Lewis Acid Catalyzed Stereoselective Synthesis of Trisubstituted Tetrahydrofurans

**Significance:** Reported is a Lewis acid (BF₃·OEt₂) 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 σ-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 → 2b). Both aryl- and alkyl-substituted tetrahydrofurans were easily obtained, but there was a decrease in stereoselectivity when α-branched aldehydes were used. Thiethyl-substituted heterocycles showed a high tendency to isomerize; consequently, slightly lower dr values were observed. Single X-ray crystal analysis confirmed the 2,3,5-all-cis configuration of the compound 2c (R¹ = Ph; R² = 4-BrC₆H₄). Tetrahydrofuran 2d (R¹ = R² = Ph) underwent rapid epimerization on reaction with triethylamine to give the thermodynamically more favorable 2,3-trans,2,5-cis diastereomer (yield 82%, 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; dr = 80:20 to 95:5) (A. C. Jackson, B. E. Goldman, B. B. Snider J. Org. Chem. 1984, 49, 3988).