

Catalytic Effect of Five-Coordinate Organotin Bromide or Tetraphenylstibonium Bromide on the Chemo- and Stereoselective Addition of Tin Enolate to α -Halo Ketone

Makoto Yasuda,^{1a)} Tatsuhiro Oh-hata, Ikuya Shibata, Akio Baba,* Haruo Matsuda,^{1b)} and Noboru Sonoda

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

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Two types of catalysts, five-coordinate organotin bromides and tetraphenylstibonium bromide, similarly promoted the selective addition of tin enolates to the carbonyl moiety in α -halo ketones. The reaction with 2-chlorocyclohexanones and the enolates gave chlorohydrins bearing chloro- and hydroxyl groups in the *cis*-conformation. Chemoselective carbonyl addition to acyclic α -halo ketones was followed by effective cyclization to 2-(2-oxoethyl)oxiranes. The structural and bonding analogy of both catalysts may be responsible for the similar catalytic activities which induced the chemo- and stereoselective addition.

An organotin enolate is one of the most versatile tools for carbon-carbon bond formation.²⁾ Of particular interest is the addition to carbonyl compounds.³⁾ Organotin enolates **1** exist as tautomeric mixtures of keto- and/or enol-forms,⁴⁾ and the large dependence of the ratio on their substituents and conditions frequently disturbs the unified reaction modes (Scheme 1). We recently demonstrated that coordination to a tin atom increases the ratio of the enol form, and that the resulting high-coordinate tin enolates are effective reagents for a halo-selective reaction toward α -halo carbonyls.⁵⁾ On the other hand, a fine carbonyl-selective addition was reported⁶⁾ by Stille and co-workers to finally produce 2-(2-oxoethyl)oxiranes, where a palladium catalyst is indicated to act as a Lewis acid; the possibility of an oxidative addition of palladium(0) with the carbon-halogen bond is excluded. This fact indicates that a mild Lewis acid, like palladium(II), is appropriate to activate the carbonyl group in the presence of an acid-sensitive tin enolate.

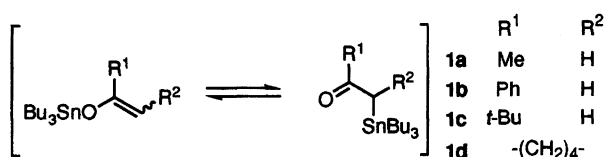
During the course of an investigation utilizing high-coordinate tin enolates,⁷⁾ we found an example of the formation of 2-(2-oxoethyl)oxiranes from 2-bromo-1-phenylethanone and tin enolate **1a** in the presence of $\text{Bu}_3\text{SnBr}-\text{Bu}_4\text{NBr}$ or $\text{Bu}_3\text{SnBr}-\text{HMPA}$.^{7b)} In addition,

we recently observed⁸⁾ that tetraphenylstibonium bromide⁹⁾ (Ph_4SbBr) catalytically promotes a highly stereoselective addition of tin enolates to 2-chlorocycloalkanones. These two types of catalysts both plausibly activate the carbonyl function in α -halo ketones. In previous studies, we found some examples in which high-coordinate Bu_3SnI complexes and Ph_4SbI act as similar catalysts in a reaction of CO_2 with oxirane¹⁰⁾ or oxetane.¹¹⁾ Moreover, in the cycloaddition of monosubstituted oxiranes and heterocumulenes, both Ph_4SbI ¹²⁾ and $\text{Bu}_3\text{SnI}-\text{Bu}_3\text{PO}$ ¹³⁾ were found to catalyze an unusual cleavage of oxirane rings at the substituted site. In this paper, we focus on the analogous activity of five-coordinate tributyltin bromides and tetraphenylstibonium bromide as catalysts for the formation of 2-(2-oxoethyl)oxiranes via the chemoselective addition of tin enolate **1** to carbonyl groups of α -halo ketones.

Results and Discussion

Diastereoselective Addition to 2-Chlorocyclohexanones.

The control of the stereochemistry in nucleophilic addition to substituted cyclic ketones is a current subject in organic syntheses.¹⁴⁾ As briefly reported,⁸⁾ the Ph_4SbBr -catalyst could control the stereoselective addition of tin enolate **1** to 2-chlorocyclohexanone (**2a**). Because **2** exists as a mixture of conformers, **2(eq)** and **2(ax)**, in comparable ratios, as shown in Scheme 2,¹⁵⁾ isomeric mixtures of **3** and **4** (for example, **3aa/4aa**=48/52) were obtained under noncatalyzed conditions. The effects of catalysts on the reaction of **1** with **2** are summarized in Table 1. The combination catalysts of tributyltin bromide

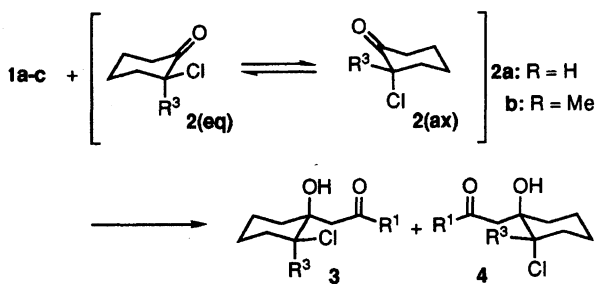


Scheme 1.

Table 1. Effect of Catalyst in the Reaction of Tin Enolates **1** with 2-Chlorocyclohexanones **2**^{a)}

Entry	Tin enolate	Chloroketone	Catalyst	Yield/%	Ratio		
					3	:	4
1	1a	2a	None	aa : 95	48	:	52
2	1a	2a	Bu ₄ NBr	aa : 24	100	:	—
3	1a	2a	Bu ₄ PBr	aa : 24	97	:	3
4	1a	2a	Ph ₄ SbBr	aa : 68	95	:	5
5	1a	2a	Bu ₃ SnBr–Bu ₄ NBr	aa : 59	100	:	—
6	1a	2a	Bu ₃ SnBr–Bu ₄ PBr	aa : 44	97	:	3
7	1a	2a	Bu ₃ SnBr–Ph ₄ SbBr	aa : 70	100	:	—
8	1a	2a	Bu ₃ SnBr	aa : 85	50	:	50
9	1b	2a	None	ba : 100	60	:	40
10	1b	2a	Ph ₄ SbBr	ba : 75	100	:	—
11	1c	2a	None	ca : 79	63	:	37
12	1c	2a	Ph ₄ SbBr	ca : 44	100	:	—
13	1a	2b	None	ab : 56	82	:	18
14	1a	2b	Ph ₄ SbBr	ab : 91	100	:	—

a) Tin enolate **1** (6.0 mmol), chloro ketone **2** (3.0 mmol), catalyst (0.3 mmol), THF (3 mL), 40 °C, 24 h.



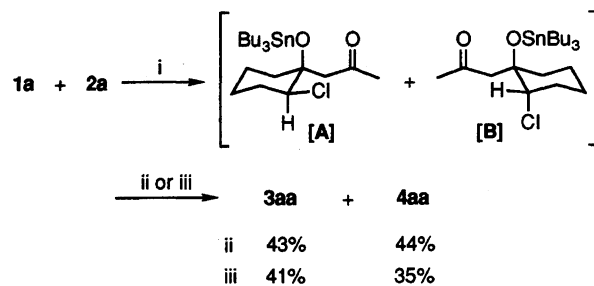
Scheme 2.

(Bu₃SnBr) with such onium salts as Bu₄NBr, Bu₄PBr and Ph₄SbBr effected the exclusive formation of the chlorohydrin derivative **3aa**. These onium bromides alone gave lower yields of **3aa**, except for Ph₄SbBr. The sole use of Bu₃SnBr only led to a similar result as that of a noncatalyzed run (Entries 8 and 1). It is notable that Bu₃SnBr-onium salt showed a similar catalytic effect to Ph₄SbBr alone.

We should consider the equilibrium in the addition step for tin enolate to carbonyl carbon, resulting in isomerization caused by Ph₄SbBr between intermediate tin halo alkoxides [A] and [B]. Following experiments excluded the presence of isomerization (Scheme 3). The reaction of **1a** with **2a** in THF at 40 °C for 12 h afforded **3aa** (43%) and **4aa** (44%) after the hydrolysis of [A] and [B], respectively. However, without hydrolysis, further stirring for 12 h after adding a catalytic amount of Ph₄SbBr caused a slight change in the selectivity (41% of **3aa** and 35% **4aa**). These results apparently showed the absence of isomerization between [A] and [B], and suggested a direct face-control of the direction of nucleophilic addition, where exclusive equatorial and axial attacks would be controlled in the equatorial-chloro-**2(eq)** and axial-chloro form **2(ax)**, respectively, finally furnishing adduct **3**.

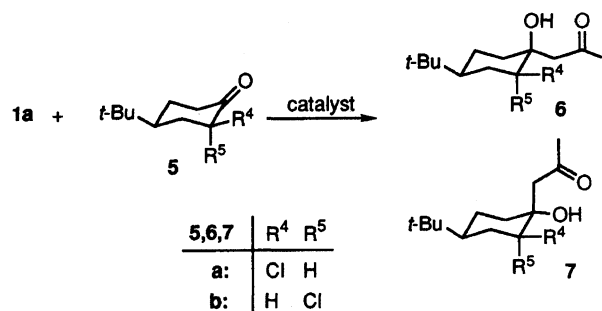
Next, more details were investigated using sterically

fixed conformers, *cis*- and *trans*-4-*tert*-butyl-2-chlorocyclohexanones (**5a** and **5b**) (Scheme 4, Table 2). An equatorial attack to **5a** was exclusive, irrespective of the presence of a catalyst to produce **6a**, as already reported.⁸⁾ In contrast, **5b** was completely controlled to only an axial attack by Ph₄SbBr or Bu₃SnBr–Bu₄NBr, furnishing adduct **7b** with a *cis*-conformation for the chloro and hydroxy groups; in the absence of the catalyst, however, a mixture of adducts arising from equatorial and axial attacks (75/25) was obtained. In this case too, Ph₄SbBr and Bu₃SnBr–Bu₄NBr showed a similar



Reagents and conditions: (i) 40 °C, 12 h, THF; (ii) H₂O; (iii) Ph₄SbBr (0.1 equiv), 40 °C, 12 h, and then H₂O.

Scheme 3.



Scheme 4.

Table 2. Stereoselectivity in the Addition of **1a** to **5**^{a)}

Entry		Chloroketone		Catalyst	Yield/%	Ratio		
		5	R ⁴	R ⁵		6	:	7
1	a:	Cl	H	None	76	100	:	—
2	a:	Cl	H	Ph_4SbBr	61	100	:	—
3	b:	H	Cl	None	72	75	:	25
4	b:	H	Cl	Ph_4SbBr	60	—	:	100
5	b:	H	Cl	$\text{Bu}_3\text{SnBr}-\text{Bu}_4\text{NBr}$	71	—	:	100

a) Tin enolate **1a** (6.0 mmol), chloro ketone **5** (3.0 mmol), catalyst (0.3 mmol), THF (3 mL), 40 °C, 24 h.

catalytic activity, as shown in Table 2 (Entries 4 and 5).

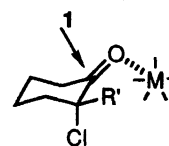
The interaction between onium salts and Bu_3SnBr was examined by ^{119}Sn NMR spectroscopy, as listed in Table 3. The signal for Bu_3SnBr was remarkably moved upfield upon the addition of Bu_4NBr or Bu_4PBr . These upfield shifts indicate the formation of five-coordinate tin species coordinated by a bromide anion.¹⁶⁾ These tin species have trigonal bipyramidal structures with a substituent Br and a ligand Br in both axial positions,^{16a)} in which the original Sn–Br bond becomes somewhat ionic. On the contrary, the relative small shift of δ (^{119}Sn) in Entry 4 indicates a small interaction between Bu_3SnBr and Ph_4SbBr . This small shift is in good accordance with the fact that Ph_4SbBr acted as a catalyst with little assistance of Bu_3SnBr in the addition step to the carbonyl moiety (Entries 4 and 7 in Table 1). This weak coordination ability of Ph_4SbBr is explained in terms of the low-ionic Sb–Br bond¹⁷⁾ in compared with the other onium bromides which have typical ionic bonds. Tetraphenylstibonium bromide is also known to have a trigonal bipyramidal structure in which the Sb–Br bond occupies an axial position.¹⁷⁾ Structural and bonding analogies between tetraphenylstibonium bromide and five-coordinate organotin bromide may be responsible for the similar catalytic activities.

This catalytic stereocontrol could be rationalized based on the rate acceleration effect of these organometallics, because a facile addition to the carbonyl moiety took place without any catalysts. We assume that these catalysts would act as Lewis acids, and could cause an unusual addition to **2(ax)**, where the coordinating carbonyl group and axial chlorine pre-

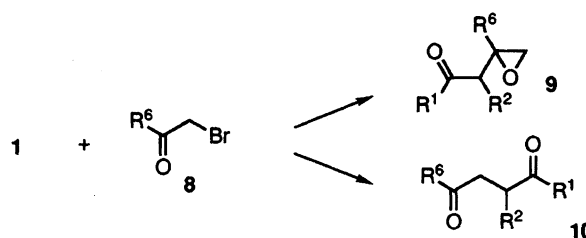
vent an equatorial attack of tin enolate, as illustrated in Scheme 5. Although the details are not clear, the catalytic cycle could be accomplished owing to both the appropriate Lewis acidity and the lower oxo-affinity compared with other metals, such as Al reported by Yamamoto.¹⁸⁾

Application to Oxirane Formation. Stille reported on the Pd-catalyzed formation of 2-(2-oxoethyl)-oxiranes **9** from α -halo ketones **8** via a carbonyl addition of tin enolate **1** in THF reflux.⁶⁾ The milder conditions are required in order to prevent a transformation of the product 2-(2-oxoethyl)oxiranes into furan derivatives (Scheme 6). We previously reported on the formation of 1,4-diketones **10** under mild conditions by a coordination procedure of tin enolates, in which the generation of small amounts of oxirane was assumed to be responsible for the catalysis of the complex of Bu_3SnBr and the ligands.^{7b)} The by-product, Bu_3SnBr , arising from destannylation, increases in progress along with the formation of 1,4-diketones. The coordination of the ligands to the resulting Bu_3SnBr leads to a lack of high-coordinate tin enolates. This is the reason why excess amounts of such ligands as HMPA and Bu_4NBr are indispensable for the predominant formation of 1,4-diketones.

For the selective formation of oxiranes under mild conditions, we carried out a further investigation into numerous tin complex catalysts and Ph_4SbBr . The catalytic effects in the reaction of tin enolate **1** with



Scheme 5.



Scheme 6.

Table 3. ^{119}Sn NMR Chemical Shifts of Bu_3SnBr Effected by Onium Salt^{a)}

Entry	Tin compound (complex)	$\delta(^{119}\text{Sn})/\text{ppm}$
1	Bu_3SnBr	106
2	$\text{Bu}_3\text{SnBr}-\text{Bu}_4\text{NBr}$	−34
3	$\text{Bu}_3\text{SnBr}-\text{Bu}_4\text{PBr}$	−26
4	$\text{Bu}_3\text{SnBr}-\text{Ph}_4\text{SbBr}$	84

a) The samples were prepared from Bu_3SnBr (0.125 mmol) and onium salt (0.125 mmol) in THF (0.4 mL) and $\text{THF}-d_8$ (0.1 mL).

Table 4. Effect of Catalysts in the Reaction of Tin Enolate **1** with 2-Bromo-1-phenylethanone (**8a**)^{a)}

Entry	Tin enolate	Catalyst	Time/h	Yield/%			
				9	10		
1	1a	None	2	aa:	3	3	18 ^{b)}
2		Bu ₃ SnBr–Bu ₄ NBr	2		66	14	
3		Bu ₃ SnBr–Bu ₄ PBr	2		63	12	
4		Bu ₃ SnBr–Ph ₄ SbBr	2		95	5	
5		Bu ₃ SnBr–Et ₄ NBr	2		29	4	
6		Bu ₃ SnBr–Me ₄ NBr	21		28	4	
7		Bu ₃ SnBr–HMPA	21		65	15	
8		Bu ₃ SnBr–Bu ₃ PO	21		61	13	
9		Bu ₂ SnBr ₂ –Bu ₄ NBr	2		49	7	
10		Bu ₃ SnBr	7		0	0	
11	Bu ₄ NBr	3	44	18			
12	Ph ₄ SbBr	3	78	5			
13 ^{c)}	Bu ₄ NBr	2	14	43			
14 ^{c)}	Bu ₄ PBr	3	16	34			
15 ^{c)}	Ph ₄ SbBr	2	71	8			
16	1b	Ph ₄ SbBr	3	ba:	73	11	
17		1d	Ph ₄ SbBr		4	da:	36
18	Bu ₃ SnBr–Bu ₄ NBr		3	38	5		

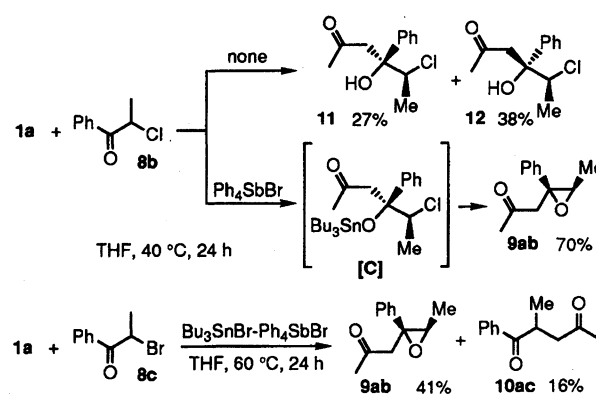
a) Tin enolate **1** (1.2 mmol), **8a** (1.0 mmol), catalyst (0.1 mmol), THF (1 mL), 25 °C. b) The adduct product 5-Bromo-4-hydroxy-4-phenyl-2-pentanone derived via carbonyl attack was obtained.^{7b)} c) Onium halide (1.8 mmol) was used.

2-bromo-1-phenylethanone (**8a**) are summarized in Table 4. The use of Bu₃SnBr-onium salts as catalysts caused the selective formation of oxirane **9aa** by carbonyl addition at room temperature for 2 h (Entries 2, 3, and 4), although a noncatalyzed reaction resulted in a low conversion (Entry 1). The low yields upon using Bu₃SnBr–Et₄NBr or –Me₄NBr were perhaps due to their low solubility in the reaction mixture (Entries 5 and 6). The use of phosphine oxides, HMPA or Bu₃PO, as ligands gave high yields (Entries 7 and 8) in spite of requiring longer reaction times. The addition of only Bu₃SnBr did not promote oxirane-formation at all, similar to the noncatalyzed run (Entry 10). Even without Bu₃SnBr, a catalytic amount of Ph₄SbBr promoted the selective formation of **9aa** (Entry 12).

Also, in the reaction of **1** with **8**, Ph₄SbBr and five-coordinate organotin bromide showed similar and effective catalytic activities under milder conditions than those of a Pd-catalyst reaction.⁶⁾

The addition of an equimolar amount of onium salt afforded interesting results (Entries 13, 14, and 15). High-coordinate tin enolates were generated by the coordination of the bromide anion from Bu₄NBr or Bu₄PBr because of their ionic N–Br or P–Br bonds, giving 1,4-diketone **10aa** in halide substitution.^{5,7)} On the contrary, 2-(2-oxoethyl)oxirane **9aa** was formed selectively even in the presence of an equimolar amount of Ph₄SbBr. No significant coordination to tin enolate would occur, due to the low-ionic character of the Sb–Br bond,¹⁷⁾ although no NMR study concerning the mixture of tin enolate **1a** with Ph₄SbBr could not be carried out because of the poor solubility.

A stereoselective addition to the carbonyl carbon was found in the reaction with acyclic secondary α -halo ketones **8b** or **8c** in Scheme 7. The Ph₄SbBr-catalyzed reaction of **1a** with 2-chloro-1-phenyl-1-propanone (**8b**) proceeded at 40 °C to give the oxirane **9ab** in 70% yield as a single isomer bearing *cis*-conformation for Ph and Me groups, while no stereoselective addition was observed without the catalyst to give a mixture of chlorohydrin derivatives (**11/12**=42/58). The reaction with 2-bromo-1-phenyl-1-propanone (**8c**) gave the oxirane **9ab** in 41% yield along with 1,4-diketone **10ac** in the presence of Bu₃SnBr–Ph₄SbBr. In contrast, noncatalyzed oxirane formation from **1a** and **8c** required heating at 80 °C in benzene, and showed low selectivity.⁷⁾ In these reactions the formation of Cram products was enhanced by the coordination of Ph₄SbBr to the carbonyl group. It is noteworthy that in the case of these



Scheme 7.

α -chloro ketones, no oxirane was produced in the absence of catalysts, only chlorohydrin derivatives being obtained. This result strongly indicated that these catalysts promoted a destannylation, even though the formation of a stable complex between Ph_4SbBr and Bu_3SnBr was not detected in the aforementioned NMR study. Although the details are not clear, we tentatively assume that a weak interaction between Ph_4SbBr and Bu_3SnBr plays an important role in the elimination of Bu_3SnBr to yield oxiranes catalytically.

Since these catalytic reactions proceeded at lower temperature than in the Pd-catalyst system, the 2-(2-oxoethyl)oxiranes formed could be hardly rearranged to furan derivatives.⁶⁾

In conclusion, both five-coordinate organotin bromide complexes and tetraphenylstibonium bromide, which have similar structures, trigonal bipyramid, including axial metal-Br bonds, showed analogous catalytic activities. These catalytic systems could be treated under milder conditions than those of Pd-catalyst, and induced chemo- and stereoselective additions to α -halo ketone at the carbonyl group efficiently. They are convenient and useful catalysts for the stereoselective synthesis of oxiranes.

Experimental

General. Melting points were taken on a Yanagimoto melting-point apparatus and are uncorrected. IR spectra (KRS-5 windows or KBr pellets) were recorded on a Hitachi 260-30 spectrophotometer. 1H and ^{13}C NMR spectra were obtained with a Hitachi R-90H (90 and 22.6 MHz) or a JEOL JNM-GSX-400 (400 and 100 MHz) spectrometer, respectively with TMS as an internal standard. ^{119}Sn NMR spectra were obtained with a JEOL JNM-GSX-400 (149 MHz) spectrometer with Me_4Sn used as an internal standard. Mass spectra were recorded on a JEOL JMS-DS303 or a Shimadzu GCMS-QP2000A spectrometer. GLC analyses were performed on a Shimadzu GC-8A with FID using a 2 m $\times$ 3 mm column packed with SE-52. Flash chromatography was performed on silica gel (Wakogel C-300). Bulb-to-bulb distillation (Kugelrohr) was accomplished in a Sibata GTO-250RS at the indicated oven temperature and pressure. The yields were determined by GLC or 1H NMR using internal standards.

Materials. THF was distilled from sodium and benzophenone. HMPA was distilled from CaH_2 . The onium salts, $(Bu_4N)Br$, $(Bu_4P)Br$, $(Me_4N)Br$, and $(Et_4N)Br$ were commercial products and were dried in vacuo before using. Tetraphenylstibonium bromide (Ph_4SbBr) was prepared from commercial Ph_3Sb , $AlCl_3$, and $PhBr$ using a method reported in the literature.⁹⁾ Tin enolates **1a**–**d** were prepared by known methods.⁴⁾ 2-Chlorocyclohexanone (**2a**), 2-bromo-1-phenylethanone (**8a**) and 2-bromo-1-phenyl-1-propanone (**8c**) were commercial products. 2-Chloro-2-methylcyclohexanone (**2b**) and 2-chloro-1-phenyl-1-propanone (**8b**) were prepared according to the described methods.¹⁹⁾ Compounds **5a** and **5b**, *cis*- and *trans*-2-chloro-4-*tert*-butylcyclohexanone, were prepared by the standard procedure.²⁰⁾

General Procedure for Synthesis of Chlorohydrins

3 and 4. 2-Chlorocyclohexanone **2** (3.0 mmol) was added to a stirred solution of a tin enolate **1** (6.0 mmol) and catalyst (0.3 mmol) in dry THF (3 mL); the mixture was stirred at 40 °C for 24 h. After diethyl ether (100 mL) and aqueous NH_4F (15%; 40 mL) were added, the organic layer was separated and washed with water (50 mL $\times$ 2), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel and/or distillation to give the chlorohydrin **3**. In a noncatalyzed reaction, chlorohydrin **4** was obtained according to the above-mentioned method.

1-Acetonil-c-2-chlorocyclohexan-r-1-ol (3aa): Obtained from **1a** and **2a** according to the general procedure using flash chromatography (eluted by hexane-diethyl ether, 5:1) and distillation: Bp 100 °C/1.5 mmHg (1 mmHg = 133.322 Pa); IR (neat) 3450 (OH) and 1700 (C=O) cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ = 4.05 (1H, dd, J = 11.5 and 4.6 Hz, 2-H), 3.27 (1H, s, OH), 2.95, 2.64 (each 1H, each d, each J = 16.6 Hz, $CH_2C=O$), 2.21 (3H, s, CH_3), 2.15–1.2 (8H, m); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ = 208.8 (s, C=O), 72.5 (s, C-1), 67.8 (d, C-2), 51.7 (t, $CH_2C=O$), 36.1 (t), 32.1 (t), 32.0 (q, Me), 25.6 (t), 20.4 (t); MS m/z 192 ($M^+ + 2$), 190 (M^+). Found: m/z 190.0735. Calcd for $C_9H_{15}ClO_2$: M, 190.0762. Found: C, 56.46; H, 8.01; Cl, 18.29%. Calcd for $C_9H_{15}ClO_2$: C, 56.69; H, 7.93; Cl, 18.59%.

1-Acetonil-t-2-chlorocyclohexan-r-1-ol (4aa): Obtained from **1a** and **2a** according to the general procedure using flash chromatography (eluted by hexane-diethyl ether, 10:1): IR (neat) 3450 (OH) and 1690 (C=O) cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ = 4.26 (1H, d, J = 1.3 Hz, OH), 4.13 (1H, t, J = 3.8 Hz, 2-H), 3.07, 2.54 (each 1H, each d, each J = 17.6 Hz, $CH_2C=O$), 2.22 (3H, s, CH_3), 2.35–2.20 (1H, m), 1.8–1.4 (7H, m); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ = 211.0 (s, C=O), 73.0 (s, C-1), 63.9 (d, C-2), 48.9 (t, $CH_2C=O$), 32.9 (t), 31.8 (q, Me), 30.1 (t), 20.7 (t), 20.3 (t); MS m/z 192 ($M^+ + 2$), 190 (M^+). Found: m/z 190.0728. Calcd for $C_9H_{15}ClO_2$: M, 190.0762.

c-2-Chloro-1-phenacylcyclohexan-r-1-ol (3ba): Obtained from **1b** and **2a** according to the general procedure using flash chromatography (eluted by hexane-diethyl ether, 20:1) and distillation: Bp 123 °C/0.7 mmHg; IR (neat) 3450 (OH) and 1670 (C=O) cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ = 7.88–7.85 (2H, m), 7.51–7.35 (3H, m), 4.11 (1H, dd, J = 11.7 and 4.4 Hz, 2-H), 3.52 (1H, s, OH), 3.38, 3.13 (each 1H, each d, each J = 16.6 Hz, $CH_2C=O$), 2.1–1.2 (8H, m); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ = 200.0 (s, C=O), 137.1 (s), 133.2 (d), 128.3 (d), 127.8 (d), 72.9 (s, COH), 67.7 (d, CCl), 46.3 (t, $CH_2C=O$), 36.3 (t), 32.1 (t), 25.7 (t), 20.3 (t); MS m/z 254 ($M^+ + 2$), 252 (M^+). Found: m/z 252.0908. Calcd for $C_{14}H_{17}ClO_2$: M, 252.0918.

t-2-Chloro-1-phenacylcyclohexan-r-1-ol (4ba): Obtained from **1b** and **2a** according to the general procedure using flash chromatography (eluted by hexane-diethyl ether, 20:1): Mp 71–72 °C; IR (neat) 3480 (OH) and 1665 (C=O) cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ = 7.99–7.96 (2H, m), 7.62–7.46 (3H, m), 4.64 (1H, s, OH), 4.26 (1H, t, J = 3.30 Hz, 2-H), 3.63, 3.01 (each 1H, each d, each J = 17.6 Hz, $CH_2C=O$), 2.37–2.29 (1H, m), 1.94–1.47 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.2 (–, C=O), 137.0, 133.8 (+), 128.7 (+), 128.2 (+), 73.5 (–, C-1), 63.9 (+, C-2), 44.0 (–, $CH_2C=O$), 33.1 (–), 30.1 (–), 20.7 (–), 20.2 (–); MS m/z 254 ($M^+ + 2$), 252 (M^+). Found: m/z 252.0900. Calcd for $C_{14}H_{17}ClO_2$: M, 252.0918.

c-2-Chloro-1-(3,3-dimethyl-2-oxobutyl)cyclohexan-r-1-ol (3ca): Obtained from **1c** and **2a** according to the general procedure using flash chromatography (eluted by hexane–diethyl ether, 60:1); IR (neat) 3400 (OH) and 1690 (C=O) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ =4.07 (1H, dd, J =11.7 and 4.4 Hz, 2-H), 3.83 (1H, s, OH), 2.94, 2.71 (each 1H, each d, each J =17.6 Hz, $\text{CH}_2\text{C}=\text{O}$), 2.1–1.2 (8H, m); 1.14 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, CDCl_3) δ =217.4 (s, C=O), 72.8 (s, C-1), 67.7 (d, C-2), 45.0 (s, CMe_3), 44.7 (t, $\text{CH}_2\text{C}=\text{O}$), 36.3 (t), 32.1 (t), 26.2 (q, CMe_3), 20.4 (t), 20.4 (t); MS m/z 232 (M^+), 197 ($\text{M}^+ - \text{Cl}$). Found: m/z 232.1237. Calcd for $\text{C}_{12}\text{H}_{21}\text{ClO}_2$: M, 232.1231.

t-2-Chloro-1-(3,3-dimethyl-2-oxobutyl)cyclohexan-r-1-ol (4ca): Obtained from **1c** and **2a** according to the general procedure using flash chromatography (eluted by hexane–diethyl ether, 60:1); IR (neat) 3430 (OH) and 1675 (C=O) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ =4.72 (1H, s, OH), 4.17 (1H, t, J =3.42 Hz, 2-H), 3.13, 2.48 (each 1H, each d, each J =18.1 Hz, $\text{CH}_2\text{C}=\text{O}$), 2.32–2.29 (1H, m), 1.8–1.4 (7H, m), 1.16 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, CDCl_3) δ =219.3 (s, C=O), 73.0 (s, C-1), 63.4 (d, C-2), 45.0 (s, CMe_3), 42.8 (t, $\text{CH}_2\text{C}=\text{O}$), 32.8 (t), 29.9 (t), 26.2 (q, CMe_3), 20.6 (t), 20.0 (t); MS m/z 234 ($\text{M}^+ + 2$), 232 (M^+), 197 ($\text{M}^+ - \text{Cl}$). Found: m/z 232.1242. Calcd for $\text{C}_{12}\text{H}_{21}\text{ClO}_2$: M, 232.1231.

1-Acetyl-2-chloro-2-methylcyclohexan-r-1-ol (3ab): Obtained from **1a** and **2b** according to the general procedure using flash chromatography (eluted by hexane–diethyl ether, 10:1) and distillation: Bp 75 °C/0.7 mmHg; IR (neat) 1720 (C=O) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ =2.86, 2.61 (each 1H, each d, each J =17.1 Hz, $\text{CH}_2\text{C}=\text{O}$), 2.18 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.96–1.25 (8H, m), 1.26 (3H, s, 2- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ =206.0 (s, C=O), 62.1 (s), 61.7 (s), 49.8 (t, $\text{CH}_2\text{C}=\text{O}$), 31.3 (t), 30.4 (q, $\text{MeC}=\text{O}$), 29.9 (t), 20.7 (t), 20.5 (q, 2-Me), 25.3 (t); MS m/z 207 ($\text{M}^+ + 3$), 205 ($\text{M}^+ + 1$), 169 ($\text{M}^+ - \text{Cl}$). Found: m/z 205.0985. Calcd for $\text{C}_{10}\text{H}_{18}\text{ClO}_2$: M+1, 205.0996.

1-Acetyl-2-chloro-2-methylcyclohexan-r-1-ol (4ab): Obtained from **1a** and **2b** according to the general procedure using flash chromatography (eluted by hexane–diethyl ether, 10:1) and distillation: Bp 90 °C/0.7 mmHg; IR (neat) 1710 (C=O) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ =3.36 (1H, s, OH), 2.94, 2.47 (each 1H, each d, each J =15.1 Hz, $\text{CH}_2\text{C}=\text{O}$), 2.18 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 1.9–1.2 (8H, m), 1.56 (3H, s, 2- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ =209.6 (s, C=O), 80.1 (s), 75.2 (s), 47.9 (t, $\text{CH}_2\text{C}=\text{O}$), 39.1 (t), 33.7 (t), 32.5 (q, $\text{MeC}=\text{O}$), 26.3 (q, 2-Me), 23.0 (t), 21.0 (t); MS m/z 207 ($\text{M}^+ + 3$), 205 ($\text{M}^+ + 1$), 169 ($\text{M}^+ - \text{Cl}$). Found: m/z 205.1004. Calcd for $\text{C}_{10}\text{H}_{18}\text{ClO}_2$: M+1, 205.0996.

1-Acetyl-4-tert-butyl-2-chlorocyclohexan-r-1-ol (6a): Obtained from **1a** and *cis*-4-tert-butyl-2-chlorocyclohexanone (**5a**) in THF at 40 °C for 24 h and purified by flash chromatography (eluted by hexane–diethyl ether, 3:2); mp 56–58 °C; IR (neat) 3480 (OH) and 1690 (C=O) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ =4.06 (1H, dd, J =12.2 and 4.4 Hz, 2-H), 3.25 (1H, s, OH), 2.98, 2.61 (each 1H, each d, each J =16.6 Hz, $\text{CH}_2\text{C}=\text{O}$), 2.20 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.1–1.75 (3H, m), 1.55–1.4 (3H, m), 1.25–1.05 (1H, m), 0.87 (9H, s, *t*-Bu); ^{13}C NMR (22.6 MHz, CDCl_3) δ =208.8 (–, C=O), 72.0 (–, C-1), 68.7 (+, C-2), 51.9 (–, $\text{CH}_2\text{C}=\text{O}$), 48.3 (+, C-4), 36.1 (–), 33.4 (–), 32.4 (–, CMe_3), 32.0 (+, $\text{CH}_3\text{C}=\text{O}$), 27.4 (+, CMe_3), 21.2 (–); MS m/z 248 ($\text{M}^+ + 2$),

246 (M^+). Found: C, 63.10; H, 9.36; Cl, 14.46%. Calcd for $\text{C}_{13}\text{H}_{23}\text{ClO}_2$: C, 63.27; H, 9.39; Cl, 14.37%. The stereochemistry of the title compound **6a** which has a fixed conformation was established by ^1H NMR spectroscopy. When the proton at δ =4.06 (2-H) was irradiated, NOEs with the methylene protons (δ =2.98, d) and (δ =2.61, d) were observed.

1-Acetyl-4-tert-butyl-2-chlorocyclohexan-r-1-ol (6b): Obtained from **1a** and **5b** under the condition noted in Table 2 and purified by flash chromatography (eluted by hexane–diethyl ether, 10:1); bp 80 °C/0.08 mmHg; IR (neat) 3480 (OH) and 1708 (C=O) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ =4.27 (1H, t, J =2.4 Hz, 2-H), 4.21 (1H, d, J =1.5 Hz, OH), 3.09, 2.49 (each 1H, each d, each J =18.1 Hz, $\text{CH}_2\text{C}=\text{O}$), 2.22 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.1–1.4 (7H, m), 0.86 (9H, s, *t*-Bu); ^{13}C NMR (22.6 MHz, CDCl_3) δ =211.4 (–, C=O), 72.4 (–, C-1), 63.4 (+, C-2), 50.3 (–, $\text{CH}_2\text{C}=\text{O}$), 40.0 (+, C-4), 32.3 (–), 31.8 (–, CMe_3), 31.6 (+, $\text{CH}_3\text{C}=\text{O}$), 30.4 (–), 27.4 (+, CMe_3), 21.2 (–); MS m/z 248 ($\text{M}^+ + 2$), 246 (M^+). Found: m/z 246.1371. Calcd for $\text{C}_{13}\text{H}_{23}\text{ClO}_2$: M, 246.1388.

1-Acetyl-4-tert-butyl-2-chlorocyclohexan-r-1-ol (7b): Obtained from **1a** and **5b** under the catalyzed condition noted in Table 2 and purified by flash chromatography (eluted by hexane–diethyl ether, 10:1); IR (neat) 3480 (OH) and 1710 (C=O) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ =4.50 (1H, br s, 2-H), 2.98 (1H, s, OH), 2.77, 2.66 (each 1H, each d, each J =14.2 Hz, $\text{CH}_2\text{C}=\text{O}$), 2.26 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.1–2.0 (1H, m), 1.9–1.8 (1H, m), 1.75–1.65 (4H, m), 1.2–1.0 (1H, m), 0.87 (9H, s, *t*-Bu); ^{13}C NMR (22.6 MHz, CDCl_3) δ =208.6 (–, C=O), 72.5 (–, C-1), 68.3 (+, C-2), 48.2 (–, $\text{CH}_2\text{C}=\text{O}$), 39.7 (+, C-4), 33.4 (–), 32.8 (+, $\text{CH}_3\text{C}=\text{O}$), 32.3 (–), 31.7 (–, CMe_3), 27.5 (+, CMe_3), 23.7 (–); MS m/z 248 ($\text{M}^+ + 2$), 246 (M^+). Found: m/z 246.1394. Calcd for $\text{C}_{13}\text{H}_{23}\text{ClO}_2$: M, 246.1388.

Determination of Stereochemistry. The stereochemistries of **3** and **4** were determined as follows. The ^1H and ^{13}C NMR spectra of **3aa** and **4aa** were in good analogy with 1-acetyl-4-tert-butyl-2-chlorocyclohexan-r-1-ol (**6a**)⁸ and 1-acetyl-4-tert-butyl-2-chlorocyclohexan-r-1-ol (**6b**), respectively. The other chlorohydrins **3** and **4** showed analogous peaks to the NMR spectra of **3aa** and **4aa**, respectively.

Synthesis of 2-(2-Oxoethyl)oxirane (9). Typical procedure for the synthesis of **9aa** catalyzed by the Bu_3SnBr – Bu_4NBr complex. — After a mixture of tributyltin bromide (0.1 mmol) and tetrabutylammonium bromide (0.1 mmol) in THF (1 mL) was stirred for 20 min and tin enolate **1a** (1.2 mmol) and 2-bromo-1-phenylethanone (**8a**) (1.0 mmol) were added, the mixture was stirred for 2 h under nitrogen.

The spectral data of compounds **9aa**, **9ba**, **9da**, **9ab**, **10aa**, **10ba**, **10da**, and **10ac** were described in our previous papers.^{5,7b)}

Noncatalyzed Reaction of 1a with 8b. After 2-chloro-1-phenyl-1-propanone (**8b**) (5.0 mmol) was added to a stirred solution of a tin enolate **1a** (10.0 mmol) in dry THF (6 mL), the mixture was stirred at 40 °C for 24 h. Diethyl ether (100 mL) and aqueous NH_4F (15%; 40 mL) were then added, and the organic layer was separated and washed with water (50 mL $\times$ 2), dried (MgSO_4) and evaporated. The crude product was purified by flash chromatography on silica

gel (eluted by hexane-diethyl ether, 5:1) to give **11** and **12** in this order. The stereochemistries of these compounds, **11** and **12**, were determined by cyclization of the intermediate carbonyl adduct as follows. After stirring a mixture of **8b** (1.0 mmol) and **1a** (2.0 mmol) in THF (2 mL) at 40 °C for 24 h, 2.0 mmol of HMPA was added, the solution was stirred at 40 °C for 3 h. After a work-up, cyclized product **9ab** (18%) from [C], non-cyclized **12** (32%), and **11** (6%) were obtained. The structure of **9ab** was identified by comparing it with a sample obtained previously.^{7b)}

(4R*,5R*)-5-Chloro-4-hydroxy-4-phenylhexan-2-one (11): IR (neat) 3425 (OH) and 1700 (C=O) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ =7.55–7.25 (5H, m), 4.79 (1H, s, OH), 4.27 (1H, q, J =6.67 Hz, 5-H), 3.38, 3.22 (each 1H, each d, each J =17.1 Hz, 3-H₂), 2.18 (3H, s, 1-H₃), 1.29 (3H, d, J =6.67 Hz, 6-H₃); ¹³C NMR (22.6 MHz, CDCl₃) δ =210.1 (s, C-2), 141.1 (s), 127.7 (d), 127.4 (d), 126.0 (d), 77.2 (s, C-4), 63.6 (d, C-5), 48.7 (t, C-3), 31.7 (q, C-1), 19.3 (q, C-6); MS m/z 229 (M^+ +3), 227 (M^+ +1). Found: C, 63.42; H, 6.88; Cl, 15.52%. Calcd for C₁₂H₁₅ClO₂: C, 63.58; H, 6.67; Cl, 15.64%.

(4S*,5R*)-5-Chloro-4-hydroxy-4-phenylhexan-2-one (12): IR (neat) 3450 (OH) and 1700 (C=O) cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ =7.42–7.25 (5H, m), 4.73 (1H, s, OH), 4.19 (1H, q, J =6.67 Hz, 5-H), 3.28 (2H, s), 2.04 (3H, s, 1-H₃), 1.27 (3H, d, J =6.67 Hz, 6-H₃); ¹³C NMR (22.6 MHz, CDCl₃) δ =209.7 (s, C-2), 142.9 (s), 128.4 (d), 127.5 (d), 125.4 (d), 77.6 (s, C-4), 65.7 (d, C-5), 51.1 (t, C-3), 32.0 (q, C-1), 18.9 (q, C-6); MS m/z 229 (M^+ +3), 227 (M^+ +1). Found: C, 63.18; H, 6.68; Cl, 15.78%. Calcd for C₁₂H₁₅ClO₂: C, 63.58; H, 6.67; Cl, 15.64%.

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- 1) a) Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists; b) Present address: Department of Applied Chemistry, Osaka Institute of Technology, 5-16-1 Omiya, Asahi, Osaka 535, Japan.
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