. Anal. Calc'd for $C_{25}H_{43}NO_6$: C, 66.20; H, 9.55; N, 3.09. Found: C, 66.27; H, 9.49; N, 3.13.

β-isomer **14**: 6 mg (14%, 18% brsm) of a colorless oil, R_f = 0.52 (hex/EtOAc 5/1). IR (neat): 3375, 2929, 2855, 1700, 1646, 1510, 1435, 1366, 1239, 1169 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.76 (s, 1H), 5.57-5.48 (m, 2H), 4.60 (d, *J* = 10 Hz, 1H), 3.96 (m, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.31 (m, 2H), 2.29 (t, *J* = 7 Hz, 2H), 1.97 (m, 2H), 1.60 (m, 2H), 1.43 (s, 9H), 1.28 (m, 8H), 0.91 (d, *J* = 7 Hz, 3H), 0.84 (d, *J* = 7 Hz, 3H).

Eq. 3*:*

The residue was purified by flash chromatography with hexanes/EtOAc 3/1 to give partially separated products. Total yield: 26 mg (56%, 89% brsm). α-isomer **16**: 21 mg (47%, 76% brsm) of a colorless oil, R_f = 0.30 (hex/EtOAc 3/1). IR (neat): 3340, 2926, 2854, 1714, 1530, 1439, 1226, 1038, 988 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.12 (m, 5H), 6.40-5.30 (m, 7H), 5.16 (m, 1H), 4.76 (br, 1H), 3.76 (s, 3H), 3.60 (s, 3H), 3.03-2.85 (m, 4H), 2.18-1.95 (m, 4H), 1.73 (d, *J* = 6 Hz, 3H), 1.27 (m, 10H). ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 167.5, 156.2, 141.4, 134.6, 133.4, 132.2, 131.7, 130.2, 129.6, 129.1, 128.4, 126.7, 126.2, 125.3, 52.0, 51.6, 51.0, 40.8, 36.7, 32.5, 29.4 (3x), 29.3, 29.2, 29.1, 18.0. HRMS: Calc'd for $C_{29}H_{41}NO_4$: 467.3036. Found: 467.3014.

β-isomer: 5 mg (12%, 18% brsm) of a colorless oil, R_f = 0.39 (hex/EtOAc 3/1). IR (neat): 3346, 2962, 2926, 2854, 1720, 1260, 1091, 1021, 799 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31-7.11 (m, 5H), 6.40-5.40 (m, 6H), 5.73 (s, 1H), 4.73 (m, 1H), 4.51 (m, 1H), 3.68 (s, 3H), 3.58 (s, 3H), 3.45-2.60 (m, 4H), 2.17-1.99 (m, 4H), 1.72 (d, *J* = 6 Hz, 3H), 1.45-1.14 (m, 10H).

Eq. 4.

The residue was purified by flash chromatography with hexanes/EtOAc 3/1 to give a mixture of products. α-isomer **18** and β-isomer [not separable]: 18 mg (58%) of a colorless oil, R_f = 0.17 (hex/EtOAc 3/1). IR (neat): 3348, 2964, 1715, 1530, 1367, 1228, 1152 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.78 (s, 1H), 5.67 (d, J = 10 Hz, 1H), 4.92-4.85 (m, 1H/1H), 4.69-4.66 (m, 1H/1H), 4.25 (q, *J* = 7 Hz, 2H), 4.14 (q, J = 7 Hz, 2H), 3.66 (s, 3H), 3.63 (s, 3H), 2.59-2.41 (m, 4H/4H), 2.15 (s, 3H), 2.12 (s, 3H), 1.34 (t, *J* = 7 Hz, 3H), 1.27 (t, J = 7 Hz, 3H), 0.95 (s, 9H), 0.90 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.7,167.3,160.3, 156.8, 156.3, 137.4, 132.9, 119.5, 60.8, 60.5, 56.7, 52.0, 42.7, 42.5, 34.6, 30.1, 29.7, 29.2, 27.2, 26.0, 25.8, 14.2, 14.1. Anal. Calc'd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.12; H, 8.44; N, 4.34.

Cyclization reaction

N-Moc-3-(10-methoxycarbonyl-E-2-decen-1yl)-5-benzyl-3-pyrrolidin-2-on **19**

Uncyclized compound **11** (30 mg, 65 mmol) was dissolved in benzene (2 mL) and 2.0 mg (3.0 mmol, 0.05 equiv.) of tributyltinoxide were added. The mixture was heated in a

sealed tube at 130°C (oil-bath) for 2 d. The solvent was removed *in vacuo* and the residue was purified by flash chromatography with hexanes/EtOAc 1/1 to give 24 mg (86%) of a colorless oil, R_f = 0.45, hex/EtOAc 1/1). IR (neat): 2928, 2854, 1784, 1737, 1439, 1360, 1314 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.11 (m, 5H), 6.68 (d, *J* = 2 Hz, 1H), 5.46-5.30 (m, 2H), 4.72-4.68 (m, 1H), 3.95 (s, 3H), 3.66 (s, 3H), 3.50 (dd, *J* = 13 Hz, 4 Hz, 1H), 2.85 (d, *J* = 6 Hz, 2H), 2.77 (dd, *J* = 13 Hz, 9 Hz, 1H), 2.30 (t, *J* = 7 Hz, 2H), 1.99-1.92 (m, 2H), 1.62 (m, 2H), 1.28 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 168.7, 152.0, 143.2, 137.9, 135.6, 133.7, 129.5, 128.5, 127.0, 124.5, 61.1, 53.5, 51.5, 38.3, 34.1, 32.4, 29.2, 29.1 (2x), 28.9, 28.5, 24.9. Anal. Calc'd for $C_{25}H_{33}NO_5$: C, 70.23; H, 7.78; N, 3.28. Found: C, 70.45; H, 7.91; N, 3.01.