Aldol Reactions of α-Bromoalkyl Phenyl Ketones and Aldehydes with Tin(IV) Iodide and Tetrabutylammonium Iodide

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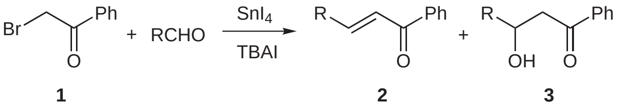
Abstract: Aldol reactions of α-bromoacetophenone and aldehydes in dichloromethane produced the corresponding *E*-α,β-unsaturated ketones at 25 °C with one equimolar amount of tin(IV) iodide, one equimolar amount of tetrabutylammonium iodide and one equimolar amount of *N*,*N*-diisopropylethylamine, and produced the corresponding β-hydroxy ketones at –80 °C with one equimolar amount of tin(IV) iodide and two equimolar amounts of tetrabutylammonium iodide. Using one equimolar amount of tin(IV) iodide and two equimolar amounts of tetrabutylammonium iodide at –80 °C in dichloromethane, α-bromopropiophenone reacted with aldehydes to afford the corresponding *syn*-α-methyl-β-hydroxy ketones selectively.

Key words: aldol reactions, diastereoselectivity, tin, enones, β-hydroxyketones

The crossed aldol reaction is one of the most versatile synthetic tools for carbon–carbon bond formation, and many convenient methods for generating metal enolates have been developed.[1] α-Halo ketones such as α-bromoacetophenone undergo reductive dehalogenation with low-valent metal reagents to yield the corresponding metal enolates that are applied to crossed aldol reactions.[2–15] We have found that a combo-reagent of tin(IV) iodide and tetrabutylammonium iodide (TBAI) can be applied to a carbonyl allylation with 2-propenyl chlorides and a carbonyl propargylation and allenylation with 2-propynyl mesylates.[16] For example, in the carbonyl allylation, triiodostannate(II) ion (SnI_3^-), derived by the reduction of SnI_4 with I^-,[4,17] would cause nucleophilic substitutions in 2-propenyl chlorides to yield 2-propenyltriiodotins that would function as allylic anions. We thus hoped that the triiodostannate(II) ion would mediate the formation of triiodotin enolates from α-bromo ketones to cause crossed aldol reactions with aldehydes.



Equation 1

The aldol reaction of α-bromoacetophenone (**1**) and benzaldehyde with tin(IV) iodide and TBAI was investigated under various conditions. The results are summarized in Table 1 (Equation 1, R = Ph). The addition of two equimolar amounts of TBAI to tin(IV) iodide caused the aldol condensation of **1** and benzaldehyde in dichloromethane at 25 °C to produce an α,β-unsaturated ketone, namely (*E*)-chalcone (**2**, R = Ph), selectively (entry 1). The aldol condensation proceeded poorly with one equimolar amount of TBAI. The use of one equimolar amount of TBAI and one equimolar amount of *N*,*N*-diiso-

Table 1 Aldol Reaction of **1** and Benzaldehyde[a]

Entry	TBAI (mmol)	*i*-Pr_2NEt (mmol)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	
						2	**3**
1	2.0	–	CH_2Cl_2	25	48	57	–
2	1.0	1.0	CH_2Cl_2	25	48	68	–
3	1.0	1.0	THF	25	48	67	–
4	1.0	1.0	DMF	25	67	38	–
5	2.0	–	CH_2Cl_2	–80	48	–	52
6	1.0	1.0	CH_2Cl_2	–80	48	25	51

[a] The reaction of **1** (1.1 mmol) and benzaldehyde (1.0 mmol) was carried out with tin(IV) iodide (1.0 mmol) in solvent (2 mL).
[b] Isolated yields.

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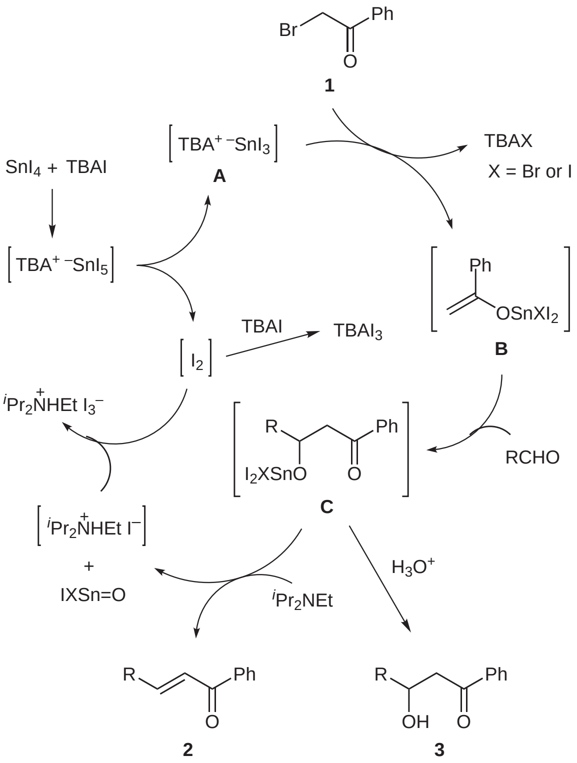
propylethylamine as a base to tin(IV) iodide enhanced the yield of **2** (R = Ph) (entry 2). The aldol reaction with two equimolar amounts of TBAI at –80 °C selectively afforded β-hydroxy ketone **3** (R = Ph) (entry 5), while the aldol reaction with one equimolar amount of TBAI and one equimolar amount of *N*,*N*-diisopropylethylamine at –80 °C afforded a mixture of **2** (R = Ph) and **3** (R = Ph) (entry 6). The aldol reaction did not occur without either tin(IV) iodide or TBAI. Tin(II) iodide instead of tin(IV) iodide under the same conditions as those of entry 1 did not cause the aldol reaction.[2,4,6]

The reaction conditions of entry 2 or entry 5 in Table 1 can be applied to various aldehydes to selectively prepare the corresponding *E*-α,β-unsaturated ketones **2** or the corresponding β-hydroxy ketones **3**, respectively (Equation 1, Table 2). The use of tetrahydrofuran as a solvent at –80 °C facilitated the aldol reaction with 4-chlorobenzaldehyde to enhance the yield of **2** together with **3** (entry 8). The combo-reagent of SnI_4 and TBAI did not cause pinacol coupling of any aldehyde or **1** in the reactions in Tables 1 and 2.

A plausible mechanism for the aldol reaction of **1** with aldehydes is illustrated in Scheme 1. Tin(IV) iodide is first reduced to triiodostannate(II) ion **A** with TBAI via the reductive elimination of iodine from pentaiodostannate(IV) ion. The stannate(II) ion **A** causes nucleophilic substitution in **1** to give triiodotin enolate **B**, which undergoes nucleophilic addition to aldehydes to afford β-triiodostannyloxy ketones **C**. *N*,*N*-Diisopropylethylamine promotes β-elimination from **C** to produce *E*-α,β-unsaturated ketones **2** together with IXSn=O and *N*-ethyl-*N*,*N*-diisopropylammonium iodide. The *N*-ethyl-*N*,*N*-diisopropylammonium iodide captures iodine by the reductive elimination from pentaiodostannate(IV) ion. A second TBAI performs a part of the capture of iodine in the aldol reaction without *N*,*N*-diisopropylethylamine. In addition, β-triiodostannyloxy ketones **C** formed at –80 °C can be treated with acetic acid to produce β-hydroxy ketones **3**.



Scheme 1 A plausible mechanism for the aldol reaction of **1** with aldehydes

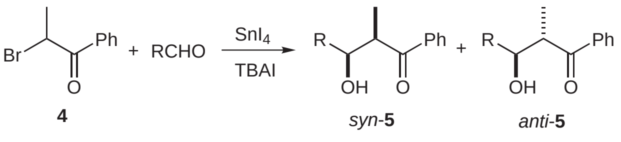
Table 2 Selective Preparation of *E*-α,β-Unsaturated Ketones **2** and β-Hydroxy Ketones **3**

Entry	R	Temp (°C)	Time (h)	Yield (%)[a]	
				2	**3**
1	4-ClC_6H_4	25	48	67	–
2	4-$MeOC_6H_4$	25	48	59	–
3	4-MeC_6H_4	25	48	59	–
4	PhCH=CH	25	54	64	–
5	PhCHMe	25	72	43	–
6	C_6H_{13}	25	48	52	–
7	*c*-C_6H_{11}	25	49	53	–
8[b]	4-ClC_6H_4	–80	49	19	55
9	4-$MeOC_6H_4$	–80	48	6	47
10	4-MeC_6H_4	–80	50	3	53
11	PhCH=CH	–80	51	–	63
12	PhCHMe	–80	50	–	43
13	C_6H_{13}	–80	60	–	44
14	*c*-C_6H_{11}	–80	66	–	31

[a] Isolated yields.

[b] THF (3 mL) was used as a solvent, because 4-chlorobenzaldehyde was hardly soluble in CH_2Cl_2 at –80 °C.

α-Bromopropiophenone (**4**) reacted with various aldehydes under the same conditions as those of entry 5 in Table 1 to produce the corresponding *syn*-α-methyl-β-hydroxy ketones *syn*-**5** selectively (Equation 2). The results are summarized in Table 3. The *syn* diastereoselectivity might be explained by the formation of *Z* enolate **E** from a σ*–π*-dominated Felkin–Anh model **D**[18] followed by the nucleophilic addition of **E** to aldehydes via a chair-formed six-membered cyclic transition state **F**, as shown in Scheme 2.



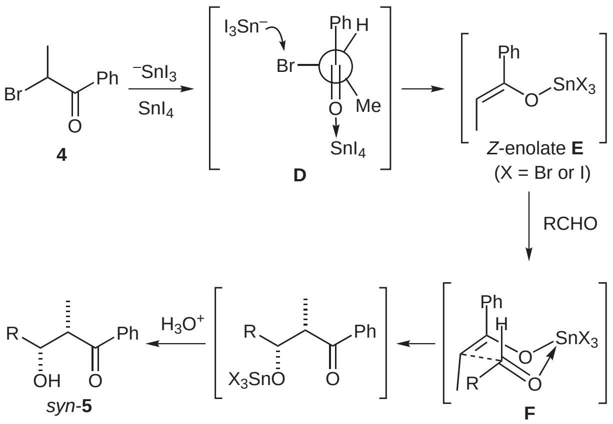
Equation 2

Table 3 Selective Preparation of *syn*-α-Methyl-β-hydroxy Ketones *syn*-**5**

Entry	R	Temp (°C)	Time (h)	**5**, Yield (%)[a] (*syn*/*anti*)[b]
1	Ph	–80	47	41 (93:7)
2	4-MeC_6H_4	–80	48	43 (96:4)
3	PhCH=CH	–80	49	45 (94:6)
4	$PhCH_2CH_2$	–80	50	50 (89:11)
5	C_6H_{13}	–80	69	32 (92:8)
6	*c*-C_6H_{11}	–80	68	30 (100:0)

[a] Isolated yields.

[b] The isomer ratios were determined by ^1H NMR analysis (JEOL JNM-LA500); see ref.[14]



Scheme 2 Diastereoselective crossed aldol reaction

Preparation of α,β-Unsaturated Ketones; Typical Procedure (Table 1, Entry 2)

To a solution of tin(IV) iodide (0.63 g, 1.0 mmol) and α-bromoacetophenone (**1**; 0.22 g, 1.1 mmol) in CH_2Cl_2 (2 mL) were successively added TBAI (0.37 g, 1.0 mmol), benzaldehyde (0.11 g, 1.0 mmol) and *N*,*N*-diisopropylethylamine (0.13 g, 1.0 mmol) at 25 °C under a nitrogen atmosphere. After stirring the mixture for 48 h, it was diluted with CH_2Cl_2 (100 mL) and washed successively with aq NH_4Cl solution (20 mL), aq $NaHCO_3$ solution (20 mL), H_2O (20 mL) and brine (20 mL). The extract was dried over anhyd $MgSO_4$. After evaporation of solvent, purification by column chromatography (silica gel, hexane–EtOAc, 7: 1) and then HPLC (Japan Analytical Industry Co. Ltd., LC-908, JAIGEL-2H, $CHCl_3$) afforded (*E*)-chalcone (**2**; 0.14 g, 68%; R = Ph).

Preparation of β-Hydroxy Ketones; Typical Procedure (Table 1, Entry 5)

To a solution of tin(IV) iodide (0.63 g, 1.0 mmol) and α-bromoacetophenone (**1**; 0.22 g, 1.1 mmol) in CH_2Cl_2 (2 mL) were successively added TBAI (0.74 g, 2.0 mmol) and benzaldehyde (0.11 g, 1.0 mmol) at –80 °C under a nitrogen atmosphere. After this mixture was stirred for 48 h at –80 °C, Et_2O (5 mL) containing AcOH (0.2 mL) was added. The mixture was diluted with CH_2Cl_2 (100 mL) and washed successively with aq $NaHCO_3$ solution (20 mL), H_2O (20 mL) and brine (20 mL). The CH_2Cl_2 extract was dried over anhyd $MgSO_4$. After evaporation of solvent, purification by column chromatography (silica gel, hexane–EtOAc, 5: 1) and then HPLC (Japan Analytical Industry Co. Ltd., LC-908, JAIGEL-2H; $CHCl_3$) afforded β-hydroxy ketone **3** (0.12 g, 52%; R = Ph).

References and Notes

(1) In *Comprehensive Organic Syntheses*, Vol. 2; Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.; Pergamon: Oxford, **1991**, 99.

(2) Sn: (a) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 467. (b) Chan, T. H.; Li, C. J.; Wei, Z. Y. *J. Chem. Soc., Chem. Commun.* **1990**, 505.

(3) $CrCl_2$: Dubois, J.-E.; Axiotis, G.; Bertounesque, E. *Tetrahedron Lett.* **1985**, *26*, 4371.

(4) CeI_3, $CeCl_3$–NaI or $SnCl_2$: Fukuzawa, S.; Tsuruta, T.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1473.

(5) Et_3B–Ph_3SnH: Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403.

(6) $SnCl_2/Na_2SO_3$: Lin, R.; Yu, Y.; Zhang, Y. *Synth. Commun.* **1993**, *23*, 271.

(7) SmI_2: Aoyagi, Y.; Yoshimura, M.; Tsuda, M.; Tsuchibuchi, T.; Kawamata, S.; Tateno, H.; Asano, K.; Nakamura, H.; Obokata, M.; Ohta, A.; Kodama, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 689.

(8) Et_2Zn, Et_3B, Me_3Al, EtMgBr: Aoki, Y.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1995**, 463.

(9) $Co(PMe_3)_4$: Orsini, F. *J. Org. Chem.* **1997**, *62*, 1159.

(10) $BiCl_3$–Al: Shen, Z.; Zhang, J.; Zou, H.; Yang, M. *Tetrahedron Lett.* **1997**, *38*, 2733.

(11) GaI_3: Han, Y.; Huang, Y.-Z. *Tetrahedron Lett.* **1998**, *39*, 7751.

(12) GeI_2–K: Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691.

(13) $Bu_3SnSnBu_3$–Bu_2SnI_2: Shibata, I.; Kawasaki, M.; Yasuda, M.; Baba, A. *Chem. Lett.* **1999**, 689.

(14) $TiCl_2$: Kagayama, A.; Igarashi, K.; Shiina, I.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2579.

(15) Bi–ZnF_2: Lee, Y. J.; Chan, T. H. *Can. J. Chem.* **2003**, *81*, 1406.

(16) (a) Masuyama, Y.; Takeuchi, K.; Kurusu, Y. *Tetrahedron Lett.* **2005**, *46*, 2861. (b) Masuyama, Y.; Yamazuki, R.; Ohtsuka, M.; Kurusu, Y. *Synlett* **2006**, 1750.

(17) Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, *65*, 5066.

(18) Since tin(II) iodide is not applicable for the aldol reactions with **1** or **4**, in contrast to the carbonyl allylation with 2-propenyl chlorides and the carbonyl propargylation or allenylation with 2-propynyl mesylates,[16b,19] tin(IV) iodide probably plays an important role in the aldol reactions. That is to say, the coordination of tin(IV) to carbonyl oxygen of **1** or **4** should mediate the preparation of tin(IV) enolates from **1** and **4**. Thus, we proposed that **4** was reduced to *Z* enolate **E** via the σ*–π*-dominated Felkin–Anh model **D**. For the σ*–π*-dominated Felkin–Anh model **D**, see: Atkinson, R. S. *Stereoselective Synthesis*; Wiley: Chichester, **1995**, 300.

(19) (a) Masuyma, Y. *Recent Res. Dev. Org. Chem.* **2000**, *4*, 373. (b) Masuyama, Y.; Watabe, A.; Ito, A.; Kurusu, Y. *Chem. Commun.* **2000**, 2009.