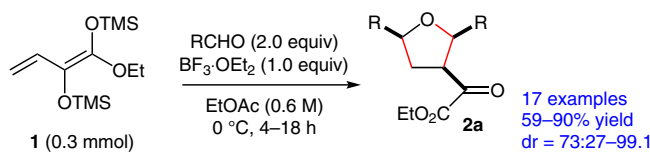
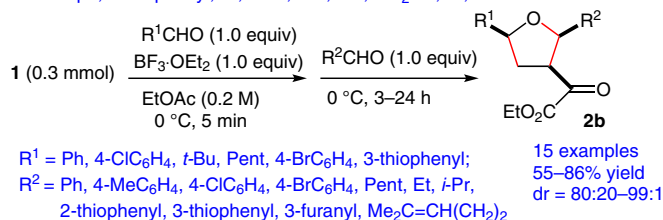


# Lewis Acid Catalyzed Stereoselective Synthesis of Trisubstituted Tetrahydrofurans



R = Ph, 2-MeC<sub>6</sub>H<sub>4</sub>, 3-MeC<sub>6</sub>H<sub>4</sub>, 4-MeC<sub>6</sub>H<sub>4</sub>, 2-ClC<sub>6</sub>H<sub>4</sub>, 3-ClC<sub>6</sub>H<sub>4</sub>,  
4-ClC<sub>6</sub>H<sub>4</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 4-PhC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 2-Naph,  
1-Naph, 3-thiophenyl, Et, Pent, *i*-Pr, CN, CO<sub>2</sub>Me, Cl, Br



**Significance:** Reported is a Lewis acid (BF<sub>3</sub>·OEt<sub>2</sub>) 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. Thienyl-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** (R<sup>1</sup> = Ph; R<sup>2</sup> = 4-BrC<sub>6</sub>H<sub>4</sub>). Tetrahydrofuran **2d** (R<sup>1</sup> = R<sup>2</sup> = 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).

**Review:** A. de La Torre, C. Cuyamendous, V. Bultel-Poncé, T. Durand, J.-M. Galano, C. Oger *Tetrahedron* **2016**, *72*, 5003–5025.