New Tandem Catalysis. Preparation of Cyclic Enol Ethers through a Ruthenium-Catalyzed Ring Closing Metathesis–Olefin Isomerization Sequence

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Supporting Information

General: Starting materials and reagents were purchased from commercial suppliers and used without further purification except the following: tetrahydrofuran and dichloromethane were dried on alumina columns using a solvent dispensing system;¹ pentane, hexanes and ether used in chromatography were distilled prior to use. Acetonitrile was distilled from CaH₂. All reactions were conducted in oven (135 °C) or flame-dried glassware under an inert atmosphere of dry nitrogen. K₂CO₃ was purchased from Fisher and was oven-dried (140 °C) before use. Since the purity and activity of commercially available tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (Grubbs' ruthenium catalyst, **2**) was variable, silica gel chromatography (5:1 pentane:ether) was used to purify the catalyst **2**. The vibrant cranberry red fractions were collected to yield pure **2**.

Infrared (IR) spectra were recorded on a Nicolet Avatar 360 spectrophotometer, ν_{max} cm⁻¹. Bands are characterized as broad (br), strong (s), medium (m) and weak (w). ¹H NMR spectra were recorded on a Varian Unity 300 (300 MHz), Varian Gemini 400 (400 MHz) or Varian Gemini 500 (500 MHz). Chemical shifts are reported with the solvent as the internal standard (CHCl₃ δ 7.26 ppm, C₆H₆ δ 7.16 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ¹³C NMR spectra were recorded on a Varian Gemini 400 (100 MHz) or Varian Gemini 500 (125 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent as an internal

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

reference (CDCl_3 δ 77.2 ppm, C_6H_6 δ 128.3 ppm). ^{31}P NMR spectra were recorded on a Varian Gemini 400 (162 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with 85% H_3PO_4 as an external reference (δ 0.0 ppm). A Hewlett Packard HP 6890 Series II Gas Chromatograph was used for all reactions monitored by GC utilizing an HP-5 Cross-Linked 5% Phenyl Methyl Silicone column. Enantiomeric ratios were determined by chiral GC utilizing either a Beta Dex 120 (30 m x 0.25 mm x 0.25 μm film thickness) or Gamma Dex 120 (30 m x 0.25 mm x 0.25 μm film thickness) columns by Supelco. Elemental Analysis were performed by Robertson Microlit Laboratories, Inc., Madison, NJ and are reported in percent abundance.

General Etherification Procedure to Synthesize Dienes: An excess of 60% sodium hydride (NaH) in mineral oil was added to a flame-dried flask. A solution of the alcohol in tetrahydrofuran was slowly added to the NaH. The resultant suspension was stirred for 1-2 hours at room temperature. The alkyl bromide was added and the reaction was stirred at room temperature until complete conversion of the alcohol to the desired diene. In some cases addition of 0.5-2.0 mL of anhydrous dimethylformamide was found to facilitate complete conversion of the alcohol to diene. The reaction suspension was chilled in an ice bath and the excess NaH was quenched with saturated aqueous ammonium chloride. The reaction mixture was partitioned between ether and H_2O . The aqueous layer was extracted with ether (3x). The combined organics were washed with H_2O and brine, dried over MgSO_4 and concentrated. The crude dienes were purified by silica gel (EM Science Silica Gel 60 Geduran 35-75 μm) chromatography.

The general procedure was followed with allylic alcohol **28** (298 mg, 2.22 mmol), 60% NaH (180 mg), 5-bromo-1-pentene (1.0 mL, 8.5 mmol, 3.9 equiv) in tetrahydrofuran (10 mL) and dimethylformamide (1.5 mL). The reaction mixture was allowed to stir for 6 h at 22 °C. Silica gel chromatography (50:1

pentane:ether) afforded diene **15** as a colorless oil (298 mg, 67% yield). **(1-Pent-4-enyloxy-allyl)-benzene (15)**: IR (neat): 3074 (w), 3027 (w), 2945 (s), 2853 (s), 1644 (m), 1443 (m), 1098 (s) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) 7.35 (m, 4H), 7.29 (m, 1H), 5.95 (1H, ddd, $J = 10.4, 6.8, 3.6$ Hz), 5.82 (1H, ddt, $J = 10.4, 6.8, 2.8$ Hz), 5.26 (1H, d, $J = 17.2$ Hz), 5.19 (1H, d, $J = 10.4$ Hz), 5.02 (1H, d, $J = 17.2$ Hz), 4.95 (1H, d, $J = 10.4$ Hz), 4.73 (1H, d, $J = 6.8$ Hz), 3.49 (1H, dt, $J = 9.2, 6.8$ Hz), 3.40 (1H, dt, $J = 9.2, 6.8$ Hz), 2.15 (2H, q, $J = 7.6$ Hz), 1.72 (2H, qi, $J = 6.8$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) 141.4, 139.3, 138.4, 128.5, 127.6, 126.8, 116.1, 114.8, 83.2, 68.2, 30.7, 29.4; Anal calcd for $\text{C}_{14}\text{H}_{19}\text{O}$: C, 83.12; H, 8.97. Found C, 83.40; H, 8.69.

General RCM-Isomerization Procedure for 6-Membered Ring Systems:

Purified Grubbs' catalyst **2** was weighed into an oven-dried pyrolysis tube inside a N_2 atmosphere glovebox. The tube was capped with a septum, the edges sealed with electrical tape, and removed from the glovebox. The reaction vessel was put under positive N_2 pressure and dichloromethane was added via syringe. A solution of the diene in dichloromethane was added via syringe pump over 1 h yielding a final reaction concentration of 0.05 M. Upon complete addition a mixture of 95:5 $\text{N}_2:\text{H}_2$ was bubbled vigorously through the solution and the septum was replaced by teflon screw-cap. The sealed reaction vessel was heated to 65-70 $^\circ\text{C}$ for 6-24 (generally 8-12) hours. The reaction solution was absorbed on alumina (FisherBrand Alumina Adsorption Chromatography Grade 80-200 mesh) and purified by alumina chromatography.

The general procedure was followed with diene **9** (50.6 mg, 0.23 mmol) in dichloromethane (1.0 mL), catalyst **2** (19.0 mg, 0.023 mmol), dichloromethane (3.5 mL), 95:5 $\text{N}_2:\text{H}_2$ ($t = 3$ min). The reaction mixture was stirred at 65-70 $^\circ\text{C}$ for 20 h. Alumina chromatography (100% pentane to 95:5 pentane:ether) afforded the enol ether **10** (25.0 mg, 0.13 mmol, 57%) as a colorless oil. **2-(4-Chlorophenyl)-3,4-dihydro-2H-pyran (10)**: IR (neat): 3062 (w), 2936 (s), 2867 (m), 1727

(m), 1690 (w), 1645 (w), 1495 (s), 1243 (m), 1086 (s), 1060 (s), 1010 (s), 806(w) cm^{-1} ; ^1H NMR (C_6D_6 , 400 MHz) δ 7.11 (2H, dt, J = 8.4, 2.4 Hz), 6.93 (2H, dt, J = 8.4, 2.4 Hz), 6.48 (2H, d, J = 6.0 Hz), 4.60 (1H, ddd, J = 10.8, 6.0, 2.8 Hz), 4.50 (1H, dd, J = 6.4, 6.4 Hz), 1.91-1.81 (1H, m), 1.71-1.62 (1H, m) 1.60-1.55 (2H, m); ^{13}C NMR (C_6D_6 , 100 MHz) δ 144.6, 141.4, 133.8, 129.0, 127.9, 101.1, 76.7, 31.1, 20.0; Anal. calcd for $\text{C}_{11}\text{H}_{11}\text{ClO}$: C, 67.87; H, 5.70. Found C, 68.17; H, 5.54.

General RCM-Isomerization Procedure for 7-Membered Ring Systems:

Purified Grubbs' catalyst **2** was weighed into an oven-dried pyrolysis tube inside a N_2 atmosphere glovebox. The tube was capped with a septum, the edges sealed with electrical tape, and removed from the glovebox. The reaction vessel was put under positive N_2 pressure and dichloromethane was added via syringe. A solution of the diene in dichloromethane was added via syringe pump over 1 h yielding a final reaction concentration of 0.03 M. Upon complete addition a mixture of 95:5 N_2 : H_2 was bubbled vigorously through the solution and the septum was replaced by teflon screw-cap. The sealed reaction vessel was heated to 65-70 $^\circ\text{C}$ for 6-8 h. The reaction solution was absorbed on alumina (FisherBrand Alumina Adsorption Chromatography Grade 80-200 mesh) and purified by alumina chromatography.

General RCM-Isomerization Procedure for 5-Membered Ring Systems:

Purified Grubbs' catalyst **2** was weighed into an oven-dried pyrolysis tube inside a N_2 atmosphere glovebox. The tube was capped with a septum, the edges sealed with electrical tape, and removed from the glovebox. The reaction vessel was put under positive N_2 pressure and dichloromethane was added via syringe. A solution of the diene in dichloromethane was added via syringe pump over 2 h yielding a final reaction concentration of 0.05 M. Upon complete addition a mixture of 95:5 N_2 : H_2 was vigorously bubbled through the solution and the septum was replaced by teflon screw-cap. The sealed reaction vessel was heated to 45-50 $^\circ\text{C}$ for 6-8 h. The reaction solution was absorbed on alumina (FisherBrand Alumina Adsorption Chromatography Grade 80-200 mesh) and purified by alumina chromatography.

RCM-Isomerization for 6-membered nitrogen-containing substrate:

Allyl bromide (35.0 μL , 0.39 mmol) was added to a stirring mixture of tosylamide **29** (100.0 mg, 0.33 mmol) and K_2CO_3 (250.0 mg, 1.78 mmol) in dry acetonitrile (3.3 mL). The mixture was refluxed for 7 h and judged complete by TLC. The reaction mixture was diluted with brine (5 mL) and extracted with CH_2Cl_2 (3 x 3 mL). Drying with MgSO_4 followed by silica gel chromatography (3:2, hexanes:ether) yielded the desired diene **16** as a colorless oil (99.0 mg, 0.29 mmol, 88%). **N-Allyl-4-methyl-N-(1-phenylbut-3-en-1-yl)benzenesulfonamide (16)**: IR (neat): 3068 (m), 3030 (m), 2974 (m), 2917 (m), 2854 (w), 1639 (m), 1595 (m), 1501 (m), 1457 (s), 1337 (s), 1161 (s), 1086 (s), 1048 (m), 1010 (m), 916 (s), 815 (m), 777 (s), 746 (m), 707 (s), 658 (s), 613 (m) cm^{-1} ; ^1H NMR (C_6D_6 , 500 MHz) δ 7.70 (2H, d, J = 8.0 Hz), 7.15 (2H, d, J = 7.0 Hz), 7.03-6.90 (3H, m), 6.73 (2H, d, J = 8.0 Hz), 5.64-5.53 (2H, m), 5.27 (1H, t, J = 5.0 Hz), 4.93 (1H, dt, J = 17.0, 2.0 Hz), 4.86-4.79 (2H, m), 4.73 (1H, dd, J = 10.0, 1.5 Hz), 3.75 (1H, dd, J = 17.0, 5.5 Hz), 3.50 (1H, dd, J = 16.0, 1.5 Hz), 2.61 (1H, ddd, J = 15.0, 7.5, 7.5 Hz), 2.53 (1H, ddd, J = 14.0, 7.0, 7.0 Hz), 1.87 (3H, s); ^{13}C NMR (CDCl_3 , 100 MHz) δ 143.0, 138.4, 137.8, 135.7, 134.6, 129.4, 128.6, 128.3, 127.8, 127.3, 117.6, 117.0, 60.7, 47.2, 38.5, 21.7; Anal. calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_2\text{S}$ C, 70.35; H, 6.79; N, 4.10. Found C, 70.35; H, 6.92; N, 4.17.

Catalyst **2** (19.0 mg, 0.023 mmol) was weighed into an oven-dried pyrolysis tube inside a N_2 atmosphere glovebox. The tube was capped with a septum, the edges sealed with electrical tape, and removed from the glovebox. The reaction vessel was put under positive N_2 pressure and dichloromethane (2.0 mL) was

added by syringe. A solution of diene **16** (51.0 mg, 0.015 mmol) in dichloromethane (1.0 mL) was added with a syringe pump over 1 h (final reaction concentration of 0.05 M). Fifteen minutes after the addition was completed a mixture of 95:5 N₂:H₂ was bubbled vigorously through the solution for 4 min and the septum was replaced by PTFE screw-cap. The sealed reaction vessel was heated to 65-70 °C for 13 h. The reaction mixture was concentrated and purified by silica gel chromatography (0.5% triethylamine in 7:3 benzene:hexanes) to yield enamine **17** as a white solid (34.0 mg, 0.10 mmol, 74%).

2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (17): IR (neat): 3093 (w), 3062 (w), 3033 (w), 2923 (w), 2841 (w), 1646 (m), 1595 (w), 1495 (m), 1406 (m), 1344 (s), 1167 (s), 1098 (m), 1010 (w), 941 (m), 828 (m), 689 (s) cm⁻¹; ¹H NMR (CDCl₃, 500MHz) δ 7.65 (2H, d, *J* = 8.5 Hz), 7.27-7.21 (7H, m), 6.92 (1H, d, *J* = 8.0 Hz), 5.19 (1H, s), 5.06 (1H, t, *J* = 7.0 Hz), 2.43 (3H, s), 1.93 (1H, br d, *J* = 13.5 Hz), 1.80 (1H, dt, *J* = 18.0, 5.0 Hz), 1.66-1.59 (1H, m), 1.45 (1H, tt, *J* = 12.5, 5.0 Hz); ¹³C NMR (C₆D₆, 100MHz) δ 143.2, 141.0, 137.7, 129.9, 128.8, 127.6, 127.4, 126.6, 125.5, 108.4, 56.6, 26.8, 21.6, 17.6; Anal. calcd for C₁₈H₁₉NO₂S: C, 68.98; H, 6.11; N, 4.47. Found C, 69.31; H, 6.40; N, 4.39.