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Diastereoselective Reductive Aldol Reaction of Enones to Ketones Catalyzed by Halogenotin Hydride

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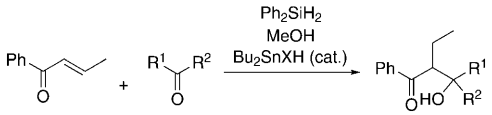
In memory of Professor Haruo Matsuda

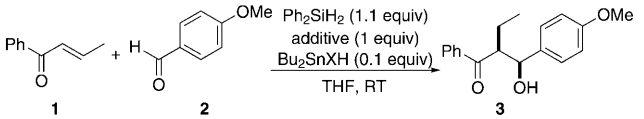
The reductive aldol reaction promoted by metal hydrides is a valuable method for obtaining β-hydroxycarbonyls in a one-pot synthesis. The advantage of this reaction is that there is no need to isolate metal enolates. To date, catalytic reductive aldol reaction of enones[1] or unsaturated esters[2a–d] to aldehydes have been reported. In particular, enantioselective reactions have been developed for the reaction using unsaturated esters.[2] However, the reductive aldol reaction of enones to ketones instead of aldehydes is uncommon due to the low reactivity of intermediate enolates and low electrophilicity to ketones.[3] We have previously reported that use of dibutylhalogenotin hydride (Bu_2SnIH)[4] as stoichiometric metal hydride promoted reductive aldol reaction of enones to aldehydes. We investigated catalytic use of dibutylhalogenotin hydride (Bu_2SnClH or Bu_2SnIH) for reductive aldol reaction of enones, and found here that high reactivity, high chemo- and diastereoselectivity of intermediate tin enolates toward ketones. (Scheme 1).



Scheme 1. Reductive aldol reaction of enones.

Initially, we examined the reductive aldol reaction of 1-phenyl-2-buten-1-one (**1**) with *p*-methoxybenzaldehyde (**2**) in the presence of a catalytic amount of Bu_2SnIH and stoichiometric Ph_2SiH_2 (Table 1, entry 1). However, aldol product **3** was obtained in only 15% yield. In addition, the diastereoselectivity of **3** was low. We previously reported on the Bu_2SnClH complex-catalyzed reductive amination of carbonyl compounds with primary amines by using hydrosilanes as hydride sources.[5] In this reaction, the presence of water was critical for the catalytic reaction. Accordingly, herein addition of water (1 equiv) promoted the reductive aldol reaction to give **3** in 51% yield with high *syn*-selectivity (entry 2). A side reaction took place to give 1-phenylbutan-1-one, generated by conjugate reduction of **1**, in 47% yield. The yield of **3** was increased by using MeOH as an additive and by-products such as 1-phenyl-butan-1-one were not obtained in significant amounts (entry 3). Furthermore,

Table 1. Optimization of reductive aldol reaction of enone **1** to aldehyde **2**.



1 2 3

Entry	Bu_2SnXH	Additive	*t* [h]	Yield [%] (*syn*/*anti*)[a]
1	Bu_2SnIH	none	24	15 (34:66)
2	Bu_2SnIH	H_2O	3	51[b] (89:11)
3	Bu_2SnIH	MeOH	3	76 (91:9)
4	Bu_2SnClH	MeOH	4	93 (89:11)
5	Bu_2SnClH	MeOH[c]	4	52 (93:7)
6[d]	Bu_2SnClH	MeOH	4	67 (86:14)
7[e]	Bu_2SnClH	MeOH	4	88 (44:56)
8	Bu_2SnClH	*i*PrOH	24	97 (66:34)

[a] Conditions: Bu_2SnClH (0.1 mmol), Ph_2SiH_2 (1.1 mmol), **1a** (1 mmol), **2a** (1 mmol), Additive (1 mmol), THF (1 mL). [b] 1-Phenyl-butan-1-one was obtained in 47% yield. [c] MeOH (3 mmol) was used. [d] $PhSiH_3$ (1.1 mmol) was used instead.

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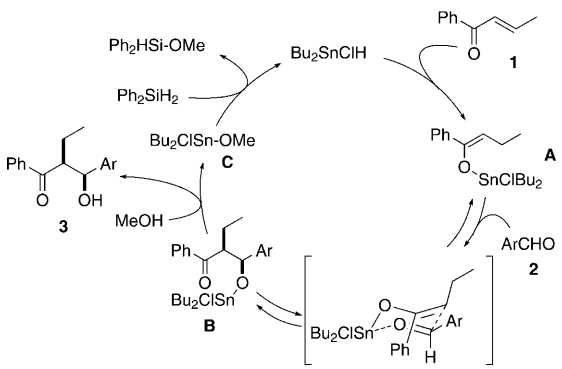
Bu_2SnClH-catalyzed reaction quantitatively afforded **3** while retaining the high *syn*-selectivity (entry 4). On the other hand, addition of excess MeOH (3 equiv) resulted in a lower yield (52%) (entry 5), and use of $PhSiH_3$ as a hydride source decreased the yield of **3** (entry 6). Using CH_2Cl_2 also afforded high yield although *syn*-selectivity was not so good (entry 7). Reaction rate and *syn*-selectivity were reduced in the case using *i*PrOH as an additive (entry 8).

A plausible catalytic cycle is shown in Scheme 2. Initially, Bu_2SnClH undergoes conjugate addition to enone **1** to give (*Z*)-tin enolate **A**.[6] In this step, Bu_2SnClH does not reduce aldehyde **2**. Next, generated (*Z*)-tin enolate **A** reacts with **2**

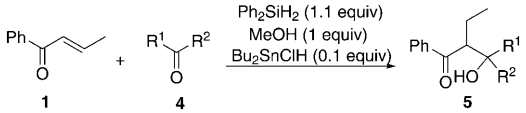


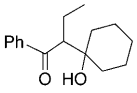
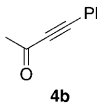
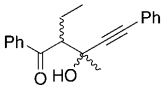
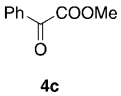
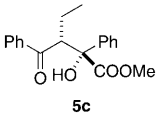
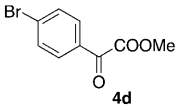
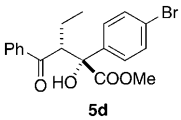
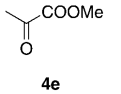
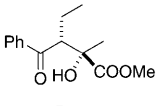
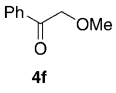
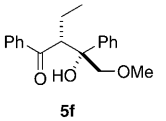
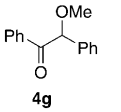
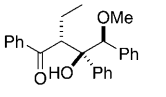
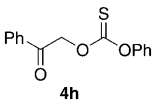
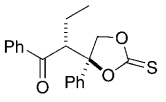
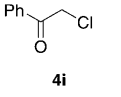
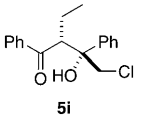
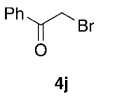
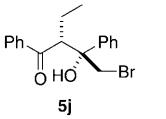
Scheme 2. Plausible catalytic cycle.

via Zimmerman–Traxler six-membered cyclic transition state[7] to form *syn*-tin aldolate **B**; **B** is protonated by MeOH. We assume that this is the rate-determining step. Thus, *syn*-aldol product **3** is obtained with generation of tin methoxide **C**. In the final step, methoxide **C** reacts with Ph_2SiH_2 to regenerate Bu_2SnClH. In this system, the choice of additive is important. Thus MeO group has effects on both steps of trapping of tin aldolate **B** and of regeneration of Bu_2SnClH. When water is used as an additive, tin enolate **A** is protonated to give saturated ketone as by-product. On the other hand, *i*PrOH unlikely promotes protonation of tin aldolate and regeneration of catalyst due to less acidity and generation of sterically hindered tin alkoxide compared with MeOH. *syn*-Selectivity would be reduced via retro-aldol reaction and reaction time increases.[8]

It is noteworthy that this catalytic system was applicable to the reductive aldol reaction of enone **1** with ketones (Table 2). In the reaction of **1** with cyclohexanone (**4a**), aldol product **5a** was obtained in 37% yield in THF (entry 1) in which remaining product was 1-phenyl-butan-1-one by conjugate reduction of **1**. Changing solvent to CH_2Cl_2 afforded **5a** selectively in 80% yield (entry 2). Table 2 shows the reaction using various ketones in which indicated conditions are the result of optimization process. Ketones bearing electron-withdrawing group **4b** could be employed to give product **5b** in high yield without reduction of **4b** (entry 3). Furthermore, the reaction with α-ketoesters **4c–e** also afforded aldol products **5c–e** with high diastereoselectivities (entries 4–6). In particular, despite only small

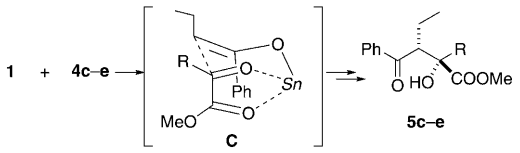
Table 2. Reductive aldol reaction of enones **1a** with various ketones.



Entry	Ketone **4**	Conditions	Product **5**	Yield [%] (d.r.)[a]
1[b]	 **4a**	THF, RT, 3 h	 **5a**	37
2		CH_2Cl_2, RT, 3 h		80
3[b]	 **4b**	CH_2Cl_2, RT, 3 h	 **5b**	76 (80:20)
4	 **4c**	THF, RT, 4 h	 **5c**	86 (>99:1)
5	 **4d**	THF, RT, 4 h	 **5d**	74[d] (>99:1)
6[c]	 **4e**	CH_2Cl_2, RT, 24 h	 **5e**	80 (89:11)
7[c]	 **4f**	THF, RT, 24 h	 **5f**	66 (>99:1)
8	 **4g**	CH_2Cl_2, RT, 3 h	 **5g**	66[d] (96:4)
9	 **4h**	THF, reflux, 5 h	 **5h**	70 (92:8)
10	 **4i**	CH_2Cl_2, RT, 3 h	 **5i**	80 (90:10)
11	 **4j**	CH_2Cl_2, RT, 3 h	 **5j**	79 (90:10)

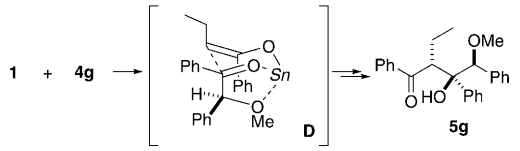
[a] Conditions: Bu_2SnClH (0.1 mmol), Ph_2SiH_2 (1.1 mmol), **1** (1 mmol), **4** (1 mmol), Additive (1 mmol), THF (1 mL). [b] Ketone **4** (2 mmol) was used. [c] *i*PrOH (1 mmol) was used instead of MeOH. [d] Stereochemistry was determined by X-ray analysis.

stereogenic difference between methyl and methyl ester on carbonyl moiety of methyl pyruvate (**4e**), considerably diastereoselectivity was obtained (entry 6). These results could be rationalized by chelated bicyclic transition state **C** as shown in Scheme 3.



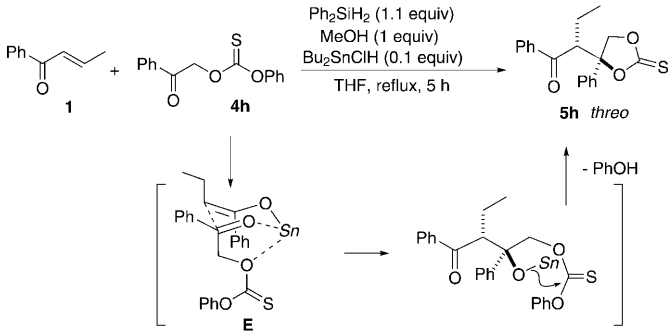
Scheme 3. Plausible mechanism through chelated cyclic transition state.

The use of α-alkoxyketone **4f** also afforded highly diastereoselective reaction in which OMe acts as the coordinating group to tin (entry 7). Surprisingly, the reaction of with benzoin methyl ether (**4g**) afforded diastereoseolective product **5g** with three contiguous stereogenic centers (entry 8). In this reaction, among possible chelated cyclic transition states, an excellent stereocontrol was achieved through **D** as sterically least hindered Cram's cyclic transition state (Scheme 4).



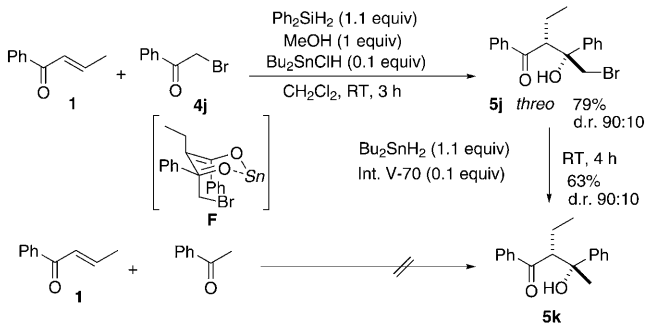
Scheme 4. Control of diastereoselectivity of three contiguous streogenic centers.

We were able to perform the one-pot synthesis of heterocyclic compounds starting from thiocarbonate **4h** (entry 9). Thus, heating of **1** with **4h** gave cyclic thionocarbonate **5h** in 70% yield with high diastereoselectivity. The reaction proceeds through cyclic transition state **E**, followed by intramolecular esterification (Scheme 5).



Scheme 5. One-pot and diastereoselective synthesis of heterocycle.

The highly diastereoselective reaction was also applicable to α-haloketones **4i** and **4j** (entries 10 and 11). In this case the reactions proceeded through transition state **F** (Scheme 6). The presented reductive aldol reaction has limited application for simple ketone such as acetophenone. However, dehalogenation of product **5j** afforded adduct **5k** which corresponds with the reaction product using acetophenone.



Scheme 6. Chelation-controlled reductive aldol reaction of enone **1a** with α-haloketone **4j**. Int. V-70 = initiatior, see ref. [9] and Supporting Information.

In conclusion, we have established that Ph_2SiH_2 and alcohol promoted reductive aldol reaction of enones in the presence of a catalytic amount of dibutylhalogenotin hydride (Bu_2SnClH). Highly chemo- and diastereoselective aldol products were obtained in the case using α-ketoester, α-alkoxyketone and α-haloketones. We are now enlarging the scope of substrates.

Experimental Section

A typical experimental procedure for reductive aldol reaction of enone with ketone: To a dry nitrogen-filled 10 mL round-bottomed flask containing Bu_2SnH_2 (0.05 mmol) in THF (1 mL) was added Bu_2SnCl_2 (0.05 mmol) at RT. The mixture was stirred at RT for 5 min. To the solution were added enone **1** (1 mmol), ketone **4** (1 mmol), MeOH (1 mmol) and Ph_2SiH_2 (1.1 mmol), and the resulting mixture was stirred at RT for 4 h. After quenching with H_2O (5 mL), the reaction mixture was extracted with diethyl ether (2×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was subjected to column chromatography eluting with hexane/EtOAc. Tin and silane residues were removed by this treatment. Further purification was performed by TLC eluting with hexane/Et_2O. Product was determined by ^1H NMR. For products **5d**, **5g**, and **5h**, further purification was performed by recrystallization. The structures of crystalline products were determined by X-ray analysis. CCDC 777382 (**5d**), 777388 (**5g**) and 777384 (**5h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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Keywords: aldol reaction · diastereoselectivity · enones · ketones · reduction

[1] For rhodium-catalyzed reductive aldol reaction of enones to aldehydes mediated by silane: a) I. Matsuda, K. Takahashi, S. Sato, *Tetrahedron Lett.* **1990**, *31*, 5331–5334; For rhodium-catalyzed reductive aldol reaction of enones mediated by hydrogen, see: b) H.-Y. Jang,

R. R. Huddleston, M. J. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 15156–15157; c) C.-K. Jung, S. A. Garner, M. J. Krische, *Org. Lett.* **2006**, *8*, 519–522; d) C. Bee, S. B. Han, A. Hassan, H. Iida, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 2746–2747. For copper-catalyzed reductive aldol reaction of enones to aldehydes mediated by silane: e) T. Ooi, K. Doda, D. Sakai, K. Maruoka, *Tetrahedron Lett.* **1999**, *40*, 2133–2136. For platinum-catalyzed reductive aldol reaction of enones to aldehydes mediated by silane or hydrogen: f) H. Lee, M.-S. Jang, Y.-J. Song, H.-Y. Jang, *Bull. Korean Chem. Soc.* **2009**, *30*, 327–333; For Lewis base catalyzed reductive aldol reaction of enones to aldehydes mediated by silane: g) M. Sugiura, N. Sato, S. Kotani, M. Nakajima, *Chem. Commun.* **2008**, 4309–4311; For indium-catalyzed reductive aldol reaction of enones to aldehydes mediated by silane: h) I. Shibata, H. Kato, T. Ishida, M. Yasuda, A. Baba, *Angew. Chem.* **2004**, *116*, 729–732; *Angew. Chem. Int. Ed.* **2004**, *43*, 711–714; i) K. Miura, Y. Yamada, M. Tomita, A. Hosomi, *Synlett* **2004**, 1985–1989.

[2] For transition-metal-catalyzed enantioselective reductive aldol reaction of unsaturated esters to aldehydes mediated by silane, see: a) S. J. Taylor, M. O. Duffey, J. P. Morken, *J. Am. Chem. Soc.* **2000**, *122*, 4528–4529; b) C.-X. Zhao, M. O. Duffey, S. J. Taylor, J. P. Morken, *Org. Lett.* **2001**, *3*, 1829–1831; c) H. Nishiyama, T. Shiomi, Y. Tsuchiya, I. Matsuda, *J. Am. Chem. Soc.* **2005**, *127*, 6972–6973; d) O. Chuzel, J. Deschamp, C. Chausteur, O. Riant, *Org. Lett.* **2006**, *8*, 5943–5946; For copper-catalyzed enantioselective reductive aldol reaction of unsaturated esters to ketones mediated by silane, see: e) D. Zhao, K. Oisaki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2006**, *47*, 1403–1407; f) J. Deschamp, O. Chuzel, J. Hannedouche, O. Riant, *Angew. Chem.* **2006**, *118*, 1314–1319; *Angew. Chem. Int. Ed.* **2006**, *45*, 1292–1297; g) D. Zhao, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 14440–14441.

[3] For intramolecular reaction, enantioselective one has been reported using methyl ketones: B. H. Lipshutz, B. Amorelli, J. B. Unger, *J. Am. Chem. Soc.* **2008**, *130*, 14378–14379.

[4] T. Kawakami, M. Miyatake, I. Shibata, A. Baba, *J. Org. Chem.* **1996**, *61*, 376–379.

[5] H. Kato, I. Shibata, Y. Yasaka, S. Tsunoi, M. Yasuda, A. Baba, *Chem. Commun.* **2006**, 4189–4191.

[6] (*Z*)-Tin enolate can be considered to be generated initially because of the preferred conjugate addition of Bu_2SnXH to the *s-cis* form of enone: a) G. P. Boldrini, F. Mancini, E. Tagliavini, C. Trombini, A. U. Ronchi, *J. Chem. Soc. Chem. Commun.* **1990**, 1680–1681; b) G. P. Boldrini, M. Bortolotti, F. Mancini, E. Tagliavini, C. Trombini, A. U. Ronchi, *J. Org. Chem.* **1991**, *56*, 5820–5826.

[7] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

[8] We have proposed retro-aldol mechanism in the dibromoindium hydride (Br_2InH) prompted reaction. K. Inoue, T. Ishida, I. Shibata, A. Baba, *Adv. Synth. Catal.* **2002**, *344*, 283–287.

[9] M. Matsugi, K. Gotanda, C. Ohira, M. Suemura, A. Sano, Y. Kita, *J. Org. Chem.* **1999**, *64*, 6928–6930.

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