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Chemo- and Stereoselective Reduction of α,β-Epoxyketones with Diisopropoxytitanium(III) Tetrahydroborate

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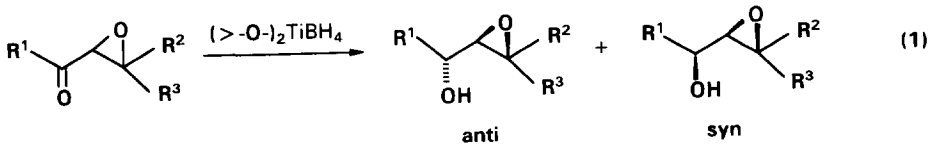
Abstract: Reduction of α,β-epoxyketones with diisopropoxytitanium(III) tetrahydroborate in dichloromethane under mild conditions (-78°→ -20°C) provides *anti*- (or erythro-) α,β-epoxy alcohols in high yields with high degree of chemo- and stereoselectivity.

The chemo- and stereoselective reduction of α,β-epoxyketones is a challenging problem in organic synthesis and the α,β-epoxyalcohols that are formed are versatile intermediates which can be elaborated efficiently into polyhydroxy compounds with multiple chiral centers.[1] A few reports are available for the stereoselective reduction of α,β-epoxyketones.[2] While the reduction of α,β-epoxyketones with $NaBH_4$ leads to the corresponding α,β-epoxyalcohols with modest stereoselectivity,[2a] the reduction with $NaBH_4$ in the

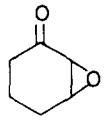
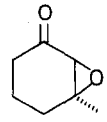
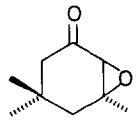
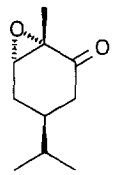
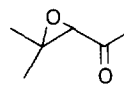
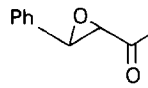
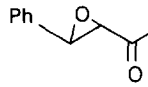
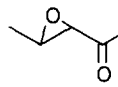


(1)

presence of $CaCl_2$ or $LaCl_3$ in methanol,[2f] $NaBH_4/CeCl_3/MeOH$[2d] and $Zn(BH_4)_2/Et_2O$[2c] have been reported to give high *anti*-stereoselectivity. Shibata reported a highly stereoselective reduction of α,β-epoxyketones with halodibutyltinhydride[2e] and Hosomi showed divergent stereoselectivity using hydridosilicates.[2g]

Recently, we demonstrated that diisopropoxytitanium(III) tetrahydroborate, $(>\text{-O-})_2TiBH_4$, **1** is a useful reagent for the highly chemoselective 1,2-reduction of α,β-unsaturated carbonyl compounds to the

Table 1.

Entry	Substrate	Time (min)	Product[a] (α,ß-epoxyalcohol) syn : anti		Yield[b] (%)
1.	 2	20	10[2e]	18 : 82	86
2.	 3	45	11[2b]	2 : 98	93
3.	 4	45	12[9]	1 : 99	91
4.	 5	90	13[2a]	1 : 99	73[c]
5.	 6	45	14[8c]	3 : 97	92
6.	 7	45	15[2e]	23 : 77	88
7.	 8	90	16[2e,8d]	25 : 75	90
8.	 9	90	17[2e]	31 : 69	93

a. Ratio determined by GC (10 - 14) or ^{1}H NMR (15 - 17). b. Isolated yield. c. Yield based on recovered starting material.

corresponding allylic alcohols.[3] In continuation of our work in this area, we report that the use of titanium(III) tetrahydroborate **1** for the reduction of acyclic and cyclic α,β-epoxy ketones constitutes a highly chemo- and stereoselective method for the synthesis of *anti*-α,β-epoxy alcohols (**eq. 1.**).

The tetrahydroborate, **1** was generated *in situ* from diisopropoxytitanium dichloride[4] and benzyltriethylammonium borohydride[5] in dry CH_2Cl_2 at -20°C and was allowed to react with a number of acyclic and cyclic α,β-epoxy ketones in CH_2Cl_2 (-78°→-20°C; 20-90 min) and the corresponding *anti*-α,β-epoxy alcohols are obtained with high degree of stereoselectivity. The results are summarized in **Table 1.** While the reaction of **1** with unsubstituted cyclic α,β-epoxy ketone **2** gave the *anti*-α,β-epoxy alcohol **10** with 82% stereoselectivity, the substituted epoxy ketones **3**, **4**, and **5** afforded the *anti*-α,β-epoxy alcohols **11**, **12**, and **13** respectively in >98% stereoselectivity. Even the acyclic α,β-epoxy ketone **6** on reaction with **1** provided the *anti*-α,β-epoxy alcohol **14** with excellent selectivity (>97%). However, the phenyl substituted epoxy ketones **7** and **8** gave the *anti*-α,β-epoxy alcohols **15** and **16** respectively in 75-77% stereoselectivity.

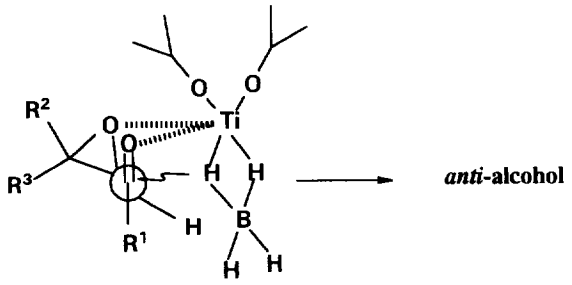


Fig. 1.

Interestingly the methyl substituted epoxy ketone **9** on reaction with **1** gave the epoxy alcohol **17** with only moderate *anti*- selectivity (69%). The *anti*- selective reduction with titanium(III) tetrahydroborate **1** can be explained in terms of Cram's chelation model[6] (**Fig. 1**). Titanium forms a tightly coordinated chelate with the epoxy ketone and subsequent intramolecular hydride transfer from the less hindered side to the carbonyl carbon affords the expected *anti*-isomer.

In summary, it has been demonstrated that diisopropoxytitanium(III) tetrahydroborate **1** is a convenient reagent for the stereoselective reduction of both cyclic and acyclic α,β-epoxy ketones to the corresponding *anti*-α,β-epoxy alcohols in very good yields.

EXPERIMENTAL SECTION

General Remarks. ^{1}H NMR spectra were recorded at 90 MHz and 300 MHz in $CDCl_3$. TLC were performed on 0.25-mm precoated silica plates (60F-254). Gas chromatographic (GLC) analyses of product mixtures and purified samples were performed on SE-30 on chromosorb W-HW 80/100 (3 mm x 2 m) column. All the reduction experiments were carried out under nitrogen. All α,β-epoxy ketones were prepared according to the literature procedures.[7] The diastereomeric mixture of products were purified and isolated by flash chromatography on silica gel (tlc grade). A stock solution of diisopropoxytitanium dichloride in dry CH_2Cl_2 (11.8% w/v) was used.[4] The ratio of diastereomers[2,8] was determined by GLC (**10** - **14**) or ^{1}H NMR (**15** - **17**).

General Procedure for the Preparation of Diisopropoxytitanium(III) Tetrahydroborate, 1.

To a stirred solution of diisopropoxytitanium dichloride (2 mL, 1 mmol) was slowly added benzyltriethylammonium tetrahydroborate (0.414 g, 2 mmol) in dry CH_2Cl_2 (4 mL) under N_2 at -20°C, and the reaction mixture was stirred for 30 min and used as such for reductions.

General Procedure for the Reduction of α,β-Epoxyketones.

The solution of tetrahydroborate **1** obtained as above was cooled to -78°C and the α,β-epoxyketone, **2** (0.224 g, 2 mmol) in dry CH_2Cl_2 (2 mL) was added. The reaction mixture was brought to -20°C over a period of 15 min and stirred for 30 min. A solution of saturated K_2CO_3 (5 mL) was added and stirred for an additional 15 min (25°C). The reaction mixture was extracted with ether (3x20 mL) and it was washed with brine and dried (Na_2SO_4). Removal of solvent followed by flash chromatography on silica gel (tlc grade; ether-petroleum ether, 30:70) afforded the diastereomeric mixture of *syn* and *anti*-α,β-epoxyalcohol **10** as an oil[2e] (0.196 g, 86%). GC analysis of the purified product indicated the presence of *syn*/*anti* alcohols in a ratio of 18:82. IR (neat): ν 3450, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.9 (m, CHOH, ***syn***-), 4.15 (m, CHOH, ***anti***-).

***anti-2,3-Epoxy-3-methylcyclohexanol,* 11.**[2b] Yield: 93%; IR (neat): ν 3420, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.4 (s, 3H), 1.45-2.10 (m, 6H), 2.3 (br, 1H, exchangeable, **OH**), 2.95 (s, 1H), 4.0 (t, J = 6.4 Hz, 1H).

***anti-3,5,5-Trimethyl-2,3-epoxycyclohexanol,* 12.**[9] Yield: 91%; IR (neat): ν 3380, 825 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H), 0.95 (s, 3H), 1.35 (s, 3H), 1.95 (br, 1H, exchangeable **OH**), 2.95 (s, 1H), 4.15 (t, J = 6.4 Hz, 1H).

***anti-1,2-Epoxy-p-menth-6-ol,* 13.**[2a] Yield: 73% (based on the starting material recovered);IR (neat): ν 3380,

835 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.9 (d, J = 5.5 Hz, 6H), 1.4 (s, 3H), 3.1 (s, 1H), 3.5-4.1 (br m, 2H).

***anti-3,4-Epoxy-4-methyl-2-pentanol*, 14.**[8c] Yield: 92%; IR (neat): ν 3350, 835 cm^{-1}; ^1H NMR ($CDCL_3$): δ 1.28 (br s, 6H), 1.35 (d, J = 6.3 Hz, 3H), 2.6 (d, 1H, **OH**), 3.45 (m, 1H).

syn- and anti-3,4-Epoxy-4-phenylbutan-2-ol*, 15.**[2e] Yield: 88%; IR (thin film): ν 3400, 900 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32 (d, J = 6.4 Hz, 3H, CH_3, ***syn-), 1.36 (d, J = 6.6 Hz, 3H, CH_3, ***anti-***), 3.87 (d, J = 2.3 Hz, 1H, PhC**H**, ***anti-***), 3.96 (d, J = 2.1 Hz, 1H, PhC**H**, ***syn-***).

syn- and anti-2,3-Epoxy-1,3-diphenylpropan-1-ol*, 16.**[2e,8d] Yield: 90%; IR (thin film): ν 3400, 900 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.00 (d, J = 2.1 Hz, 1H, PhC**H**, ***syn-), 4.14 (d, J = 2.1 Hz, 1H, PhC**H**, ***anti-***), 4.70 (d, J = 4.9 Hz, 1H, C**H**OH, ***syn-***), 4.98 (d, J = 2.9 Hz, 1H, C**H**OH, ***anti-***).

syn- and anti-2,3-Epoxy-1-phenylbutan-1-ol*, 17.**[2e] Yield: 93%; IR (neat): ν 3440, 835 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (d, J = 5.1 Hz, CH_3, ***anti-), 1.31 (d, J = 5.1 Hz, CH_3, ***syn-***), 4.50 (d, J = 5.4 Hz, CHOH, ***syn-***), 4.74 (d, J = 3.4 Hz, CHOH, ***anti-***).

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