Synthesis of Unsaturated Amino Alcohols Through Unexpectedly Selective Ru-Catalyzed Cross-Metathesis Reactions

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Supplementary Information

Experimental Section

General Information

All the chemicals used herein were purchased from commercial vendors and used as received. Diethyl ether (Et₂O) was distilled over sodium/benzophenone and MeOH was distilled over magnesium/iodine. Anhydrous dichloromethane (DCM), 1,2-dichloroethane and DMSO were purchased from EM Science in Sure-Seal™ bottles. Flash column chromatography¹ was performed using silica gel 60 (230-400 mesh) (EMD Chemicals). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F₂₅₄ pre-coated plates (0.25 mm thickness) with a fluorescent indicator from EMD Chemicals. All reactions were conducted using anhydrous solvent(s) under nitrogen atmosphere unless noted otherwise.

NMR spectra were recorded on a Varian Mercury-VX instrument at ambient temperature. The residual solvent protons (¹H) or solvent carbons (¹³C) was used as internal standards. ¹H NMR data are presented, using the standard abbreviations, as follows: chemical shift (δ) in ppm (multiplicity, integration, coupling constant(s)). The following abbreviations are used for denoting signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, and m = multiplet. ¹H-¹H COSY spectroscopy was used

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

to verify ^1H NMR assignments (selected data shown for compound **7b**). High resolution mass spectra were recorded at the Université de Sherbrooke, Mass Spectrometry Service Laboratory on a ZAB-1F instrument (VG model) using electron impact (EI) ionization technique. Determination of the Ru content in samples was performed using inductively-coupled plasma emission spectroscopy (ICP-ES) at Robertson Microlit Laboratories, Inc. (NJ, USA). The melting point measurements were obtained using a MEL-TEMP 3.0 instrument (Barnstead International) and are uncorrected.

The Ru complexes **2-3** are defined as follows:

Synthetic Procedures

Representative Procedure for Ru-Catalyzed Cross Metathesis Reaction.

Compound 7b: 7-Hydroxy-hept-3-enenitrile. In a predried round-bottom flask,² allyl cyanide (7.8 g, 116 mmol, 2 equiv) was added to a solution of pen-4-en-1-ol (5 g, 58 mmol, 1 equiv) in DCM (350 mL) at room temperature. To this solution was added Ru complex **2** (2.5 g, 3 mmol, 5 mol%) in one portion and the round-bottom flask was fitted with a pre-dried reflux condenser.² This reaction mixture was then heated to reflux (45 °C) for 2 h whereupon the reaction allowed to return to room temperature. Ethyl vinyl ether (14 mL, 50 equiv) and DMSO (10 mL, 50 equiv) were then added to the reaction mixture and the solution was agitated for 1 h in air. After removal of the volatiles under reduced pressure, the resultant dark-colored oil was immediately passed through a short silica gel column (2 x 10 cm) using EtOAc/hexanes (3:1) as eluant to remove the bulk of the colored impurity.³ The brown oil thus obtained was further purified by silica gel flash column chromatography (EtOAc/hexanes, 1:1 to 3:1 gradient elution). The purified

(2) Oven-dried glassware was brought to room temperature under nitrogen atmosphere.

(3) This was conducted under gravity *without* applying nitrogen or air pressure.

product was obtained as a pale yellow-orange oil in 75% yield⁴ (5.4 g) as a 6:1 (*E*:*Z*) mixture. TLC (EtOAc/hexanes, 1:1) R_f = 0.20 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 1.6 (m, 2H), 1.9 (s, 1H), 2.1 (m, 2H), 3.0-3.1 (m, 2H), 3.6 (t, 2H, J = 6.5 Hz), 5.3-5.4 (m, 1H), 5.6-5.8 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 17.7, 20.6, 23.7, 28.6, 31.6, 31.9, 61.7, 62.1, 117.8, 117.9, 135.5, 135.7. HRMS: calcd for C₇H₁₂NO (M+H)⁺ 126.0919, found 126.0922. %Ru (ICP-ES): 192 ppm.⁶

All the cross-metathesis reactions below were conducted according to the representative procedure described above for compound 7b.

Compound 7a: 6-Hydroxy-hex-2-enenitrile. The following quantity of reagents were used: acrylonitrile (1.23 g, 23.3 mmol, 2.0 equiv), pen-4-en-1-ol (1.0 g, 11.6 mmol, 1.0 equiv), Ru complex **3** (0.363 g, 0.58 mmol, 0.05 equiv) in 500 mL DCM. After workup and column chromatography (EtOAc/hexanes, 1:1), the purified product (**7a**) was obtained as a yellow pale oil in 74% yield (954 mg) as a 1:2 (*E*:*Z*) mixture. TLC (EtOAc/hexanes, 1:1) R_f = 0.22 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 1.6-1.8 (m, 2H), 2.1 (s, 1H), 2.3-2.5 (m, 2H), 3.6-3.7 (m, 2H), 5.3-5.4 (m, 1H), 6.5-6.8 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 28.7, 30.0, 30.1, 31.2, 61.6, 61.8, 100.0, 100.3, 116.2, 117.7, 155.0, 155.8. HRMS: calcd for C₆H₁₀NO (M+H)⁺ 112.0762, found 112.0766.

Compound 7c: 8-Hydroxy-oct-4-enenitrile. The following quantity of reagents were used: pent-4-enenitrile (0.94 g, 11.6 mmol, 2.0 equiv), pen-4-en-1-ol (0.5 g, 5.8 mmol, 1.0 equiv), Ru complex **2** (0.247 g, 0.29 mmol, 0.05 equiv) in 35 mL DCM. After workup and column chromatography (EtOAc/hexanes, 1:1), the purified product (**7c**) was obtained as an orange oil in 72% yield (581 mg) as a 5:1 (*E*:*Z*) mixture.⁷ TLC (EtOAc/hexanes, 1:1) R_f = 0.26 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 1.6-1.7 (m, 2H), 1.7 (s, 1H), 2.1-2.2 (m, 2H), 2.2-2.4 (m, 4H), 3.6 (t, 2H, J = 6.5 Hz), 5.2-5.5 (m, 1H), 5.5-5.7 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 17.8, 17.9, 23.4, 23.7, 28.5, 28.9, 32.2,

(4) This value reflects the unoptimized yield. When this reaction was conducted on a 5.8 mmol scale, **7b** was obtained in 81% isolated purified yield as indicated in Table 1.

(5) Aqueous potassium permanganate – prepared by mixing 1g KMnO₄ and 2g K₂CO₃ in 100 mL H₂O – was used as the revealing agent for the TLC experiment.

(6) With Ru complex **3**, using the same workup procedure, the %Ru = 479 ppm (ICP-ES).

(7) Due to signal overlap in the ¹H NMR spectrum, the *E/Z* ratio was approximated using ¹³C NMR data.

32.4, 62.1, 62.4, 119.6, 125.9, 126.5, 133.1, 133.6. HRMS: calcd for $C_8H_{12}NO$ (M-H)⁺ 138.0919, found 138.0917.

Compound 7d: *5-Hydroxy-pent-3-enenitrile*. The following quantity of reagents were used: allyl cyanide (0.78 g, 11.6 mmol, 2.0 equiv), allyl alcohol (0.34 g, 5.8 mmol, 1.0 equiv), Ru complex **2** (0.247 g, 0.29 mmol, 0.05 equiv) in 35 mL DCM. After workup and column chromatography (EtOAc/hexanes, 1:1), the purified product (**7d**) was obtained as a yellow oil in 38% yield (215 mg) as a 15:1 (*E:Z*) mixture. TLC (EtOAc/hexanes, 1:1) R_f = 0.20 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 1.6 (s, 1H), 3.1-3.2 (m, 2H), 4.1-4.3 (m, 2H), 5.6-5.7 (m, 1H), 6.0-6.1 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 20.4, 36.5, 60.6, 62.5, 117.5, 118.7, 134.7. HRMS: calcd for C_5H_8NO (M+H)⁺ 98.0606, found 98.0609.

Compound 7e: *6-Hydroxy-hex-3-enenitrile*. The following quantity of reagents were used: allyl cyanide (0.78 g, 11.6 mmol, 2.0 equiv), but-3-en-1-ol (0.42 g, 5.8 mmol, 1.0 equiv), Ru complex **2** (0.247 g, 0.29 mmol, 0.05 equiv) in 35 mL DCM. After workup and column chromatography (EtOAc/hexanes, 1:1), the purified product (**7e**) was obtained as a yellow pale oil in 77% yield (496 mg) as a 3.5:1 (*E:Z*) mixture. TLC (EtOAc/hexanes, 1:1) R_f = 0.24 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 1.6 (s, 1H), 2.3-2.4 (m, 2H), 3.1-3.2 (m, 2H), 3.7-3.7 (m, 2H), 5.4-5.6 (m, 1H), 5.7-5.9 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 16.0, 20.7, 30.9, 35.6, 61.5, 61.7, 117.9, 118.4, 119.6, 120.1, 132.4, 132.6. HRMS: calcd for $C_6H_{10}NO$ (M+H)⁺ 112.0762, found 112.0765.

Compound 9: *7-Trityloxy-hept-3-enenitrile*. The following quantity of reagents were used: allyl cyanide (0.78 g, 11.6 mmol, 2.0 equiv), **8** (1.90 g, 5.8 mmol, 1.0 equiv), Ru complex **2** (0.247 g, 0.29 mmol, 0.05 equiv) in 35 mL DCM. After workup and column chromatography (EtOAc/hexanes, 1:9), the purified product (**9**) was obtained as a brown solid in 23% yield (485 mg) as a 2.5:1 (*E:Z*) mixture. TLC (EtOAc/hexanes, 1:3) R_f = 0.60 (UV and KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 1.6-1.8 (m, 2H), 2.1-2.2 (m, 2H), 2.9-3.0 (m, 2H), 3.0-3.1 (m, 2H), 5.2-5.4 (m, 1H), 5.5-5.8 (m, 1H), 7.2-7.3 (m, 9H), 7.4-7.5 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 15.7, 20.6, 24.3, 29.2, 29.4, 62.7, 86.6, 117.6, 117.7, 118.1, 127.1, 128.0, 128.9, 135.5, 135.9, 144.6. HRMS: calcd for $C_{26}H_{25}NO$ (M)⁺ 367.1936, found 367.1930. Melting point: 80-82 °C.

Compound 11: *2-Hydroxy-hex-3-enenitrile*. The following quantity of reagents were used: allyl cyanide (0.78 g, 11.6 mmol, 2.0 equiv), but-3-en-2-ol (0.42 g, 5.8 mmol, 1.0 equiv), Ru complex **2** (0.247 g, 0.29 mmol, 0.05 equiv) in 35 mL DCM. After workup and

column chromatography (EtOAc/hexanes, 1:1), the purified product (**11**) was obtained as a yellow pale oil in 21% yield (135 mg) as a 5:1 (*E:Z*) mixture. TLC (EtOAc/hexanes, 1:1) R_f = 0.27 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 1.3 (d, 3H, J = 6.5 Hz), 1.7 (s, 1H), 3.1-3.3 (m, 2H), 4.3-4.6 (m, 1H), 5.4-5.64 (m, 1H), 5.67-6.0 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 16.1, 20.1, 23.3, 23.5, 63.9, 67.7, 117.2, 117.8, 139.4, 139.6. HRMS: calcd for C₆H₈NO (M-H)⁺ 110.0606, found 110.0602.

Compound 14: 4-[1,3]-Dioxolane-2-yl-but-3-enenitrile. The following quantity of reagents were used: allyl cyanide (0.78 g, 11.6 mmol, 2.0 equiv), 2-vinyl-1,3-dioxolane (0.58 g, 5.8 mmol, 1.0 equiv), Ru complex **2** (0.247 g, 0.29 mmol, 0.05 equiv) in 35 mL DCM. After workup and column chromatography (EtOAc/hexanes, 1:1), the purified product (**14**) was obtained as an orange oil in 26% yield (208 mg) as a 2.5:1 (*E:Z*) mixture. TLC (EtOAc/hexanes, 1:1) R_f = 0.44 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 3.1-3.2 (m, 2H), 3.9-4.0 (m, 4H), 5.28-5.32 (m, 1H), 5.8-5.9 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 20.3, 20.4, 65.2, 65.3, 102.4, 102.5, 116.7, 116.8, 123.3, 123.5, 131.6, 132.0. HRMS: calcd for C₇H₈NO₂ (M-H)⁺ 138.0555, found 138.0550.

Compound 16: 4-Phenyl-but-3-enenitrile. The following quantity of reagents were used: allyl cyanide (0.78 g, 11.6 mmol, 2.0 equiv), styrene (0.60 g, 5.8 mmol, 1.0 equiv), Ru complex **2** (0.247 g, 0.29 mmol, 0.05 equiv) in 35 mL DCM. After workup and column chromatography (EtOAc/hexanes, 1:4), the purified product (**16**) was obtained as a brown pale solid in 10% yield (83 mg) as the *E* isomer. TLC (EtOAc/hexanes, 1:4) R_f = 0.39 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 3.3 (dd, 2H, J = 5.9, 1.7 Hz), 6.1 (dt, 1H, J = 15.8, 5.6 Hz), 6.7 (d, 1H, J = 15.8 Hz), 7.2-7.4 (m, 5H). ¹³C NMR (75 MHz, CDCl₃): δ 21.0, 117.0, 117.6, 126.7, 128.5, 129.0, 134.9, 135.9. HRMS: calcd for C₁₀H₉N (M)⁺ 143.0735, found 143.0731. Melting point: 56-58 °C.

Compound 17: 8-Trityloxy-oct-4-en-1-ol. The following quantity of reagents were used: **8** (3.80 g, 11.6 mmol, 2.0 equiv), pent-4-en-1-ol (0.50 g, 5.8 mmol, 1.0 equiv), Ru complex **2** (0.247 g, 0.29 mmol, 0.05 equiv) in 35 mL DCM. After workup and column chromatography (EtOAc/hexanes, 1:3), the purified product (**17**) was obtained as a brown pale oil in 60% yield (1.35 g) as a 2.5:1 (*E:Z*) mixture. TLC (EtOAc/hexanes, 1:3) R_f = 0.20 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 1.2 (br s,⁸ 1H), 1.5-1.7 (m, 4H), 2.0-2.4 (m, 4H), 3.0-3.1 (m, 2H), 3.5-3.7 (m, 2H), 5.3-5.5 (m, 2H), 7.2-7.3 (m, 9H), 7.4-7.5

(8) The triplet signals of residual EtOAc partially overlap this broad singlet signal.

(m, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 29.1, 29.5, 30.1, 32.6, 36.2, 62.7, 63.0, 63.1, 86.5, 127.0, 127.1, 127.9, 128.9, 130.0, 130.7, 144.6, 144.7. HRMS: calcd for $\text{C}_{27}\text{H}_{30}\text{O}_2$ (M) $^+$ 386.2246, found 386.2251.

Representative Procedure for the One-Pot Nitrile Reduction/Amine Protection Reaction.

Compound 18a: (7-Hydroxy-hept-3-enyl)-carbamic acid 9H-fluoren-9-ylmethyl ester. A solution of **7b** (2.6 g, 21 mmol, 1 equiv) in Et_2O (200 mL) was added into a predried² three neck round-bottom flask. The reaction flask was subjected to three rapid cycles of vacuum/nitrogen purge and the reaction mixture was then cooled to $-78\text{ }^\circ\text{C}$. Subsequently, DIBAL-H (1.0 M in DCM; 85 mL, 84 mmol, 4.0 equiv) was slowly added over 1 h, manually using a syringe. The resulting solution was stirred at $-78\text{ }^\circ\text{C}$ for 2 h. TLC was used to determine the extent of **7b** remaining, thus establishing the extent of progress of reaction.⁹ If the reaction was found to be incomplete, an additional equivalent of DIBAL-H was introduced into the reaction mixture followed by stirring for an additional 1 h at $-78\text{ }^\circ\text{C}$. Once **7b** was fully consumed (TLC), Fmoc-OSu (29 g, 85 mmol, 4 equiv) was added at $-78\text{ }^\circ\text{C}$ in one portion and within 10 minutes a solution of NaBH_4 (8 g, 210 mmol, 10 equiv) in MeOH (200 mL)¹⁰ was introduced into the reaction mixture in one portion. After 15 minutes, the dry ice/acetone bath was replaced with an ice bath, thus allowing the reaction mixture to gradually warm to $0\text{ }^\circ\text{C}$. The reaction was stirred at $0\text{ }^\circ\text{C}$ for 1 h before it was allowed to attain room temperature. Thereafter NaHCO_3 (2.1 g, 25 mmol, 1.2 equiv) was added to the reaction mixture and the resultant mixture was

(9) TLC (EtOAc /hexanes, 1:1 with 2% Et_3N) R_f = 0.31 (KMnO_4).⁵

(10) The methanolic sodium borohydride was prepared immediately prior to use in predried glassware under an inert atmosphere. Upon addition of sodium borohydride to methanol, mild bubbling was observed (hydrogen gas evolution).

A variant to the above procedure was initially attempted wherein NaBH_4 was introduced as a solid followed by addition of MeOH (see: Gallagher T. F.; Adams, J. L. *J. Org. Chem.* **1992**, *57*, 3347-3353). Using this procedure, the secondary amine dimeric side-product formation was still observed. Thus, we resorted to a pre-made solution of methanolic NaBH_4 , as aforementioned, which proved to be significantly more effective in suppressing the dimer side-reaction, presumably through a more rapid reduction of the nitrile intermediate given that NaBH_4 does not require additional time to dissolve in the reaction medium.

As a further practical remark, we wish to note that when NaBH_4 was added as a solid (followed by addition of MeOH), vigorous bubbling occurred while warming the reaction mixture to room temperature – which required extreme caution and adequate head space in reaction container. In contrast, the procedure described above was easier to handle and more controlled, since the bubbling observed when preparing the methanolic NaBH_4 was a much less vigorous event, and upon warming the reaction mixture to room temperature no further precautions were found to be necessary.

stirred overnight at room temperature. For workup, Et₂O (500 mL) and saturated aqueous NaHCO₃ solution (500 mL) were introduced into the reaction mixture and the aqueous phase was extracted further with Et₂O (3x 300 mL). The organic extracts were then combined, washed with brine (1x 500 mL), dried (MgSO₄), filtered and the volatiles removed under reduced pressure. The crude product thus obtained was then subjected to silica gel flash column chromatography (EtOAc/hexanes: 1:1 to 3:1 gradient elution). The title compound was obtained as a white solid in 97% yield (7.1 g). TLC (EtOAc/hexanes, 1:1) R_f = 0.25 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 1.5-1.7 (m, 3H), 2.1-2.3 (m, 4H), 3.2 (br s, 2H), 3.6 (t, 2H, J = 6.3 Hz), 4.2 (t, 1H, J = 6.6 Hz), 4.4 (d, 2H, J = 6.7 Hz), 4.9 (br s, 1H), 5.3-5.6 (m, 2H), 7.2-7.3 (m, 2H), 7.4-7.5 (m, 2H), 7.6 (d, 2H, J = 7.3 Hz), 7.8 (d, 2H, J = 7.3 Hz). ¹³C NMR (75 MHz, CDCl₃): δ 23.6, 27.8, 29.3, 32.1, 32.4, 33.2, 40.8, 47.5, 62.6, 66.6, 120.2, 125.2, 127.2, 127.3, 127.9, 133.1, 141.5, 144.2, 156.7. HRMS: calcd for C₂₂H₂₄NO₃ (M+H)⁺ 352.1913, found 352.1920. Melting point: 94-96 °C.

Compound 18b. *7-Hydroxy-hept-3-enyl)-carbamic acid tert-butyl ester.* The same procedure as that described above for **18a** was used with the following exceptions: Boc₂O was used instead of Fmoc-OSu and the reaction was performed on a 100 mg (0.8 mmol) scale; other reagent stoichiometries were modified accordingly. After workup and silica gel flash column chromatography (EtOAc/hexanes, 1:1), the purified product was obtained as a colorless oil in 78% yield (143 mg). TLC (EtOAc/hexanes, 1:1) R_f = 0.32 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃): δ 1.4 (s, 9H), 1.5-1.7 (m, 2H), 1.8 (br s, 1H), 2.0-2.2 (m, 4H), 3.1 (t, 2H, J = 6.7 Hz), 3.6 (t, 3H, J = 6.3 Hz), 4.5 (br s, 1H), 5.3-5.5 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 18.3, 22.8, 23.3, 23.4, 23.9, 27.0, 27.1, 28.0, 35.1, 56.6, 57.2, 72.2, 74.1, 121.6, 122.2, 126.7, 127.4, 150.9. HRMS: calcd for C₁₂H₂₅NO₃ (M+H)⁺ 230.1756, found 230.1751.

Compound 8: *5-Trityloxy-pent-1-ene.* To a solution of triphenylmethane chloride (6.9 g, 25 mmol, 1 equiv) in DCM (300 mL) at 0 °C was added pent-4-en-1-ol (3.2 g, 37.5 mmol, 1.5 equiv) and triethylamine (7.6 g, 75 mmol, 3 equiv). The resulting solution was allowed to warm to room temperature and stirred for an additional 3 h. The organic phase was washed with saturated aqueous NH₄Cl solution (3x 200 mL), water (1x 200 mL), brine (1x 200 mL), dried (MgSO₄), filtered and the solvent was removed under reduced pressure. The crude oil thus obtained was then subjected to silica gel flash column chromatography (EtOAc/hexanes: 1:24). The title compound was obtained as a

colorless oil in 75% yield (6.1 g). TLC (EtOAc/hexanes, 1:9) R_f = 0.60 (KMnO₄).⁵ ¹H NMR (300 MHz, CDCl₃) δ 1.7-1.9 (m, 2H), 1.9-2.3 (m, 2H), 3.1 (t, 2H, J = 6.4 Hz), 4.9-5.1 (m, 2H), 5.7-5.9 (m, 1H), 7.2-7.4 (m, 9H), 7.5-7.6 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 29.5, 30.8, 63.3, 86.6, 114.8, 127.1, 128.0, 129.0, 138.9, 144.7; HRMS calcd for C₂₄H₂₄O (M)⁺ 328.1827, found 328.1831.

Compound 7a

Compound 7b

Compound 7d

Compound 7e

Compound 11

Compound 14

Compound 18a

Compound **18b**