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Unique Synthetic Utility of BF_3·OEt_2 in the Highly Diastereoselective Reduction of Hydroxy Carbonyl and Dicarbonyl Substrates

Takashi Ooi, Daisuke Uraguchi, Junko Morikawa, and Keiji Maruoka*

Departments of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan, and Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan

maruoka@kuchem.kyoto-u.ac.jp

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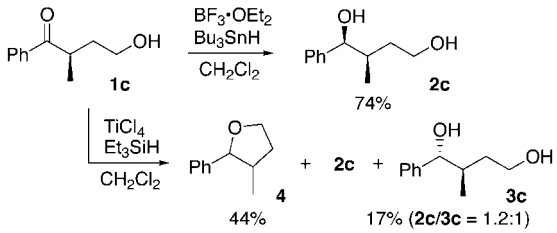
ABSTRACT



A new aspect of commonly used BF_3·OEt_2 has been illuminated by successfully demonstrating the unique but highly stereoselective reactions of hydroxy carbonyl and dicarbonyl substrates. For example, treatment of γ-hydroxy ketone 1c with BF_3·OEt_2/Bu_3SnH in CH_2Cl_2 at −78 to −40 °C afforded the corresponding 1,4-diol 2c with virtually complete diastereoselection, while use of $TiCl_4$ 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.[1] 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 β-hydroxycarbonyl compounds and 1,3-polyols.[2] Boron trifluoride etherate (BF_3·OEt_2), which is apparently one of the most familiar and thoroughly investigated Lewis acids,[3−7] has been utilized as a reliable carbonyl activator in this field as exemplified by *erythro*-selective addition of allyltrialkylstannane to aldehydes.[8] However, the full synthetic potential of BF_3·OEt_2 in organic synthesis has yet to be realized especially in terms of functional group compatibility and

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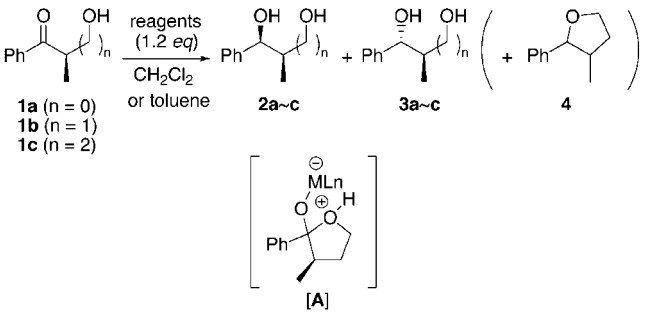
stereoselectivity. Here we wish to report the unique synthetic utility of BF_3·OEt_2 in stereoselective reactions of hydroxy carbonyl and dicarbonyl substrates, clearly demonstrating its advantage over ordinary transition-metal Lewis acids.[9]

With information on the commercial availability of several BF_3·ROH's in hand, we first examined the stereoselectivity in the reduction of a series of hydroxy ketones with BF_3·OEt_2 (Scheme 1), since direct use of free hydroxy groups

Scheme 1



without a protection−deprotection sequence is quite convenient for functional transformation. Selected data are summarized in Table 1. Thus, initial treatment of α-hydroxypropiophenone **1a** with BF_3·OEt_2 (1.2 equiv) in toluene at −78 °C and subsequent addition of Bu_3SnH (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 TiX_4 (X = Cl, F) was used as the chelating Lewis acid, regardless of the reaction temperature (entries 2−5).[10] Using $SnCl_4$, the reduction did not proceed and most of the starting α-hydroxy ketone was recovered (entry 6). In the case of *β*-hydroxy ketone **1b**, high levels of diastereoselectivities were uniformly observed with BF_3·OEt_2, TiX_4 (X = Cl, F), and $SnCl_4$ (entries 7−10). Moreover, even *γ*-hydroxy ketone **1c** on reaction with BF_3·OEt_2/Bu_3SnH gave rise to the corresponding 1,4-diol **2c** with virtually complete diastereoselection (entry 11). In sharp contrast, however, use of $TiCl_4$ 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 TiF_4 and $SnCl_4$ (entries 13 and 14).[11]

The distinct advantage of BF_3·OEt_2 over ordinary transition-metal Lewis acids is further illustrated by the stereoselective reactions of substituted *γ*-keto aldehydes **5a**,**b** and **8** as shown in Table 2. Here again, BF_3·OEt_2 works well 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**.

Table 1. Diastereoselective Reduction of Hydroxy Ketones **1a**−**c**[a]

entry	ketone	reagents	condition	*syn*/*anti* ratio[b,c] (% yield)[d]
1	**1a**	BF_3·OEt_2/Bu_3SnH	−78, 2	13:1 (80)
2		$TiCl_4$/Bu_3SnH	−78, 1	− (trace)[e]
3		$TiCl_4$/Et_3SiH	−78, 1, 25, 8	1:1.6 (75)
4		$TiCl_4$/$PhMe_2SiH$	−78, 0.5, −40, 12	1:1.3 (75)
5		TiF_4/Bu_3SnH	−78, 0.1; 25, 20[f]	1:1.8 (87)
6		$SnCl_4$/Et_3SiH	−78, 0.1; 25, 20	− (trace)
7	**1b**	BF_3·OEt_2/Bu_3SnH	−78, 0.5	>20:<1 (98)
8		$TiCl_4$/Et_3SiH	−78, 1, −20, 2	19:1 (84)
9		TiF_4/Bu_3SnH	−78, 0.1; 25, 4[f]	>20:<1 (87)
10		$SnCl_4$/Et_3SiH	−78, 6	14:1 (<8)
11	**1c**	BF_3·OEt_2/Bu_3SnH	−78, 12; −40, 1	>20:<1 (74)
12		$TiCl_4$/Et_3SiH	−78, 9; −40, 0.5	1.2:1 (17) [44][g]
13		TiF_4/Bu_3SnH	−78, 0.1; 25, 12[f]	− (trace) [49][g]
14		$SnCl_4$/Et_3SiH	−78, 6; −40, 2	− (trace) [86][g]

[a] The reaction was carried out in toluene or CH_2Cl_2 with 1.2 equiv of each reagent under the indicated conditions. [b] *syn*/*anti* ratio was determined by 300 MHz ^{1}H NMR analysis. [c] The relative configuration of the major isomer was determined as follows: Correlation to the authentic sample independently synthesized from *trans*-*β*-methylstylene 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}H NMR analysis of the corresponding acetonide derived with catalytic PPTS and dimethoxypropane in CH_2Cl_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). [d] Isolated yield. [e] Bu_3SnH was consumed instantaneously to give probably Bu_3SnCl and the reduction did not proceed further even after warming to room temperature. [f] Higher reaction temperature was necessary because of the insolubility of TiF_4 in both CH_2Cl_2 and toluene. [g] Yield of 2,3-disubstituted furan **4** as a side product is given in brackets.

Table 2. Diastereoselective Reduction of Substituted *γ*-Keto Aldehydes **5a**,**b** and **8**[a]

entry	keto aldehyde	reagents	condition	*syn*/*anti* ratio[b] (% yield)[c]
1	**5a**	BF_3·OEt_2/Bu_3SnH	−78, 6; −40, 4.5	12:1 (99)
2			−78, 4; −40, 2.5	>20:<1 (52)[d]
3		$TiCl_4$/Et_3SiH	−78, 6, 0, 4.5	3.6:1 (23)[e]
4	**5b**	BF_3·OEt_2/Bu_3SnH	−78, 4; −40, 6	10:1 (40)[d,f]
5	**8**	BF_3·OEt_2/Bu_3SnH	−78, 3; −40, 0.5	10:1 (94)[g]

[a] Unless otherwise specified, the reaction was carried out in CH_2Cl_2 with 1.05 equiv of Lewis acid and 2.1 equiv of Bu_3SnH under the indicated conditions. [b] *syn*/*anti* ratio was determined by 300 MHz ^{1}H NMR analysis. [c] Isolated yield. [d] Use of toluene as solvent. [e] Starting *γ*-keto aldehyde was recovered with concomitant formation of the partially reduced hydroxy ketone. [f] The *syn* configuration was confirmed by correlation to the authentic sample prepared from 4-phenyl-3-buten-1-ol by OsO_4-catalyzed dihydroxylation (Xu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495). [g] The stereochemical assignment was made by comparison of the signals of hydroxy bearing carbons in the ^{13}C NMR spectrum (Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: Weinheim, 1987).

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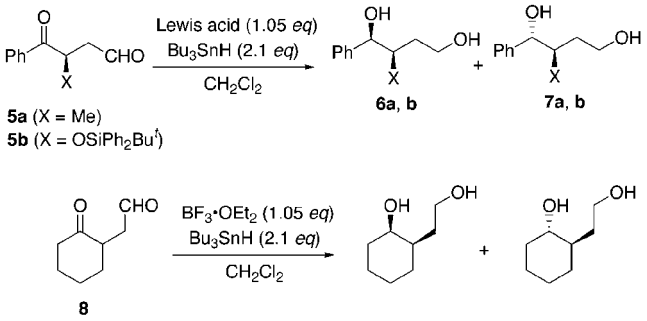
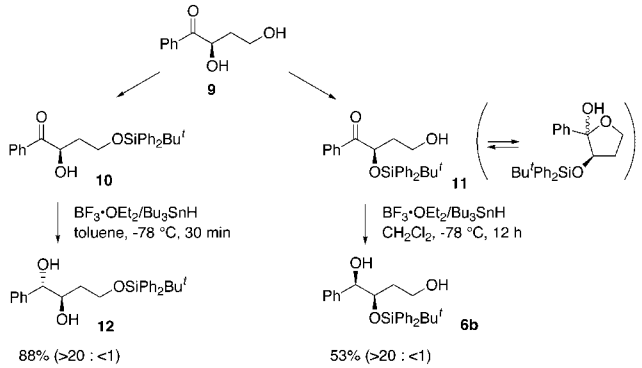


Since hydroxy ketones **10** and **11**[12] can be reduced to **12** and **6b**, respectively, by the $BF_3{\cdot}OEt_2/Bu_3SnH$ system with high diastereoselectivity, either *syn*- or *anti*-stereoisomeric triols of type **6b** or **7b** can be synthesized from the single starting material, dihydroxy ketone **9**, by appropriately protecting the hydroxy functionalities (Scheme 2). This picture demonstrates that the present $BF_3{\cdot}OEt_2$-mediated method certainly offers a new stereoselective approach for the construction of polyhydroxy backbones.

In conclusion, we observed characteristic features of $BF_3{\cdot}OEt_2$ in the stereocontrolled reduction of hydroxycarbonyl 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.

Scheme 2



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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) $PhMe_2SiH$ exhibited higher reactivity than Et_3SiH 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_2O, pyridine and catalytic DMAP in CH_2Cl_2 afforded the corresponding keto acetate (80% yield) which was completely characterized spectroscopically. See Supporting Information.