Lewis Acid Catalyzed Stereoselective Synthesis of Trisubstituted Tetrahydrofurans

**Significance:** Reported is a Lewis acid (BF\(_3\cdot\)OEt\(_2\)) catalyzed synthesis of 2,3,5-trisubstituted tetrahydrofurans 2a by the reaction of bis(silyloxy)diene 1 with aldehydes in good yields and with excellent stereoselectivity. The reaction involves a domino process in which three new \(\sigma\)-bonds and three stereogenic centers are produced. Tetrahydrofurans 2b with different 2- and 5-substituents were obtained by using two different aldehydes through a sequential reaction (1 \(\rightarrow\) 2b). Both aryl- and alkyl-substituted tetrahydrofurans were easily obtained, but there was a decrease in stereoselectivity when \(\alpha\)-branched aldehydes were used. Thiophenyl-substituted heterocycles showed a high tendency to isomerize; consequently, slightly lower \(\text{dr}\) values were observed. Single X-ray crystal analysis confirmed the 2,3,5-all-cis configuration of the compound 2c (\(R^1 = \text{Ph}; R^2 = 4-\text{BrC}_6\text{H}_4\)). Tetrahydrofuran 2d (\(R^1 = R^2 = \text{Ph}\)) underwent rapid epimerization on reaction with triethylamine to give the thermodynamically more favorable 2,3-trans,2,5-cis diastereomer (yield 82\%, \(\text{dr} = 87:13\)).

**Comment:** The tetrahydrofuran heterocycle is a key scaffold in various natural products and medicinally active molecules (see Review below), and various methods are known for their synthesis (see, for example: B. List and co-workers *J. Am. Chem. Soc.* 2016, 138, 14538). However, these methods are limited to the use of the same aldehyde (2.0 equiv) resulting in equal 2- and 5-substitution of the tetrahydrofurans, and they provide racemic products. The reported method employs a diastereoselective one-pot synthesis of 2a and 2b from readily available substrates. A probable mechanism is proposed involving a vinylogous aldol reaction followed by a Prins-type cyclization (M. Boomhoff, C. Schneider *Chem. Eur. J.* 2012, 18, 4185). Two of the tetrahydrofuran products 2 were converted into bi- and tricyclic compounds by carbonyl–ene reactions (71–95\% yield; \(\text{dr} = 80:20\) to 95:5) (A. C. Jackson, B. E. Goldman, B. B. Snider *J. Org. Chem.* 1984, 49, 3988).