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

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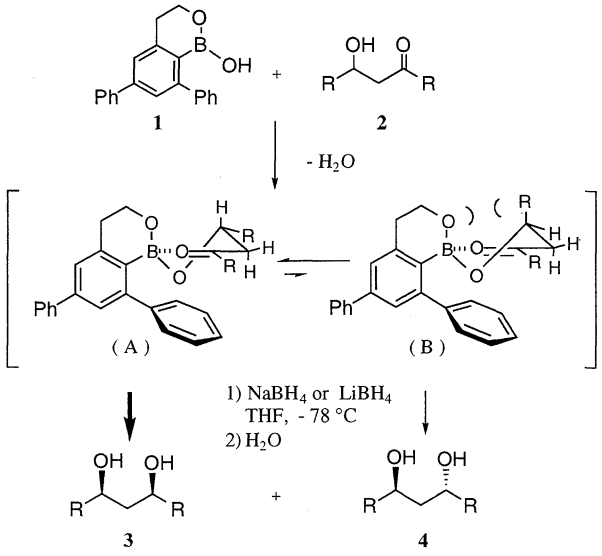
1-Hydroxy-6,8-diphenyl-1,2,3,4-tetrahydro-2-oxa-1-boranaphthalene (terphenylboronic acid **1**), is employed for stereoselective reduction of acyclic and cyclic β-hydroxy ketones. The terphenylboronic acid **1** and acyclic β-hydroxy ketones **2** are converted to the corresponding boronates by azeotropic 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.

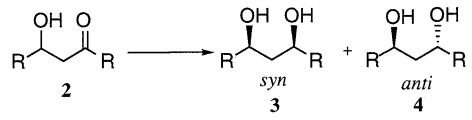


Scheme 1.

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. $NaBH_4$ (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 ^{1}H-NMR analysis.[1a] The ratio of the *syn* isomer **3a** and the *anti* isomer **4a** was estimated on the basis of relative intensity of ^{13}C signals of the stereogenic carbon atoms.[1c]

Similarly, **2b** and **2c** were reduced with $NaBH_4$ or $LiBH_4$. 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 (Et_2BOMe-$NaBH_4$).[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.

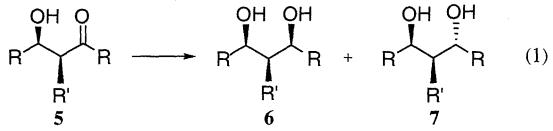
Table 1. Stereoselective Reduction of **2**



β-Hydroxy ketones		Reducing reagent	Yield	Ratio 3 : 4
2a	R : *n*-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 : *cyclo*-C_6H_{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 $NaBH_4$,

$LiBH_4$ 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]

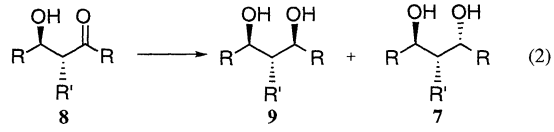


(1)

5a R : *i*-Pr, R' : Me (2 h, 81%) 93 : 7

5b R : *n*-Pr, R' : Et (32 h, 25%) 67 : 33

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 $NaBH_4$[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.

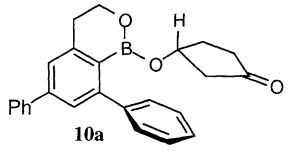


(2)

8a R : *i*-Pr, R' : Me (2 h, 84%) 95 : 5

8b R : *n*-Pr, R' : Et (52 h, 92%) 95 : 5

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, $LiEt_3BH$ as a nucleophilic reagent and *i*-Bu_2AlH (DIBAH) as a 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.

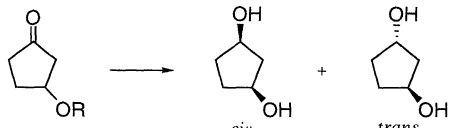


10a

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

With $LiEt_3BH$, 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*-Bu_2AlH, 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 ^{1}H-NMR spectra in DMSO-d_6 : *cis* **11** ; the methylene protons of C-2 appeared at δ1.30 ppm (1H, dt, *J*=13.3 and 5.7 Hz) and δ1.99 ppm (1H, dt, *J*=13.3 and 6.7 Hz) : *trans* **12** ; at δ1.59 ppm (2H, t, *J*=5.4 Hz). The *cis*/*trans* ratio was estimated by the ^{1}H-NMR spectra in DMSO-d_6 on the basis of integrated intensity of alcoholic methine proton, *cis* **11** ; δ3.9-4.0 ppm (m) : *trans* **12** ; δ4.1-4.2 ppm (m).

Table 2. Stereoselective Reduction of **10**



10 → *cis* **11** + *trans* **12**

Substrate	Reducing reagent	Yield	Ratio **11** : **12**
10a	$LiEt_3BH$	88%	98 : 2
	DIBAH	86%	95 : 5
10b[a] R = TBDMS	$LiEt_3BH$	71%	98 : 2
	DIBAH	72%	67 : 33

[a]The silyl group was removed by treatment with *aq.* HCl.

References and Notes

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3 H. Yamashita, K. Amano, S. Shimada, and K. Narasaka, the preceeding paper in this issue.