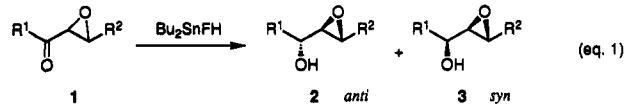
Chemo- and Stereoselective Carbonyl Reduction of α,β-Epoxy Ketones by Bu_2SnFH

Takayo Kawakami, Ikuya Shibata,* Akio Baba, and Haruo Matsuda

Department of Applied Chemistry, Faculty of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565, Japan

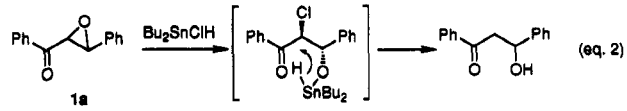
Received July 2, 1993

Organotin hydrides which provide mild and selective reductions are widely used in organic synthesis.[1] Tri-*n*-butyltin hydride (Bu_3SnH) is most conventionally used as a selective dehalogenating agent under radical conditions.[2] On the other hand, although halodibutyltin hydrides (Bu_2SnXH, X = Cl, Br, I) are readily available, their utility in organic synthesis has been limited.[3] We have recently demonstrated the ionic use of chlorodibutyltin hydride (Bu_2SnClH) in highly *anti*-stereoselective reductions of α-alkoxy ketones.[4] This fact encouraged us to investigate the reduction of ketones bearing other functional groups. Although the *anti*-selective carbonyl reduction of α,β-epoxy ketones has been carried out by employing other reducing agents,[5] the control under mild conditions by using organotin hydrides has not been achieved so far.[6] So we tried to bring about this purpose and here report the chemo- and stereoselective reduction of α,β-epoxy ketones 1 by using Bu_2SnFH (eq 1).



1 2 *anti* 3 *syn*

We initially used Bu_2SnClH for the reduction of **1a**. However, the use of this reagent resulted in the formation of an aldol in 83% yield. Perhaps the nucleophilicity of the tin chloride effects the ring cleavage of the oxirane[7] and reduction of the chlorine–carbon bond would lead to the aldol product (eq 2). Since Bu_2SnClH could not be



1a

used for the chemoselective carbonyl reduction of α,β-epoxy ketones, we next tried fluorodibutyltin hydride (Bu_2SnFH). It seemed that this reagent would be a good candidate for this purpose because the tin–fluorine bond is assumed to have a lower ability to cleave the epoxide ring.[8] However, Bu_2SnFH could not be prepared by the simple reaction of Bu_2SnH_2 and Bu_2SnF_2, in analogy to the synthesis of Bu_2SnClH.[9] The difficulty with the redistribution reaction to form Bu_2SnFH is because of the lack of solubility of both tin fluorides.[10] Fortunately, we found that the equimolar addition of HMPA was found to effect the redistribution of Bu_2SnH_2 and Bu_2SnF_2 dramatically, thus allowing the preparation of Bu_2SnFH within 5 min at room temperature. Although the isolation of Bu_2SnFH was difficult, the mixture so obtained was a clear liquid, and the IR absorption at 1869 cm^{-1} was detected along with disappearance of the absorption shown by Bu_2SnH_2 in HMPA at 1837 cm^{-1}. This shift of the IR absorption suggested the formation of Bu_2SnFH, because similar results have been reported by Sawyer et al.[10]

As was expected, Bu_2SnFH effectively reduced α,β-epoxy ketones (Table I). In the reduction of **1a**, epoxy alcohols **2a** and **3a** were obtained in good yields. Thus the chemoselective carbonyl reduction took place and no byproducts derived from the ring cleavage were detected. This tin hydride reaction could be applied to various epoxy ketones **1b–f**. Even in the reaction of **1c**, which has a reactive terminal epoxide, no detectable ring cleavage occurred, and epoxy alcohols **2c** and **3c** were obtained in good yield (entry 3). Besides aromatic ketones, the reduction of methyl ketone **1d** afforded **2d** and **3d** in good yield (entry 4). Cyclic substrates **1e** and **1f** were also reactive and gave the corresponding epoxy alcohols (entries 5 and 6). In addition to this chemoselectivity, equally impressive is the highly stereoselective carbonyl reduction to form *anti*-epoxy alcohols **2**. As shown in Scheme I, the *anti*-selective reaction is explained in terms of Cram's chelation model **A**.[11] Because a fluorine atom has a high electron-withdrawing ability, the acidity of the tin center is enhanced and a tightly-coordinated chelate is most probably formed.[12] The high Lewis acidity and lower halogen nucleophilicity of Bu_2SnFH compared to Bu_2SnClH afforded the chemo- and stereoselective reduction.

In summary, the novel tin hydride reagent, Bu_2SnFH, was formed and was used to prepare *anti*-epoxy alcohols from α,β-epoxy ketones.

Experimental Section

Analysis. Boiling points are uncorrected. NMR spectra were recorded at 400 MHz. Sample were examined in deuteriochloroform ($CDCl_3$) containing 0.03% by volume of tetramethylsilane (TMS). GLC analyses were performed with a FFAP coated 2-m × 3-mm glass column. Column chromatography was performed by using Wakogel C-200 or C-300 mesh silica gel. Preparative TLC was carried out on Wakogel B-5F mesh silica gel.

Materials. Di-*n*-butyltin dihydride (Bu_2SnH_2) was prepared by the reduction of di-*n*-butyltin dichloride (Bu_2SnCl_2) with $LiAlH_4$.[13] Di-*n*-butyltin difluoride (Bu_2SnF_2) was synthesized by the reaction of 18.46 g (60.8 mmol) of di-*n*-butyltin dichloride

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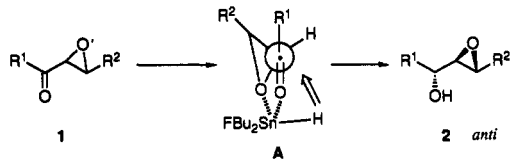
Table I. Reduction of α,β-Epoxy Ketones by Bu_2SnFH[a]

entry	1 R¹	1 R²	1 no.	conditions	yield of 2 + 3 (%)[b]	ratio 2:3
1	Ph	Ph	1a	rt, 1 h	90	87:13[c]
2	Ph	Me	1b	rt, 3 h	100	82:18[c]
3	Ph	H	1c	0 °C to rt, 1.5 h	81	86:14[c]
4	Me	Ph	1d	rt, 1.5 h	96	69:31[c]
5	$(CH_2)_4$		1e	0 °C, 7 h	88	86:14[d,e]
6	$(CH_2)_3$		1f	0 °C, 3 h	88	>98:2[d,e]

[a] α,β-epoxy ketone 1 1 mmol, Bu_2SnH_2 0.5 mmol, Bu_2SnF_2 0.5 mmol, HMPA 1 mmol, THF 1 mL. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by GLC. [e] Cis:trans.

Scheme I



(Bu_2SnCl_2) and 5.50 g (148 mmol) of ammonium fluoride (NH_4F) in 300 mL of MeOH at rt overnight.[14] Fluorodibutyltin hydride (Bu_2SnFH) was obtained by the redistribution Bu_2SnF_2 and Bu_2SnH_2 in the presence of HMPA. α,β-Epoxy ketones were prepared by the oxidation of the corresponding α,β-unsaturated ketones using alkaline hydrogen peroxide.[15] THF was freshly distilled over sodium benzophenone ketyl and HMPA was distilled over finely powdered calcium hydride.

Representative Procedure for *anti*-Selective Carbonyl Reduction of α,β-Epoxy Ketones. All reactions were carried out under dry nitrogen. To the solution of Bu_2SnH_2 (0.5 mmol) in 1 mL of THF was added HMPA (1 mmol). Bu_2SnF_2 (0.5 mmol) was added, and the mixture was stirred at rt for 10 min. The IR band at 1835 cm^{-1} due to the Sn–H bond of Bu_2SnH_2 changed to 1869 cm^{-1}, which indicated the formation of Bu_2SnFH. α,β-Epoxy ketone (1 mmol) was added at 0 °C to rt and this solution was stirred for 1–7 h. After the reaction was quenched with MeOH (5 mL), the solvent was removed under reduced pressure. The residue was subjected to column chromatography with hexane–EtOAc (1:1) to give an *anti*-rich mixture of epoxy alcohols. The ratio of diastereomers was determined by ^1H NMR (**2a-d** and **3a-d**) or GLC (**2e,f** and **3e,f**). Further purification of diastereomers **2** and **3** was performed by TLC with hexane–diethyl ether (1:1). The stereochemistry of diastereomers was assigned by ^1H NMR comparison with stereochemically defined authentic samples.

***anti*- and *syn*-1,3-diphenyl-2,3-epoxy-1-propanol (2a and 3a)**: colorless liquid, purified by TLC; IR (neat) 3400 cm^{-1}; HRMS calcd for $C_{15}H_{14}O_2$ 226.0994, found 226.0999; ^1H NMR ($CDCl_3$) **2a** δ 2.53 (d, 1H, J = 2.0 Hz), 3.28–3.31 (m, 1H), 4.14 (d, 1H, J = 2.0 Hz), 5.00 (dd, 1H, J = <1 and 2.0 Hz), 7.24–7.46 (m, 10H); **3a** δ 2.64 (d, 1H, J = 5.4 Hz), 3.28–3.31 (m, 1H), 4.0 (d, 1H, J = 2.0 Hz), 4.72 (dd, 1H, J = 4.9 and 5.4 Hz), 7.24–7.46 (m, 10H); ^{13}C NMR ($CDCl_3$) **2a** δ 54.9, 64.9, 71.2, 125.7–128.7, 136.5, 139.2; **3a** δ 56.9, 65.7, 73.3, 125.7–128.7, 163.3, 140.1.

***anti*-1-Phenyl-2,3-epoxy-1-butanol (2b)**: colorless liquid, purified by TLC; IR (neat) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, 1H, J = 5.4 Hz), 2.57 (br, 1H), 2.90 (dd, 1H, J = 2.4 and 3.4 Hz), 3.19 (qd, 1H, J = 2.4 and 5.4 Hz), 4.74 (d, 1H, J = 3.4 Hz), 7.24–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.9, 51.4, 62.2, 71.1, 126.3, 127.9, 128.4, 139.8; HRMS calcd for $C_{10}H_{12}O_2$ 164.0838, found 164.0838.

***syn*-1-Phenyl-2,3-epoxy-1-butanol (3b)**: colorless liquid, purified by TLC; IR (neat) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (d, 3H, J = 5.4 Hz), 2.62 (br, 1H), 2.95 (dd, 1H, J = 2.4 and 5.4 Hz), 3.13 (qd, 1H, J = 2.4 and 5.4 Hz), 4.50 (d, 1H, J = 5.4 Hz), 7.29–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.1, 53.2, 63.1, 73.8, 126.1, 128.1, 128.6, 140.3; HRMS calcd for $C_{10}H_{12}O_2$ 164.0838, found 164.0845.

***anti*-1-Phenyl-2,3-epoxy-1-propanol (2c)**: colorless liquid, purified by TLC; IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (dd, 1H, J = 3.9 and 5.4 Hz), 2.90 (br, 1H), 2.92 (dd, 1H, J = 2.9 and 5.4 Hz), 3.16–3.19 (m, 1H), 4.85 (d, 1H, J = 2.9 Hz), 7.28–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 43.6, 55.0, 70.8, 126.3, 128.1, 128.4, 139.5; HRMS calcd for $C_9H_{10}O_2$ 150.0681, found 150.0667.

***syn*-1-Phenyl-2,3-epoxy-1-propanol (3c)**: colorless liquid, purified by TLC; IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76 (dd, 1H, J = 2.9 and 4.9 Hz), 2.77–2.81 (m, 1H), 3.16–3.19 (m, 1H), 3.25 (br, 1H), 4.40 (t, 1H, J = 4.9 Hz), 7.27–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 45.3, 56.0, 74.5, 126.2, 128.0, 128.5, 140.0; HRMS calcd for $C_9H_{10}O_2$ 150.0681, found 150.0694.

***anti*-4-Phenyl-3,4-epoxy-2-butanol (2d)**: colorless liquid, purified by TLC; IR (neat) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (d, 1H, J = 6.4 Hz), 2.06 (br, 1H), 3.01 (t, 1H, J = 2.4 Hz), 3.88 (d, 1H, J = 2.4 Hz), 4.02 (qd, 1H, J = 2.4 and 6.4 Hz), 7.18–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.7, 54.6, 64.8, 65.6, 125.7, 128.2, 128.5, 136.9; HRMS calcd for $C_{10}H_{12}O_2$ 164.0838, found 164.0824.

***syn*-4-Phenyl-3,4-epoxy-2-butanol (3d)**: colorless liquid, purified by TLC; IR (neat) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, 1H, J = 6.8 Hz), 2.56 (br, 1H), 3.06 (dd, 1H, J = 2.0 and 2.9 Hz), 3.94 (d, 1H, J = 2.0 Hz), 4.06 (qd, 1H, J = 2.9 and 6.8 Hz), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.7, 54.8, 64.9, 65.6, 125.6, 128.1, 128.4, 136.9; HRMS calcd for $C_{10}H_{12}O_2$ 164.0838, found 164.0835.

^1H NMR data of cyclic compounds **2e**, **3e**, **2f**, and **3f** were consistent with the ones reported previously.[16]

***trans*-2,3-Epoxycyclohexanol (2e)**: colorless liquid, purified by TLC; IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15–2.00 (m, 6H), 2.45 (br, 1H), 3.02 (dd, 1H, J = <1 and 3.42 Hz), 3.21–3.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.39, 24.00, 53.08, 65.85; HRMS (CI) [M + H] calcd for $C_6H_{11}O_2$ 115.0759; found 115.0745.

***cis*-2,3-Epoxycyclohexanol (3e)**: colorless liquid, purified by TLC; IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–2.00 (m, 6H), 2.05 (d, 1H, J = 18.07), 3.24 (dd, 1H, J = 2.93 and 3.91 Hz), 3.40–3.70 (m, 1H), 3.97–4.60 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.10, 23.07, 28.92, 55.32, 55.45, 58.26; HRMS calcd for $C_6H_{10}O_2$ 114.0681, found 114.0687.

***trans*-2,3-Epoxycyclopentanol (2f)**: colorless liquid, purified by TLC; IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15–2.15 (m, 4H), 2.17 (br, 1 H), 3.46–3.50 (m, 2H), 4.25–4.31 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.96, 27.09, 56.25, 58.91, 73.63; HRMS (CI) [M + H] calcd for $C_5H_9O_2$ 101.0603, found 101.0609.

***cis*-2,3-Epoxycyclopentanol (3f)**: (reference data which was prepared with another reducing agent) colorless liquid, purified by TLC; IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–2.10 (m, 4H), 1.78 (d, 1H, J = 9.28 Hz), 3.39–3.42 (m, 2H), 4.17–4.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.00, 27.15, 56.25, 58.88, 73.66; HRMS calcd for $C_5H_8O_2$ 100.0524, found 100.0528.

Acknowledgment. This work was supported by the JSPS Fellowships for Japanese Junior Scientists from Ministry of Education, Science and Culture. Thanks are due to Mrs. Y. Miyaji and Mr. H. Moriguchi, Faculty of Engineering, Osaka University, for assistance in obtaining NMR and HRMS spectra.

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