## **Reductive Aldol Reaction**

## Catalytic Generation of Indium Hydride in a Highly Diastereoselective Reductive Aldol Reaction\*\*

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The reductive aldol reaction of metal hydrides, enones, and aldehydes is a valuable route to  $\beta$ -hydroxyketones because it is a convenient one-pot method without the need to synthesize metal enolates. However, a difficulty of this reaction is that aldehydes are more sensitive than enones to

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## Communications

conventional metal hydrides.<sup>[1]</sup> Furthermore, reagents that achieve high diastereoselectivity have scarcely been reported. We have already reported the initiation of reductive aldol reactions by dihaloindium hydrides (Cl<sub>2</sub>InH and Br<sub>2</sub>InH), generated by transmetalation of *n*Bu<sub>3</sub>SnH and In<sup>III</sup> halides InX<sub>3</sub>.<sup>[2]</sup> However, since indium hydrides should be generated prior to the addition of enones or aldehydes, equimolar amounts of InX<sub>3</sub> must be treated with *n*Bu<sub>3</sub>SnH before the reaction.<sup>[3,4]</sup> Here we report a superior method in which no presynthesis of indium hydrides is required and where *n*Bu<sub>3</sub>SnH is not used. In particular, the catalytic use of InBr<sub>3</sub> was acieved (Scheme 1).



Scheme 1. Reductive aldol reaction.

We focused on hydrosilanes as hydride sources instead of *n*Bu<sub>3</sub>SnH. Active metal hydrides such as NaBH<sub>4</sub> and LiAlH<sub>4</sub> are not appropriate as they readily reduce aldehydes in the absence of InX<sub>3</sub>. Trialkyl silanes are stable liquids that are easy to handle and have low toxicity.<sup>[5]</sup> They have no reactivity towards carbonyl compounds in the absence of additives.<sup>[5b]</sup> When transmetalation with InX<sub>3</sub> occurs, only indium hydrides could act as reactive species in reactions with electrophiles.

Initially, we applied the Et<sub>3</sub>SiH/InCl<sub>3</sub> system to the reductive aldol reaction. Thus, 1-phenyl-2-buten-1-one (1a, 1.2 mmol) and *p*-methoxybenzaldehyde (2, 1 mmol) were added in one portion to a solution of InCl<sub>3</sub> (1 mmol) and Et<sub>3</sub>SiH (1.2 mmol) in THF, but only a trace of silyl aldolate **3a** was obtained. However, when the reaction was performed in EtCN, the yield of **3a** was increased to 59% based on **2** (Scheme 2).



Scheme 2. Reductive aldol reaction with an equimolar amount of InCl<sub>3</sub>.

For the  $nBu_3SnH/InX_3$  system, we earlier reported the formation of thermodynamically stable *anti*-aldol adducts under aprotic conditions.<sup>[2]</sup> Furthermore, a serious problem was the reduction of the starting aldehydes, which gave **4** as an unavoidable side product. In contrast, the hydrosilane-

promoted reaction in Scheme 2 has opposite diastereoselectivity and gives *syn*-aldolate **3a** even under aprotic conditions. Moreover, the result given in Scheme 2 is noteworthy because the reduction of aldehyde scarcely occurred.

Next, we investigated the generation of indium hydride by transmetalation. Et<sub>3</sub>SiH/InCl<sub>3</sub> was chosen for comparison with our previously reported generation of Cl<sub>2</sub>InH from *n*Bu<sub>3</sub>SnH/InCl<sub>3</sub>.<sup>[6]</sup> When InCl<sub>3</sub> and Et<sub>3</sub>SiH were mixed in CD<sub>3</sub>CN at -10°C for 5 min, <sup>1</sup>H NMR analysis showed a new peak at  $\delta = 6.6$  ppm besides the Et<sub>3</sub>SiH peak at  $\delta =$ 3.6 ppm.<sup>[6a]</sup> The peak at  $\delta = 6.6$  ppm is consistent with our previously reported value for Cl<sub>2</sub>InH generated from the nBu<sub>3</sub>SnH/InCl<sub>3</sub> system, for which transmetalation occurred smoothly at -78°C in THF. After stirring the solution of Et<sub>3</sub>SiH/InCl<sub>3</sub> at -10°C for 20 min, the peak of Cl<sub>2</sub>InH gradually decreased because of its instability, while the peak of Et<sub>3</sub>SiH still remained. When the <sup>1</sup>H NMR analysis was performed in [D<sub>8</sub>]THF, no peaks other than that of Et<sub>3</sub>SiH were observed. Although the transmetalation was slow compared with the *n*Bu<sub>3</sub>SnH/InCl<sub>3</sub> system, it was found that Cl<sub>2</sub>InH was generated from Et<sub>3</sub>SiH/InCl<sub>3</sub> in nitrile solvents.

Thus, the effective reaction shown in Scheme 2 is explainable: Indium hydride generated in situ promotes 1,4-reduction of enone **1a** to the indium enolate, which gives aldolate **3** by reaction with aldehyde **2**. The formation of *syn*-aldolates **3a** indicates that immediate trapping of kinetically controlled *syn*-indium aldolate would occur by  $Et_3SiH$ . This result suggests the possibility of using indium halides as catalysts, because the silicon trapping agent generates indium hydride.

Next we investigated the catalytic use of indium halides. As shown in Table 1, the use of InCl<sub>3</sub> (10 mol%) resulted in an unsatisfacory yield of silyl aldolate 3a (entry 1). However, 3a was obtained in 75% yield when InBr<sub>3</sub> was used as the catalyst (entry 2). p-Nitrobenzaldehyde and benzaldehyde gave 3b and 3c, respectively (entries 3 and 4). Aliphatic aldehydes were also applicable to give 3d-f (entries 5-7). It is noteworthy that no reduction of aldehydes 2 took place in these cases. Thus, the present system exhibits high chemo- and regioselectivity for enones. As mentioned previously, these results represent an advantage over the nBu<sub>3</sub>SnH/InBr<sub>3</sub> system, which is seriously limited to the reaction with panisaldehyde because the system could not prevent the reduction of electrophilic aldehydes such as p-nitrobenzaldehyde. Enones bearing aromatic and aliphatic substituents were also reactive (entries 8-12).

A plausible catalytic cycle for InBr<sub>3</sub> is shown in Scheme 3. Initially, Br<sub>2</sub>InH is generated by the slow transmetalation of InBr<sub>3</sub> with Et<sub>3</sub>SiH. The generated Br<sub>2</sub>InH next undergoes 1,4addition with enone **1** to give indium enolate A. In this step, Br<sub>2</sub>InH does not reduce the coexistent aldehydes **2**. The absence of aldehyde reduction is due to the low concentration of Br<sub>2</sub>InH from the slow transmetalation. In contrast, in the case of *n*Bu<sub>3</sub>SnH/InBr<sub>3</sub>, Br<sub>2</sub>InH is formed in high concentration because of the easy transmetalation of *n*Bu<sub>3</sub>SnH with InBr<sub>3</sub> and the equimolar reaction, which was accompanied by partial reduction of the aldehydes. (*Z*)-Indium enolate A can be considered to be generated initially because of the preferred 1,4-addition of indium hydride to the *s-cis* form of enone **1**.<sup>[7]</sup> Indium enolate A reacts with **2** via a Zimmerman-

Table 1: Diastereoselective reductive aldol reactions.<sup>[a]</sup>

	$R^1 \rightarrow R^2$ 0 1	+ R <sup>3</sup> CHO	Et <sub>3</sub> SiH <sub>3</sub> (10 mol%) EtCN 0 °C, 4 h	$R^{1} \rightarrow R^{3} O OSiEt_{3}$	
Entry	Enone <b>1</b>	Aldehyde <b>2</b>	Product	Yield [%]	syn:anti
1 2	Ph O 1a	МеО- СНО	3 a 3 a	33 <sup>[b]</sup> 75	> 99:1 90:10
3		02N-СНО	3 b	59	>99:1
4 5 6 7	Ph Ph	PhCHO PhCH <sub>2</sub> CHO #BuCHO Et <sub>2</sub> CHO	3 c 3 d 3 e 3 f	78 40 73 87	92:8 > 99:1 > 99:1 90:10
8 9	U 1b	PhCHO	3 g 3 h	82 65 <sup>[c]</sup>	>99:1 78:22
10	∬	МеО-{}СНО	) 3i	61	>99:1
11	Mo o Ph	PhCHO	3 j	40	>99:1
12	0 1d	МеО-	3 k	46	>99:1

[a] Conditions: Et<sub>3</sub>SiH (1.2 mmol), InBr<sub>3</sub> (0.1 mmol), enone 1 (1 mmol), EtCN (1 mL). [b]  $InCl_3$  was used instead of InBr<sub>3</sub>. [c] Product was isolated as desilylated aldol adduct.



Scheme 3. Plausible catalytic cycle.



Scheme 4. Trapping of indium aldolate by a trialkyl silane.

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Traxler six-membered cyclic transition state<sup>[8]</sup> to form syn-indium aldolate B, which is immediately trapped by Et<sub>3</sub>SiH. Thus, syn-silyl aldolate 3 is obtained with regenation of Br<sub>2</sub>InH. In this step, there is the possibility of trapping of indium aldolate B with Et<sub>3</sub>SiBr to regenerate InBr<sub>3</sub>, because Et<sub>3</sub>SiBr is produced by the initial transmetalation step. However, we consider that the trapping of indium aldolate A by Et<sub>3</sub>SiH is plausible considering the initial concentrations of Et<sub>3</sub>SiH and Et<sub>3</sub>SiBr. Moreover, it was confirmed that the Et<sub>3</sub>SiBr-free indium aldolate generated by *n*Bu<sub>3</sub>SnH/InBr<sub>3</sub><sup>[2]</sup> is easily trapped by Et<sub>3</sub>SiH (Scheme 4).

In summary, the  $Et_3SiH$ -promoted diastereoselective reductive aldol reaction has been established by using  $InBr_3$  as a catalyst. This three-component reaction afforded only silyl aldolates as products without any side reactions. The silicon compounds, including the  $Et_3SiH$ 

starting material, could be easily removed by evaporation after the reaction. The *syn* selectivity obtained here is higher than that of any other reductive aldol reaction, including those promoted by tin hydride.

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