

# Unique Synthetic Utility of $\text{BF}_3 \cdot \text{OEt}_2$ in the Highly Diastereoselective Reduction of Hydroxy Carbonyl and Dicarbonyl Substrates

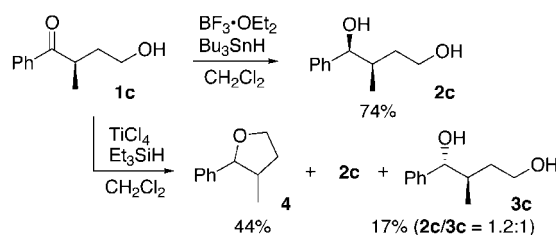
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## ABSTRACT



A new aspect of commonly used  $\text{BF}_3 \cdot \text{OEt}_2$  has been illuminated by successfully demonstrating the unique but highly stereoselective reactions of hydroxy carbonyl and dicarbonyl substrates. For example, treatment of  $\gamma$ -hydroxy ketone **1c** with  $\text{BF}_3 \cdot \text{OEt}_2/\text{Bu}_3\text{SnH}$  in  $\text{CH}_2\text{Cl}_2$  at  $-78$  to  $-40$  °C afforded the corresponding 1,4-diol **2c** with virtually complete diastereoselection, while use of  $\text{TiCl}_4$  as a Lewis acid under similar reaction conditions caused a total lack of diol yield and selectivity (17%;  $2c/3c = 1.2:1$ ), accompanied by a significant formation of 2,3-disubstituted tetrahydrofuran **4** (44%).

Undoubtedly, stereochemical control in acyclic and cyclic systems (1,*n* asymmetric induction) has been of great and continuous interest for synthetic organic chemists.<sup>1</sup> Lewis acid catalyzed regio- and/or stereoselective addition of organosilicon and organotin compounds to carbonyl substrates has certainly played an essential role, and a number of simple but highly sophisticated methodologies have been developed particularly for the stereocontrolled syntheses of  $\beta$ -hydroxycarbonyl compounds and 1,3-polyols.<sup>2</sup> Boron trifluoride etherate ( $\text{BF}_3 \cdot \text{OEt}_2$ ), which is apparently one of the most familiar and thoroughly investigated Lewis acids,<sup>3–7</sup> has been utilized as a reliable carbonyl activator in this field

as exemplified by *erythro*-selective addition of allyltrialkylstannane to aldehydes.<sup>8</sup> However, the full synthetic potential of  $\text{BF}_3 \cdot \text{OEt}_2$  in organic synthesis has yet to be realized especially in terms of functional group compatibility and

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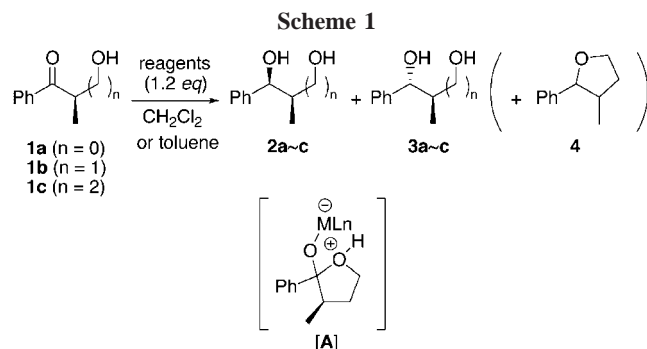
(2) Reviews: (a) Denmark, S. E.; Willson, T. M. In *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic Publishers: 1989; p 247. (b) Fleming, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 563. (c) Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 629. (d) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, 1995.

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stereoselectivity. Here we wish to report the unique synthetic utility of  $\text{BF}_3 \cdot \text{OEt}_2$  in stereoselective reactions of hydroxy carbonyl and dicarbonyl substrates, clearly demonstrating its advantage over ordinary transition-metal Lewis acids.<sup>9</sup>

With information on the commercial availability of several  $\text{BF}_3 \cdot \text{ROH}$ 's in hand, we first examined the stereoselectivity in the reduction of a series of hydroxy ketones with  $\text{BF}_3 \cdot \text{OEt}_2$  (Scheme 1), since direct use of free hydroxy groups



without a protection–deprotection sequence is quite convenient for functional transformation. Selected data are summarized in Table 1. Thus, initial treatment of  $\alpha$ -hydroxy-

**Table 1.** Diastereoselective Reduction of Hydroxy Ketones **1a–c**<sup>a</sup>

entry	ketone	reagents	condition	<i>syn/anti</i> ratio <sup>b,c</sup> (% yield) <sup>d</sup>
1	<b>1a</b>	$\text{BF}_3 \cdot \text{OEt}_2 / \text{Bu}_3\text{SnH}$	–78, 2	13:1 (80)
2		$\text{TiCl}_4 / \text{Bu}_3\text{SnH}$	–78, 1	– (trace) <sup>e</sup>
3		$\text{TiCl}_4 / \text{Et}_3\text{SiH}$	–78, 1, 25, 8	1:1.6 (75)
4		$\text{TiCl}_4 / \text{PhMe}_2\text{SiH}$	–78, 0.5, –40, 12	1:1.3 (75)
5		$\text{TiF}_4 / \text{Bu}_3\text{SnH}$	–78, 0.1; 25, 20 <sup>f</sup>	1:1.8 (87)
6		$\text{SnCl}_4 / \text{Et}_3\text{SiH}$	–78, 0.1; 25, 20	– (trace)
7	<b>1b</b>	$\text{BF}_3 \cdot \text{OEt}_2 / \text{Bu}_3\text{SnH}$	–78, 0.5	>20: <1 (98)
8		$\text{TiCl}_4 / \text{Et}_3\text{SiH}$	–78, 1, –20, 2	19:1 (84)
9		$\text{TiF}_4 / \text{Bu}_3\text{SnH}$	–78, 0.1; 25, 4 <sup>f</sup>	>20: <1 (87)
10		$\text{SnCl}_4 / \text{Et}_3\text{SiH}$	–78, 6	14:1 (<8)
11	<b>1c</b>	$\text{BF}_3 \cdot \text{OEt}_2 / \text{Bu}_3\text{SnH}$	–78, 12; –40, 1	>20: <1 (74)
12		$\text{TiCl}_4 / \text{Et}_3\text{SiH}$	–78, 9; –40, 0.5	1.2:1 (17) [44] <sup>g</sup>
13		$\text{TiF}_4 / \text{Bu}_3\text{SnH}$	–78, 0.1; 25, 12 <sup>f</sup>	– (trace) [49] <sup>g</sup>
14		$\text{SnCl}_4 / \text{Et}_3\text{SiH}$	–78, 6; –40, 2	– (trace) [86] <sup>g</sup>

<sup>a</sup> The reaction was carried out in toluene or  $\text{CH}_2\text{Cl}_2$  with 1.2 equiv of each reagent under the indicated conditions. <sup>b</sup> *syn/anti* ratio was determined by 300 MHz  $^1\text{H}$  NMR analysis. <sup>c</sup> The relative configuration of the major isomer was determined as follows: Correlation to the authentic sample independently synthesized from *trans*- $\beta$ -methylstyrene according to the Sharpless protocol (Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515) (entries 1–6). Evaluation of *J* values in the  $^1\text{H}$  NMR analysis of the corresponding acetonide derived with catalytic PPTS and dimethoxypropane in  $\text{CH}_2\text{Cl}_2$  (entries 7–10). Comparison with the known (1*R*,2*S*)-2-methyl-1-phenyl-1,4-butanediol (Matsumoto, K.; Aoki, Y.; Oshima, K.; Utimoto, K.; Rahman, N. A. *Tetrahedron* **1993**, *49*, 8487) (entries 11–14). <sup>d</sup> Isolated yield. <sup>e</sup>  $\text{Bu}_3\text{SnH}$  was consumed instantaneously to give probably  $\text{Bu}_3\text{SnCl}$  and the reduction did not proceed further even after warming to room temperature. <sup>f</sup> Higher reaction temperature was necessary because of the insolubility of  $\text{TiF}_4$  in both  $\text{CH}_2\text{Cl}_2$  and toluene. <sup>g</sup> Yield of 2,3-disubstituted furan **4** as a side product is given in brackets.

propiophenone **1a** with  $\text{BF}_3 \cdot \text{OEt}_2$  (1.2 equiv) in toluene at –78 °C and subsequent addition of  $\text{Bu}_3\text{SnH}$  (1.2 equiv) resulted in clean formation of the corresponding diols **2a** and **3a** in 80% yield with high *syn* selectivity (*syn/anti* = 13:1; entry 1), while the selectivity was dramatically lowered when  $\text{TiX}_4$  (*X* = Cl, F) was used as the chelating Lewis acid, regardless of the reaction temperature (entries 2–5).<sup>10</sup> Using  $\text{SnCl}_4$ , the reduction did not proceed and most of the starting  $\alpha$ -hydroxy ketone was recovered (entry 6). In the case of  $\beta$ -hydroxy ketone **1b**, high levels of diastereoselectivities were uniformly observed with  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{TiX}_4$  (*X* = Cl, F), and  $\text{SnCl}_4$  (entries 7–10). Moreover, even  $\gamma$ -hydroxy ketone **1c** on reaction with  $\text{BF}_3 \cdot \text{OEt}_2 / \text{Bu}_3\text{SnH}$  gave rise to the corresponding 1,4-diol **2c** with virtually complete diastereoselection (entry 11). In sharp contrast, however, use of  $\text{TiCl}_4$  as a Lewis acid under similar reaction conditions caused a total lack of selectivity, and 2,3-disubstituted tetrahydrofuran **4** was obtained as a major product via facile hemiacetal formation [A] and subsequent reduction under the reaction conditions (entry 12). Such hemiacetal formation took precedence over the desired reduction with  $\text{TiF}_4$  and  $\text{SnCl}_4$  (entries 13 and 14).<sup>11</sup>

The distinct advantage of  $\text{BF}_3 \cdot \text{OEt}_2$  over ordinary transition-metal Lewis acids is further illustrated by the stereoselective reactions of substituted  $\gamma$ -keto aldehydes **5a,b** and **8** as shown in Table 2. Here again,  $\text{BF}_3 \cdot \text{OEt}_2$  works well

**Table 2.** Diastereoselective Reduction of Substituted  $\gamma$ -Keto Aldehydes **5a,b** and **8**<sup>a</sup>

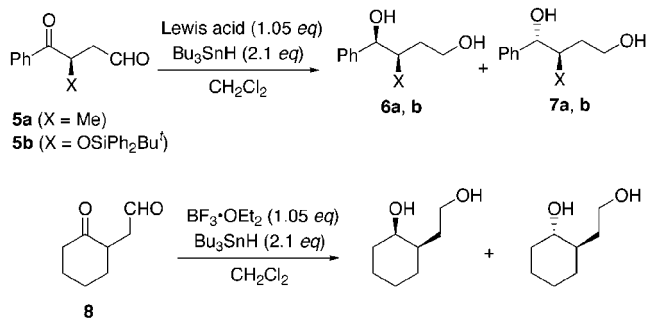
entry	ketone aldehyde	reagents	condition	<i>syn/anti</i> ratio <sup>b</sup> (% yield) <sup>c</sup>
1	<b>5a</b>	$\text{BF}_3 \cdot \text{OEt}_2 / \text{Bu}_3\text{SnH}$	–78, 6; –40, 4.5	12:1 (99)
2			–78, 4; –40, 2.5	>20: <1 (52) <sup>d</sup>
3		$\text{TiCl}_4 / \text{Et}_3\text{SiH}$	–78, 6, 0, 4.5	3.6:1 (23) <sup>e</sup>
4	<b>5b</b>	$\text{BF}_3 \cdot \text{OEt}_2 / \text{Bu}_3\text{SnH}$	–78, 4; –40, 6	10:1 (40) <sup>d,f</sup>
5	<b>8</b>	$\text{BF}_3 \cdot \text{OEt}_2 / \text{Bu}_3\text{SnH}$	–78, 3; –40, 0.5	10:1 (94) <sup>g</sup>

<sup>a</sup> Unless otherwise specified, the reaction was carried out in  $\text{CH}_2\text{Cl}_2$  with 1.05 equiv of Lewis acid and 2.1 equiv of  $\text{Bu}_3\text{SnH}$  under the indicated conditions. <sup>b</sup> *syn/anti* ratio was determined by 300 MHz  $^1\text{H}$  NMR analysis. <sup>c</sup> Isolated yield. <sup>d</sup> Use of toluene as solvent. <sup>e</sup> Starting  $\gamma$ -keto aldehyde was recovered with concomitant formation of the partially reduced hydroxy ketone. <sup>f</sup> The *syn* configuration was confirmed by correlation to the authentic sample prepared from 4-phenyl-3-buten-1-ol by  $\text{OsO}_4$ -catalyzed dihydroxylation (Xu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495). <sup>g</sup> The stereochemical assignment was made by comparison of the signals of hydroxy bearing carbons in the  $^{13}\text{C}$  NMR spectrum (Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: Weinheim, 1987).

not only to obtain the desired alcohols with high stereoselectivity but also to suppress the otherwise favorable hemiacetalization leading to cyclic ethers such as **4**.

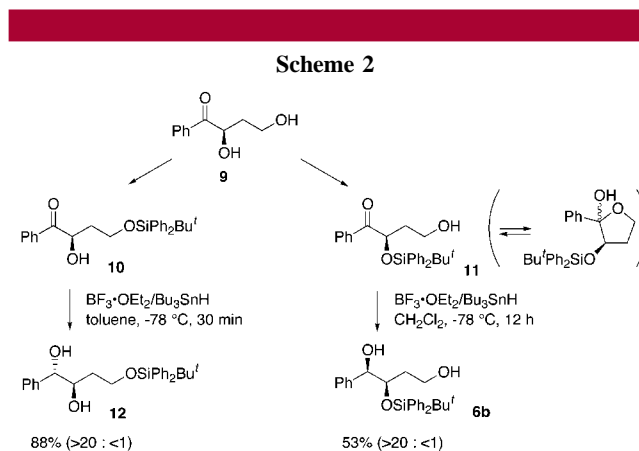
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Since hydroxy ketones **10** and **11**<sup>12</sup> can be reduced to **12** and **6b**, respectively, by the BF<sub>3</sub>·OEt<sub>2</sub>/Bu<sub>3</sub>SnH system with high diastereoselectivity, either *syn*- or *anti*-stereoisomeric triols of type **6b** or **7b** can be synthesized from the single starting material, dihydroxy ketone **9**, by appropriately protecting the hydroxy functionalities (Scheme 2). This picture demonstrates that the present BF<sub>3</sub>·OEt<sub>2</sub>-mediated method certainly offers a new stereoselective approach for the construction of polyhydroxy backbones.

In conclusion, we observed characteristic features of BF<sub>3</sub>·OEt<sub>2</sub> in the stereocontrolled reduction of hydroxycar-



bonyl and dicarbonyl substrates, which provides 1,*n*-diols (*n* = 2–4) with almost complete diastereoselection. Aside from the clear synthetic utility of the present system, the origin of selectivity is unclear and is under current investigation.

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**Supporting Information Available:** Representative experimental procedure as well as spectroscopic characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) PhMe<sub>2</sub>SiH exhibited higher reactivity than Et<sub>3</sub>SiH and allowed the reduction to be performed at lower temperature. However, the diastereoselectivity was not improved.

(11) Reduction of hemiacetal of **1c** leading to 2,3-disubstituted tetrahydrofuran of type **4** has been reported, see, for example: Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, 52, 1273.

(12) Hydroxy ketone **11** was found to be in equilibrium with its hemiacetal in solution. Treatment of **11** with Ac<sub>2</sub>O, pyridine and catalytic DMAP in CH<sub>2</sub>Cl<sub>2</sub> afforded the corresponding keto acetate (80% yield) which was completely characterized spectroscopically. See Supporting Information.