

# Highly efficient and regioselective cyclization catalyzed by titanium silicate-1

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## Highly regioselective cyclization of 3,4, 4,5 and 5,6 unsaturated alcohols to tetrahydrofuranols and tetrahydropyranols is reported using the TS-1–H<sub>2</sub>O<sub>2</sub> system for the first time.

Since the discovery of the titanium silicate molecular sieve, TS-1,<sup>1</sup> and its use in liquid phase heterogeneous oxidation catalysis<sup>2</sup> in the presence of dilute hydrogen peroxide, it has been the subject of tremendous research activity to establish its applicability to various organic transformations.<sup>3–7</sup>

Substituted tetrahydrofuran and tetrahydropyran rings are common in many natural products, and thus play an important role as building blocks for the synthesis of various biologically active organic target molecules.<sup>8</sup> Hence, new methods for the synthesis of these oxacyclic compounds have long been sought. A strategy involving electrophilic activation of the double bond<sup>9,10</sup> in pent-4-en-1-ol or hex-5-en-1-ol followed by intramolecular nucleophilic attack of the oxygen atom of the hydroxy group offers a convenient route for the stereoselective synthesis of these compounds. Ring closure of substituted pent-4-en-1-yloxy and hex-5-en-1-yloxy radicals<sup>11,12</sup> is also of notable synthetic utility. Here, we report a highly efficient regioselective cyclization of such olefinic alcohols over TS-1, under mild reaction conditions using dilute hydrogen peroxide as oxidant. A similar oxidative cyclization (bifunctional behavior, epoxidation followed by acid catalyzed cyclization) was observed in the oxidation of linalool<sup>13</sup> over Al-Ti-Beta and Al-Ti-MCM-41, where the acidity at the Al sites was responsible for the cyclization.

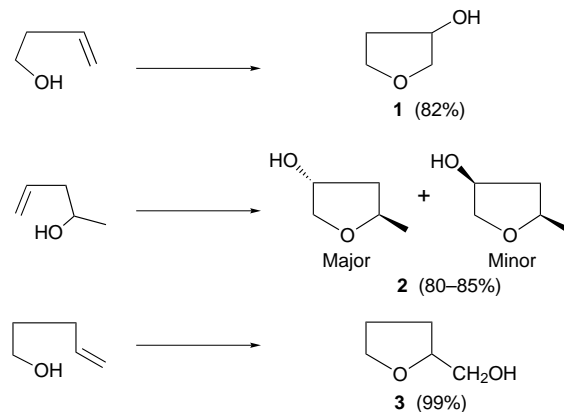
TS-1 used in the present study was synthesized by the standard literature procedure<sup>1</sup> and thoroughly characterized *via* X-ray diffraction and FT-IR and UV-VIS spectroscopy. The liquid phase reaction was carried out in a two-necked glass reactor fitted with a water condenser under an N<sub>2</sub> atmosphere at the required temperature (298 and 333 K) with vigorous stirring. In a typical reaction the following constituents were employed: substrate (0.02 mol), aq. H<sub>2</sub>O<sub>2</sub> (0.02 mol, 30 wt%), catalyst (TS-1, Si/Ti = 27, 20 wt% with respect to the substrate), acetone (10 g), butan-2-ol or H<sub>2</sub>O (in a three phase system). At various reaction times products were analyzed *via* capillary gas chromatography (Shimadzu 14 A, OV-1 and Chiraldex G-TA with Flame Ionization Detector). Products were identified *via* GC retention times and GC-MS using authentic reference samples. When authentic samples were unavailable identification was performed *via* <sup>1</sup>H NMR spectroscopy.

Cyclization of the simplest molecule in this series, but-3-en-1-ol, occurs at room temperature using the TS-1–H<sub>2</sub>O<sub>2</sub> system. In butan-2-ol the reaction rate is slow and it takes 18 h to reach a yield of 82%, 3-hydroxytetrahydrofuran **1** being the sole product (Scheme 1). However, in the presence of water as the dispersion medium (solid catalyst, aq. H<sub>2</sub>O<sub>2</sub> and organic substrate initially forms three distinct phases) reaction proceeds at a faster rate (93.6% conversion after 6 h). Selectivity towards **1** decreases to 75.5%. In this case oxirane ring opening *via* attack of external H<sub>2</sub>O molecules from the medium competes with intramolecular cyclization, leading to dihydroxylation (butane-1,2,4-triol, selectivity 24.5%). Interestingly, increasing the reaction temperature to 333 K in the latter case decreases the yield of **1** to 2.5% with selective dihydroxylation.<sup>14</sup> Unlike the benzenesulfonyl chloride system,<sup>10</sup> the cyclization of but-3-en-

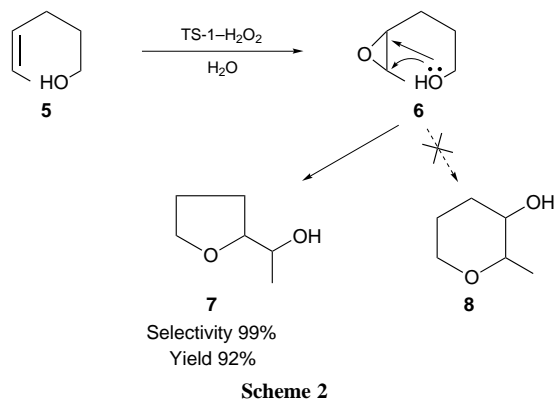
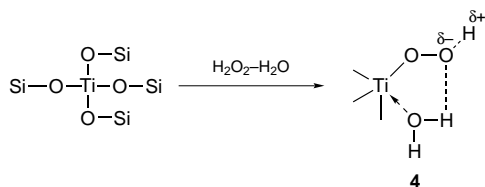
1-ol is relatively efficient in the present TS-1–H<sub>2</sub>O<sub>2</sub> system. Another important aspect of the TS-1 catalyzed cyclization is that, unlike the radical addition reaction, the products are hydroxy-substituted oxacyclic compounds.

The tetrahydrofuran derivative 2-methyl-4-hydroxytetrahydrofuran **2** (*trans* : *cis* ratio 70 : 30) was formed from (±)-pent-4-en-2-ol in acetone (80% yield at room temperature after 18 h). In water at room temperature, the selectivity for **2** drops to 70%, with a *trans* : *cis* ratio of 67 : 33 after 12 h. At higher temperature in a water dispersion medium the dihydroxylation product predominates in a manner similar to that for but-3-en-1-ol. Interestingly, here also the intermediate epoxide is highly reactive and undergoes very rapid oxirane ring opening *via* either intramolecular cyclization or hydrolysis. However, using butan-2-ol as solvent **2** forms as the sole product in 84% yield (*trans* : *cis* ratio 72 : 28). The high *trans* selectivity among the diastereomers of **2** may be due to the higher stability of the transition state at the active site.

The cyclization of pent-4-en-1-ol occurred regioselectively to the 5-*exo* product tetrahydrofuran-2-methanol **3**. Attack of the hydroxy nucleophile definitely does not take place at the other carbon atom of the intermediate oxirane ring. Irrespective of the reaction medium (butan-2-ol, acetone or water), **3** was exclusively obtained in 98–99% yield. This is interesting, since 2,4,6,6-tetrabromocyclohexa-2,4-dienone-induced<sup>9</sup> cyclization leads to a mixture of tetrahydropyran to tetrahydrofuran in the ratio 3 : 1. In water at high temperature (333 K) no dihydroxylation product is formed. Although theoretical calculations on the transition state energies for the pent-4-en-1-yloxy radical<sup>11</sup> indicates that the 5-*exo* product is strongly favored, and in the TS-1–H<sub>2</sub>O<sub>2</sub> system oxidation is believed to occur *via* titanium hydroperoxo species **4**<sup>15</sup> (Scheme 2) and is thus essentially ionic in nature. Restricted geometry inside the TS-1 channel (MFI topology with intersecting 10-membered rings of 5.3 × 5.6 and 5.1 × 5.5 Å pore diameters and 0.10 cm<sup>3</sup> g<sup>-1</sup> internal void volume helps in bending the chain) might play a crucial role in the regioselectivity of the cyclization. The decreasing trend for the ratio of tetrahydropyran to tetrahydrofuran from mesoporous MCM-41 to large pore Beta<sup>13</sup> followed by exclusive formation of tetrahydrofuran rings over medium pore TS-1 supports the above proposition.

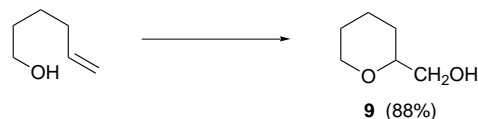


Scheme 1



One might suggest that the 5-*exo* product formation from **3** could be accounted for by the acidic nature of TS-1; if the reaction follows an  $S_N1$  pathway, the hydroxy group would attack preferentially at the more substituted carbon atom due to the higher stability of the corresponding carbocation. On the contrary, alkyl group substitution at C<sub>5</sub> does not cause any change in the regioselectivity of cyclization as observed for *cis*-hex-4-en-1-ol **5** (Scheme 2). Between the two possibilities for the ring-opening of the intermediate oxirane **6**, the 5-*exo* product, 1-(tetrahydro-2-furyl)ethanol **7**, forms exclusively in 92% yield in acetone at 333 K. The 6-*endo* product, 2-methyl-3-hydroxytetrahydropyran **8**, is not formed. The titanium hydroperoxo species **4** protonates the oxirane **6** and thus activates<sup>13</sup> it for the nucleophilic attack of the hydroxy groups at C<sub>1</sub>.

For the cyclization of hex-5-en-1-ol, where two products are possible, tetrahydropyran-2-methanol **9** only is formed in 90% yield in acetone at 333 K (Scheme 3). Interestingly, no intermediate epoxide was detected while studying the kinetics of various constituents of the reaction mixture by GC, indicating that TS-1 catalyzed the present cyclization process at a very fast rate and that ring closure takes place inside the cages of the zeolite immediately after the epoxidation.



**Scheme 3**

In conclusion, we can say that, in the presence of aq. H<sub>2</sub>O<sub>2</sub>, TS-1 generates titanium hydroperoxo species **4**, which not only efficiently epoxidizes the double bond of the olefinic alcohols, but catalyzes epoxy ring-opening *via* intramolecular attack of the hydroxy nucleophile leading to oxacyclic ring formation. This reaction not only has enormous potential for the regioselective synthesis of substituted tetrahydrofuran and tetrahydropyran derivatives, but also opens up a new area involving the use of titanium silicates in cyclization reactions.

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## Note and References

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