Supporting Information

Rhodium-Catalyzed Addition of Alkynes to Activated Ketones and Aldehydes

Pawan K. Dhondi and John D. Chisholm*

1-014 Center for Science and Technology, Department of Chemistry, Syracuse University, Syracuse, NY 13244

Experimental Section

General procedures: Routine ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz for ^1H , 75 MHz for ^{13}C) using Me_4Si (δ 0.0) as the internal reference. Two-dimensional NMR experiments were performed on a Bruker Avance DRX-500 spectrometer. Ratios of isomers were determined from ^1H NMR spectra. Infrared spectra were recorded on a Thermo Nicolet IR-100 spectrometer, and were obtained from samples prepared as thin films between NaCl plates. High resolution mass spectra were obtained using the positive ion electrospray ionization mode with $\text{MeOH/THF} + \text{NaCl}$ as solvent on a 3-Tesla FT mass spectrometer at The Ohio State University. Elemental analyses were performed by Complete Analysis Laboratories Inc., Parsippany, New Jersey. Flash column chromatography was performed using Silia-P flash silica gel (40-63 μm) from Silicycle, Inc. Precoated plates of silica gel 60 F₂₅₄ from EMD Chemicals Inc. were employed for thin-layer chromatography.

All anhydrous reactions were run under a positive pressure of argon or nitrogen. All syringes, hypodermic needles, cannulae, and reaction flasks required for anhydrous reactions were dried in an oven and cooled under a N_2 atmosphere or in a desiccator. Benzene, dichloromethane, diethyl ether, and THF were dried by passage through an alumina column (solvent purification system from Solv-Tek, Inc.) following the method of Grubbs.¹ Triethylamine was distilled from CaH_2 and stored over 4 Å molecular sieves. All other reagents and solvents were purchased from Aldrich, Acros Organics, Fluka, GFS Chemicals, Lancaster, Sigma, and Strem Chemicals and used without further purification.

Representative Experimental Procedures:

3,8-Dihydroxy-3-methyl-oct-4-yn-2-one (13): A degassed solution of 2,3-butanedione (**11**) (104.4 mg, 1.2 mmol) and 4-pentyne-1-ol (**12**) (34.7 mg, 0.4 mmol) in 0.5 ml THF was added to a degassed mixture of Rh(acac)(CO)₂ (0.012 mmol, 3.1 mg, 3 mol %) and 2-di-*t*-butylphosphinobiphenyl (0.036 mmol, 10.9 mg, 9 mol %) under an argon atmosphere (degassing was performed by bubbling argon through the solution for approximately 10 min. Solid substrates were degassed in the same reaction tube as the catalyst and ligand). The reaction tube was then placed in a preheated oil bath at 40°C (unless specified otherwise) and stirred for 24 hours. The reaction mixture was then pre-adsorbed on silica gel and purified by silica gel chromatography (30-50% ethyl acetate/CH₂Cl₂). This sequence provided **13** (62.1 mg, 91% yield) as a thick oil. TLC *R*_f = 0.31 (50% ethyl acetate/50% CH₂Cl₂). IR (neat): 3415, 2936, 2243, 1723 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 4.16 (s, 1H), 3.69 (t, *J* = 6.1 Hz, 2H), 2.36 (s, 3H), 2.33 (t, *J* = 7.0 Hz, 2H), 2.08 (s, 1H), 1.73 (p, *J* = 6.6 Hz, 2H), 1.56 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 206.2, 85.5, 79.6, 72.2, 60.3, 30.5, 26.4, 23.0, 14.7. Anal Calc'd for C₉H₁₄O₃: C, 63.51; H, 8.29. Found: C, 63.51; H, 8.22.

2-Hydroxy-2-methyl-dec-3-ynoic acid ethyl ester (3): A degassed solution of octyne (**2**) (44.5 mg, 0.4 mmol) and ethyl pyruvate (**1**) (142.2 mg, 1.2 mmol) in 0.5 ml of 1,4-dioxane was added to a degassed mixture of Rh(acac)(CO)₂ (5.2 mg, 0.02 mmol, 5 mol %) and 2-di-*t*-butylphosphinobiphenyl (12 mg, 0.04 mmol, 10 mol %) under argon preheated to 90°C. After 24 h the reaction was pre-adsorbed on silica gel and purified by silica gel chromatography (80% CH₂Cl₂/hexane-0.7% acetone/CH₂Cl₂) providing **3** (75.4 mg, 83% yield) as a yellow oil. TLC *R*_f = 0.23 (0.7% acetone/99.3% CH₂Cl₂). IR (neat): 3502, 2934, 2860, 2250, 1739 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 4.28 (q, *J* = 7.1 Hz, 2H), 3.42 (s, 1H), 2.18 (t, *J* = 7.0 Hz, 2H), 1.64 (s, 3H), 1.53-1.42 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.40-1.19 (m, 6H), 0.87 (t, *J* = 6.7 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 173.4, 85.2,

80.0, 68.1, 62.9, 31.5, 28.6, 28.5, 27.5, 22.7, 18.8, 14.2 (only 12 signals are seen due to overlapping peaks in the alkyl region). Anal Calc'd for C₁₃H₂₂O₃: C, 68.99; H, 9.80. Found: C, 68.67; H, 9.74.

4-Ethyl-4,9-dihydroxy-non-5-yn-3-one (15): Purification by silica gel chromatography (15-35% ethyl acetate/CH₂Cl₂) provided **15** in 95% yield. TLC *R_f* = 0.36 (40% ethyl acetate/60% CH₂Cl₂). IR (neat): 3435, 2937, 2880, 2235, 1720 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 4.14 (s, 1H), 3.66 (t, *J* = 6.1 Hz, 2H), 2.88 (dq, *J* = 18.1, 7.3 Hz, 1H), 2.52 (dq, *J* = 18.1, 7.3 Hz, 1H), 2.36 (s, 1H), 2.30 (t, *J* = 7.0 Hz, 2H), 1.97-1.85 (m, 1H), 1.77-1.65 (m, 3H), 1.10 (t, *J* = 7.3 Hz, 3H) 0.89 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 209.7, 86.2, 79.6, 76.1, 61.4, 33.3, 31.2, 29.3, 15.4, 8.2, 7.9. Anal Calc'd for C₁₁H₁₈O₃: C, 66.64; H, 9.15. Found: C, 66.64; H, 9.20

2,7-Dihydroxy-2-methyl-hept-3-ynoic acid ethyl ester (16): Purification by silica gel chromatography (30-50% ethyl acetate/CH₂Cl₂) provided **16** in 94% yield. TLC *R_f* = 0.39 (50% ethyl acetate/50% CH₂Cl₂). IR (neat): 3449, 2985, 2940, 2248, 1741 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 4.16 (q, *J* = 7.1 Hz, 2H), 3.59 (t, *J* = 6.2 Hz, 2H), 2.21 (t, *J* = 7.0 Hz, 2H), 1.63 (p, *J* = 6.6 Hz, 2H), 1.53 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) (the protons for both alcohols had exchanged with deuterium in the spectra for this compound, and are therefore not reported). ¹³C NMR (75 MHz, CDCl₃) δ 172.9, 84.2, 80.3, 67.9, 62.5, 60.9, 30.8, 37.4, 15.1, 13.9. Anal Calc'd for C₁₀H₁₆O₄: C, 59.98; H, 8.05. Found: C, 60.22; H, 8.11.

Tridec-4-yne-1,6-diol (18): Purification by silica gel chromatography (10-20% acetone/CH₂Cl₂) provided **18** in 68% yield. TLC *R_f* = 0.31 (20% acetone/80% CH₂Cl₂). IR (neat): 3338, 2927, 2857, 2233 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 4.29 (t, *J* = 6.6 Hz, 1H), 3.70 (t, *J* = 6.1 Hz, 2H), 3.31 (s, 2H), 2.30 (t, *J* = 6.9 Hz, 2H), 1.73-1.58 (m, 4H), 1.41-1.39 (m, 2H), 1.25 (m, 8H), 0.87-0.83 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 84.5, 82.3,

62.6, 61.3, 38.3, 32.0, 31.3, 29.5, 29.4, 25.5, 22.8, 15.4, 14.3. Anal Calc'd for C₁₃H₂₄O₂: C, 73.54; H, 11.39.

Found: C, 73.50; H, 11.39.

1-Cyclohexyl-hex-2-yne-1,6-diol (20): Purification by silica gel chromatography (0-40% acetone/hexane) provided alcohol **20** in 80% yield. TLC R_f = 0.31 (40% acetone/60% hexane). IR (neat): 3368, 2927, 2853, 2234 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 4.07 (d, J = 6.0 Hz, 1H), 3.69 (t, J = 6.2 Hz, 2H), 3.09 (s, 2H), 2.30 (dt, J = 6.9, 2.0 Hz, 2H), 1.81-1.61 (m, 7H), 1.51-1.39 (m, 1H), 1.27-0.93 (m, 5H). ¹³C NMR (75 MHz, CDCl₃) δ 85.3, 81.0, 67.3, 61.4, 44.4, 31.3, 28.8, 28.3, 26.5, 26.0, 15.4 (only 11 signals are seen due to overlapping peaks). HRMS (Electrospray): m/z Calc'd for C₁₂H₂₀O₂Na⁺ (M⁺): 219.1355 Found: 219.1351.

1-Phenyl-hex-2-yne-1,6-diol (22): Purification by silica gel chromatography (0-10% acetone/CH₂Cl₂) provided **22** in 34% yield. TLC R_f = 0.34 (50% ethyl acetate/50% CH₂Cl₂). IR (neat): 3299, 2947, 2225 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.50 (d, J = 7.7 Hz, 2H), 7.37-7.26 (m, 3H), 5.39 (s, 1H), 3.70 (t, J = 6.2 Hz, 2H), 2.33 (dt, J = 6.9, 1.8 Hz, 2H), 1.70 (p, J = 6.6 Hz, 2H) (the protons for both alcohols had exchanged with deuterium in the spectra for this compound, and are therefore not reported). ¹³C NMR (75 MHz, CDCl₃) δ 141.4, 128.6, 128.2, 126.7, 86.5, 80.9, 64.5, 61.2, 31.0, 15.4. Anal Calc'd for C₁₂H₁₄O₂: C, 75.76; H, 7.42. Found: C, 75.37; H, 7.39.

1-(4-Nitro-phenyl)-hex-2-yne-1,6-diol (24): 4-Nitrobenzaldehyde is a solid and was therefore degassed along with the catalyst and ligand to which the degassed solution of 4-pentyne-1-ol in THF was added. Purification by silica gel chromatography (6-18% acetone/CH₂Cl₂) followed by recrystallization from chloroform provided **24** in 94% yield. mp = 53.5-54.5°C (CHCl₃); TLC R_f = 0.32 (50% ethyl acetate/50% CH₂Cl₂). IR (neat): 3347, 2949, 2227, 1606, 1519 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 8.22 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.9 Hz, 2H),

5.53 (s, 1H), 3.75 (t, $J = 6.1$ Hz, 2H), 2.95 (s, 1H), 2.40 (dt, $J = 7.0, 2.1$ Hz, 2H), 1.78 (p, $J = 6.5$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 148.4, 147.7, 127.5, 123.8, 87.7, 79.9, 63.6, 61.5, 30.9, 15.5. Anal Calc'd for $\text{C}_{12}\text{H}_{13}\text{NO}_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.22; H, 5.72; N, 6.11.

3-Hydroxy-3-methyl-undec-4-yn-2-one (25): Purification by silica gel chromatography (CH_2Cl_2) provided **25** in 83% yield. TLC $R_f = 0.29$ (CH_2Cl_2). IR (neat): 3466, 2932, 2859, 2246, 1723 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 4.02 (s, 1H), 2.32 (s, 3H), 2.14 (t, $J = 7.0$ Hz, 2H), 1.52 (s, 3H), 1.33-1.19 (m, 8H), 0.82 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 206.4, 86.7, 79.6, 72.6, 31.3, 28.5, 28.4, 27.2, 23.2, 22.6, 18.7, 14.0. Anal Calc'd for $\text{C}_{12}\text{H}_{20}\text{O}_2$: C, 73.43; H, 10.27. Found: C, 73.87; H, 10.33.

3-Hydroxy-3-methyl-5-phenyl-pent-4-yn-2-one (27): Purification by silica gel chromatography (0-1% ethyl acetate/ CH_2Cl_2) provided **27** in 82% yield. TLC $R_f = 0.27$ (CH_2Cl_2). IR (neat): 3447, 2890, 2933, 1724 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.45-7.42 (m, 2H), 7.33-7.29 (m, 3H), 4.28 (s, 1H), 2.46 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 205.8, 131.8, 128.9, 128.4, 121.9, 88.2, 85.6, 73.0, 27.0, 23.4. Anal Calc'd for $\text{C}_{12}\text{H}_{12}\text{O}_2$: C, 76.57; H, 6.43. Found: C, 76.32; H, 6.41.

3-Hydroxy-3-methyl-5-triisopropylsilyl-pent-4-yn-2-one (29): Purification by silica gel chromatography (10-30% ethyl acetate/ CH_2Cl_2) provided **29** in 99% yield. TLC $R_f = 0.51$ (CH_2Cl_2). IR (neat): 3468, 2944, 2866, 2169, 1726 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 4.04 (s, 1H), 2.39 (s, 3H), 1.60 (s, 3H), 1.04 (s, 21H). ^{13}C NMR (75 MHz, CDCl_3) δ 205.8, 106.6, 87.4, 73.1, 27.4, 23.3, 18.7, 11.3. Anal Calc'd for $\text{C}_{15}\text{H}_{28}\text{O}_2\text{Si}$: C, 67.11; H, 10.51. Found: C, 67.37; H, 10.55.

7-Hydroxy-7-methyl-8-oxo-non-5-ynenitrile (30): Purification by silica gel chromatography (0-2% acetone/ CH_2Cl_2) provided **30** in 98% yield. TLC R_f = 0.36 (3% acetone/97% CH_2Cl_2). IR (neat): 3447, 2938, 2249, 1723 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 4.06 (s, 1H), 2.39 (t, J = 7.1 Hz, 2H), 2.33 (t, J = 6.9 Hz, 2H), 2.29 (s, 3H), 1.78 (p, J = 6.9 Hz, 2H), 1.49 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 205.9, 119.0, 83.4, 81.4, 72.4, 26.9, 24.1, 23.2, 17.7, 16.1. Anal Calc'd for $\text{C}_{10}\text{H}_{13}\text{NO}_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.23; H, 7.47; N, 7.91

3,6-Dihydroxy-3,6-dimethyl-hept-4-yn-2-one (33): Purification by silica gel chromatography (0-15% acetone/ CH_2Cl_2) provided **33** in 63% yield. TLC R_f = 0.32 (40% ethyl acetate/60% CH_2Cl_2). IR (neat): 3418, 2984, 2935, 1723 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 4.20 (s, 1H), 2.83 (s, 1H), 2.36 (s, 3H), 1.56 (s, 3H), 1.48 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ 206.2, 90.7, 81.3, 72.6, 65.1, 31.3, 27.1, 23.5 (only 8 signals are seen due to overlapping peaks). Anal Calc'd for $\text{C}_9\text{H}_{14}\text{O}_3$: C, 63.51; H, 8.29. Found: C, 63.33; H, 8.38.

3,7-Dihydroxy-3-methyl-hept-4-yn-2-one (35): Purification by silica gel chromatography (30-50% ethyl acetate/ CH_2Cl_2) provided **35** in 94% yield. TLC R_f = 0.31 (50% ethyl acetate/50% CH_2Cl_2). IR (neat): 3401, 2937, 2250, 1723 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 4.55 (s, 1H), 3.65 (t, J = 6.0 Hz, 2H), 3.47 (s, 1H), 2.41 (t, J = 6.2 Hz, 2H), 2.33 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 206.5, 83.8, 81.1, 72.7, 60.6, 27.0, 23.5, 23.1. Anal Calc'd for $\text{C}_8\text{H}_{12}\text{O}_3$: C, 61.52; H, 7.74. Found: C, 61.33; H, 7.70.

3,14-Dihydroxy-3-methyl-tetradec-4-yn-2-one (37): Purification by silica gel chromatography (0-10% acetone/ CH_2Cl_2) provided **37** in 96% yield. TLC R_f = 0.29 (10% acetone/90% CH_2Cl_2). IR (neat): 3429, 2930,

2856, 2247, 1723 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 4.22 (s, 1H), 3.49 (t, $J = 6.7$ Hz, 2H), 2.61 (s, 1H), 2.27 (s, 3H), 2.09 (t, $J = 7.0$ Hz, 2H), 1.46 (s, 3H), 1.43-1.36 (m, 4H), 1.24-1.19 (m, 10H). ^{13}C NMR (75 MHz, CDCl_3) δ 206.5, 86.6, 79.6, 72.5, 62.5, 32.6, 29.3, 29.3, 28.9, 28.7, 28.2, 27.0, 25.7, 23.2, 18.6. Anal Calc'd for $\text{C}_{15}\text{H}_{26}\text{O}_3$: C, 70.83; H, 10.30. Found: C, 70.58; H, 10.23.

12-Ethyl-12-hydroxy-13-oxo-pentadec-10-ynoic acid (39): A degassed solution of dry and distilled triethylamine (81 mg, 0.8 mmol) in 1 ml of THF, followed by a degassed solution of 3,4-hexanedione (**14**) (288.4 mg, 2.4 mmol) was added to a degassed mixture of 10-undecynoic acid (**38**) (153.5 mg, 0.8 mmol) $\text{Rh}(\text{acac})(\text{CO})_2$ (6.3 mg, 0.024 mmol, 3 mol%) and 2-di-*t*-butylphosphinobiphenyl (21.7mg, 0.072 mmol, 9 mol%) under an argon atmosphere. The reaction was then warmed to 40°C . The reaction was quenched by the addition of 17 drops of glacial acetic acid after 24h. The reaction mixture was then pre-adsorbed on silica gel and purified by silica gel chromatography (5% acetone/ CH_2Cl_2) providing alcohol **39** in 94% yield. TLC R_f = 0.20 (4% acetone/96% CH_2Cl_2). IR (neat): 3438, 2936, 2857, 2234, 1716, 1646 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 2.86 (dq, $J = 18.0, 7.3$ Hz, 1H), 2.48 (dq, $J = 18.0, 7.3$ Hz, 1H), 2.25 (t, $J = 7.4$ Hz, 2H), 2.13 (t, $J = 7.0$ Hz, 2H), 1.87 (sextet, $J = 7.3$ Hz, 1H), 1.67 (sextet, $J = 7.0$ Hz, 1H), 1.56-1.49 (m, 2H), 1.46-1.37 (m, 2H), 1.22 (m, 8H), 1.05 (t, $J = 7.3$ Hz, 3H), 0.85 (t, $J = 7.4$ Hz, 3H) (the protons for the alcohol and the carboxylic acid had exchanged with deuterium in the spectra for this compound, and are therefore are not reported). ^{13}C NMR (75 MHz, CDCl_3) δ 209.7, 179.7, 86.8, 79.0, 76.0, 34.0, 33.2, 29.1, 29.0, 28.9, 28.8, 28.7, 28.3, 24.6, 18.6, 8.1, 7.8. Anal Calc'd for $\text{C}_{17}\text{H}_{28}\text{O}_4$: C, 68.89; H, 9.52. Found: C, 68.77; H 9.46.

References

- (1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-20.

Spectral Data

^1H and ^{13}C spectral data is provided for selected compounds.

220
200
180
160
140
120
100
80
60
40
20
ppm