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Operationally Simple, Efficient, and Diastereoselective Synthesis of *cis*-2,6-Disubstituted-4-Methylene Tetrahydropyrans Catalyzed by Triflic Acid

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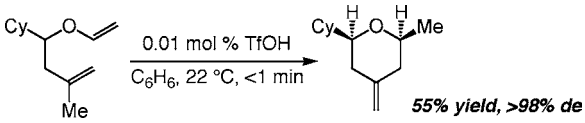
ABSTRACT



A highly efficient (0.01 mol % of TfOH), operationally simple (room temperature, inexpensive, and commercially available catalyst), and diastereoselective (up to >98% de) method for Brønsted acid-catalyzed reaction of enol ethers to form *cis*-2,6-disubstituted tetrahydropyrans is disclosed.

Practical, environmentally friendly, and efficient methods for stereoselective synthesis of heterocycles are critical to the synthesis of medicinally relevant organic molecules. An important class of heterocyclic synthesis targets is functionalized chiral pyrans.[1] Accordingly, a number of synthesis strategies have been recently developed that involve stereoselective conversions of appropriately functionalized acyclic O-containing precursors to 2,6-disubstituted pyrans. In one set of transformations, a highly electrophilic oxocarbenium ion, generated from reaction of an alcohol and an aldehyde in the presence of a Lewis acid, is intramolecularly trapped by an electron-rich neighboring alkene through an oxonium-ene process (Prins-type cyclizations).[2] The above strategy requires sub-stoichiometric (0.5 equiv) or super-stoichiometric (2 equiv) amounts of strong Brønsted or Lewis acids. In a related study, the only catalytic method disclosed thus far in this general class of transformations, 5−20 mol % of a Lewis acid catalyst ($In(OTf)_3$), is used in the presence of 1.2−2.5 equiv of trimethyl silyl halides to promote intermolecular oxonium-ene cyclizations; these diastereoselective transformations afford *cis*-2,6-disubstituted pyrans that bear a C-halide bond at the C4 position.[3] In another set of investigations, electron-donating silyl units are installed to enhance the reactivity of the nucleophilic olefin (allylsilanes).[4] The latter approach delivers excellent yields of pyrans in high diastereoselectivities. However, additional operations

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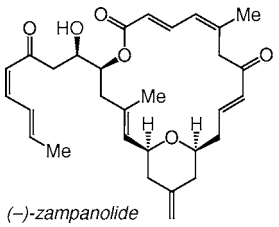
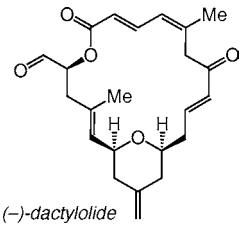
must be carried out to incorporate the requisite silyl group, and the use of 1−2 equiv of a strong acid (e.g., camphorsulfonic acid, TMSOTf) is often required.[5]

An alternative protocol, developed by Hart and Rychnovsky,[6] involves the formation of oxocarbenium ions, generated by reaction of an enol ether with an acid, that is then intercepted by an unfunctionalized alkene (i.e., not activated by an α-silyl group); such a strategy is attractive since it does not require silyl group activation. To the best of our knowledge, an example of an efficient *catalytic* variant of the latter approach has not yet been reported.

Research in these laboratories, during the past several years, has focused on the design and development of a range of new metal-based chiral catalysts and methods for diastereo- and enantioselective synthesis of chiral pyrans.[7] In this communication, we report an efficient, practical, and highly stereoselective protocol that involves the use of a simple and inexpensive Brønsted superacid catalyst for conversion of unsaturated enol ethers to *cis*-2,6-disubstituted-4-methylene tetrahydropyrans: six-membered heterocyclic units found in a variety of biologically active natural products, such as dactylolide and zampanolide (shown below).[8] Thus, low catalyst loadings (≤0.01 mol %; turnover number = 10 000) of commercially available triflic acid (TfOH, pK_a = −13 to −14) initiate stereoselective formation of the desired pyrans. Catalytic reactions are typically carried out at room temperature (22 °C) and proceed to >98% conversion in only a few minutes.



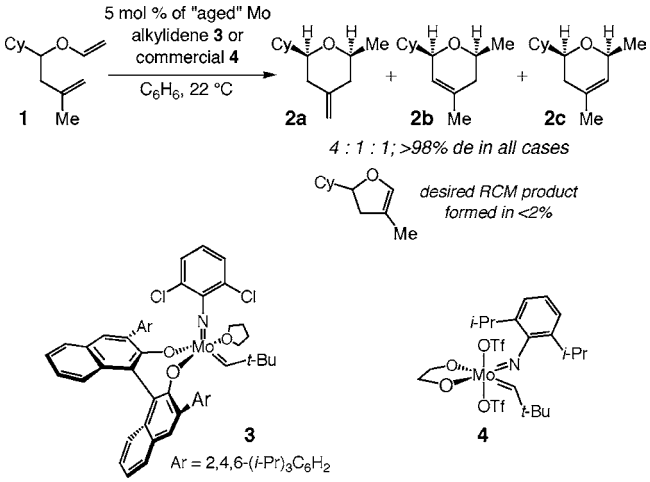
(−)-zampanolide



(−)-dactylolide

The present protocol was discovered inadvertently during investigations concerning the development of Mo-catalyzed asymmetric ring-closing metathesis (ARCM) of enol ethers.[9] In the course of these studies, we noted that, when **1** is subjected to a particular batch of Mo-based alkylidene **3**,[10] unsaturated pyrans **2a**, **2b**, and **2c** are formed efficiently and diastereoselectively (>98% de, as judged by analysis of 400 MHz ^{1}H NMR spectra) instead of the expected ring-closing metathesis (RCM) product (Scheme 1).

Scheme 1. Initial Observations with Mo−Based Alkylidenes



Despite the appreciable Lewis acidity of Mo-based alkylidenes, particularly those bearing electron-deficient ligands, such as dichloroaryl imidate **3**,[11] we suspected that this and related olefin metathesis precatalysts may not be responsible for promoting cyclizations. Accordingly, we systematically investigated the reaction of **1** in the presence of a range of Mo-based alkylidenes (5 mol % loading in all cases), including freshly prepared chiral complexes **3**, which only promote RCM. In contrast, their Mo triflate precursors (e.g., **4**, Scheme 1) proved to be effective cyclization catalysts.

Next, we established that other metal triflates, such as Ag(OTf), $Hg(OTf)_2$, $Zn(OTf)_2$, $Mg(OTf)_2$, $Sn(OTf)_2$, and $Al(OTf)_3$, can be used as catalysts, whereas $Yb(OTf)_3$, which is relatively stable to hydrolytic decomposition[12] (does not readily generate TfOH through exposure with moisture), fails to promote conversion of **1** to **2a**−**c** (<2% conv). Finally, we determined that, in the above studies, cyclization efficiency (% conv) and reaction times are dependent on the age and quality of the metal triflate used. Collectively, the

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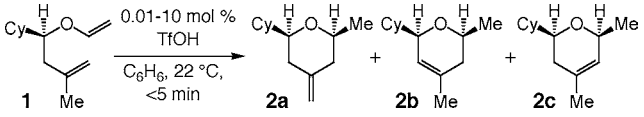
above findings suggested that small amounts of TfOH are likely responsible for the observed catalytic activity.

On the basis of the above findings, we examined the effect of pure TfOH on promoting the conversion of enol ether **1** to pyrans **2**. As the data in entries 1 and 2 of Table 1 indicate,

Table 1. Effect of Catalyst Loading on Product Distribution[a]



entry	mol % TfOH	**2a**:**2b**:**2c**[b]
1	10	(polymer)
2	5	(polymer)
3	1	1:3:3
4	0.1	1.5:1:1
5	0.01	4:1:1

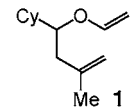
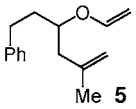
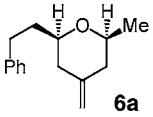
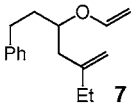
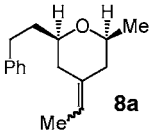
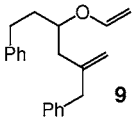
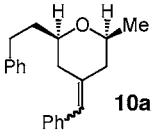
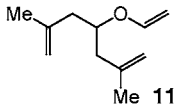
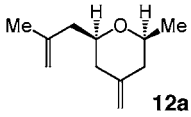
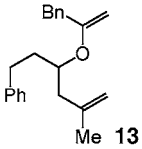
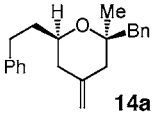
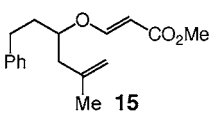
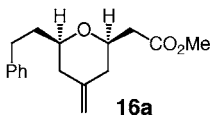
[a] All conversions and de >98%, determined by 400 MHz ^{1}H NMR analysis of the unpurified product. [b] Determined by 400 MHz ^{1}H NMR analysis of the unpurified product.

treatment of **1** with 5 or 10 mol % of TfOH gives rise to rapid polymerization (<2% **2**). However, upon decreasing the catalyst loading considerably (≤1 mol %), the desired tetrahydropyrans **2** can be isolated (entries 3−5, Table 1). The ratio of the olefin isomers is affected by catalyst loading, with 0.01 mol % of TfOH providing a 4:1:1 ratio of **2a**:**2b**:**2c**. Attempts at improving the above product distribution by further lowering the catalyst loading resulted in >98% recovery of the starting material.

Next, we examined the scope of the cyclization process. The results of these studies are summarized in Table 2. As shown in entry 1, we established that pyran **2a**, from the reaction of enol ether **1**, can be obtained in the pure form in 55% isolated yield. Similar levels of reactivity and diastereoselectivity are observed with diene **5** (entry 2); dihydropyran **6a** is obtained in 64% isolated yield. The acid-catalyzed cyclization of enol ethers **7** and **9**, where the 1,1-disubstituted olefins bear a longer alkyl chain (vs Me in **1**), leads to the formation of **8a** and **10a** as 1.6−1:1 mixtures of olefin stereoisomers in 53 and 75% isolated yields. The transformations depicted in entries 3 and 4 proceed with improved levels of product selectivity (**a**:**b**:**c** = 10−11:1:1), presumably because isomerization of the trisubstituted exocyclic alkene is now thermodynamically less favored (vs with disubstituted exocyclic olefins in **2a** and **6a**). Desymmetrization of triene **11** proceeds smoothly to afford dihydropyran **12a** in 60% isolated yield and >98% de. Catalytic cyclization of 1,1-disubstituted enol ether **13** (entry 6, Table 2) is noteworthy as it affords **14a**, bearing a tertiary ether site, in 90% de and 46% isolated yield. The acid-catalyzed transformation of **15**, which carries a sterically more hindered and electron-deficient enol ether, requires 18 h to proceed to completion, delivering **16a**−**c** in reduced selectivity (2:2:1); diastereomerically pure **16a** was isolated in 27% yield.

Several other noteworthy points regarding the acid-catalyzed cyclization merit mention. (1) Catalytic cyclizations

Table 2. Diastereoselective TfOH-Catalyzed Synthesis of *cis*-2,6-Disubstituted-4-Methylene Tetrahydropyrans[a]

entry	substrate	major product	**a**:**b**:**c**[b]	yield of **a** (%)[c]
1	 **1**	 **2a**	4:1:1	55
2	 **5**	 **6a**	3.5:1:1	64
3	 **7**	 **8a**	11:1:1	53
4	 **9**	 **10a**	10:1:1	75
5	 **11**	 **12a**	4:1:1	60
6	 **13**	 **14a**	4:3:1	46[d]
7	 **15**	 **16a**	2:2:1	27[e]

[a] Conditions: 0.01 mol % of TfOH for entry 1 and 0.1 mol % of TfOH for entries 2−7, C_6H_6, 22 °C, 10 min, N_2 atm. All conversions and de >98%, determined by 400 MHz ^{1}H NMR analysis of the unpurified product. [b] Determined by 400 MHz ^{1}H NMR analysis of the unpurified product. [c] Isolated yields after chromatography on silica gel impregnated with $AgNO_3$ (5% w/w). [d] Diastereomeric excess = 90%. [e] Reaction time = 18 h.

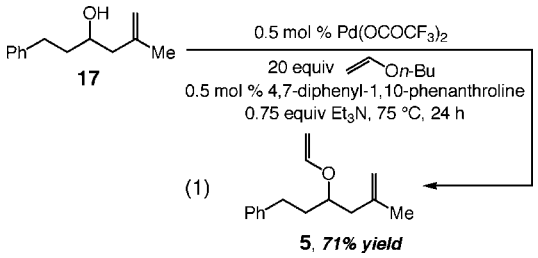
can be carried out efficiently in various other common solvents, such as pentane, toluene, Et_2O, THF, dichloromethane, and dimethoxyethane with similar levels of efficiency as that observed in benzene; however, product selectivity (**a**:**b**:**c**) is consistently higher in benzene. For example, with 0.1 mol % of TfOH at 22 °C, a 1:1:1 mixture of **2a**:**2b**:**2c** is formed when catalytic cyclization of **1** is carried out in THF; a 3:1:1 selectivity is observed with Et_2O as solvent. (2) Catalytic cyclizations can be carried out at −78 °C (toluene). Under these conditions, reactions proceed to completion (0.01 mol % of TfOH) but without any improvement in product selectivity (**a**:**b**:**c**). (3) Longer reaction times lead to an increase in the amount of endocyclic products; for example, after 5 days, **1** is converted to **2b** and **2c** with <2% **2a** remaining (established by analysis of 400 MHz ^{1}H NMR). Moreover, when pure **2a** is re-subjected to the reaction conditions, it is converted to **2b** and **2c** in the presence of 0.01 mol % of TfOH after 1 h at 22 °C. The above observations indicate that products **a** are likely the

exclusive kinetic products which then isomerize to **b** and **c** olefin isomers. (4) One limitation of the present catalytic protocol is that there is <2% conv with substrates bearing a terminal alkene.

Examination of other Brønsted and Lewis acids as catalysts for this class of cyclization reactions clearly indicates that TfOH is unique in its ability to promote efficient and selective C−C bond formations. Thus, when enol ether **1** is subjected to camphorsulfonic acid or trifluoroacetic acid (5 mol %), <2% of the desired product is obtained (>98% recovered starting material). In contrast, Amberlyst 15E (0.5 g resin/mmol substrate) gives rise to >98% conversion after 1 h (22 °C) to afford **2a**:**2b**:**2c**, albeit with diminished product selectivity (1:1:1) and diastereoselectivity (33 vs >98% de with TfOH in favor of the *cis* diastereomer). Lewis acids $BF_3{\cdot}Et_2O$ and $TiBr_4$ induce cyclization, but significantly less efficiently: with 5 mol % of $BF_3{\cdot}Et_2O$, >98% conv to an equimolar mixture of **2a**, **2b**, and **2c** is observed (18 h), whereas $TiBr_4$ (∼90% conv after 18 h) provides a complex mixture of products, including **2a**, **2b**, and **2c** and ∼10% unreacted starting material.

The starting vinyl ethers required for TfOH-catalyzed cyclizations can be accessed from the corresponding homoallylic alcohols in one Pd-catalyzed step; the procedure shown in eq 1 is representative.[13] Subjection of homoallylic alcohol **17** to 0.5 mol % of commercially available $Pd(OCOCF_3)_2$ and 4,7-diphenyl-1,10-phenanthroline in the presence of 0.75 equiv of Et_3N and 20 equiv of *n*-butyl vinyl ether (75 °C, 24 h) gives rise to the formation of **5** in 71% yield after silica gel chromatography (eluted with 1% Et_3N). Because a variety of homoallylic alcohols are available in highly optically enriched form,[14] the present protocol can be easily applied to the enantioselective synthesis of *cis*-2,6-disubstituted-4-methylene tetrahydropyrans.

1,1-Disubstituted vinyl ether **13** (entry 6, Table 2) was prepared through Tebbe olefination[15] of the corresponding phenyl acetate; **15** (entry 7, Table 2) was accessed through a conjugate addition[6a] method. It is important to note that the more substituted and functionalized oxocarbenium ions generated from enol ether precursors, such as **13** and **15** (entries 6 and 7, Table 2), cannot be readily prepared in situ through Prins-type protocols.[2−4]



In summary, we present a method for catalytic and diastereoselective cyclizations of unsaturated enol ethers that afford *cis*-2,6-disubstituted-4-methylene tetrahydropyrans. The overall process is direct and operationally simple: vinyl ether substrates can be accessed from easily available homoallylic alcohols, and cyclizations are readily promoted, typically in less than 10 min, in the presence of 0.01−0.1 mol % of commercially available TfOH (∼$6/gram) at room temperature. The effectiveness of the present protocol and the significance of 2,6-disubstituted pyrans in chemical synthesis should render the present method of synthetic utility. Moreover, the recent emergence of chiral Brønsted acid catalysts[16] suggests that a highly efficient approach for an enantioselective variant of the present process may be achievable. Studies along these lines are in progress and will be disclosed in due course.

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Supporting Information Available: Experimental procedures and spectral data for products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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