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Acid-Catalyzed Regioselective Sulfetherification of Alkenols and Stereoselective Rearrangement of Tetrahydrofuran to Tetrahydropyran

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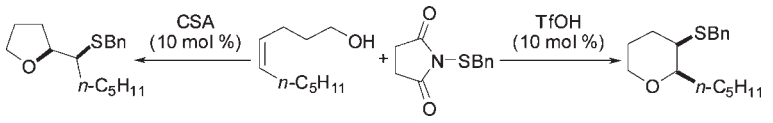
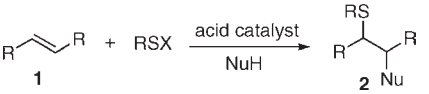
ABSTRACT



An efficient acid-catalyzed sulfetherification of various unsaturated alcohols with sulfenamides to form tetrahydrofurans and tetrahydropyrans regioselectively is described. Mechanistic studies have shown that the tetrahydrofurans can stereoselectively rearrange to the corresponding tetrahydropyrans.

Functionalizations of olefins represent important synthetic transformations. As a part of our general interest in the area of oxidation of olefins to introduce various heteroatoms onto C−C double bonds,[1,2] we have been investigating acid-catalyzed electrophilic sulfur additions to olefins using sulfenamides and related sulfur reagents with the aim of eventually developing an asymmetric process using a chiral catalyst (Scheme 1).[3−7] During our studies on intramolecular sulfetherification of alkenols, we have found that either 5-*exo* or 6-*endo* cyclization products can be regioselectively formed with sulfenamides depending upon the acid catalyst used (Scheme 2). It appears that the 5-*exo* product can undergo an acid-catalyzed stereoselective rearrangement to form the 6-*endo* product. Herein we report our preliminary efforts on this subject.

Scheme 1



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(1) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.
(2) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762.
(3) For a leading review on electrophilic sulfur additions to olefins, see: Rayner, C. M. In *Organosulfur Chemistry: Synthetic Aspects*; Page, P., Ed.; Academic Press: London, 1995; p 89.
(4) For a leading review on sulfenamides, see: Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689.
(5) For leading references on acid-promoted addition of RS or RSe to olefins with RS-N or RSe-N reagents, see: (a) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704. (b) Caserio, M. C.; Kim, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3231. (c) Brownbridge, P. *Tetrahedron Lett.* **1984**, *25*, 3759. (d) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *Tetrahedron* **1986**, *42*, 1145. (e) Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1280.
(6) For leading references on acid-promoted addition of RS to olefins with RSSR or RSOR reagents, see: (a) Trost, B. M.; Ochiai, M.; McDougal, P. G. *J. Am. Chem. Soc.* **1978**, *100*, 7103. (b) Edstrom, E. D.; Livinghouse, T. *J. Am. Chem. Soc.* **1986**, *108*, 1334. (c) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723. (d) Taniguchi, N. *J. Org. Chem.* **2006**, *71*, 7874. (e) Yamagiwa, N.; Suto, Y.; Torisawa, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6197.
(7) For leading references on Lewis base promoted addition of RSe to olefins with RSe-N reagents, see: (a) Denmark, S. E.; Collins, W. R. *Org. Lett.* **2007**, *9*, 3801. (b) Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752.

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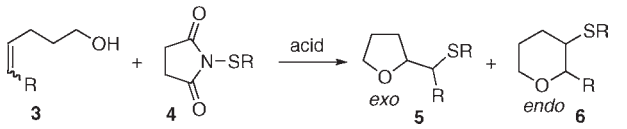
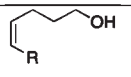
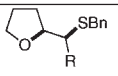
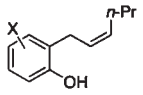
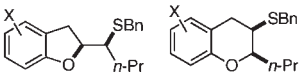
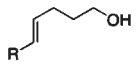
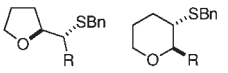
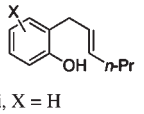
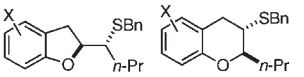
Scheme 2



Initial studies were carried out with *cis*-4-decen-1-ol (**3a**). Treating **3a** with *N*-(benzylthio)succinimide (**4a**, R = Bn) led to no reaction in the absence of acid catalysts. However, the cyclization proceeded smoothly with high conversions in the presence of various acid catalysts such as $Sc(OTf)_3$, $InCl_3$, $In(OTf)_3$, CSA, TsOH, and TfOH. In all these cases except for TfOH, 5-*exo* product **5a** was formed predominantly. For example, **5a** was obtained as the only product in 88% yield with 10 mol % of CSA at 25 °C for 24 h (Table 1, entry 1). In the case of TfOH, it was observed that 6-*endo* product **6a** was formed in significant amounts and became the major product with prolonged reaction time. As shown in Table 1 (entry 2), **6a** was obtained in 95% yield (**6a**:**5a** = 94:6) with 10 mol % of TfOH at 25 °C for 24 h. The switch between the 5-*exo* and 6-*endo* selectivity was also observed for a wide variety of alkenols, with CSA or TsOH favoring the 5-*exo* product and TfOH favoring the 6-*endo* products. Generally speaking, *cis*-olefins (Table 1, entries 1, 3, 5, 7, 9, and 11) gave higher *5-exo* selectivity than *trans*-olefins (Table 1, entries 13, 15, 17, 19, and 21). The disfavoring of *6-endo* product for *cis*-olefins as compared to *trans*-olefins could be due to the steric effect during the cyclization. However, high 6-*endo* selectivity was observed for both *cis*- and *trans*-olefins (Table 1, entries 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22). Importantly, in all these cases, both 5-*exo* and 6-*endo* products were formed stereoselectively. The assigned stereochemistry was supported by the X-ray structures of compounds **5e** and **6e** (Figures 1 and 2) as well as analogues of **5a**, **6a**, and **6h** (see the Supporting Information).[8]

Further studies showed that when isolated 5-*exo* products were treated with 10 mol % of TfOH at 25 °C, 6- *endo*

Table 1. Acid-Catalyzed Sulfetherification of Alkenols[a]

entry	substrate **3**	acid	ratio **5** : **6**[c]	yield %[d]
				
1	**3a**, R = *n*-C_5H_{11}	CSA	>99 : 1	88
2		TfOH	6 : 94	95
3	**3b**, R = Me	CSA	>99 : 1	99
4		TfOH	14 : 86	93
				
5	**3c**, X = H	TsOH	>99 : 1	70
6		TfOH[b]	5 : 95	95
7	**3d**, X = *o*-Me	TsOH	>99 : 1	88
8		TfOH[b]	8 : 92	86
9	**3e**, X = *p*-Br	TsOH	>99 : 1	99
10		TfOH[b]	4 : 96	89
11	**3f**, X = *p*-F	TsOH	>99 : 1	99
12		TfOH[b]	4 : 96	99
				
13	**3g**, R = Me	CSA	82 : 18	82
14		TfOH	4 : 96	86
15	**3h**, R = *n*-C_5H_{11}	CSA	85 : 15	70
16		TfOH	4 : 96	96
				
17	**3i**, X = H	TsOH	71 : 29	75
18		TfOH[b]	5 : 95	89
19	**3j**, X = *o*-Me	TsOH	91 : 9	75
20		TfOH[b]	7 : 93	90
21	**3k**, X = *p*-Br	TsOH	60 : 40	88
22		TfOH[b]	4 : 96	93

[a] Reactions were carried out with substrate **3** (1.0 equiv), **4a** (1.2 equiv), and acid (0.1 equiv) in CH_2Cl_2 at 25 °C for 24 h unless otherwise noted. [b] Reactions were carried out with substrate **3** (1.0 equiv), **4a** (1.2 equiv), and TfOH (0.1 equiv) in $ClCH_2CH_2Cl$ at 80 °C for 24 h. [c] The ratio was determined by ^1H NMR spectroscopic analysis of the crude product. [d] Isolated yield of **5** and **6**.

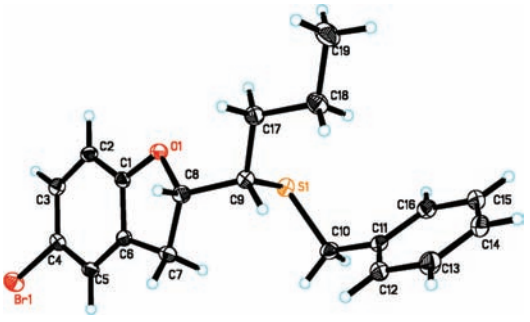


Figure 1. X-ray structure of compound **5e**.

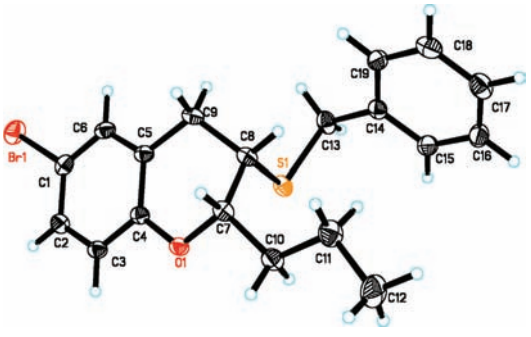
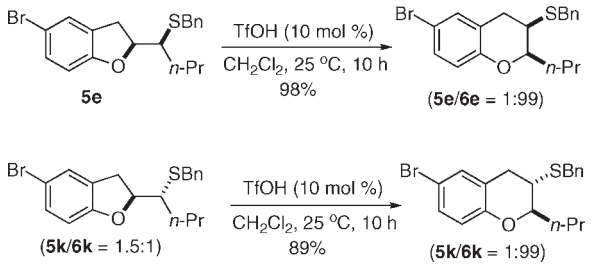


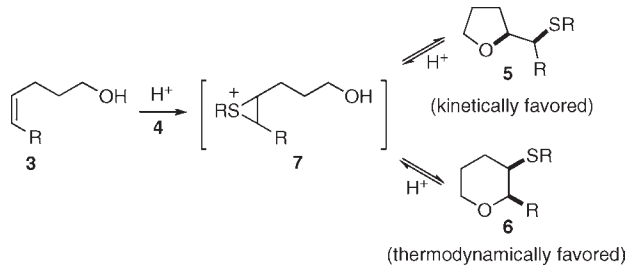
Figure 2. X-ray structure of compound **6e**.

Scheme 3



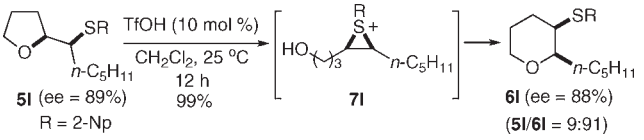
products were formed cleanly in high yields (Scheme 3).[9] These results indicate that the kinetically favored 5-*exo* product can be stereoselectively converted to the thermodynamically favored 6-*endo* product in the presence of acid catalysts such as TfOH, likely via a thiiranium intermediate (Scheme 4).[9]

Scheme 4



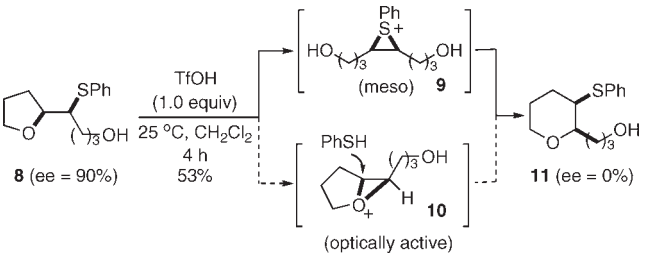
Significantly, the ee was maintained during the rearrangement when optically active **5l** was subjected to the reaction conditions (Scheme 5), suggesting that thiiranium

Scheme 5



intermediate **7l** is configurationally stable.[10,11] To further probe the reaction mechanism, enantiomerically enriched compound **8** was prepared and subjected to the reaction conditions (Scheme 6). Only racemic product **11** was obtained (Figure 3), likely via *meso* thiiranium intermediate **9**, which further supports the reaction mechanism described in Scheme 4.

Scheme 6



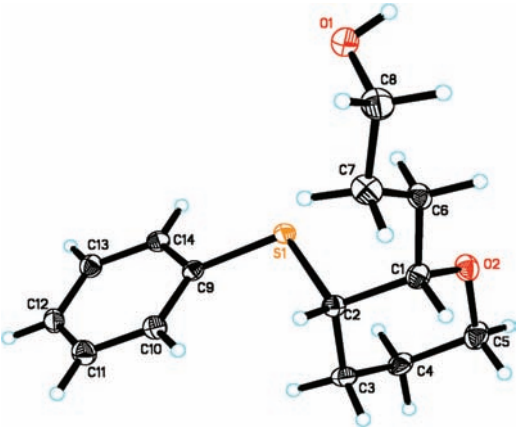


Figure 3. X-ray structure of compound **11**.

In summary, we have developed an efficient acid-catalyzed regioselective and stereoselective sulfetherification of alkenols, forming either 5-*exo* or 6-*endo* products by the choice of acid catalyst. Studies show that kinetically favored 5-*exo* products undergo a stereoselective rearrangement to thermodynamically favored 6-*endo* products via a thiiranium intermediate in the presence of strong acid such as TfOH. The current procedures provide an efficient method to prepare synthetically useful tetrahydrofurans and -pyrans in high yield. Studies also show that an optically active tetrahydrofuran can be converted into the corresponding tetrahydropyran without loss of ee. The observed configurational stability of the chiral thiiranium intermediate under the current reaction conditions

(8) For *cis*-5-octen-1-ol, only 6-*exo* product was detected with both TsOH and TfOH.

(9) For leading references on tetrahydofuran rearrangement to tetrahydropyran via thiiranium and seleniranium, see: (a) Gruttadauria, M.; Lo Meo, P.; Noto, R. *Tetrahedron* **2001**, *57*, 1819. (b) Gruttadauria, M.; Noto, R. *J. Heterocycl. Chem.* **2001**, *38*, 765. (c) Fox, D. J.; House, D.; Warren, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2462. (d) Gruttadauria, M.; Aprile, C.; Noto, R. *Tetrahedron Lett.* **2002**, *43*, 1669. (e) Aprile, C.; Gruttadauria, M.; Amato, M. E.; D'Anna, F.; Lo Meo, P.; Riela, S.; Noto, R. *Tetrahedron* **2003**, *59*, 2241.

(10) For leading references on enantiomerically enriched thiiranium ions, see: (a) Blanchette, H. S.; Branchaud, B. P. *Tetrahedron Lett.* **2002**, *43*, 351. (b) Denmark, S. E.; Vogler, T. *Chem.—Eur. J.* **2009**, *15*, 11737.

(11) For a leading reference on studies of stability of thiiranium ions, see: Denmark, S. E.; Collins, W. R.; Cullen, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 3490.

provides a prospect for a possible asymmetric process with a chiral acid catalyst.[12−14] Such studies are under investigation.

(12) For a leading reference on chiral sulfur reagent-mediated reactions, see: Bürgler, F. W.; Fragale, G.; Wirth, T. *ARKIVOC* **2007**, 21.

(13) For leading reviews on chiral selenium reagent-mediated reactions, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3740. (b) Freudendahl, D. M.; Shahzad, S. A.; Wirth, T. *Eur. J. Org. Chem.* **2009**, 1649.

(14) For a reference on chiral Lewis base catalyzed selenoetherification, see ref 7b.

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Supporting Information Available. Experimental procedures, characterization data, HPLC data, and X-ray structures along with NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.