Gold-Catalyzed Dehydrative Cyclization of Allylic Diols

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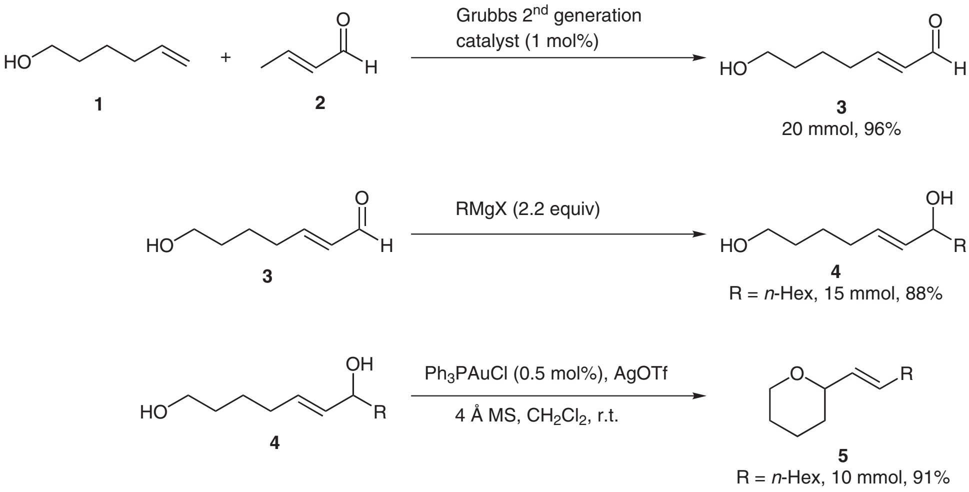
Abstract: The gold(I)-catalyzed cyclization of monoallylic diols is an efficient method for the formation of tetrahydropyrans from readily available, easily prepared substrates. The reaction has been shown to be general and high yielding with low catalyst loadings. Several new synthetically useful substrates and efficient methods for both their preparation and cyclization are reported.

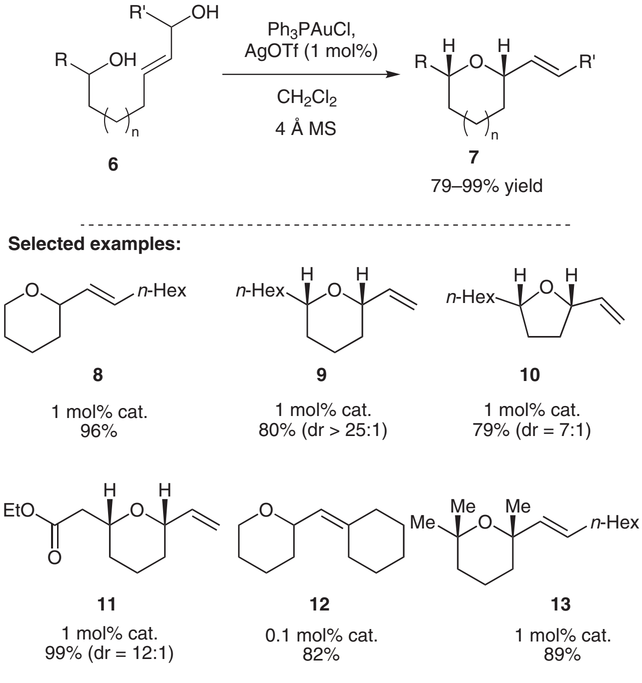
Key words: allylic diol, dehydrative cyclization, tetrahydropyran, gold-catalysis, cross-metathesis



Scheme 1

Introduction

Highly functionalized marine natural products have long garnered the interest of the synthetic community, having been heartily pursued due to interest in their novel, complex structures and promising biological activities.[1] A broad spectrum of differing structural elements are present in these compounds, but saturated oxygen heterocycles are one of the most common motifs.[2] We recently reported a new strategy for the preparation of 2-alkenyltetrahydrofurans and -pyrans **7** from monoallylic diols **6** (Scheme 2).[3] The reaction was shown to be an efficient method that was operationally simple to execute, providing the products in high yield from easily prepared starting materials. Herein we report our efforts to prepare several more substrates that we envision to be synthetically useful (vide infra) and a procedure for the gram scale preparation of 2-alkenyltetrahydropyrans (**1** → **5**, Scheme 1).



Scheme 2

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Scope and Limitations

Homogeneous gold-catalysis has become a powerful new method in organic synthesis, largely due to the selective reaction of alkynes or allenes under mild conditions.[4] The current report, however, relies on the activation of allylic alcohols containing a tethered nucleophile **4** to effect a gold-catalyzed cyclization. In the course of our studies, we required an efficient method for the preparation of such substrates and found that the most direct route necessitated an aldehyde such as **3** or a suitably protected derivative.

Initial studies were focused on using silyl-protected 5-hexen-1-ol (e.g., **TBS-1**) in cross metathesis reactions with crotonaldehyde using Grubbs second generation catalyst (Scheme 1).[5] This method worked fairly well using 3 mol% of the ruthenium catalyst and directly generated a silyl-protected version of aldehyde **3**.[6] Unfortunately, it proved difficult to fully purify the material by flash chromatography, with varying amounts of catalyst byproducts remaining depending on the workup employed, and as such an alternative method was sought.[7,8] Fortunately, this small problem was overcome by simply reducing the catalyst loading to 1 mol% and using the free alcohol **1** instead of its silyl ether (Scheme 1). Reactions ranging from 5 to 20 mmol scale reproducibly gave 95–98% yield of a material that was sufficiently pure for the ensuing reactions.

Substrate preparation is then easily accomplished by the addition of organometallics to the α,β-unsaturated aldehyde. When the Grignard or lithium reagent is not particularly precious, it is most convenient to use just over 2 molar equivalents to both deprotonate the free alcohol and add to the carbonyl. As illustrated in Scheme 1, when 2.2 equivalents of *n*-hexylmagnesium bromide was allowed to react with **3**, the 1,2-addition product **4** was obtained in 88% yield (Scheme 1). The Au-catalyzed cyclization then smoothly provided 1.8 g of the tetrahydropyran **5** (91%) with a 0.5 mol% loading. With the exception of increased reaction times, to date we have never encountered any difficulty performing these reactions at any scale and predict that much larger batches could be prepared with significantly reduced catalyst loadings.

To further test functional group compatibility and generate products with groups suited for further synthetic transformations, we have also prepared the tetrahydropyrans **14**–**18** (Figure 1). For these examples, the substrates were prepared by reaction of **3** with the corresponding Grignard or lithium reagents and the cyclization reactions were carried out using a 1 mol% catalyst loading at ambient temperature. Interestingly, the cyclization reaction to form **16** was a great deal more difficult and required 5 mol% catalyst at reflux. Although most of the functional groups present are known to be stable under typical gold-catalyzed reaction conditions,[4] we were unsure about how the cationic metal complex would perform in the presence of an allylsilane. To our surprise, the allylsilane product **17** produced by the dehydrative cyclization was well tolerated and did not appear to affect the reaction.

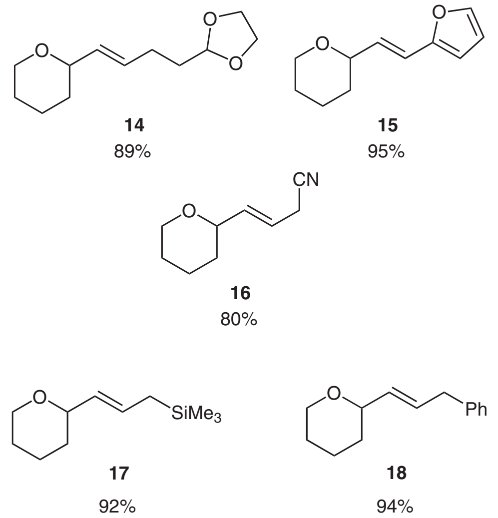

Figure 1

In conclusion, we have developed an efficient method for the preparation of oxygen heterocycles by a gold-catalyzed cyclization of monoallylic diols. The reaction is scalable and tolerates extremely low catalyst loadings giving synthetically useful products in three steps with high overall yield from commercially available materials. Further studies on the use of this method in total synthesis are underway and will be reported in due course.

THF and CH_2Cl_2 were dried using an mBraun solvent purification system. Analytical TLC was performed using 250 μm Silica Gel 60 F254 precoated plates (EMD Chemicals Inc.). Flash column chromatography was performed using 230–400 mesh 60 Å Silica Gel (Whatman Inc.). ^1H NMR spectra were recorded using Varian Mercury 300 MHz spectrometers; ^{13}C NMR spectra were recorded using a Varian Unity Mercury 300 spectrometer at 75 MHz. Chemical shift is reported in ppm relative to the carbon resonance of $CDCl_3$ (77.23 ppm). IR spectra were recorded on a Bruker Vector 22 IR spectrometer at 4.0 cm^{-1} resolution. High-resolution mass spectral data (HRMS) were obtained by the Mass Spectrometry Core Laboratory of University of Florida. Accurate masses are reported for the molecular ion (M^+) or a suitable fragment ion.

Gram Scale Preparation

(*E*)-7-Hydroxyhept-2-enal (3)

A solution of Grubbs 2nd generation catalyst (169.6 mg, 0.2 mmol, 1 mol%) in anhyd CH_2Cl_2 (50 mL, degassed by bubbling with argon for 30 min) was prepared in a flame-dried 250 mL flask equipped with a reflux condenser. To the reaction vessel, a solution of 5-hexen-1-ol (2.0032 g, 20 mmol) and crotonaldehyde (7.0050 g, 100 mmol) in anhyd CH_2Cl_2 (50 mL, degassed by bubbling with argon for 30 min) was added and the mixture was immediately heated to reflux for 2 h by immersing into an oil bath that had been preheated to 50 °C, at which point TLC analysis indicated a complete reaction. The crude mixture was then cooled to r.t., silica gel (8 g) was added to the flask, and the resulting slurry was vigorously stirred open to air for 30 min. The mixture was then adsorbed onto the silica gel under reduced pressure and purified by flash chromatography (50% EtOAc–hexanes) to give 2.4601 g (96%) of the title compound as a brown oil; $R_f = 0.25$ (50% EtOAc–hexanes).

IR (neat): 3418, 2937, 2863, 2741, 1683, 1635, 1134, 1060, 977 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.49 (d, *J* = 7.8 Hz, 1 H), 6.87 (dt, *J* = 15.6, 6.6 Hz, 1 H), 6.13 (ddt, *J* = 15.6, 7.8, 1.8 Hz, 1 H), 3.68 (t, *J* = 6.2 Hz, 2 H), 2.43–2.35 (m, 2 H), 2.01 (br, 1 H), 1.67–1.59 (m, 4 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 194.4, 159.1, 133.0, 62.1, 32.4, 32.0, 24.1.

HRMS (ESI): *m*/*z* calcd for $C_7H_{16}NO_2$ (M + NH$_4$)$^+$: 146.1176; found: 146.1165.

(*E*)-Tridec-5-ene-1,7-diol (4)

A solution of *n*-hexylmagnesium bromide (0.97 M in Et$_2$O, 34.02 mL, 2.2 equiv) was added in a dropwise fashion to a solution of **3** (1.9225 g, 15.0 mmol) in THF (75 mL) at 0 °C. The mixture was stirred 30 min at the same temperature and then quenched with aq sat. NH$_4$Cl (50 mL), diluted with H$_2$O (100 mL), and extracted with EtOAc (3 × 80 mL). The combined organic layers were dried (MgSO$_4$), concentrated, and the residue was purified by flash chromatography (40% EtOAc–hexanes) to give 2.8244 g (88%) of the title compound as a yellow oil: R_f = 0.33 (50% EtOAc–hexanes).

IR (neat): 3346, 2929, 2857, 1457, 1058, 968 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.62 (dt, *J* = 15.6, 6.3 Hz, 1 H), 5.45 (dd, *J* = 15.6, 6.9 Hz, 1 H), 4.02 (q, *J* = 6.3 Hz, 1 H), 3.63 (t, *J* = 6.0 Hz, 2 H), 2.06 (q, *J* = 6.9 Hz, 2 H), 1.94 (br, 1 H), 1.60–1.23 (m, 14 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 133.7, 131.6, 73.3, 62.8, 37.5, 32.3, 32.0, 32.0, 29.4, 25.6, 25.5, 22.8, 14.2;

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{23}$ (M + H – 2H$_2$O)$^+$: 179.1794; found: 179.1790.

(*E*)-2-(Oct-1-enyl)tetrahydro-2*H*-pyran (5)

Anhyd CH$_2$Cl$_2$ (25 mL, degassed by bubbling with argon for 30 min) was added to an aluminum foil covered, flame dried, 100 mL flask containing Ph$_3$PAuCl (24.8 mg, 0.05 mmol, 0.5 mol%), AgOTf (12.8 mg, 0.05 mmol, 0.5 mol%), and activated 4 Å MS (950 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the diol **4** (2.1432 g, 10.0 mmol) in anhyd CH$_2$Cl$_2$ (25 mL, degassed by bubbling with argon for 30 min) was then added. After 5 h, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (30 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (5% EtOAc–hexanes) to give 1.7944 g (91%) of the title compound as a colorless oil; R_f = 0.95 (5% EtOAc–hexanes).

IR (neat): 2927, 2854, 2728, 1463, 1086, 967 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.65 (ddt, *J* = 15.6, 6.6, 0.9 Hz, 1 H), 5.44 (ddt, *J* = 15.6, 6.3, 1.5 Hz, 1 H), 4.01–3.95 (m, 1 H), 3.75–3.70 (m, 1 H), 3.46 (dt, *J* = 11.4, 1.5 Hz, 1 H), 2.00 (q, *J* = 6.3 Hz, 2 H), 1.85–1.22 (m, 14 H), 0.86 (t, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 132.1, 131.3, 78.5, 68.5, 32.5, 32.4, 31.9, 29.3, 29.1, 26.1, 23.6, 22.8, 14.2.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{25}O$ (M + H)$^+$: 197.1891; found: 197.1900.

Representative Procedure for Small Scale Reactions

(*E*)-Trimethyl[3-(tetrahydro-2*H*-pyran-2-yl)allyl]silane (17)

Anhyd CH$_2$Cl$_2$ (1.6 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (2.3 mg, 0.0046 mmol, 1.0 mol%), AgOTf (1.2 mg, 0.0046 mmol, 1.0 mol%), and activated 4 Å MS (30 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol (100.2 mg, 0.46 mmol) in anhyd CH$_2$Cl$_2$ (1.6 mL) was then added. After 40 min, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (4 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (5% EtOAc–hexanes) to give 83.8 mg (92%) of the title compound **17** as a colorless oil; R_f = 0.95 (50% EtOAc–hexanes);

IR (neat): 3418, 2937, 2863, 2741, 1683, 1635, 1134, 1060, 977 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): d = 5.61 (dt, *J* = 15.3, 7.8 Hz, 1 H), 5.30 (dd, *J* = 15.3, 6.3 Hz, 1 H), 4.95 (d, *J* = 11.4 Hz, 1 H), 3.69 (t, *J* = 8.4 Hz, 1 H), 3.43 (t, *J* = 11.1 Hz, 1 H), 1.81–1.34 (m, 8 H), –0.03 (s, 9 H).

^{13}C NMR (75 MHz, CDCl$_3$): d = 130.2, 128.5, 78.9, 69.46, 32.8, 26.1, 23.7, 22.9, –1.8.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{23}OSi$ (M + H)$^+$: 199.1513; found: 199.1525.

(*E*)-2-[4-(1,3-Dioxolan-2-yl)but-1-enyl]tetrahydro-2*H*-pyran (14)

Colorless oil; R_f = 0.92 (50% EtOAc–hexanes).

IR (neat): 2935, 2850, 1808, 1083, 1048 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.61 (ddt, *J* = 15.3, 7.4, 1.5, Hz, 1 H), 5.43 (ddt, *J* = 15.3, 6.0, 0.9 Hz, 1 H), 4.80 (t, *J* = 4.8 Hz, 1 H), 3.95–3.64 (m, 5 H), 3.40 (dt, *J* = 11.7, 3.3 Hz, 2 H), 2.10 (q, *J* = 7.4 Hz, 2 H), 1.79–1.18 (m, 8 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 132.0, 130.8, 104.3, 78.3, 68.5, 65.1, 33.5, 32.4, 27.0, 26.1, 23.6.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{21}O_3$ (M + H)$^+$: 213.1485; found: 213.1482.

(*E*)-2-[2-(Furan-2-yl)vinyl]tetrahydro-2*H*-pyran (15)

Yellow oil; R_f = 0.95 (50% EtOAc–hexanes).

IR (neat): 2937, 2848, 1726, 1083, 1013 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.32 (d, *J* = 1.8 Hz, 1 H), 6.41 (dd, *J* = 16.2, 1.5 Hz, 1 H), 6.34 (dd, *J* = 3.9, 1.8 Hz, 1 H), 6.21 (d, *J* = 3.3 Hz, 1 H), 6.15 (dd, *J* = 16.2, 5.4 Hz, 1 H), 3.46 (dt, *J* = 11.7, 2.7 Hz, 1 H), 4.08–4.03 (m, 1 H), 3.94 (ddt, *J* = 10.8, 5.4, 1.8 Hz, 1 H), 3.52 (dt, *J* = 11.4, 3.0 Hz, 1 H), 1.90–1.41 (m, 6 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 152.9, 141.9, 129.7, 118.1, 111.4, 107.9, 77.6, 68.6, 32.4, 26.1, 23.7.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{14}O_2$ (M)$^+$: 178.0984; found: 178.0994.

(*E*)-2-[2-(Cyanomethyl)vinyl]tetrahydro-2*H*-pyran (16)

Pale yellow oil; R_f = 0.78 (5% EtOAc–hexanes).

IR (neat): 2920, 2849, 2732, 2251, 1723, 1119, 1083 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.88 (ddt, *J* = 15.6, 5.1, 1.5 Hz, 1 H), 5.61 (ddt, *J* = 15.6, 5.4, 1.5 Hz, 1 H), 4.04–3.99 (m, 1 H), 3.85–3.79 (m, 1 H), 3.48 (dt, *J* = 5.4, 2.7 Hz, 1 H), 3.11 (dt, *J* = 11.4, 1.5 Hz, 2 H), 1.89–1.25 (m, 6 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 136.7, 117.9, 117.5, 76.9, 68.6, 32.0, 25.9, 23.5, 20.5.

HRMS (ESI): *m*/*z* calcd for $C_9H_{14}NO$ (M + H)$^+$: 152.1075; found: 152.1072.

(*E*)-2-(3-Phenylprop-1-enyl)tetrahydro-2*H*-pyran (18)

Colorless oil; R_f = 0.95 (50% EtOAc–hexanes).

IR (neat): 3026, 2934, 2843, 1495, 1452, 1085, 698 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.30–7.16 (m, 5 H), 5.82 (dt, *J* = 15.3, 6.9 Hz, 1 H), 5.53 (dd, *J* = 15.3 6.3 Hz, 1 H), 3.99 (dt,

J = 11.4, 2.1 Hz, 1 H), 3.81–3.75 (m, 1 H), 3.46 (dt, J = 11.4, 2.7 Hz, 1 H), 3.36 (d, J = 6.9 Hz, 2 H), 1.66–1.26 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.3, 132.9, 130.3, 128.8, 128.6, 128.6, 78.2, 68.5, 38.9, 32.3, 26.0, 23.6.

HRMS (ESI): m/z calcd for $C_{14}H_{17}O$ $(M - H)^+$: 209.1302; found: 201.1279.

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