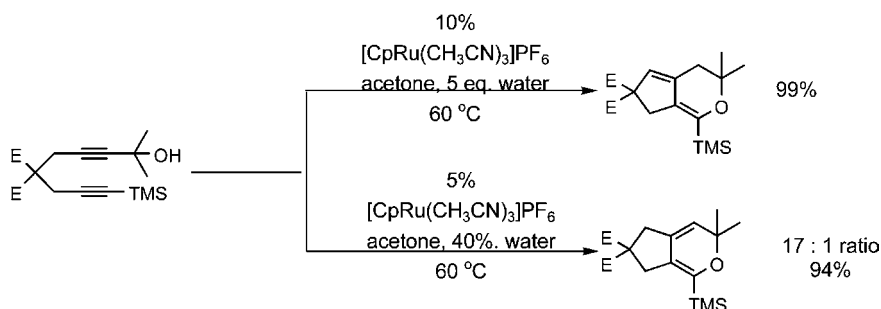# Regioselectivity Control in a Ruthenium-Catalyzed Cycloisomerization of Diyne-ols

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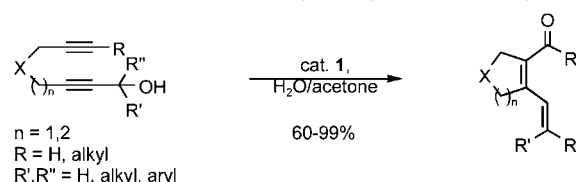*bmtrost@stanford.edu*

ABSTRACT

The ruthenium-catalyzed cycloisomerization of diynes containing one silyl alkyne and one propargyl alcohol yields 2-silyl-[6*H*]-pyrans instead of the expected unsaturated acylsilanes except when additional conjugation of a aromatic ring is present at the *δ*-position. Under certain conditions, a facile ruthenium-catalyzed isomerization of the product takes place as well. This regioselectivity of the cyclization can be controlled by the choice of solvent system. DFT calculations confirm the expected greater stability of the silyl-pyrans relative to the acylsilanes.

Recently, we disclosed a variety of transformations[1−5] of propargyl alcohols and diynes catalyzed by the cationic ruthenium complex [CpRu(CH$_3$CN)$_3$]PF$_6$ (**1**).[6] Cyclization of 1,6- and 1,7-diynes containing a propargylic alcohol occurs readily in the presence of water and a catalytic amount of **1** to produce $\alpha,\beta,\gamma,\delta$-unsaturated ketones and aldehydes in high yields[2] (Scheme 1). This methodology gives access to aldol condensation-type products in a chemoselective and atom economical[7] fashion. It was envisioned that this method could be extended to the construction of unsaturated acylsilanes,[8−10]

which are versatile synthetic intermediates, through incorporation of an alkynylsilane (Scheme 1: R = SiR$_3$). The simplicity of synthesis of alkynylsilanes as compared to acylsilanes motivates this endeavor, even though the ease of protodesilylation of silyl-alkynes under protic conditions raised concern regarding the feasibility of the process. In the event, simple alkynylsilyl-diyne-ol **2** underwent complete conversion when treated with 10 mol % **1** in aqueous acetone at 60 °C. However, instead of the expected acylsilane **3**, the

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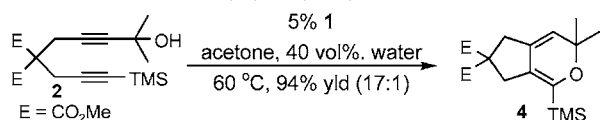(10) Page, P. C. B.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147.

Scheme 1. Ruthenium-Catalyzed Cyclization of Diyne-ols

n = 1,2
R = H, alkyl
R',R" = H, alkyl, aryl

60-99%

only product, isolated in 99% yield, was the doubly cyclized isomeric dihydropyran **5** (Scheme 2).
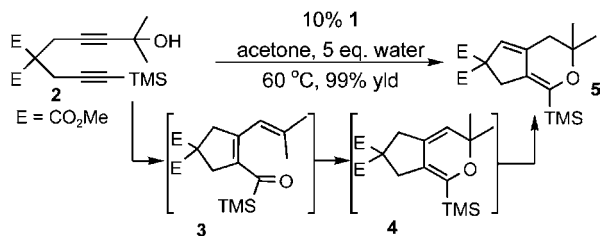
It was discovered that the amount of water present in the reaction mixture has a large effect on the product composition. Increasing the amount of water from 5 equiv to 10 vol % in acetone led to isolation of a 1:1 mixture of **5** and isomeric [6H]-pyran **4**. Further increasing the percentage of water led to increased amounts of **4**. Addition of 40 vol % water in acetone allowed isolation of **4** in 94% yield as a 17:1 mixture with **5** (Scheme 3). Higher percentages of water

or use of only water led to lower yields of **4**/**5** because turnovers of **1** were limited. Thus, the regioselectivity of the cycloisomerization can be controlled by simple change of solvent.

We reasoned that **5** was formed through three consecutive isomerization reactions. The reaction involves initial cycloisomerization to acylsilane **3** (Scheme 2), spontaneous 6π-electrocyclization to **4**, and ruthenium-catalyzed isomerization to **5** (see below). Presumably, these subsequent isomerizations proceed due to the thermodynamic equilibrium between the acylsilane and the 2-silyl-[6H]-pyran and the strain of the latter relative to the isomerized dihydropyran **5**. To support these claims we have calculated the relative stabilities of the three isomers. Using the Gaussian 98 suite of programs,[11] the gas-phase free energies were computed using the B3LYP/6-31G(d) level[12] of density functional theory (DFT). The most important term in the free energy is the electronic energy, and more accurate calculations of the electronic energies were performed using the improved B3LYP/6-311G+(2d,p)//B3LYP/6-31G(d) method. Incorporation of this larger basis set did not significantly alter the results, indicating that the present calculations are sufficiently accurate. The calculations show that **5** is more stable than **4** by 4 kcal/mol and more stable than **3** by 17 kcal/mol. The relative instability of **3** explains its absence,

and the similar stabilities of **4** and **5** justify the fact that either can be isolated. A related acylsilane to 2-silyl-[6H]-pyran isomerization is also known with allenyl-acylsilanes.[13]

The isomerization of **4** to **5** is rather facile, and even standing neat at room temperature leads to some isomerization. The process is accelerated somewhat by the presence of protic acid and to a large extent by **1**, possibly through a π-allyl mechanism.[14−16] We believe that the effect of water on the reaction can be explained by proposing that water acts as a ligand for ruthenium, thus slowing the isomerization process without overly reducing the rate of the initial cycloisomerization.[17] This claim is supported by the fact that other labile ligands can function similarly. For example, DMF slows down the second isomerization as well, although, in this case, the overall rate is also significantly reduced.

The structures of **4** and **5** were assigned on the basis of ^{1}H NMR, ^{13}C NMR, IR, and HRMS/EA and in analogy to the HMBC and UV−vis of **30** and **31**. The isolated compounds were clearly not acylsilanes due to absence of the characteristic ^{13}C carbonyl peak at 230−240 ppm and the presence of singlets accounting for 6 protons at 1.27 ppm for **4** and 1.08 ppm for **5** in the ^{1}H NMR. These features indicated that the two methyl groups in each were equivalent and not allylic. The ^{13}C NMR revealed four olefinic peaks and one ether carbon resonance. The HRMS/EA data also revealed that the mass had not changed from **2**, while the OH stretch disappeared in the IR. These data led us to consider the isomeric compounds **4** and **5** on the basis of the known valence isomerism of $\alpha,\beta,\gamma,\delta$-unsaturated ketones.[18] Utilization of HMBC data along with UV−vis spectroscopy allowed us to distinguish between the two isomers. The HMBC of related compound **31** indicated that the single vinyl proton was 2−3 bonds away from the *gem*-diester quaternary carbon and that one of the aliphatic methylenes was 2−3 bonds away from the *gem*-dimethyl quaternary carbon. The HMBC of **30** revealed the opposite relationship.

Additionally, the UV−vis spectra were taken to confirm the identity of each based upon the well established differences for s-cis homoannular and s-trans heteroannular 1,3-dienes.[19−22] Dienes with an s-cis/homoannular structure are known to have smaller extinction coefficients and λ_{max} at

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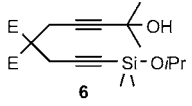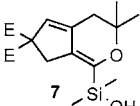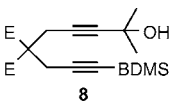(16) Trost, B. M.; Toste, F. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 1114.
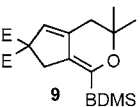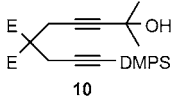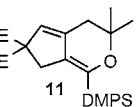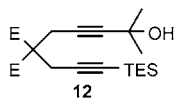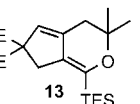(17) Rate of the initial cycloisomerization is not greatly affected by the concentration of water.
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higher wavelengths than s-trans/heteroannular dienes. The λ_{max} of 307 nm (ϵ 5000) for **30**, compared to the λ_{max} of 284 (ϵ 8000) for **31**, agrees with our structural assignment. The two isomers can also be conveniently identified by the location of the vinyl proton (~4.8 ppm for **4** and ~5.8 ppm for **5** in C_6D_6). Further examples were assigned by analogy.

The resulting vinylsilanes have potential to be valuable synthetic intermediates, and thus we wanted to examine the range of silanes that could be used (Table 1).

Table 1. Variation of the Alkynylsilane[a]

substrate	conditions	product	yield
6	A'	**7**	70%
8	A	**9**	90%
10	A	**11**	76%
12	A	**13**	85%

[a] Key: A: 10% **1**, acetone, 5 equiv of water, 60 °C. A': 10% **1**, acetone, 5 equiv of water, 50 °C. E = CO$_2$Me; BDMS = benzyldimethylsilyl-; DMPS = dimethylphenylsilyl-; TES = triethylsilyl-.

A variety of silanes are tolerated in this cyclization, including the easily functionalizable dimethylisopropoxy- and benzyldimethylsilyl[23] groups. The isopropoxy group in **6** is removed under the aqueous Lewis-acidic conditions of the reaction, and thus the product is isolated as the silanol (**7**). The disiloxane dimer also forms readily but can be minimized if desired by carrying out the reaction at lower temperatures. To demonstrate some of the potential utility of these unusual vinylsilanes, we attempted to carry out various cross-coupling reactions with aryl-iodides and either **7** or **9**. However, rapid protodesilylation occurs with TBAF as the fluoride source to yield the dihydropyran **14** in nearly quantitative yield (Scheme 4). Standing in CDCl$_3$ for several hours results in isomerization to the unsubstituted [2H]-pyran, followed by ring opening to the corresponding $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde[2] (**40**), likely due to the presence of residual HCl.
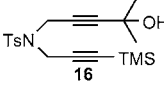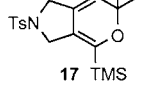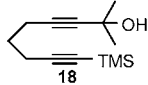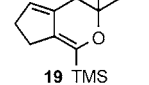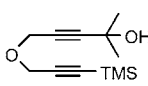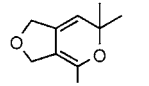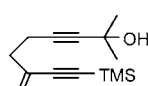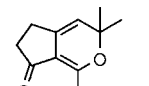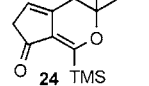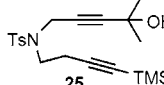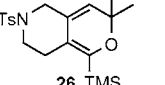
Utilization of the Denmark fluoride-free cross-coupling conditions[24−26] with **7** did lead to low (10−20%) yields of coupling products; however, this method was not pursued

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Scheme 4. Elaboration of Silyl-pyrans
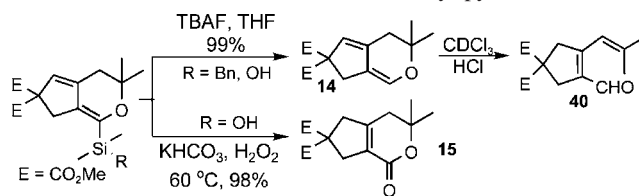
further. On the other hand, oxidation of silanol **7** under standard Tamao−Fleming[27] oxidation conditions proceeded very well to yield the unsaturated lactone **15** in quantitative yield (Scheme 4). The scope of the reaction in terms of varying the tether, the ring size, and the nature of the propargyl alcohol was also explored (Table 2). Protected

Table 2. Variation of the Tether[a]

substrate	conditions	product	yield
16	A	**17**	95%
18	A	**19**	69%
20	A	**21**	69%
22	B''	**23**	78%
22	A	**24**	85%
25	B'	**26**	46%

[a] Key: A: 10% **1**, acetone, 5 equiv of water, 60 °C. B'': B at rt. B: 10% **1**, 60 vol % acetone/40 vol % H$_2$O, 60 °C. B': B with 15% **1**.

amines (**16**), ethers (**20**), and even unsubstituted carbon (**18**) tethers are all permitted in this reaction. When the resulting allylic protons are adjacent to a heteroatom (**17**, **21**, **26**), the isomerization reaction is suppressed and the products are generally isolated as the initially formed 2-silyl-[6H]-pyran under any conditions. The β-silyl-α,β-unsaturated alkynone **22** also performs well in the cyclization to yield either isomeric pyran (**23** and **24**) depending on the conditions of the reaction. Six-membered rings can be formed (**26**); however, the turnover number of the catalyst is limited. This result is in contrast to the reactions without the alkynylsilyl

groups, in which six-membered rings are formed in only slightly reduced yields.[2] The main limitations in the makeup of the tether are that internal propargylic alcohols and ethers (e.g., **27**) and carbonyl functionality in conjugation with the leaving group (e.g., **28**) are not well tolerated.
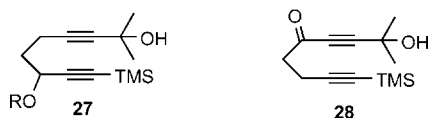
In addition to simple dimethylpropargyl alcohols, other secondary and tertiary alcohols can be used (Table 3). In

Table 3. Variation of the Propargyl Alcohol[a]

[a] Key: E = CO_2Me. A: E_E = CO_2Et; 10% **1**, acetone, 5 equiv of water, 60 °C. B: 10% **1**, 60 vol % acetone/40 vol % H_2O, 60 °C.

general, tertiary propargyl alcohols function very well in this reaction (**29**, **32**). Secondary propargyl alcohols also can be

utilized to some degree, although the yields are diminished (**35**). Additionally, unbranched secondary propargyl alcohols do not participate in the reaction to a significant extent. Benzylic secondary propargyl alcohols (**36**, **38**) react well, but instead of silylpyrans, the corresponding acylsilanes (**37**, **39**) are isolated. These products are easily identified by the presence of two olefinic proton signals along with the expected ^{13}C peak at 233 ppm (**39**) and 235 ppm (**37**). The extra conjugation of the aromatic ring presumably stabilizes the acylsilane to a sufficient extent that it is the stable isomeric form of the product, as is known for related dienone/pyran systems.[18]

In conclusion, we have shown that diyne-ols containing an alkynylsilane undergo cycloisomerization in the presence of cationic ruthenium complex **1** to form 2-silyl-[6*H*]-pyrans or isomeric dihydropyrans. The regioselectivity of the reaction can be controlled by substrate design (presence/absence of a heteroatom in the tether) or by solvent selection. Five- and six-membered rings can be formed, although cyclization to a five-membered ring is much more facile. Substrates bearing tertiary propargylic and secondary benzylic alcohols participate more readily than do simple secondary ones. If additional conjugation is present in the molecule, the acylsilane itself is the stable isomeric form. Last, the unusual ring structures formed through application of this methodology may have important applications in synthetic organic chemistry.

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