1,3-SYN DIASTEREOSELECTIVE REDUCTION OF  $\beta$ -HYDROXYKETONES WITH DIISOBUTYLALUMINUM HYDRIDE AND TRIBUTYLTIN HYDRIDE

Syun-ichi Kiyooka,≍ Hisanori Kuroda, and Yayoi Shimasaki Department of Chemistry, Kochi University Akebono-cho 2-5-1, Kochi 780, Japan

Abstract: 1,3-Syn diastereofacial selectivity (>12 : 1) has been achieved in a facile reduction of  $\beta$ -hydroxyketones with DIBAL-H. Tributyltin hydride also has shown 1,3-syn selectivity.

An acyclic stereoselective synthesis of 1,3-syn diols is still important for the synthesis of natural products, e. g., polyene macrolides.<sup>1)</sup> The reduction of acyclic  $\beta$ -hydroxyketones looks promising for this purpose; in fact Narasaka has accomplished a highly 1,3-syn selective reduction of  $\beta$ -hydroxyketones via boron chelates.<sup>2)</sup> We here report a more versatile reduction of  $\beta$ hydroxyketones with DIBAL-H<sup>3)</sup> and some reductions of them with tributyltin hydride.



Typical procedure: To a solution of  $\beta$ -hydroxyketone (1 mmol) in THF (20 mL) was added dropwise DIBAL-H (2.5 mmol; 1 mol/L THF solution) at -78°C under argon. After stirring for 2.5 h at the temperature, the solution was quenched with 10% HCl solution. The reaction mixture was extracted with ether and washed with sat. NaCl solution. The ethereal solution was dried over MgSO<sub>4</sub>. After evaporation of the solvent, the residue was purified by silica-gel flash column chromatography (10% AcOEt in hexane) to give a mixture of diols which shows high 1,3-stereoselectivity (>12 : 1).

Table 1.					,	
Diastereo	selective Re	duction c	of β-Hydroxyk	etones with [	)IBAL-H <sup>a)</sup>	
Entry	Compound	Reaction temp. (Reaction time)		Yield (%) <sup>t</sup>	) Product syn :	Ratio <sup>C)</sup> anti
1	<u>1</u> - I	0°C	(1 h)	88	70	30
2	<u>1</u> - I	-78°C	(2.5 h)	87	93	7
3	<u>1</u> - II	0°C	(1 h)	91	67	33
4	<u>1</u> - II	-78°C	(2.5 h)	85	92	8
5	<u>1</u> - III	0°C	(1 h)	84	77	23
6	<u>1</u> - III	-78°C	(2.5 h)	83	95	5
7	<u>1</u> - IV	0°C	(1 h)	85	72	28
8	<u>1</u> - IV	-78°C	(2.5 h)	81	93	7

a) DIBAL-H (2.5 mol equiv.) was used for ketone (1 mol equiv.). b) Isolated yield after column chromatography. All the products gave satisfactory spectral and elementary analyses. c) The ratios were determined by  $^{1}$ H-NMR (100 MHz) with NMR shift reagents and  $^{13}$ C-NMR (22.6 MHz) analyses.

```
Table 2.
```

Reduction	of β-Hydroxyke	tones with Tributy	ltin Hydride	at Room Te	emperature <sup>a)</sup>
Entry	Compound	Catalyst (Solvent)	Yield (%) <sup>b)</sup>	Product syn :	Ratio <sup>C)</sup> anti
1	<u>1</u> - I	AIBN <sup>d)</sup> (methanol)	26	87	13
2	<u>1</u> - I	ZnCl <sub>2</sub> <sup>e)</sup> (ether)	83	88	12
3	<u>1</u> - II	AIBN (methanol)	21	87	13
4	<u>]</u> - II	ZnCl <sub>2</sub> (ether)	87	85	15
5	<u>1</u> - III	ZnCl <sub>2</sub> (ether)	85	68	32
6	<u>1</u> - III	snCl <sub>4</sub> (CH <sub>2</sub> Cl <sub>2</sub> )	42	64	36
7	<u>1</u> - IV	ZnCl <sub>2</sub> (ether)	86	85	15

a) Overnight reaction: tributyltin hydride (2.5 mol equiv.) was employed for ketone (1 mol equiv.). b) and c) The notes are identical to those described in Table 1. d) AIBN (0.1 mol equiv.) was used. e) ZnCl<sub>2</sub> was used as a saturated solution.

The results with DIBAL-H are shown in Table 1. The reactions at -78°C achieve satisfactorily high 1,3-syn selectivity and moreover the procedure is straightforward and simple to use. Before the  $H^$ reduction of the carbonyl group of  $\beta$ -hydroxyketones excess DIBAL-H may first react with the  $\beta$ -hydroxy group to give oxygen — aluminum bond and then it leads to a six-membered ring chelation. The 1,3-syn asymmet

 $H \xrightarrow{R^{1}}_{H} \xrightarrow{R^{2}}_{Q} \xrightarrow{Q^{---}}_{Q} \xrightarrow{ML}(n)$ 

to a six-membered ring chelation. The 1,3-syn asymmetric induction in the following reduction can be effectively explained by a model shown in  $\underline{4}$ . Surprisingly the reduction with DIBAL-H did not show any selectivity in  $\mathrm{CH}_2\mathrm{Cl}_2$  toluene.

In the Lewis acid mediated reactions of  $\beta$ -alkoxyaldehyde with allylsilane stannous chloride has been recognized to be an excellent reagent which plays a role in chelation.<sup>4)</sup> Then we expected a possibility of chelating ability of organotin hydrides. Tributyltin hydride is known to be one of the more readily available and least reactive hydrides; the reduction of cyclohexanones does not occur with the hydride even at elevated temperatures, but the reduction of ketones has become feasible in the presence of zinc chloride or silica gel at room temperature.<sup>5</sup>)

The reductions were carried out with three different catalysts; 2,2'-azobisisobutyronitril (AIBN), zinc chloride, and stannous chloride. The diols were obtained in good yields in the reduction with zinc chloride. The 1,3-syn selectivity on the reaction is acceptable (7-5 : 1) as room temperature reaction except entries 5 and 6. The 1,3-syn selectivity may be due to a conformational fixation owing to some chelation abilities of tributyltin hydride and/or Lewis acids.

The stereochemistry of  $\underline{2}$  and  $\underline{3}$  was easily ascertained by conversion into the 1,3-dioxane derivatives since 1,3-syn diol  $\underline{2}$  gives only one isomer  $\underline{5}$  and 1,3-anti diol  $\underline{3}$  gives two isomers  $\underline{6}$  and  $\underline{7}$ .<sup>6</sup>) In addition, we have found the best method to assign the stereochemistry of 1,3-diols on the basis of their  $1^{3}$ C-NMR data.



1,3-Diol compounds exist in an intramolecularly hydrogen-bonded form as six-membered ring derivatives.<sup>7)</sup> The chemical shift values of two carbinol carbons for 1,3-diols 2 and 3 are listed in Table 3. The two carbinol carbons in 1,3-anti diols always resonate more upfield than those in 1,3-syn diol do  $(\Delta\delta_{syn-anti}: substituent-induced {}^{13}C$  chemical shift values).<sup>8)</sup> The upfield shft in anti diols can be clearly explained by  $\gamma$ -gauche effects,<sup>9)</sup> as shown in 8 and 9.



Table 3.

Chemical Shift Values (in CDCl $_2$ ) of Carbinol Carbons for 1,3-Diols 2 and 3 (in ppm)

Entry	Diol R <sup>1</sup>	R <sup>2</sup>	syn	anti	<sup>∆δ</sup> (syn - anti)
1	Ph	i-Pr	74.89	71.19	+ 3.70
			76.97	73.34	+ 3.63
2	Ph	t-Bu	75.43	71.65	+ 3.78
			80.43	76.04	+ 4.39
3	Ph	Me	68.18	64.94	+ 3.24
			74.50	71.26	+ 3.24
4	PhCH(Me)	t-Bu	77.74	74.04	+ 3.70
			80.97	76.27	+ 4.70

Acknowledgement: This work was supported by a Grant-in-Aid (No 60540334) for Scientific Research from the Ministry of Education, Science, and Culture (Japan).

References and Notes

- a) P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, and S. M. Viti, J. Org. Chem., <u>47</u>, 1378 (1982); b) B. H. Lipshutz and J. A. Kozlowski, ibid., <u>49</u>, 1147 (1984); c) S. -I. Kiyooka, H. Sasaoka, R. Fujiyama, and C. H.
- Heathcock, Tetrahedron Lett., 25, 5331 (1984).
  2. K. Narasaka and F. -C. Pai, Tetrahedron, 40, 2233 (1984).
  3. G. Solladie, G. Demailly, and C. Greck, Tetrahedron Lett., 26, 435 (1985): In view of 1,3-asymmetric induction, DIBAL-H has been recently used in the reduction of  $\beta$ -ketosulfoxides which proceeds in absence of any chelation.
- 4. C. H. Heathcock, S. –I. Kiyooka, and T. A. Blumenkopf, J. Org. Chem., <u>49</u>, 4214 (1984).
- 5. a) H. G. Kuivila and O. F. Beumel, J. Am. Chem. Soc., <u>83</u>, 1246 (1961); b) N. Y. M. Fung, P. de Mayo, J. H. Schauble, and A. C. Weeden, J. Org. Chem., 43, 3977 (1978).
- 6. The coupling constants in the 1,3-dioxane, especially on the carbinol methyne protons and the methylene protons in the ring, are too complex to be obtained by first-order analysis, e. g., ABXY spin system or more higher : H. Gerlach and H. Wetter, Helv. Chim. Acta, <u>57</u>, 2306 (1974).
  7. C. H. Heathcock, M. C. Pirrung, and J. E. Sohn, J. Org. Chem., <u>44</u>, 4294
- (1979).
- 8. Similar shifts were observed in their dioxane derivatives.
- 9. a) H. -J. Schneider and V. Hoppen, J. Org. Chem., <u>43</u>, 3866 (1978); b) H. Booth, J. R. Everett, and R. A. Freming, Org. Mag. Reson., <u>12</u>, 63 (1979).

(Received in Japan 24 April 1986)