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Highly Stereoselective Addition of Tin Enolate to α-Chloro Cyclic Ketone Derivatives Catalyzed by Ph_4SbBr

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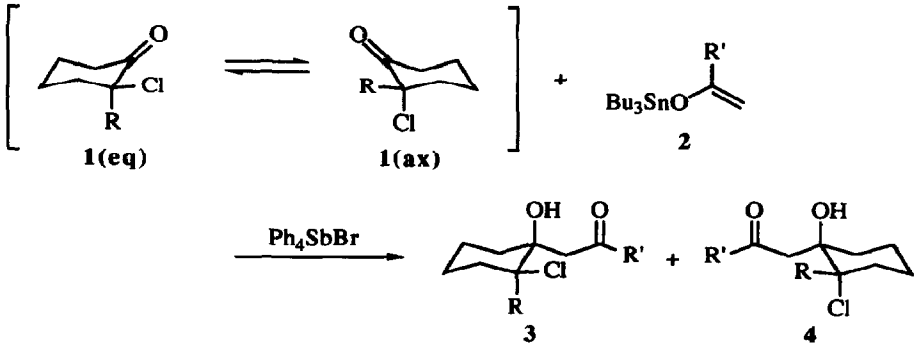
Abstract: Tetraphenylstibonium bromide was shown to be an effective catalyst for the stereoselective nucleophilic addition of tin enolates **2** to α-chloro cyclic ketone derivatives **1**, furnishing chlorohydrins **3** bearing chloro- and hydroxyl groups in *cis*-conformation selectively.

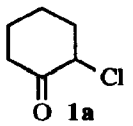
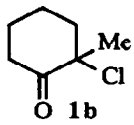
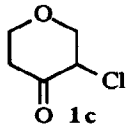
Stereoselective nucleophilic additions of organometallics to carbonyl groups in cyclic ketones,[2] especially functionalized six-membered ones, have been extensively studied.[3,4] For example, an axial substituent at C2 in cyclohexanones is reported to strongly affect the stereoselective reduction with $LiAlH_4$.[5] In the allylation of 2-methoxycyclohexanone with allyltrimethylsilane, Reetz and co-workers reported the addition of an equimolar amount of $TiCl_4$ achieved exclusive equatorial attack at the carbonyl carbon where a chelate complex of the cyclohexanone and $TiCl_4$ has been confirmed.[6] In general, a chelation control under catalytic conditions has been scarcely reported except for few acyclic systems.[7] 2-Chlorocyclohexanones are expected to be 2-functionalized ketones having some lower chelation ability than the corresponding alkoxy ketones. We recently reported the nucleophilic addition of tin enolates to α-halo cyclic ketones briefly,[8] although no stereocontrol was investigated. The stereoselective addition of tin enolate is thought to be disturbed by facile transmetallation between the tin compounds and Lewis acids like $TiCl_4$ or $SnCl_4$. We now report a catalytic stereocontrol in the reaction of tin enolates **2** with six-membered cyclic ketones **1** bearing chlorine at α-position.



Scheme 1

Since 2-chlorocyclohexanone derivatives **1** exist as equilibrium mixtures of **1(eq)** and **1(ax)**,[9] the reaction with tin enolates **2** is expected to afford mixtures of chlorohydrins **3** and **4** (Scheme 1). The results investigated are summarized in Table 1.[10,11] No stereoselectivity was observed in the addition of tin enolate **2a** to 2-chlorocyclohexanone **1a** under non-catalyzed conditions (entry 1). Using a catalytic amount (0.1 equiv) of quaternary onium salts, however, effected highly stereoselective addition, giving preferably **3aa**. The addition of Bu_4NBr or Bu_4PBr resulted in a low yield and a considerable amount of starting material **1a** did not react in spite of the high selectivities (entries 2, 3). On the contrary, Ph_4SbBr afforded both high yield and selectivity (entry 4).[12] So far as we know, this is the first example of catalytic stereocontrol of carbonyl addition in cyclic ketones. The low conversions of **1a** in entries 2 and 3 are perhaps due to the consumption of a considerable amount of Bu_4NBr or Bu_4PBr owing to their complexation with tin enolate **2a**,[8] whereas Ph_4SbBr would hardly interact with **2a** because of covalent character of the Sb-Br bond.[13] This reaction system could be applied to representative tin enolates **2a-c** and cyclic α-chloroketones **1a-c**.

Table 1. Reaction of Tin Enolate 2 with Chloroketone 1

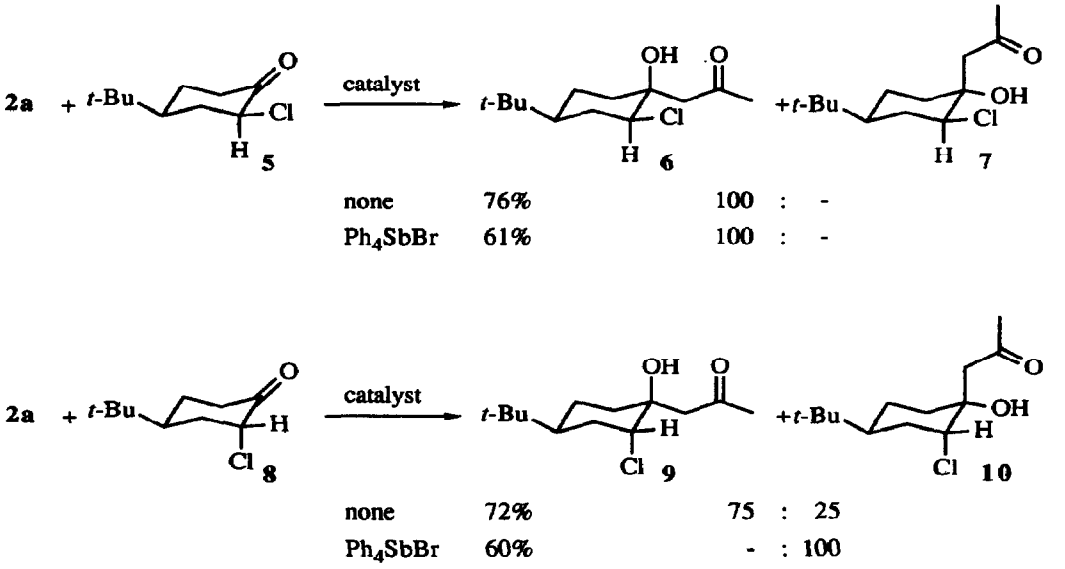
entry	1	R' in 2	catalyst	yield (%)[a]	ratio[b] 3 : 4
1	 **1a**	a: Me	none	**aa**: 95	48 : 52
2			Bu_4NBr	24	100 : -
3			Bu_4PBr	24	97 : 3
4			Ph_4SbBr	68	95 : 5
5		b: Ph	none	**ab**: 100	60 : 40
6			Ph_4SbBr	75	100 : -
7		c: *t*-Bu	none	**ac**: 79	63 : 37
8			Ph_4SbBr	44	100 : -
9	 **1b**	a: Me	none	**ba**: 56	82 : 18
10			Ph_4SbBr	91	95 : 5
11	 **1c**	a: Me	none	**ca**: 63	73 : 27
12			Ph_4SbBr	89	86 : 14

[a] Yields were determined by GLC.

[b] Isomeric ratios were determined by ^1H NMR on the crude mixture.

All compounds were isolated and showed characteristic spectral data and exact mass spectroscopic data.

In order to investigate the stereocontrol by Ph_4SbBr, the addition toward two diastereomers of 2-chloro-4-*tert*-butylcyclohexanones **5** and **8**, bearing equatorial and axial chloro groups, respectively, was examined as depicted in Scheme 2. Exclusive equatorial attack to **5** was observed irrespective of the presence of Ph_4SbBr, producing **6** in complete selectivities. Equatorial attack was also favored (75%) in the non-catalyzed reaction of **8**, whereas a drastic change of diastereoselectivity was caused by a catalytic amount of Ph_4SbBr to exclusively produce the adduct **10** *via* axial attack. Consequently, Ph_4SbBr-catalyst gave only chlorohydrins having *cis*-conformation for chloro- and hydroxy groups, **6** and **10**. In addition, a similar range of yields were obtained from both diastereomers, **5** and **8**. These results indicates that the addition of Ph_4SbBr gave *cis*-form **3** when tin enolates **2** react with either **1(eq)** or **1(ax)**. Of course, the path including conversion of **1(ax)** to **1(eq)** promoted by Ph_4SbBr can not be ruled out in this stage.



Scheme 2

This catalytic system examined is very convenient and useful for stereoselective organic syntheses. We assume that coordination of chlorine atom in **1(ax)** to Ph_4SbBr would cause the unusual nucleophilic attack, although the reaction mechanism has not yet been clear, and further investigations are in progress.

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References and Notes

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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10. Typical procedure: 2-Chlorocyclohexanone **1a** (3.0 mmol) was added to a stirred solution of a tin enolate **2a** (6.0 mmol) and tetraphenylstibonium bromide (0.3 mmol) in dry THF (3 mL) and the mixture was stirred at 40 °C for 24 h. Diethyl ether (100 mL) and aqueous NH_4F (15%; 40 mL) were added, the organic layer was separated and washed with water (50 mL × 2), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (eluted by hexane-diethyl ether, 5 :1, R_f = 0.24) on silica gel to give the chlorohydrin **3aa**. A little amount of crude isomer **4aa** (eluted by hexane-diethyl ether, 5 :1, R_f = 0.30) was identified by comparison with the ^1H NMR spectral data of **4aa** isolated from uncatalyzed reaction (entry 1 in Table 1).
11. Typical spectral data.
    3aa: IR (neat) 3450, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.05 (dd, 1H, *J* = 11.5 and 4.6 Hz), 3.27 (s, 1H), 2.95 (d, 1H, *J* = 16.6 Hz), 2.64 (d, 1H, *J* = 16.6 Hz), 2.21 (s, 3H), 2.15-1.2 (m, 8H); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 208.8, 72.5, 67.8, 51.7, 36.1, 32.1, 32.0, 25.6, 20.4; MS *m* / *z* 192 (M^+ + 2), 190 (M^+); HRMS calcd for $C_9H_{15}ClO_2$ 190.0762, found *m* / *z* 190.0735 (M^+).
    4aa: IR (neat) 3450, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (s, 1H), 4.13 (t, 1H, *J* = 3.8 Hz), 3.07 (d, 1H, *J* = 17.6 Hz), 2.54 (d, 1H, *J* = 17.6 Hz), 2.22 (s, 3H), 2.35-2.20 (m, 1H), 1.8-1.4 (m, 7H); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 211.0, 73.0, 63.9, 48.9, 32.9, 31.8, 30.1, 20.7, 20.3; MS *m* / *z* 192 (M^+ + 2), 190 (M^+); HRMS calcd for $C_9H_{15}ClO_2$ 190.0762, found *m* / *z* 190.0728 (M^+).
12. Tetraphenylstibonium bromide is stable and easy to handle. It was prepared according to the described method: Chatt, J.; Mann, F. G. *J. Chem. Soc.* **1940**, 1195.
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