

Stereoselective Reduction of β -Hydroxy Ketones to 1,3-Diols with the Aid of a Terphenylboronic Acid

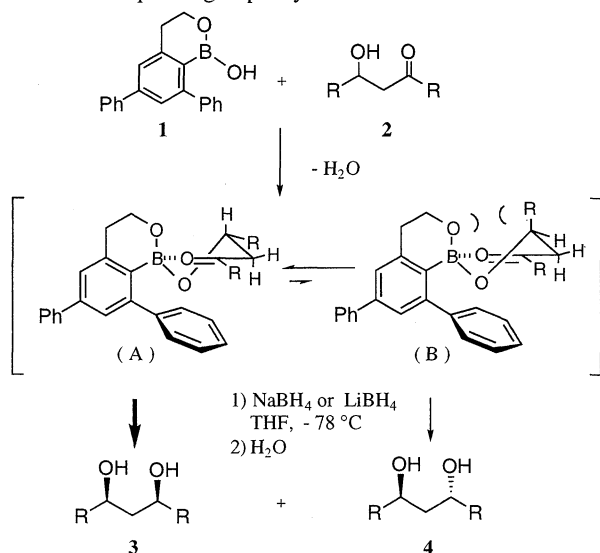
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1-Hydroxy-6,8-diphenyl-1,2,3,4-tetrahydro-2-oxa-1-boranaphthalene (terphenylboronic acid **1**), is employed for stereoselective reduction of acyclic and cyclic β -hydroxy ketones. The terphenylboronic acid **1** and acyclic β -hydroxy ketones **2** are converted to the corresponding boronates by azeotropic removal of water. The resulting boronates are treated *in situ* with reducing reagents to give *syn* 1,3-diols **3** almost exclusively. *Anti* α -substituted β -hydroxy ketones **8** are also reduced to give *anti*, *anti* 1,3-diol **9** stereoselectively. Furthermore, the reduction of 3-hydroxy-1-cyclopentanone gives a *cis* diol **11** in high selectivity.

Among the procedures developed for the preparation of acyclic 1,3-diols, the stereoselective reduction of β -hydroxy ketones has proven to be highly valuable.^{1,2} For the preparation of *syn* 1,3-diols, aid of the chelate formation with trialkylborane^{1a,b} or alkoxydialkylborane^{1c,d,e} has brought about one of the most efficient stereocontrolled methods. 1-Hydroxy-6,8-diphenyl-1,2,3,4-tetrahydro-2-oxa-1-boranaphthalene (terphenylboronic acid **1**), prepared as mentioned in the previous paper,³ was thought to exhibit potential utility for the stereocontrol in the reduction of β -hydroxy ketones. That is, when the terphenylboronate is formed from terphenylboronic acid **1** and a β -hydroxy ketone **2**, the 8-phenyl group of the terphenyl moiety would cover the α -side of the carbonyl group in the stable conformer A (Scheme 1). Accordingly, the attack of a reducing reagent from the α -side would be prevented, resulting in the formation of a *syn* 1,3-diol selectively. Based on this assumption, the reduction of β -hydroxy ketones **2** was examined via the corresponding terphenylboronates.



Scheme 1.

Representative experimental procedure is as follows (Table 1, **2a**): The terphenylboronic acid **1** (331 mg, 1.1 mmol) and 7-hydroxy-5-undecanone **2a** (187 mg, 1.0 mmol) were converted to a boronate in refluxing benzene (7 ml) for 2 h by azeotropic removal of water. After the solvent was evaporated, THF (10 ml) was added. NaBH₄ (46 mg, 1.2 mmol) was added at -78 °C and the mixture was stirred for 2 h at that temperature. After quenching, crude products were chromatographed on silica gel to give 1,3-diols **3a** and **4a** (180 mg, 95% yield) and the terphenylboronic acid **1** (317 mg, 96% recovery). The diastereomers **3a** and **4a** were converted to phenyl boronates and the structures were determined by ¹H-NMR analysis.^{1a} The ratio of the *syn* isomer **3a** and the *anti* isomer **4a** was estimated on the basis of relative intensity of ¹³C signals of the stereogenic carbon atoms.^{1c}

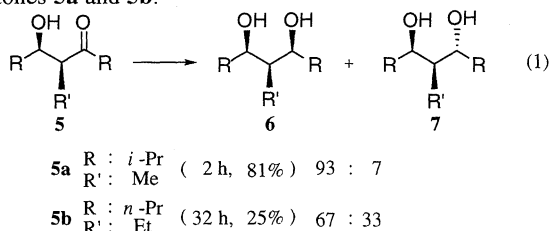
Similarly, **2b** and **2c** were reduced with NaBH₄ or LiBH₄. In all cases, high stereoselectivity was achieved and *syn* 1,3-diols **3b** and **3c** were obtained almost exclusively. The terphenylboronic acid **1** could be recovered quantitatively. The results are summarized in Table 1. Compared with a conventional method by using trialkylboranes,^{1a} the use of the terphenylboronic acid **1** achieved the higher *syn* selectivity for the reduction of β -hydroxyketones **2**, which was the comparable selectivity to the Prasad's method (Et₂BOMe-NaBH₄).^{1c} For example, in the case of the reduction of **2c** by using trialkylboranes, the *syn* isomer **3c** / the *anti* isomer **4c** ratio was 88 / 12,^{1a} while the present method gave **3c** almost exclusively.

Table 1. Stereoselective Reduction of **2**

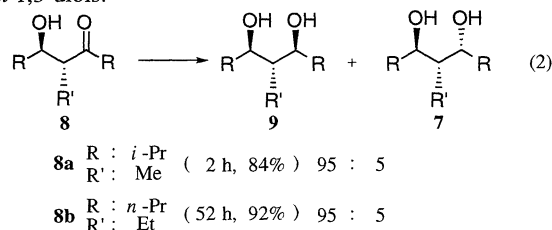
β -Hydroxy ketones	Reducing reagent	Yield	Ratio	
			3	4
2a R : <i>n</i> -Bu	NaBH ₄	95%	98	: 2
	LiBH ₄	92%	98	: 2
2b R : Ph	NaBH ₄	98%	98	: 2
	LiBH ₄	97%	97	: 3
2c R : <i>cyclo</i> -C ₆ H ₁₁	NaBH ₄	91%	99	: 1
	LiBH ₄	87%	99	: 1

This terphenylboronic acid **1** was further employed in the reduction of *syn* and *anti* α -substituted β -hydroxy ketones **5** and **8**.^{2c} As the reduction proceeded very slowly with NaBH₄,

LiBH₄ was employed as a reducing reagent.^{1e} In the present method using **1**, the reduction of *syn* hydroxy ketones **5a** and **5b** gave 1,2-*syn*, 2,3-*syn* isomers **6** as major products, but the selectivity was largely dependent on the 2-substituents R' (eq. 1). This result makes a contrast to the conventional trialkylborane method, by which only *syn*, *syn* 1,3-diols **6a** and **6b** are obtained exclusively from *syn* α -substituted β -hydroxy ketones **5a** and **5b**.^{1a}



In the reduction of *anti* α -substituted β -hydroxy ketones **8a** and **8b**, the remarkable effect of the use of **1** was presented in the stereoselectivity. The *anti*, *anti* 1,3-diol **9** was obtained in good stereoselectivity (eq. 2). The reduction of *anti* hydroxy ketones **8a** and **8b** by the conventional method using a trialkylborane and NaBH₄^{1a} did not proceed selectively. The ratios of the diols, **6**, **7**, and **9** were determined by GC analysis. Thus, the present method could be utilized for the stereoselective reduction of *anti* α -substituted β -hydroxy ketones to prepare *anti*, *anti* 1,3-diols.



A cyclic β -hydroxy ketone such as 3-hydroxy-1-cyclopentanone was also expected to be reduced in high stereoselectivity via the boronate **10a**, because the 8-phenyl group of the terphenyl moiety would cover the cyclopentane ring from the same side of the hydroxyl group (Figure 1). The reduction was examined in THF at -78 °C with two different types of reducing agents, LiEt₃BH as a nucleophilic reagent and *i*-Bu₂AlH (DIBAH) as an electrophilic reagent (Table 2). A silyl ether **10b** of the hydroxy cyclopentanone which has a large *t*-butyldimethylsilyl (TBDMS) group was also prepared as a reference compound.

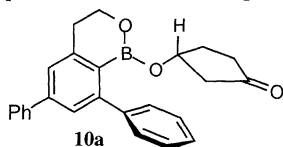


Figure 1. The supposed conformation of the boronate **10a**.

With LiEt₃BH, the reduction of both of the boronate **10a** and the silyl ether **10b** gave a *cis* diol **11** in high selectivity. In the reduction with *i*-Bu₂AlH, the boronate **10a** was reduced to the *cis* diol **11** almost exclusively, while good stereoselectivity was not observed in the reduction of the silyl ether **10b**. The structure of *cis* **11** and *trans* **12** was determined by ¹H-NMR spectra in DMSO-*d*₆: *cis* **11**; the methylene protons of C-2

Table 2. Stereoselective Reduction of **10**

Substrate	Reducing reagent	Yield	Ratio 11 : 12
10a	LiEt ₃ BH	88%	98 : 2
	DIBAH	86%	95 : 5
10b ^a	LiEt ₃ BH	71%	98 : 2
R = TBDMS	DIBAH	72%	67 : 33

^aThe silyl group was removed by treatment with aq. HCl.

appeared at δ 1.30 ppm (1H, dt, *J*=13.3 and 5.7 Hz) and δ 1.99 ppm (1H, dt, *J*=13.3 and 6.7 Hz) : *trans* **12**; at δ 1.59 ppm (2H, t, *J*=5.4 Hz). The *cis*/*trans* ratio was estimated by the ¹H-NMR spectra in DMSO-*d*₆ on the basis of integrated intensity of alcoholic methine proton, *cis* **11**; δ 3.9-4.0 ppm (m) : *trans* **12**; δ 4.1-4.2 ppm (m).

References and Notes

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