C-H Bond Functionalization via Hydride Transfer: Lewis Acid Catalyzed Alkylation Reactions by Direct Intramolecular Coupling of sp^3 C-H Bonds and Reactive Alkenyl Oxocarbenium Intermediates

Kevin M. McQuaid and Dalibor Sames*

Department of Chemistry, Columbia University, New York, NY 10027

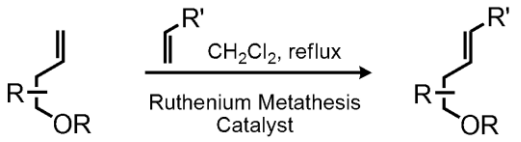
Supporting Information

I. General Introduction and Materials.

Argon was purified by passage through Drierite. Nuclear Magnetic Resonance spectra were recorded on Bruker 300, 400 or 500 Fourier transform NMR spectrometers. Spectra were recorded in $CDCl_3$ or C_6D_6 solutions and were referenced to TMS (0.0 ppm) or the solvent residual peak in $CDCl_3$ (7.26 and 77.16 for ^1H and ^{13}C NMR, respectively) or C_6D_6 (7.16 and 128.62 ^1H and ^{13}C NMR, respectively). Flash chromatography was performed on SILICYCLE silica gel (230-400 mesh). Mass spectra were recorded on a JEOL LCmate (Ionization mode: APCI+).

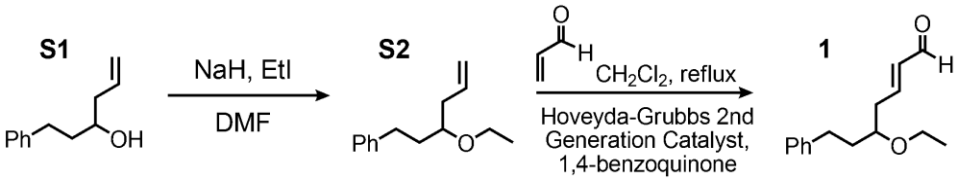
II. Synthesis of Starting Materials.

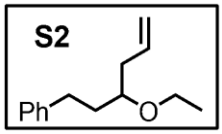
General procedure for cross-metathesis



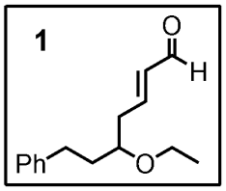
To an oven-dried two-neck round bottom flask equipped with a magnetic stir bar and reflux condenser was added the indicated metathesis catalyst. The flask was then evacuated and refilled with argon three times. Methylene chloride was added followed by the homoallylic ether or alcohol and the cross-coupling partner olefin via syringe. The septum on the two-neck round bottom flask was quickly replaced with a glass stopper and the solution was heated to reflux. During the course of the reaction, a continuous stream of argon was passed through the condenser. Reactions were generally run overnight and removed from heat in the morning. The crude reaction mixture was concentrated under reduced pressure and subjected to flash chromatography on silica gel giving the desired product as a pale brown or yellow oil. The product was spectroscopically pure by ^1H NMR but coloration indicated the presence of traces of ruthenium impurities. The amount of colored impurities could be minimized by vigorously stirring the crude reaction open to air for approximately two hours prior to chromatography, allowing for the catalyst to decompose. Re-subjecting colored products to chromatography after several days was also effective for obtaining colorless oils. However, the impurities did not appear to affect subsequent reactions.

Synthesis of enal (1).





To a solution of known alcohol **S1**[1] (1.57 g, 8.91 mmol) in DMF (40 mL), cooled to 0°C, was added sodium hydride (280 mg, 11 mmol, 95%). After stirring for 30 minutes, ethyl iodide (1.0 mL, 12 mmol) was added and allowed to warm to room temperature. After four hours, an additional portion of sodium hydride (240 mg, 9.5 mmol, 95%) and ethyl iodide (1.0 mL, 12 mmol) was added then allowed to stir overnight. The reaction was quenched with water and diluted with ether. The organic layer was separated, washed twice with water, once with brine, and dried over Na_2SO_4. Purification of the crude material via flash chromatography (2-3% ether in hexanes) gave ether **S2** as a colorless oil (1.68 g, 8.22 mmol, 92% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.25 (m, 2H), 7.20-7.15 (m, 3H), 5.85-5.77 (m, 1H), 5.09-5.03 (m, 2H), 3.62-3.54 (m, 1H), 3.49-3.41 (m, 1H), 3.35-3.29 (m, 1H), 2.80-2.73 (m, 1H), 2.67-2.59 (m, 1H), 2.34-2.25 (m, 2H), 1.82-1.76 (m, 2H), 1.21 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 142.6, 135.0, 128.6, 128.5, 125.8, 117.0, 78.2, 64.4, 38.6, 35.9, 31.9, 15.8. MS (LR-APCI): calculated for $C_{14}H_{20}O$ 204.3, measured 205.0.



Enal **1** was synthesized using the general metathesis procedure from homoallylic ether **S2** (493 mg, 2.42 mmol), freshly distilled acrolein (0.50 mL, 7.5 mmol), 1,4-benzoquinone (30 mg, 0.28 mmol) and the Hoveyda-Grubbs second-generation catalyst[2] (60 mg, 0.096 mmol) in methylene chloride (15 mL). Flash chromatography (ether/hexanes 1:5) gave enal **1** (501 mg, 2.16 mmol, 89%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.51 (d, *J*=7.9 Hz, 1H), 7.30-7.26 (m, 2H), 7.21-7.17 (m, 3H), 6.87 (dt, *J* =16 Hz, *J*=7.2 Hz, 1H), 6.15 (dd, *J*=16 Hz, *J*=7.9 Hz, 1H), 3.59-3.43 (m, 3H), 2.79-2.48 (m, 4H), 1.92-1.83 (m, 1H), 1.80-1.73 (m, 1H), 1.22 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 194.0, 154.8, 141.9, 135.0, 128.6, 128.5, 126.1, 77.2, 64.7, 37.4, 36.2, 31.8, 15.7; MS (LR-APCI): calculated for $C_{15}H_{20}O_2$ 232.3, measured 232.5.

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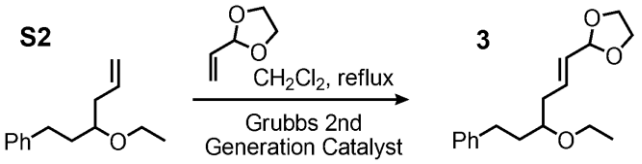
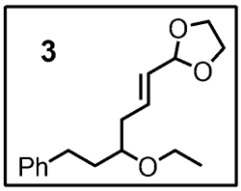
[1] Schmidt, B; *J. Org. Chem.* **2004**, *69*, 7672-7687.

[2] Garber, S.B.; Kingsbury, J.S.; Gray, B.L.; Hoveyda, A.H.; *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.

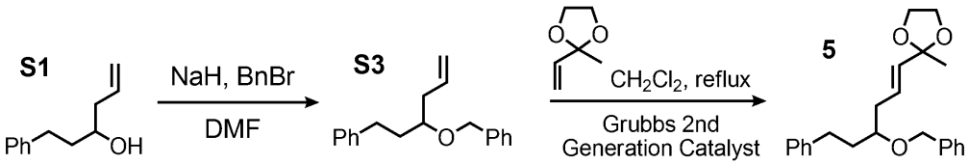
Synthesis of acetal (3).

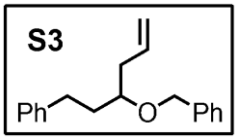




Acetal **3** was synthesized using the general metathesis procedure from homoallylic ether **S2** (617 mg, 3.02 mmol), commercially available 2-vinyl-1,3-dioxolane (0.75 mL, 7.5 mmol) and the Grubbs second-generation catalyst[3] (88 mg, 0.10 mmol) in methylene chloride (15 mL). Flash chromatography (ether/hexanes 1:5) gave acetal **3** (683 mg, 2.47 mmol, 82%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.94 (dt, *J*=16 Hz, *J*=7.2 Hz, 1H), 5.53 (dd, *J*=16, *J*= 6.4 Hz, 1H), 5.20 (d, *J*=6.4 Hz, 1H), 4.00-3.94 (m, 2H), 3.92-3.86 (m, 2H), 3.58-3.52 (m, 1H), 3.48-3.42 (m, 1H), 3.34-3.31 (m, 1H), 2.75-2.71 (m, 1H), 2.66-2.62 (m, 1H), 2.34-2.30 (m, 2H), 1.82-1.75 (m, 2H), 1.20 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 142.4, 133.6, 128.8, 128.6, 128.5, 125.8, 104.0, 77.9, 65.1, 64.5, 36.9, 36.0, 31.8, 15.7; MS (LR-APCI): calculated for $C_{17}H_{24}O_3$ 276.2, measured 277.4.

Synthesis of ketal (5).

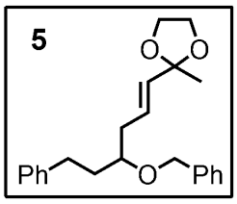




Known homoallylic alcohol **S1**[1] (1.93 g, 11.0 mmol) was dissolved in DMF (100 mL) and cooled to 0°C. Sodium hydride (295 mg, 11.7 mmol, 95%) was added in one portion and stirred for 30 minutes, followed by addition of benzyl bromide (1.64 g, 9.59 mmol). The solution was allowed to warm to room temperature and stirred over night. The reaction was quenched with a saturated ammonium chloride solution and diluted with ether. The organic phase was separated, washed three times with water then brine and dried over sodium sulfate. The solution was concentrated under reduced pressure

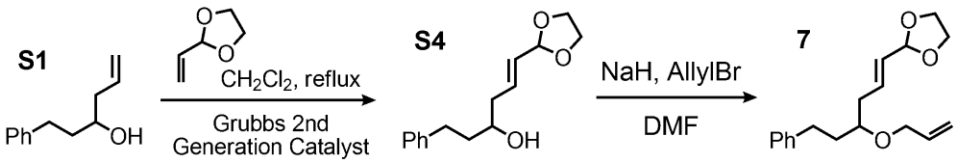
[3] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H.; *Org. Lett.*; **1999**, *1*, 953-956.

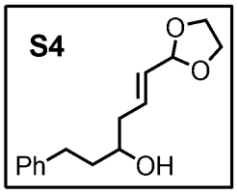
and purified by column chromatography (3% ether in hexanes) yielding **S3** as a clear oil (2.13 g, 8.00 mmol, 83% based on benzyl bromide). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.25 (m, 7H), 7.19-7.15 (m, 3H), 5.88-5.81 (m, 1H), 5.12-5.05 (m, 2H), 4.60 (d, *J*=12 Hz, 1H), 4.49 (d, *J*=12 Hz, 1H), 3.50-3.47 (m, 1H), 2.82-2.75 (m, 1H), 2.68-2.60 (m, 1H), 2.40-2.35 (m, 2H), 1.90-1.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 142.5, 139.0, 134.9, 128.6, 128.5, 127.9, 127.8, 127.7, 125.9, 117.2, 77.9, 71.1, 38.4, 35.8, 31.8; MS (LR-APCI): calculated for $C_{19}H_{22}O$ 266.2, measured 267.4.



Ketal **5** was synthesized using the general metathesis procedure from homoallylic ether **S3** (530 mg, 1.99 mmol), 2-methyl-2-vinyl-1,3-dioxolane (500 mg, 4.4 mmol) and the Grubbs second-generation catalyst[3] (54 mg, 0.063 mmol) in methylene chloride (15 mL). Flash chromatography (ether/hexanes 1:4) gave ketal **5** (507 mg, 1.44 mmol, 72%) as a pale brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.24 (m, 7H), 7.19-7.13 (m, 3H), 5.83 (dt, *J*=16 Hz, *J*=7.2 Hz, 1H), 5.50 (d, *J*=16 Hz, 1H), 5.57 (d, *J*=12 Hz, 1H), 4.48 (d, *J*=12 Hz, 1H), 3.95-3.88 (m, 2H), 3.85-3.81 (m, 2H), 3.48-3.44 (m, 1H), 2.76-2.73 (m, 1H), 2.68-2.63 (m, 1H), 2.37-2.32 (m, 2H), 1.88-1.79 (m, 2H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 142.4, 138.9, 133.1, 128.5(6C), 127.9(2C), 127.7, 127.2, 125.9, 107.4, 77.8, 71.1(2C), 64.6, 36.4, 35.9, 31.7, 25.1.

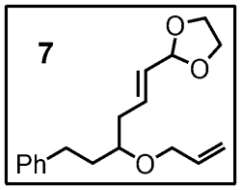
Synthesis of acetal (7).





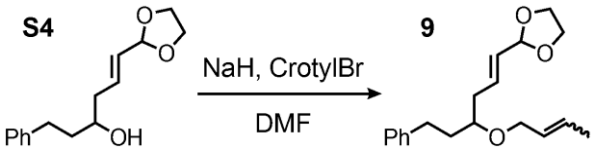
Acetal **S4** was synthesized using the general metathesis procedure from homoallylic alcohol **S1**[1] (480 mg, 2.72 mmol), commercially available 2-vinyl-1,3-dioxolane (0.7 mL, 7 mmol) and the Grubbs second-generation catalyst[3] (90 mg, 0.11 mmol) in methylene chloride (15 mL). Flash chromatography (ether/hexanes 2:3 to 1:1) gave acetal **S4** (535 mg, 2.15 mmol, 79%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.25 (m, 2H), 7.20-7.16 (m, 3H), 5.95 (dt, *J*=16 Hz, *J*=7.4 Hz, 1H), 5.59 (dd, *J*=16 Hz, *J*=6.3 Hz, 1H), 5.21 (d, *J*=6.3 Hz, 1H), 4.10-3.87 (m, 4H), 3.73-3.66 (m, 1H), 2.83-2.76 (m, 1H),

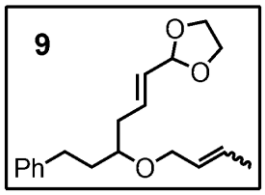
2.72-2.64 (m, 1H), 2.36-2.19 (m, 2H), 1.81-1.75 (m, 2H), 1.70 (bs, 1OH); ^{13}C NMR ($CDCl_3$, 100 MHz) 142.0, 133.2, 129.9, 128.6 (overlapping signals), 126.0, 103.8, 70.1, 65.1, 40.4, 38.6, 32.1; MS (LR-APCI): calculated for $C_{15}H_{20}O_3$ 248.3, measured 248.5.



Acetal **S4** (535 mg, 2.16 mmol) was dissolved in DMF (20 mL) and cooled to 0°C. Sodium hydride (65 mg, 2.6 mmol, 95%) was added in one portion and stirred for 30 minutes, followed by addition of allyl bromide (415 mg, 3.43 mmol). The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water and diluted with ether. The organic phase was separated, washed three times with water, then brine, and dried over sodium sulfate. The solution was concentrated under reduced pressure and purified by column chromatography (5:1 hexanes/ether) yielding **7** as a clear oil (345 mg, 1.20 mmol, 56%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.97-5.88 (m, 2H), 5.54 (dd, *J*=16 Hz, *J*=6.4 Hz, 1H), 5.31-5.25 (m, 1H), 5.21 (d, *J*=6.4 Hz, 1H), 5.18-5.15 (m, 1H), 4.07-3.84 (m, 6H), 3.43-3.37 (m, 1H), 2.79-2.71 (m, 1H), 2.67-2.59 (m, 1H), 2.38-2.30 (m, 2H), 1.88-1.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 142.3, 135.3, 133.4, 128.9, 128.6, 128.5, 125.9, 116.8, 104.0, 77.6, 70.2, 65.1, 36.7, 35.9, 31.7; MS (LR-APCI): calculated for $C_{18}H_{24}O_3$ 288.4, measured 288.4.

Synthesis of acetal (9).

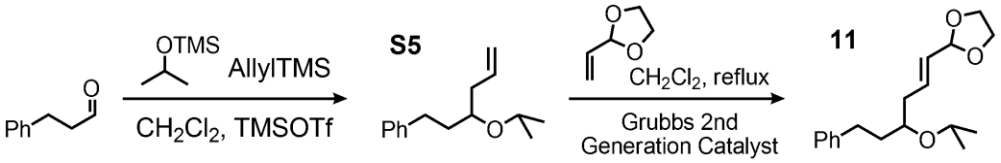


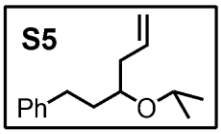


Acetal **S4** (563 mg, 2.27 mmol) was dissolved in DMF (15 mL) and cooled to 0°C. Sodium hydride (110 mg, 4.4 mmol, 95%) was added in one portion and stirred for 30 minutes, followed by addition of commercially available crotyl bromide (700 mg, 5.2 mmol) as a mixture of E/Z isomers. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water and diluted with ether. The organic phase was separated, washed three times with water, then brine, and dried over sodium sulfate. The solution was concentrated under reduced pressure and purified by column chromatography (6:1 to 5:1 hexanes/ether) yielding **9** as a clear

oil (575 mg, 1.90 mmol, 84%). GC analysis revealed approximately a 1:4 mixture of Z/E crotyl ethers. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.98-5.90 (m, 1H), 5.73-5.51 (m, 3H), 5.20 (d, *J*=6.4 Hz, 1H), 4.12-3.84 (m, 6H), 3.39-3.34 (m, 1H), 2.78-2.71 (m, 1H), 2.66-2.58 (m, 1H), 2.37-2.30 (m, 2H), 1.85-1.65 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major isomer) 142.4, 133.5, 129.3, 128.9, 128.6, 128.5, 128.1, 125.9, 104.0, 77.3, 70.0, 65.1, 36.8, 35.9, 31.8, 17.9; MS (LR-APCI): calculated for $C_{19}H_{26}O_3$ 302.4, measured 302.9.

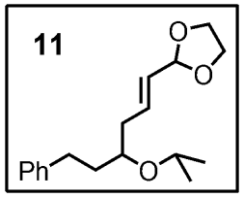
Synthesis of acetal (11).





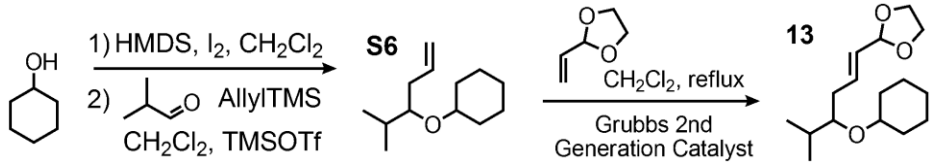
Ether **S5** was prepared using a modified Sakurai multicomponent reaction according to the procedure of Markó.[4] To a solution of freshly distilled commercially available hydrocinnamyl aldehyde (2.27 g, 16.9 mmol), commercially available isopropoxytrimethylsilane (2.5 g, 19 mmol) and commercially available allyltrimethylsilane (2.3 g, 20 mmol) in methylene chloride (40 mL), cooled to -78°C, was added trimethylsilyl trifluoromethanesulfonate (0.76 mL, 4.2 mmol) dropwise. The solution was stirred for approximately five hours then warmed to room temperature and quenched with a saturated solution of sodium bicarbonate. The aqueous phase was extracted three times with methylene chloride and the combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure and purified by flash chromatography (3% ether in hexanes) gave **S5** (2.74g, 74%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.24 (m, 2H), 7.20-7.15 (m, 3H), 5.86-5.78 (m, 1H), 5.10-5.03 (m, 2H), 3.68-3.62 (m, 1H), 3.41-3.37 (m, 1H), 2.81-2.74 (m, 1H), 2.63-2.56 (m, 1H), 2.30-2.26 (m, 2H), 1.80-1.73 (m, 2H), 1.17-1.15 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 142.7, 135.2, 128.5, 128.4, 125.8, 117.0, 76.1, 69.9, 39.6, 36.5, 32.0, 23.3, 22.7; MS (LR-APCI): calculated for $C_{15}H_{22}O$ 218.3, measured 218.9.

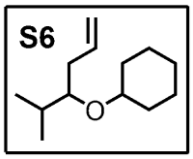
[4] Mekhalfia, A.; Markó, I.E.; *Tetrahedron Lett.* **1991**, *32*, 4779-4782.



Acetal **11** was synthesized using the general metathesis procedure from homoallylic ether **S5** (803 mg, 3.68 mmol), commercially available 2-vinyl-1,3-dioxolane (1.0 mL, 10 mmol), the Grubbs second-generation catalyst[3] (100 mg, 0.12 mmol) in methylene chloride (20 mL). Flash chromatography (ether/hexanes 1:8) gave acetal **11** (850 mg, 2.93 mmol, 80 %) as a pale brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.95 (dt, *J*=15 Hz, *J*=7.6 Hz, 1H), 5.53 (dd, *J*=15, *J*= 6.4 Hz, 1H), 5.20 (d, *J*=6.4 Hz, 1H), 4.01-3.95 (m, 2H), 3.92-3.86 (m, 2H), 3.66-3.60 (m, 1H), 3.44-3.38 (m, 1H), 2.80-2.72 (m, 1H), 2.63-2.56 (m, 1H), 2.32-2.29 (m, 2H), 1.79-1.73 (m, 2H), 1.16-1.14 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 142.5, 133.9, 128.8, 128.5, 128.4, 125.9, 104.1, 75.8, 70.0, 65.1, 37.8, 36.6, 32.0, 23.2, 22.7; MS (LR-APCI): calculated for $C_{18}H_{26}O_3$ 290.2, measured 291.4.

Synthesis of acetal (13).

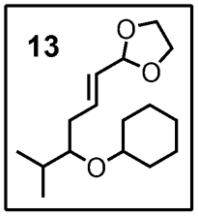




Cyclohexyloxytrimethylsilane intermediate was prepared according to the procedure of Karimi.[5] To a solution of cyclohexanol (899 mg, 8.98 mmol) and HMDS (1.5 mL, 7.1 mmol) in methylene chloride (20 mL) was added iodine (60 mg, 0.2 mmol) at room temperature. The solution was stirred for 10 minutes and quenched with solid sodium thiosulfate until the solution became clear. After stirring for an additional 30 minutes the reaction was filtered through approximately 1 cm of silica. The solution was concentrated under reduced pressure to give the trimethylsilyl ether, which was used without further purification in the next step. Ether **S6** was prepared using a silyl modified Sakurai multicomponent reaction.[4] The silyl ether intermediate was redissolved in methylene chloride (20 mL) and cooled to –78 ºC. Isobutyraldehyde (630 mg, 8.74 mmol) and allyltrimethylsilane (1.8 mL, 11 mmol) was added, followed by dropwise addition of trimethylsilyl trifluoromethanesulfonate (0.50 mL, 2.8 mmol). After five hours, the reaction was warmed to room temperature and quenched with aqueous sodium

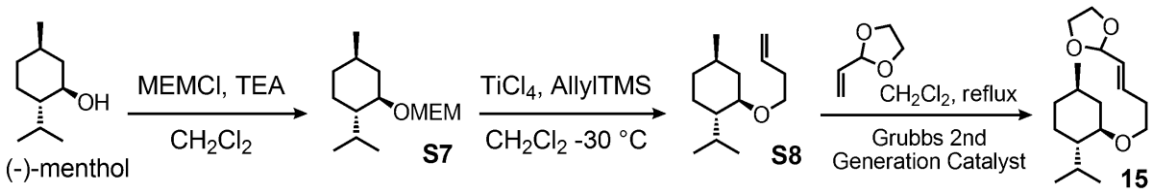
[5] Karimi, B.; Golshani, B.; *J. Org. Chem.* **2000**, *65*, 7228-7230.

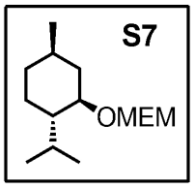
bicarbonate. The aqueous phase was extracted with methylene chloride and the combined organic phases were dried over sodium sulfate. The crude material was concentrated under reduced pressure and purified by column chromatography (2-3% ether in hexanes) to give **S6** (1.20 g, 6.10 mmol, 68% over two steps) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.92-5.82 (m, 1H), 5.08-4.99 (m, 2H), 3.25-3.19 (m, 1H), 3.15-3.11 (m, 1H), 2.27-2.15 (m, 2H), 1.09-1.70 (m, 5H), 1.54-1.50 (m, 1H), 1.31-1.15 (m, 5H), 0.90 (t, *J*=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 136.2, 116.3, 81.7, 76.6, 36.2, 33.6, 33.1, 31.4, 26.0, 24.7, 18.5; MS (LR-APCI): calculated for $C_{13}H_{24}O$ 196.3, measured 197.0.



Acetal **13** was synthesized using the general metathesis procedure from homoallylic ether **S6** (485 mg, 2.47 mmol), commercially available 2-vinyl-1,3-dioxolane (0.70 mL, 7.0 mmol), the Grubbs second-generation catalyst[3] (73 mg, 0.086 mmol) in methylene chloride (15 mL). Flash chromatography (ether/hexanes 1:6) gave acetal **13** (451 mg, 1.68 mmol, 68%) as a pale brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.00 (dt, *J*=16 Hz, *J*=7.2 Hz, 1H), 5.52 (dd, *J*=16 Hz, *J*=6.4 Hz, 1H), 5.20 (d, *J*=6.4 Hz, 1H), 4.01-3.86 (m, 4H), 3.23-3.12 (m, 2H), 2.28-2.20 (m, 2H), 1.85-1.62 (m, 5H), 1.52-1.49 (m, 1H), 1.27-1.18 (m, 5H), 0.89 (t, *J*=6.4 Hz, 6H); ^{13}C NMR (75 MHz) 134.9, 128.1, 104.3, 81.3, 76.7, 65.1, 65.0, 34.4, 33.5, 33.0, 31.4, 26.0, 24.6, 18.5, 18.4; MS (LR-APCI): calculated for $C_{16}H_{28}O_3$ 268.4, measured 268.5.

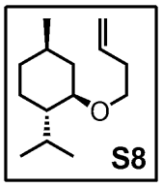
Synthesis of acetal (15).



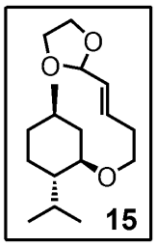


To a solution of commercially available (-)-menthol (1.67 g, 10.7 mmol) and MEMCl (1.85 g, 14.9 mmol) in methylene chloride (100 mL) at 0ºC was added diisopropylethylamine (5.3 mL, 30 mmol) and allowed to warm to room temperature overnight. The solution was diluted with ether and washed with water. The organic layer

was dried over magnesium sulfate and chromatographed (hexanes/ether 6:1) yielding **S7** (2.06 g, 8.43 mmol, 79%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.87 (d, 7.0 Hz, 1H), 4.69 (d, 7.0 Hz, 1H), 3.73-3.71 (m, 2H), 3.57-3.55 (m, 2H), 3.41-3.34 (m, 4H), 2.21-2.16 (m, 1H), 2.13-2.07 (m, 1H), 1.67-1.61 (m, 2H), 1.41-1.33 (m, 1H), 1.25-1.18 (m, 1H), 1.04-0.76 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 94.2, 77.3, 72.0, 67.2, 59.2, 48.6, 41.6, 34.6, 31.6, 25.5, 23.2, 22.4, 21.3, 15.9; MS (LR-APCI): calculated for $C_{14}H_{28}O_3$ 244.2, measured 245.4.



Ether **S8** was prepared according to the procedure of Itoh.[6] To a solution of **S7** (2.06 g, 8.43 mmol) and allyltrimethylsilane (2.0 mL, 13 mmol) in methylene chloride (100 mL) cooled to –30 ºC was added a solution of titanium tetrachloride in methylene chloride (10 mL, 10 mmol, 1M). After stirring for three hours, the reaction was allowed to warm to 0ºC and slowly quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with methylene chloride and the combined organic phases were dried over magnesium sulfate. The solvents were removed under reduced pressure and purified by flash chromatography (3% ether in hexanes) to give **S8** (1.59 g, 7.56 mmol, 90%) as a clear oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.87-5.80 (m, 1H), 5.11-5.00 (m, 2H), 3.70-3.64 (m, 1H), 3.36-3.30 (m, 1H), 3.05-2.99 (m, 1H), 2.33-2.29 (m, 2H), 2.24-2.19 (m, 1H), 2.11-2.07 (m, 1H), 1.66-1.58 (m, 2H), 1.38-1.27 (m, 1H), 1.25-1.18 (m, 1H), 1.01-0.76 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 135.8, 116.2, 79.5, 68.1, 48.4, 40.7, 34.9, 34.8, 31.7, 25.7, 23.6, 22.5, 21.1, 16.5.

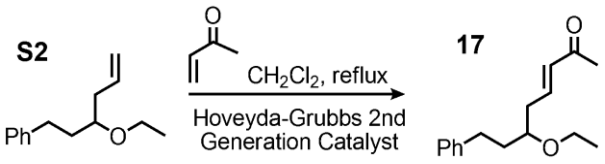


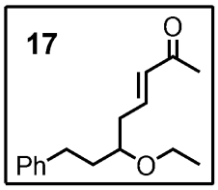
Acetal **15** was synthesized using the general metathesis procedure from homoallylic ether **S8** (604 mg, 2.87 mmol), commercially available 2-vinyl-1,3-dioxolane (0.8 mL, 8 mmol) and the Grubbs second-generation catalyst[3] (90 mg, 0.11 mmol) in methylene chloride (15 mL). Flash chromatography (ether/hexanes 1:7) gave acetal **15** (662 mg, 2.34 mmol, 82%) as a pale brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.96 (dt, *J*=16 Hz, *J*=6.8 Hz, 1H), 5.54 (dd, *J*=16 Hz, *J*=6.4 Hz, 1H), 5.19 (d, *J*=6.4 Hz, 1H), 4.01-3.95 (m, 2H), 3.93-3.87 (m, 2H), 3.70-3.65 (m, 1H), 3.36-3.30 (m, 1H), 3.04-2.98 (m, 1H), 2.38-2.32 (m, 2H), 2.22-2.18 (m, 1H), 2.09-2.05 (m, 1H), 1.66-1.57 (m, 2H), 1.38-1.30 (m, 1H), 1.23-1.17 (m, 1H), 0.99-0.75 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) 134.3, 128.1,

[6] Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496-2498.

104.2, 79.5, 67.7, 65.1, 48.4, 40.6, 34.7, 33.2, 31.7, 25.7, 23.6, 22.5, 21.1, 16.4; MS (LR-APCI): calculated for $C_{17}H_{30}O_3$ 282.2, measured 283.5.

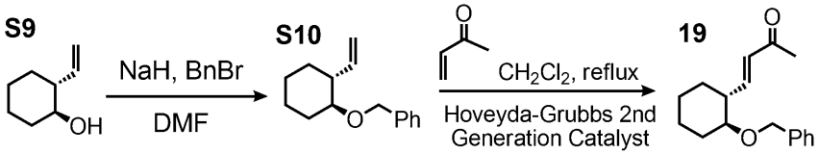
Synthesis of enone (17).

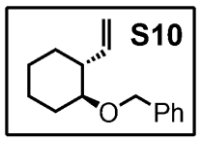




Enone **17** was synthesized using the general metathesis procedure from homoallylic ether **S2** (705 mg, 3.45 mmol), methyl vinyl ketone (0.70 mL, 8.5 mmol) and the Hoveyda-Grubbs second-generation catalyst[2] (75 mg, 0.12 mmol) in methylene chloride (20 mL). The crude reaction was concentrated under reduced pressure and purified by flash chromatography (ether/hexanes 1:4) to give enone **17** (727 mg, 2.95 mmol, 80%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3H) 6.80 (dt, *J*=16 Hz, *J*=7.2 Hz, 1H), 6.11 (d, *J*=16 Hz, 1H), 3.58-3.40 (m, 3H), 2.77-2.72 (m, 1H), 2.68-2.61 (m, 1H), 2.48-2.42 (m, 2H), 2.24 (s, 3H), 1.86-1.74 (m, 2H), 1.22 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 198.5, 144.5, 142.0, 133.4, 128.6, 128.5, 126.0, 77.4, 64.7, 37.3, 36.2, 31.8, 27.0, 15.7; MS (LR-APCI): calculated for $C_{16}H_{22}O_2$ 246.2, measured 247.4.

Synthesis of enone (19).

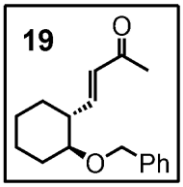




Known homoallylic alcohol **S9**[7] (912 mg, 7.23 mmol) was dissolved in DMF (75 mL) and cooled to 0°C. Sodium hydride (192 mg, 7.60 mmol, 95%) was added in one

[7] Rickborn, B.; Tobia, D.; *J. Org. Chem.* **1989**, *54*, 777-782.

portion and stirred for 30 minutes followed by addition of benzyl bromide (1.22 g, 7.13 mmol). The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a saturated ammonium chloride solution and diluted with ether. The organic phase was separated, washed three times with water, then brine and dried over sodium sulfate. The solution was concentrated under reduced pressure and purified by flash chromatography (3-5% ether in hexanes) yielding **S10** as a clear oil (1.28 g, 5.92 mmol, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.23 (m, 5H), 5.95-5.87 (m, 1H), 5.11-5.01 (m, 2H), 4.61 (d, *J*=12 Hz, 1H), 4.48 (d, *J*=12 Hz, 1H), 3.13-3.06 (m, 1H), 2.15-2.10 (m, 2H), 1.79-1.75 (m, 2H) 1.67-1.63 (m, 1H), 1.31-1.22 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 141.9, 139.3, 128.4, 127.8, 127.5, 114.2, 81.3, 70.8, 47.9, 31.4, 31.3, 25.2, 24.8.



Enone **19** was synthesized using the general metathesis procedure from homoallylic ether **S10** (530 mg, 2.45 mmol), methyl vinyl ketone (0.50 mL, 6.1 mmol) and the Hoveyda-Grubbs second-generation catalyst[2] (60 mg, 0.096 mmol) in methylene chloride (15 mL). The crude reaction was concentrated under reduced pressure and purified by flash chromatography (hexanes/ether 4:1) to give enone **19** (544 mg, 2.10 mmol, 86%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.25 (m, 5H), 6.82 (dd, *J*=16 Hz, *J*=7.4 Hz, 1H), 6.10 (d, *J*=16 Hz, 1H), 4.63 (d, *J*=12 Hz, 1H), 4.42 (d, *J*=12 Hz, 1H), 3.19-3.13 (m, 1H), 2.33-2.19 (m, 2H and CH_3), 1.83-1.76 (m, 2H), 1.72-1.69 (m, 1H), 1.35-1.18 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 199.0, 151.0, 138.8, 131.0, 128.5, 127.9, 127.8, 80.5, 70.7, 46.8, 31.2, 30.7, 27.0, 25.0, 24.5; MS (LR-APCI): calculated for $C_{17}H_{22}O_2$ 258.4, measured 259.2.

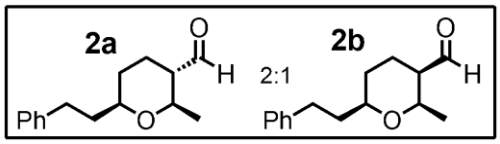
III. General Procedure for Lewis Acid Catalyzed Hydride-Transfer Reactions

Boron trifluoride etherate was purchased from Aldrich and used as received. Older bottles of catalyst (>1 year) could be employed without a noticeable decrease in performance. Reactions were monitored by GC or TLC analysis using hexanes/ethyl acetate mixtures as the eluent (visualization using permanganate stain and/or cerric ammonium molybdate stain and/or UV light). The products typically have slightly higher R_f values than starting materials. All reactions were carried out in 10 mL sample vials with pierceable Teflon caps and magnetic stir bars. All glassware was dried in the oven and allowed to cool to room temperature under vacuum prior to use. Hydrolysis of acetal starting materials and products is observed if water is not carefully excluded from the reaction setup or if the reaction is not quickly quenched immediately following completion of the reaction.

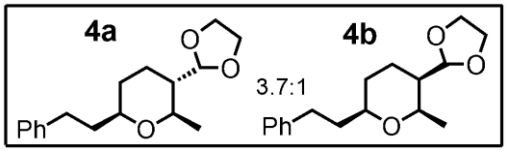
Approximately 0.2-0.3 mmol of starting material was dissolved in methylene chloride (0.025 M concentration). Boron trifluoride etherate (0.5 equiv.) was added dropwise via micro syringe and reactions were stirred at room temperature. Upon consumption of the starting material (typically 15-60 minutes), the reactions were quickly transferred to a separatory funnel containing a saturated sodium bicarbonate solution and vigorously shaken. The aqueous layer was extracted twice with methylene chloride and the combined organic phases were dried over sodium sulfate (some hydrolysis was observed when magnesium sulfate was used as a drying agent). The solvent was removed under reduced pressure and the crude material was purified by flash chromatography on silica gel to give the desired product.

Reported yields are an average of three trials. Products were typically collected as a mixture of diastereomers along with varying amounts of hydrolyzed products (usually less than 5%). In the case of **4a/b**, it was found that extended reaction times could cause a slight increase in product ratio towards the major diastereomer although gradual decomposition of the product mixture was also observed. However, when pure major and minor products **4a** and **4b** were separately resubjected to the reaction conditions, they showed no erosion of stereochemistry at C3, indicating that the reaction product mixture is determined kinetically (and not via equilibrium). Reported diastereoselectivities reflect the product ratio following total consumption of starting material. Product ratios were determined by ^{1}H NMR spectra or GC analysis of the crude reaction mixtures and/or the isolated mixtures. The relative configurations of diastereomers **4a and 4b** were assigned based on coupling constants and NOESY NMR experiments (see below). The structural assignment of other product mixtures was made by analogy.

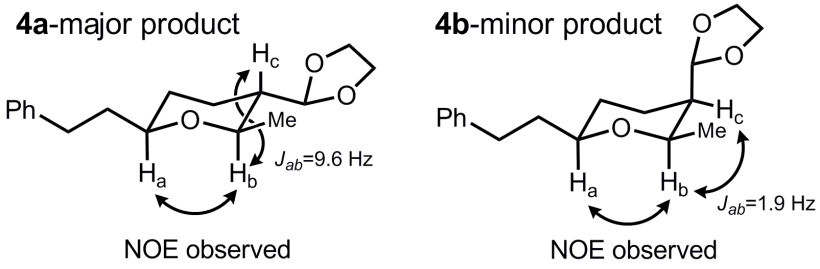
IV. Product Data for Enal, Acetal and Ketal Substrates



Enal **1** underwent cyclization using the general procedure, although a longer reaction time was required. The reaction was monitored over several days. After four days, the desired product was isolated in 44% yield as a 2:1 mixture of diastereomers **2a** (major product) and **2b** (minor product) after chromatography (1:6 ether/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) major product **2a**: δ 9.64 (d, *J*=3 Hz, 1H), 7.30-7.24 (m, 2H), 7.20-7.16 (m, 3H), , 3.60-3.53 (m, 1H), 3.28-3.22 (m, 1H), 2.81-2.65 (m, 2H), 2.28-2.15 (m, 1H), 1.99-1.93 (m, 1H), 1.90-1.81 (m, 1H), 1.76-1.64 (m, 2H), 1.62-1.26 (m, 5H); resolved characteristic peaks for minor product **2b**: 10.08 (d, *J*=3 Hz, 1H), 3.77-3.71 (m, 1H), 3.41-3.35 (m, 1H); ^{13}C NMR (75 MHz) major product **2a** 203.1, 142.2, 128.6, 128.5, 125.9, 76.3, 72.9, 55.9, 37.7, 31.8, 30.2, 24.4, 20.7; minor product **2b**: 205.8, 142.2, 128.6, 128.5, 125.9, 77.7, 74.5, 50.3, 37.8, 31.7, 27.9, 25.6, 19.7; MS (LR-APCI): calculated for $C_{15}H_{20}O_2$ 232.3, measured 232.5.



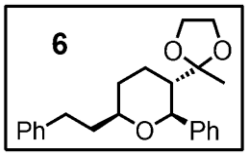
A 3.7:1 mixture of diastereomers **4a** and **4b** was isolated in 71% yield by chromatography (1:8 ether/hexanes). The product mixture contained varying amounts of the corresponding aldehydes (usually less than 5%).



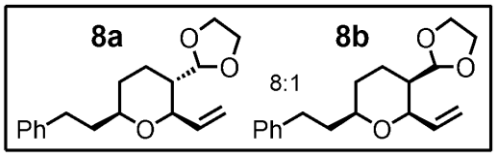
For characterization purposes, a small amount of pure **4a** and **4b** was obtained after multiple chromatography runs. The relative stereochemistry was assigned based partly on NOE experiments, which exhibited strong NOE signal between H_a and H_b in both the major and minor product. The relative stereochemistry between H_b and H_c was assigned based on *J* values from homonuclear decoupling experiments. By analogy, the stereochemistry of other product mixtures was assigned based on these observations.

Major product **4a** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28-7.25 (m, 2H and chloroform), 7.19-7.15 (m, 3H), 4.81 (d, *J*=2 Hz, 1H), 3.95-3.90 (m, 2H) 3.85-3.81 (m, 2H), 3.40-3.37 (m,

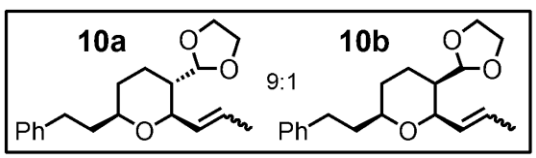
1H), 3.24-3.20 (m, 1H), 2.77-2.67 (m, 2H), 1.90-1.82 (m, 2H), 1.71-1.58 (m, 3H), 1.41-1.31 (m, 1H), 1.30-1.26 (m, 1H and CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) 142.5, 128.7, 128.4, 125.8, 104.3, 76.4, 65.1(2C), 45.7, 37.9, 31.9, 31.3, 22.8, 20.4. Minor product **4b**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.25 (m, 2H), 7.20-7.15 (m, 3H), 5.09 (d, *J*=6.6 Hz, 1H), 3.99-3.78 (m, 4H), 3.66-3.61 (m, 1H), 3.37-3.30 (m, 1H), 2.81-2.65 (m, 2H), 2.22-2.16 (m, 1H), 1.91-1.82 (m, 1H), 1.73-1.64 (m, 1H), 1.62-1.51 (m, 2H and water), 1.44-1.38 (m, 2H), 1.30 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 142.6, 128.7, 128.4, 125.8, 103.0, 77.7, 75.1, 65.0, 64.2, 41.4, 38.0, 31.9, 28.0, 26.0, 20.1; MS (LR-APCI): calculated for $C_{17}H_{24}O_3$ 276.4, measured 277.2.



Ketal **6** was isolated in 90% yield with only trace amounts of a minor diastereomer detected by NMR (>20:1 dr) after chromatography (1:5 ether/hexanes). The product contained varying amounts of the corresponding ketone (usually less than 10%), which was confirmed by independently synthesizing the corresponding ketone product and comparing the ^1H NMR spectra and GC trace with that of **6**. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.17 (m, 7H), 7.15-7.12 (m, 3H), 4.25 (d, *J*=10 Hz, 1H), 3.74-3.62 (m, 3H), 3.56-3.53 (m, 1H), 3.38-3.32 (m, 1H), 2.68-2.63 (m, 2H), 2.18-2.05 (m, 2H), 1.91-1.83 (m, 1H), 1.78-1.69 (m, 2H), 1.54-1.40 (m, 2H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 143.1, 142.5, 128.7, 128.3, 128.1, 128.0, 127.5, 125.7, 110.4, 82.9, 77.0, 64.2, 64.0, 48.8, 37.7, 31.6, 31.6, 26.0, 22.7; MS (LR-APCI): calculated for $C_{23}H_{28}O_3$ 352.5, measured 352.9.

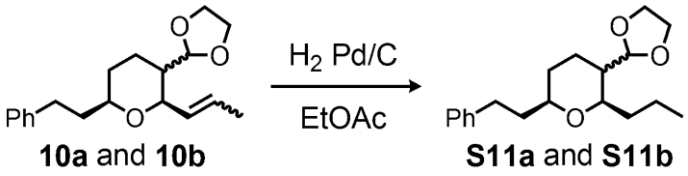


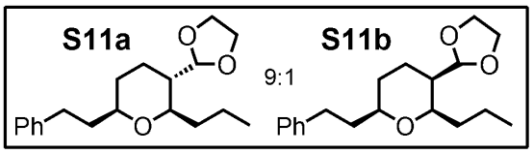
A 8:1 mixture of diastereomers **8a** and **8b** were isolated in 86% yield after chromatography (1:8 ether/hexanes). The product mixture contained varying amounts of the corresponding aldehydes (usually less than 5%). Major product **8a**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.24 (m, 2H), 7.19-7.15 (m, 3H), 5.96-5.88 (m, 1H), 5.35 (d, *J*=17 Hz, 1H), 5.22 (d, *J*=10 Hz, 1H), 4.81 (d, *J*=3 Hz, 1H), 3.94-3.73 (m, 5H), 3.31-3.25 (m, 1H), 2.79-2.65 (m, 2H), 1.93-1.84 (m, 2H), 1.78-1.65 (m, 3H), 1.51-1.41 (m, 1H), 1.36-1.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 142.4, 137.6, 128.7, 128.4, 125.8, 117.5, 103.8, 80.2, 76.3, 65.3, 65.1, 43.8, 37.8, 31.8, 31.0, 22.0; MS (LR-APCI): calculated for $C_{18}H_{24}O_3$ 288.4, measured 288.4.



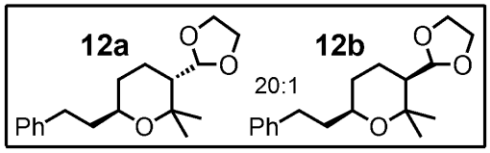
The product was isolated as a mixture of four isomers (9:1 mixture of diastereomers **10a** (major product) and **10b** (minor product), each as roughly a 5:1 mixture of E/Z alkenes) in 69% yield after chromatography (1:6 ether/hexanes). The product mixture contained varying amounts of the corresponding aldehydes (usually less than 5%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ major product **10a**: 7.28-7.24 (m, 2H), 7.19-7.14 (m, 3H), 5.83-5.70 (m, 1H), 5.56-5.43 (m, 1H), 4.81 (d, *J*=2 Hz, 1H, (E)-isomer), 4.75 (d, *J*=2 Hz, 1H, (Z)-isomer), 4.11 (t, *J*= 9.5 Hz, 1H, (Z)-isomer), 3.99-3.77 (m, 4H), 3.71 (dd, *J*=10 Hz, *J*=8.0 Hz, 1H, (E)-isomer), 3.31-3.23 (m, 1H), 2.78-2.64 (m, 2H), 1.93-1.83 (m, 2H), 1.77-1.64 (m, 6H), 1.51-1.39 (m, 1H), 1.34-1.23 (m, 1H); resolved characteristic peaks for minor product **10b**: 5.16 (d, *J*=6.1 Hz, 1H, (Z)-minor product), 5.09 (d, *J*=5.8 Hz, 1H, (E)-minor product), 3.41-3.34 (m, 1H, minor product); ^{13}C NMR ($CDCl_3$, 100 MHz) major product **10a**: 142.4, 130.8, 129.6, 128.7, 128.4, 125.8, 103.9, 79.9, 76.4, 65.4, 65.1, 44.0, 37.8, 31.8, 30.9, 21.6, 18.1; MS (LR-APCI): calculated for $C_{19}H_{26}O_3$ 302.4, measured 302.9.

Hydrogenation of the product mixture of 10.



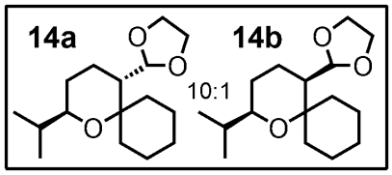


In order to further characterize the product, the mixture of **10a** and **10b** (38.0 mg, 0.126 mmol) in ethyl acetate (1.5 mL) was subjected to hydrogenation (1 atm) with Pd/C (10 mg) as the catalyst. After 4 hours, the reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification by column chromatography (8:1 hexanes/ether) afforded **S11a** (major product) and **S11b** (minor product) as a 9:1 mixture of diastereomers (31.0 mg, 0.102 mmol, 81%) as a clear oil. The product mixture contained varying amounts of the corresponding aldehydes (usually less than 5%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ major product **S11a**: 7.28-7.24 (m, 2H), 7.19-7.14 (m, 3H), 4.84 (d, *J*=3.2 Hz, 1H), 3.94-3.78 (m, 4H), 3.29-3.24 (m, 1H), 3.20-3.14 (m, 1H), 2.83-2.76 (m, 1H), 2.72-2.64 (m, 1H), 1.91-1.58 (m, 7H), 1.51-1.21 (m, 4H), 0.95 (t, *J*=7.0 Hz, 3H); resolved characteristic peaks for minor product **S11b**: 5.07 (d, *J*=6.6 Hz, 1H), 3.45-3.41 (m, 1H), 2.21-2.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) major product **S11a**: 142.6, 128.7, 128.4, 125.7, 104.1, 78.3, 76.1, 65.1, 65.0, 44.0, 38.1, 35.9, 32.0, 31.6, 22.8, 18.9, 14.3; MS (LR-APCI): calculated for $C_{19}H_{28}O_3$ 304.4, measured 305.0.



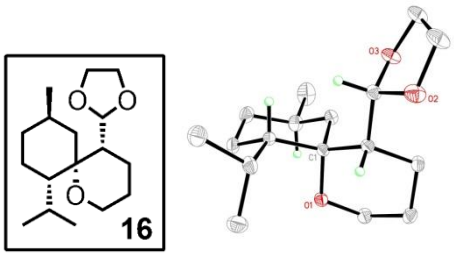
A 20:1 mixture of diastereomers **12a** (major product) and **12b** (minor product) were isolated in 89% yield after chromatography (1:9 ether/hexanes). The product mixture contained varying amounts of the corresponding aldehydes (usually less than 5%). Major product **12a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.24 (m, 2H), 7.20-7.14 (m, 3H), 4.69 (d, *J*=3.6 Hz, 1H), 3.94-3.87 (m, 2H), 3.84-3.79 (m, 2H), 3.46-3.39 (m, 1H), 2.78-2.71 (m, 1H), 2.66-2.59 (m, 1H), 1.81-1.59 (m, 5H), 1.54-1.42 (m, 1H), 1.34 (s, 3H), 1.29-1.16 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 142.7, 128.7, 128.3, 125.7, 104.7, 73.4, 69.0, 65.0, 64.8, 48.7, 38.3, 31.9, 31.7, 30.8, 20.3, 19.8; MS (LR-APCI): calculated for $C_{18}H_{26}O_3$ 290.2, measured 291.4.

Note: the structural assignment was based on the assumption that the major product (**12a**) has substituents at C3 and C6 in the equatorial position and the minor product (**12b**) differs at C3, analogous to product **4a** and **4b** where the conclusive assignment was possible due to isolation of major and minor products with hydrogen at C2 (see page S14).



A 10:1 mixture of diastereomers **14a** (major product) and **14b** (minor product) were isolated in 75% yield after chromatography (1:9 ether/hexanes). The product mixture contained varying amounts of the corresponding aldehydes (usually less than 5%). Major product: ^{1}H NMR ($CDCl_3$, 400 MHz) δ4.78 (d, *J*=3.2 Hz, 1H), 3.95-3.77 (m, 4H), 2.99-2.94 (m, 1H), 2.17-2.11 (m, 1H), 1.83-1.40 (m, 12H), 1.21-1.08 (m, 3H), 1.00 (d, *J*=6.6 Hz, 3H), 0.87 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 104.5, 73.9, 73.5, 65.1, 64.7, 48.9, 38.3, 34.2, 29.2, 26.5, 26.3, 21.5, 20.5, 19.6, 19.3, 19.2; MS (LR-APCI): calculated for $C_{16}H_{28}O_3$ 268.4, measured 268.5.

Note: the structural assignment was based on the assumption that the major product (**14a**) has substituents at C3 and C6 in the equatorial position and the minor product (**14b**) differs at C3, analogous to product **4a** and **4b** where the conclusive assignment was possible due to isolation of major and minor products with hydrogen at C2 (see page S14).

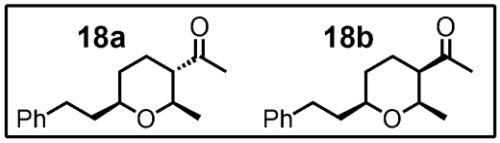


A single diastereomer, **16**, was isolated in 53% yield after chromatography (1:10 ether/hexanes). The product contained varying amounts of the corresponding aldehydes (usually less than 5%). The product spontaneously crystallized following removal of solvent and the molecular structure was confirmed by X-ray data analysis (see page S21). ^{1}H NMR ($CDCl_3$, 400 MHz) 4.73 (d, *J*=3 Hz, 1H), 3.94-3.87 (m, 2H), 3.84-3.77 (m, 2H), 3.59-3.55 (m, 1H), 3.48-3.44 (m, 1H), 2.34-2.17 (m, 3H), 1.75-1.55 (m, 7H), 1.47-1.38 (m, 2H), 0.90-0.83 (m, 10H), 0.79-0.72 (m, 1H); ^{13}C NMR (C_6D_6, 75 MHz) 104.9, 77.7, 65.5, 65.2, 60.4, 49.3, 43.8, 36.8, 36.7, 27.5, 27.0, 26.7, 24.3, 23.6, 21.0, 19.8, 19.1.

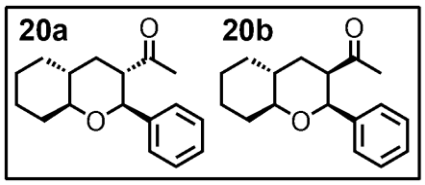
V. General Procedure for the Enone Substrate Cyclization with the Ethylene Glycol/Lewis Acid System.

Reactions of enone substrates from "Table 2" were run under similar conditions to those run with alkenyl acetals, however, a catalytic amount of ethylene glycol (0.2 equivalents) was added prior to the addition of Lewis acid. For comparison purposes, reactions were run side by side with those where ethylene glycol was omitted. As noted in the table, some reactions were heated in an oil heating bath set to 50ºC in either 15 mL sealed tubes or 10 mL sample vials capped with Teflon caps.

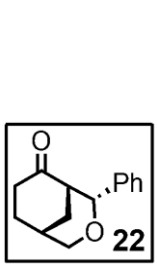
VI. Product Data of Enone Substrates

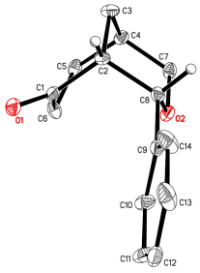


Diastereomers **18a** and **18b** were isolated by chromatography (1:6 ether/hexanes) in 86% yield as a 1.5:1 mixture of diastereomers. The product was isolated in 83% yield as a 2.4:1 mixture of diastereomers with addition of ethylene glycol. Product mixture: ^{1}H NMR ($CDCl_3$, 400 MHz) δ major product **18a:** 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 3.61-3.55 (m, 1H), 3.30-3.26 (m, 1H), 2.79-2.67 (m, 2H), 2.38-2.34 (m, 1H), 2.16 (s, 3H), 1.98-1.54 (m, 5H), 1.35-1.20 (m, 1H), 1.18 (d, *J*=6.1 Hz, 3H); resolved characteristic peaks for minor product **18b**: 2.54-2.52 (m, 1H), 2.22 (s, 3H), 1.28 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (75 MHz) major product **18a**: 211.4, 142.3, 128.6, 128.5, 125.9, 76.3, 74.4, 56.7, 37.8, 31.8, 30.8, 27.6, 20.4, resolved characteristic peaks for minor product **18b**: 210.6, 142.4, 128.6, 128.5, 125.8, 73.9, 50.9, 32.0, 30.5, 27.1, 26.1, 20.0; MS (LR-APCI): calculated for $C_{16}H_{22}O_2$ 246.2, measured 247.7.



Diastereomers **20a** and **20b** were isolated following chromatography (1:4 ether/hexanes) in 88% yield as an 8:1 mixture of diastereomers. The product was isolated in 95% yield as a 14:1 mixture of diastereomer with addition of ethylene glycol. Major product **20a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.23 (m, 5H), 4.45 (d, *J*=10 Hz, 1H), 3.19-3.13 (m, 1H), 2.99-2.92 (m, 1H), 2.04-1.79 (m, 3H), 1.71-1.65 (m, 5H), 1.59-1.49 (m, 1H), 1.42-1.24 (m, 4H), 1.11-1.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 210.5, 140.8, 128.7, 128.2, 127.2, 82.2, 81.6, 57.6, 40.9, 34.2, 32.5, 31.5, 31.2, 25.9, 25.1; MS (LR-APCI): calculated for $C_{17}H_{22}O_2$ 258.2, measured 259.2.



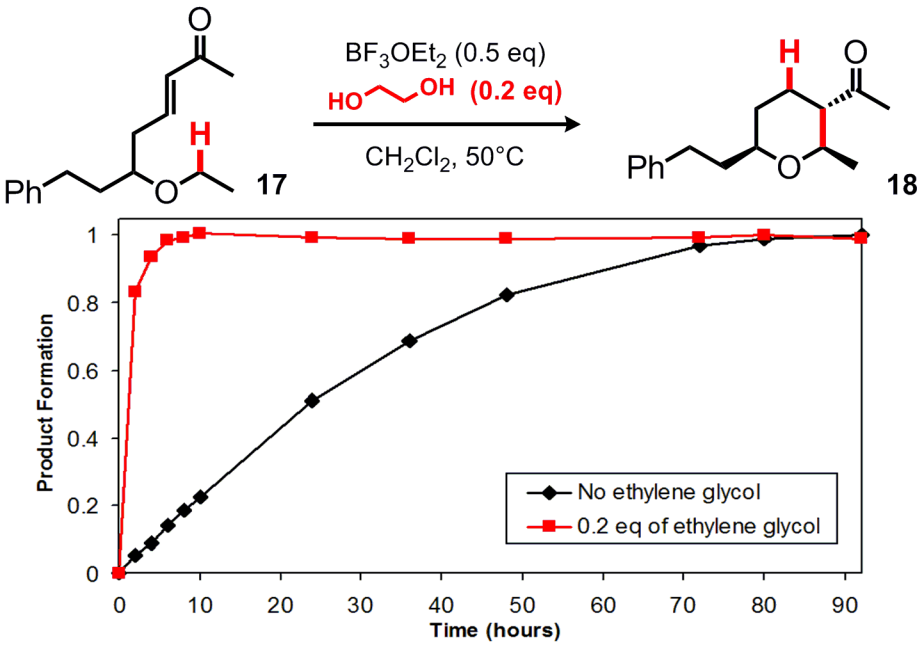


A single isomer, **22**, was isolated by column chromatography (1:4 ether/hexanes) as a clear oil in 81% yield (79% yield with addition of ethylene glycol). When starting from optically active **21**, the product spontaneously crystallized when concentrated after chromatography and the structure was confirmed by X-ray data analysis (see page S21). We are very grateful to Professor Gilbert Stork for the generous gift of an optically active sample of **21**.[8] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.08 (m, 5H), 4.75 (s, 1H), 4.31 (d, *J*=12 Hz, 1H), 4.10 (d, *J*=12 Hz, 1H), 2.95-2.88 (m, 1H), 2.76 (s, H), 2.49-2.44 (m, 1H), 2.38-2.32 (m, 1H), 2.24-2.20 (m, 1H), 2.16-2.12 (m, 1H), 2.04-1.96 (m, 1H), 1.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 211.4, 140.0, 128.5, 127.7, 125.1, 80.2, 74.4, 53.4, 41.9, 33.9, 30.8, 28.4; MS (LR-APCI): calculated for $C_{14}H_{16}O_2$ 216.1, measured 217.2.

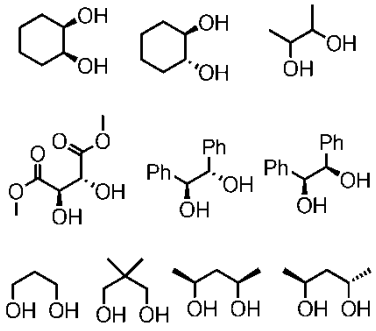
[8] Stork, G.; Tang, P.C.; Casey, M.; Goodman, B.; Toyota, M. *J. Am. Chem. Soc.* **2005**, *127*, 16255-16262.

VII. The Effect of Ethylene Glycol on the Rate of the Cyclization Reaction

The conversion of **17** to **18** was compared under standard reaction conditions with and without the addition of ethylene glycol. A 0.025 M stock solution of **17** and dodecane (internal standard) was prepared. Two 10 mL aliquots of the stock solution were added to purged reaction vials. To one vial was added 0.2 equivalents of ethylene glycol and to both was added 0.5 equivalents of boron trifluoride etherate. The vials were sealed with a Teflon cap and heated to 50 ˚C. At designated time integrals, the reactions were briefly cooled to room temperature and 0.1 mL aliquots of the reaction were removed for GC analysis. Product formation was determined by taking the combined areas of **18a** and **18b** divided by the area of the internal standard over time.



The diols to the right were screened for reactivity and diastereoselectivity as co-catalysts. All showed varying degrees of effectiveness at increasing the rate of the reaction compared to boron trifluoride etherate alone. None were more reactive or diastereoselective than ethylene glycol. A variety of alcohols were also tested but had little to no effect on the rate of the reaction. Enals undergo the cyclization reaction under these reaction conditions, however the cyclic acetals are the thermodynamically favored products. Addition of ethylene glycol produces a measurable rate enhancement but of a smaller magnitude in comparison to enones.



VIII. X-Ray Data

X-ray diffraction data were collected on a Bruker P4 diffractometer equipped with a SMART CCD detector and crystal data, data collection and refinement parameters are summarized below. The structures were solved using direct methods and standard difference map techniques and were refined by full-matrix least-squares procedures on F^2 with SHELXTL (Version 6.10).

Compound	Acetal **16**	Ketone **22**
Formula	$C_{17}H_{30}O_3$	$C_{14}H_{16}O_2$
Formula weight	282.41	216.27
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12$	$P2_12_12$
a/Å	17.0840 (9)	9.6931 (5)
b/Å	9.2508 (9)	9.8584 (5)
c/Å	10.2983 (5)	11.9252 (6)
α/°	90	90
β/°	90	90
γ/°	90	90
V/Å^3	1627.55 (14)	1139.55 (10)
Z	4	4
ρ (calc.), g·cm^{-3}	1.153	1.243
μ (Mo Kα), mm^{-1}	0.077	0.082
Temperature (K)	243 (2)	125 (2)
Radiation (λ, Å)	0.71073	0.71073
θ max, deg.	28.30	30.53
No. of data	3827	3473
No. of parameters	182	145
R_1	0.0556	0.0702
ωR_2	0.1279	0.2002
GOF	1.061	1.067

IX. NMR Spectra