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Au(I)- and Pt(II)-Catalyzed Cycloetherification of ω-Hydroxy Propargylic Esters

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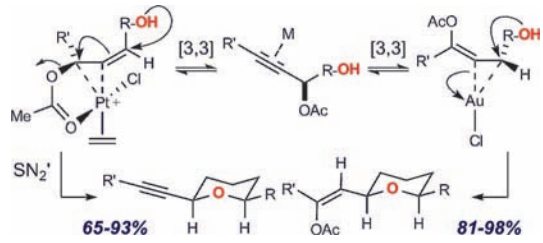
ABSTRACT



Depending on the nature of the metal catalyst, ω-hydroxy propargylic acetates choose between alternative cycloetherification manifolds to produce functionalized heterocycles in high yields. AuCl catalyzes the formation of oxacyclic enol acetates, whereas $[Cl_2Pt(CH_2CH_2)]_2$ (Zeise's dimer) will induce a propargylic substitution via an unprecedented S_N2'-type allenic substitution from within a chelated square planar cationic Pt(II) complex.

Recently, we reported a catalytic hydroalkoxylation of alkynes as an attractive strategy to ketal/spiroketal substructures present in many natural products.[1] This approach takes advantage of the alkyne functionality as a nucleus for metal-catalyzed reorganization of linear precursors into valuable heterocycles. In an extension of these studies, we decided to investigate the reactivity of ω-hydroxy propargylic esters and uncovered two distinct modes of reactivity depending on the nature of the metal catalyst that initiates electrophilic activation of the triple bond.[2] The studies reported herein culminated in a practical mild method for the synthesis of functionally diverse substituted oxygen-containing heterocycles.[3]

We envisioned that a metal with dual alkynophilic/allenophilic properties would be poised to catalyze a tandem 1,3-acyloxy migration/ cycloisomerization of ω-hydroxy propargylic esters **1** to heterocyclic enolesters **2** (eq 1).[4–6] In an initial screen with substrate **1a** (R = Me, R′ =

(1) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4908.

(2) For selected reviews, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (e) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (f) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387.

(3) For a recent review, see: (a) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683.

(4) For selected examples of reactions initiated by 1,3-acyloxy migration not cited in the reviews listed in ref 2, see: (a) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718. (b) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (c) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. (d) Barluenga, J.; Riesgo, L.; Vicente, R.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2007**, *129*, 7772. (e) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147. (f) Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207. (g) Amijs, C. H. M.; López-Carrillo, V.; Echavarren, A. M. *Org. Lett.* **2007**, *9*, 4021. (h) Marion, N.; Carlqvist, P.; Gealageas, R.; De Frémont, P.; Maseras, F.; Nolan, S. P. *Chem. Eur. J.* **2007**, *13*, 6437.

(5) For a mechanistic study of Ag(I)-catalyzed propargyl/allenyl ester isomerization, see: (a) Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 875.

(6) For a Ag(I)- and Au(I)-catalyzed *endo*-cycloisomerization for the synthesis of dihydrofurans, see: (a) Shigemasa, Y.; Yasui, M.; Ohrai, S.-I.; Sasaki, M.; Sashiwa, H.; Saimoto, H. *J. Org. Chem.* **1991**, *56*, 910. (b) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957.

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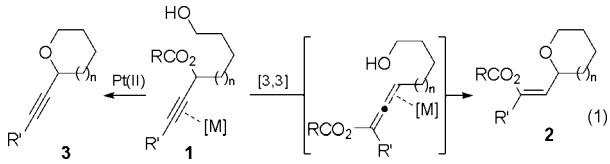
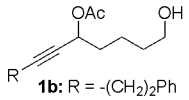
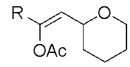
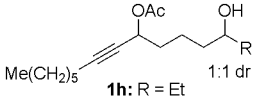
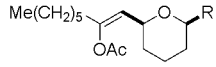
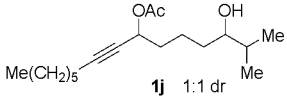
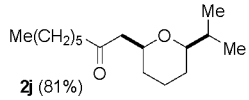
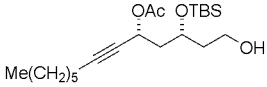
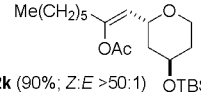
-$(CH_2)_2$Ph, $n = 0$), we found that AuCl (5 mol %) was the optimal catalyst to perform the desired transformation to enolester **2a** (CH_2Cl_2, rt, 30 min, 93% yield).[7] As will be discussed later, $[CH_2CH_2PtCl_2]_2$ was unique among the screened catalysts by initiating an alternative pathway leading to propargylic substitution products **3** (eq 1).



The AuCl-catalyzed cycloisomerisation represents a mild and general method to access stereodefined enol acetates **2** in high yields (81−98%) and generally high *Z*-selectivity (Table 1).[8] Secondary alcohols **1h** and **1i** reacted with lower

Table 1. AuCl-Catalyzed Synthesis of Oxacyclic Enolesters[a]

substrate **1**	product **2**
 **1b:** R = -$(CH_2)_2$Ph **1c:** R = -$(CH_2)_2$OTBDPS **1d:** R = -$(CH_2)_4$OTBDPS **1e:** R = Ph **1f:** R = ^{t}Bu **1g:** R = -$(CH_2)_5$Me	 **2b** (87%; *Z*:*E* = 5:1)[b] **2c** (87%; *Z*:*E* = 10:1) **2d** (82%; *Z*:*E* = 5:1) **2e** (83%; *Z*:*E* = 50:1) **2f** (89%; *Z*:*E* = 50:1) **2g** (98%; *Z*:*E* = 13:1)
 **1h:** R = Et **1i:** R = -CH_2CO_2Et	 **2h** (93%; *Z*:*E* = 2.4:1; 2.5% *trans*) **2i** (91%; *Z*:*E* = 3.1:1; 10% *trans*)
 **1j** 1:1 dr	 **2j** (81%)
 **1k**	 **2k** (90%; *Z*:*E* >50:1)

[a] Reaction conditions: propargyl acetate (0.1 M in THF), 5 mol % AuCl, rt, 30 min. Substrate **1j** was refluxed for 16 h. [b] Yields are for isolated products. Ratios/stereochemistry determined by ^{1}H NMR.

Z/*E*-selectivity but good selectivity for the 2,6-*cis*-tetrahydropyrans **2h** and **2i**. Diastereomerically pure alcohol **1k** cyclized with retention of configuration and excellent *Z*-selectivity. Finally, silyl protecting groups (**1c,d**, **1k**) were compatible with the reaction conditions and β-hydroxy ester **1i** cyclized without competing β-elimination. The more hindered, less reactive isopropyl-substituted substrate **1j** required heating for 16 h.[9]

A mechanistic hypothesis consistent with the data is provided in Figure 1. After initial AuCl-catalyzed [3,3]-

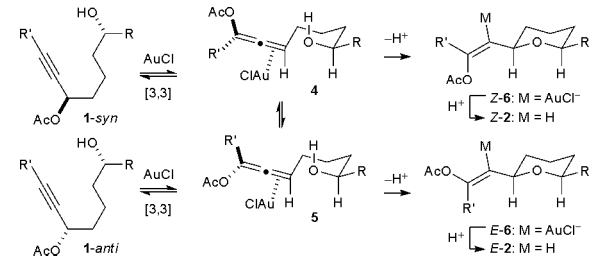


Figure 1. Proposed mechanism for Au-catalyzed cyclizations.

rearrangement of propargylic acetate **1**, the corresponding allenyl gold complex **4** or **5** undergoes intramolecular hydroalkoxylation to vinylgold species **6**. Final protodeauration yields *Z*- or *E*-enol acetate **2**. The selective formation of *Z*-products indicates that cyclization from a complex with gold coordinated *cis* to the R′-substituent (**4**) is preferred over the alternative **5**, possibly due to minimization of $A^{1,3}$ -strain. For secondary alcohols, the cycloisomerization is subject to double diastereoselection. For example, cyclization of **1**-*syn* to *Z*-**2** represents a matched case via an all-equatorial chairlike TTS (**4** → *Z*-**6**). For the corresponding **1**-*anti* diastereomer, cyclization from the gold-allenoate complex leading to the *Z*-isomer would occur via an unfavorable TTS with axial R-substituent (not shown), leading to the minor 2,6-*trans*-products (∼5%). Instead, cycloisomerization proceeds through an all-equatorial TTS leading to *E*-**2**. This represents a mismatched case, and allene-epimerization[5] (**5** → **4**) competes kinetically.[10] Consistent with this, *syn*/*anti* mixtures of substrates **1h,i** yield tetrahydropyrans **2h,i** in *Z*/*E* ratios deviating from unity.

As noted in the introduction, Zeise's dimer ($[CH_2CH_2PtCl_2]_2$) did not induce cycloisomerization according to eq 1 but instead catalyzed a propargylic substitution pathway. As shown in Table 2, treatment of propargylic acetates **1** with 2.5 mol % of Zeise's dimer (THF, 30 min, rt) efficiently affords propargylic substitution products **3**. Primary alcohols gave monosubstituted ethers **3b−e,g** or isochromans **3n,o** in yields ranging from 77−93%. Phenols also participate in this transformation yielding dihydrobenzopyran **3m**. Silyl protecting groups (**1c,d,k,l**) survived the mild reaction conditions, and β-hydroxy ester **1i** cyclized (→ **3i**) without competing β-elimination. Epimeric mixtures of δ-hydroxypropargylic acetate **1p** or **1q** yield tetrahydrofurans **3p** or

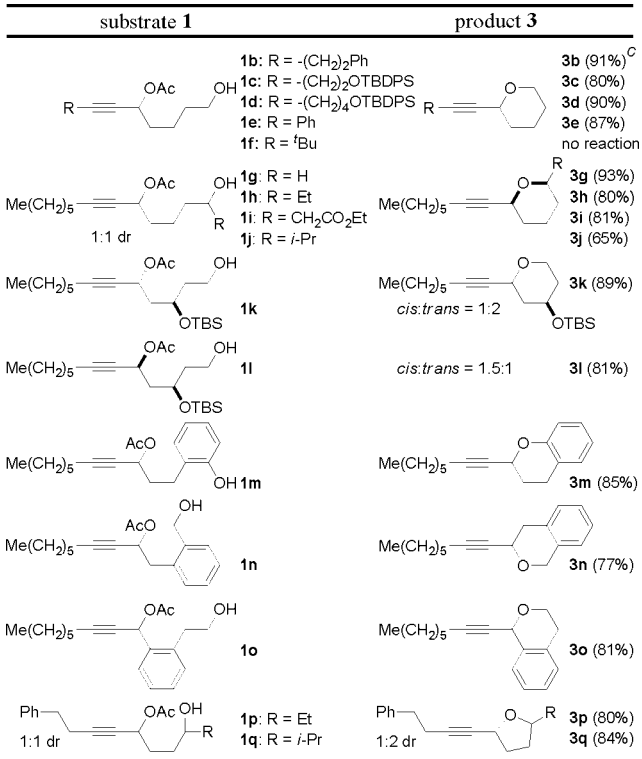
(7) Other catalysts were inactive, resulted in low conversion ($AgPF_6$), or yielded complex mixtures ($ClAuPPh_3/AgPF_6$, $MeAuPPh_3/AgPF_6$, $AuCl_3$, $NaAuCl_4$, $PtCl_2$). In THF, $NaAuCl_4 \cdot 2H_2O$ (5 mol %) did catalyze the formation of enol ester **2g** (*Z*:*E* = 8:1) from **1g** in 90% yield.

(8) For a mechanistically distinct Au-catalyzed synthesis of heterocycles from homopropargylic ethers, see: (a) Jung, H. H.; Floreancig, P. E. *J. Org. Chem.* **2007**, *72*, 7359.

(9) The enol acetate was not stable under the reaction conditions, and β-ketone **2j** was isolated instead. In all other cases presented in Table 1, the enolic esters are stable to isolation and chromatography. If desired, they can be transformed to the corresponding β-ketones under mild conditions and in high yields; see Supporting Information.

(10) The isomeric products do not equilibrate. However, AuCl and $[Cl_2PtCH_2CH_2]_2$ catalyze the racemization of homochiral 3-acetoxy-2-Me-7-Ph-4-heptyne (98% ee) at rates similar to those of the cyclizations in Tables 1 and 2; see Supporting Information.

Table 2. Pt(II)-Catalyzed Synthesis of Cyclopropargyl Ethers[a,b]



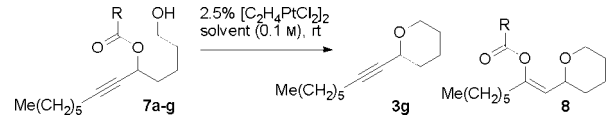
[a] Reaction conditions: propargyl acetate **1b**−**q** (0.1 M in THF), 2.5 mol % $[CH_2CH_2PtCl_2]_2$, rt, 30 min. [b] *Cis*/*trans* ratio was determined by ^{1}H NMR (**3j**, 0% *trans*; **3h** and **3i**, 7.4% *trans*). [c] Isolated products.

3q in a *cis*:*trans* ratio of 1:2 (80−84% yield), whereas epimeric mixtures of 1,5-disubstituted substrates **1h**−**j** converge to 2,6-*cis*-tetrahydropyrans **3h**−**j** (65−81% yield, 0−8% *trans*-isomer). Finally, substrates with a β-silyloxy substituent retain some degree of stereochemical memory; 1,3-*syn* substrate **1k** afforded **3k** in a *cis*:*trans* ratio of 1:2, whereas *anti*-isomer **1l** yielded **3l** in a 1.5:1 ratio.[10]

Although propargylic substitution can be achieved with the Nicholas reaction,[11] the overall transformation is not catalytic and necessitates a multistep sequence including dicobalt complex formation, (Lewis) acid-mediated ionization, and final reductive metal decomplexation. Alternatively, propargylic substitution can be catalyzed by transition metals, although the scope remains somewhat limited to substrates bearing terminal alkynes or carbocation-stabilizing substituents.[12] Various control experiments rule out a mechanism involving propargylic carbocation intermediates. For example, stirring alkyne **1g** with strong Lewis acids (cat. or equiv $TiCl_4$, $BF_3{\cdot}OEt_2$, $FeCl_3$) invariably returned starting material (>90%). Also, substrates that sterically prevent coordination to the alkyne but not the ester are inert (e.g., **1f**).

To gain some mechanistic insight, the effects of the ester leaving group and solvents were studied, and the results

Table 3. Influence of Ester and Solvent on Product Distribution



entry	substrate	conditions	**3g**[a]	**8**[a]
1	**7a**; R = Me	THF, 30 min	93%	
2	**7b**; R = Et	THF, 1 h	82%	
3	**7c**; R = Ph	THF, 1 h	50%	30%
4	**7c**	2,4-Me_2THF, 1 h	50%	
5	**7c**	CH_2Cl_2, 10 min	87%	
6	**7d**; R = 4-MeOPh	THF, 1 h	72%	11%
7	**7e**; R = 4-^{t}BuPh	THF, 1 h	73%	9%
8	**7f**; R = 4-NO_2Ph	THF, 1 h	no reaction[b]	
9	**7f**	CH_2Cl_2, 10 min	86%	
10	**7g**; R = 4-CNPh	THF, 1 h	no reaction[b]	
11	**7g**	CH_2Cl_2, 10 min	83%	

[a] Isolated product. [b] Starting material was recovered in >90%.

documented in Table 3 are illustrative. Compared to acetate and propionate esters **7a** and **7b**, which yield exclusively substitution product **3g** (entries 1 and 2), the corresponding benzoate **7c** (entry 3) provided a mixture of substitution (**3g**, 50%) and cycloisomerization products (**8c**, 30%). Interestingly, the preference for propargylic substitution increased with electron-donating *para*-substituents (entries 6 and 7), whereas electron-withdrawing *p*-nitro or *p*-CN substitution shut the reaction down (entries 8 and 10). However, exclusive propargylic substitution was observed when the solvent was switched to CH_2Cl_2 (entries 5, 9, and 11).

In Figure 2, we formulate a mechanism initiated by Pt(II)-catalyzed propargyl/allenyl isomerization. The resulting allene engages the enolester double-bond face *cis* to the smaller substituent (π-complex **10**).[13,14] In CH_2Cl_2, chloride ionization leads to cationic square-planar bidentate complex **11**.[15] In this complex, activation of the ester leaving group by Lewis acid type complexation[2c] to the cationic Pt(II) center with concomitant LUMO-lowering olefin π^* and ester C−O σ^* orbital alignment (coplanar) conspire to lower the barrier for a concerted S_N2' cyclization (→ **12**).[16,17] Elimination of acetic acid and ligand exchange (starting alkyne **7** for product alkyne **3**) completes the catalytic cycle. In the weakly coordinating solvent THF, cationic complexes **13** and **14** can compete with bidentate complex **11**,[18] thereby enabling a bifurcating hydroalkoxylation manifold to enolester **8** via activation of the olefin proximal to the alcohol (**14** → **15**).[19] This solvent effect conforms with the observa-

(11) For selected reviews, see: (a) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809. (b) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133. (c) Díaz, D. D.; Betancort, J. M.; Martín, V. S. *Synlett* **2007**, 343.

(12) For selected examples not involving allenylidene intermediates, see: (a) Matsuda, I.; Komori, K.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 9072. (b) Sherry, B. D.; Radosevich, A. T.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 6076. (c) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180. (d) Nishibayashi, Y.; Shinoda, A.; Miyake, Y.; Matsuzawa, H.; Sato, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4835. (e) Zhan, Z.; Yu, J.; Liu, H.; Cui, Y.; Yang, R.; Yang, W.; Li, J. *J. Org. Chem.* **2006**, *71*, 8298. (f) Evans, P. A.; Lawler, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4970. (g) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409. (h) Mahrwald, R.; Quint, S.; Scholtis, S. *Tetrahedron* **2002**, *58*, 9847.

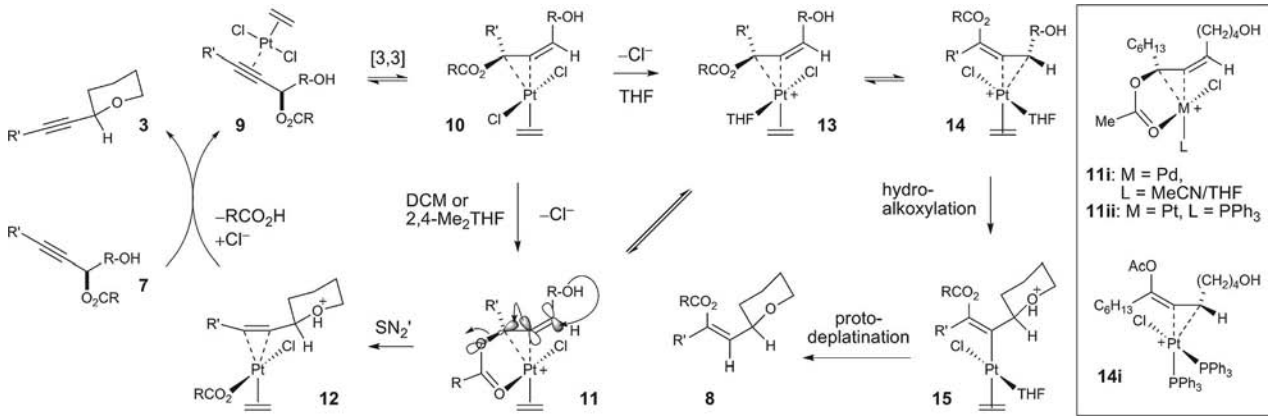


Figure 2. Mechanistic proposal for the platinum(II)-catalyzed cycloetherification of ω-hydroxypropargylic esters.

tion that reaction of benzoate **7c** in 2,4-Me_2THF (a noncoordinating substitute for THF) exclusively yields substitution product **3g** through bidentate complex **11** (compare entries 3 and 4, Table 3).[18] Our model also explains the observed correlation between ester donor-strength and product distribution in THF (Table 3). Electron-rich esters compete more efficiently with THF for coordination to the platinum center, augmenting propargylic substitution (via **11**) in going from benzoate to *p*-MeO- or *p*-^{t}Bu-benzoate to acetate and propionate esters.[20] On the other hand, THF is not as strong an ionizing solvent as CH_2Cl_2 to allow the charge buildup required for the formation of any cationic complex with the electron-withdrawing allenic *p*-NO_2Bz and *p*-CNBz esters, thereby shutting down both modes of reactivity (compare entries 8, 10 with 9, 11). Finally, other Cl_2ML_2 complexes that can accommodate bidentate allenyl ester coordination catalyze the propargylic substitution. For example, reaction of **7a** with 5 mol % of $Cl_2Pd(MeCN)_2$ in THF yielded **3g** (12% at 40% conversion, 2 h) via **11i** (box Figure 2). Also, $Cl_2Pt(PPh_3)_2$ (5 mol %) catalyzed the reaction when activated by $AgBF_4$ (5 mol %) to yield 52% of substitution product **3g** via **11ii** and 34% of enolester **8** via **14i** (CH_2Cl_2, 1 h, rt). Overall, *this mechanistically novel platinum-catalyzed propargylic substitution represents an operationally simple alternative that functions with internal alkynes lacking a carbocation-stabilizing substituent*.

In conclusion, we have developed novel catalytic cycloetherifications of ω-hydroxy propargylic esters initiated by a common propargyl/allenyl ester rearrangement. Particularly noteworthy is the observation that the incipient metal-complexed allenyl esters will partition between a hydroalkoxylation manifold and an S_N2'-type allenic substitution depending on the catalyst and solvent conditions.[21] Thus, catalysis by AuCl will lead exclusively to stereodefined oxacyclic enol acetates, whereas square planar platinum(II) chlorides catalyze the formation of propargylic substitution products. A mechanistic rationale reconciling this divergent behavior in the context of metal coordination chemistry was developed and we will continue to test this model experimentally. Finally, it is worth emphasizing that our methodology is defined by mild reaction conditions and broad substrate scope. The corresponding substituted cyclic ethers are valuable intermediates for the synthesis of biologically active polyketide natural products.

Acknowledgment. This work was supported by the Robert A. Welch Foundation and Merck Research Laboratories.

Supporting Information Available: General procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For a crystal structure of dichloro(tetramethylallene)platinum(II) dimer, see: (a) Hewitt, T. G.; De Boer, J. J. *J. Chem. Soc. A* **1971**, 817.

(14) π-Bonded allenes oscillate between the orthogonal π-systems: Ben-Shosan, R.; Pettit, R. *J. Am. Chem. Soc.* **1967**, *89*, 2231.

(15) The addition of LiCl or Bu_4NCl inhibits the reaction.

(16) For S_N' substitutions of allenyl halides involving allenyl/propargyl cation or carbene intermediates, see: (a) Kitamura, T.; Miyake, S.; Kobayashi, S. *Chem. Lett.* **1985**, 929. (b) Shiner, V. J.; Humphrey, J. S., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 622. (c) Toda, F.; Higashi, M.; Akagi, K. *Bull. Chem. Soc. Jpn.* **1969**, 829. For a proposed S_N2' hydrolysis of propargylic acetates, see ref 4h. For a propargylic substitution via a proposed S_N2' addition of alcohols to a rhenium(V)-oxo allenolate intermediate, see ref 12b.

(17) For a Au-catalyzed cyclization of monoallylic diols proceeding via a proposed S_N2' allylic substitution, see: (a) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669.

(18) No reaction is observed in 1,4-dioxane. This solvent has a lower donor strength than THF and is less polar than THF and CH_2Cl_2, thus preventing solvent-mediated stabilization of cationic intermediates.

(19) Control experiments indicate that enol ester products do not arise from subsequent Pt(II)-catalyzed hydroacetoxylation of propargylic substitution product **3**.

(20) Alternative pathways invoking a role for ester Brønsted base strength (H^+-transfer or H-bonding) on product distribution cannot explain the results in Table 3. Also, addition of 2,6-^{t}Bu$_2$-pyridine (1 equiv) to the reaction in entry 1 (Table 3) did not prevent the propargylic substitution, and product **3g** was obtained in 88% yield.

(21) For a recent example of divergent cycloisomerization of a common alleneyne substrate depending on whether the reaction was catalyzed by gold or platinum, see: (a) Zriba, R.; Gandon, V.; Aubert, C.; Fensterbank, L.; Malacria, M. *Chem. Eur. J.* **2008**, *14*, 1482.