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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 β-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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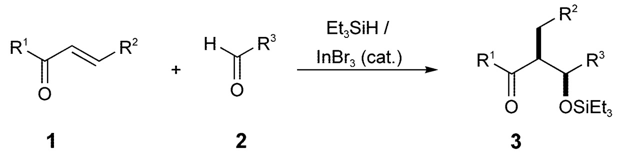
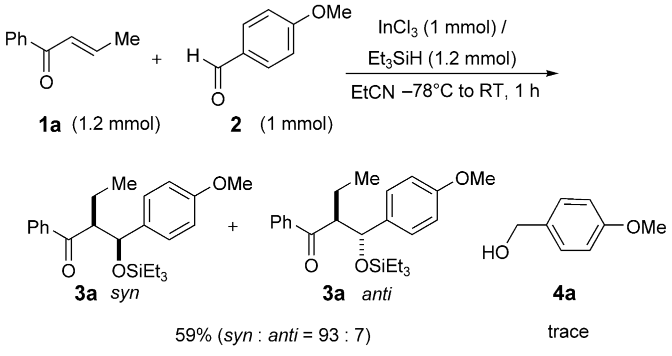
conventional metal hydrides.[1] Furthermore, reagents that achieve high diastereoselectivity have scarcely been reported. We have already reported the initiation of reductive aldol reactions by dihaloindium hydrides (Cl_2InH and Br_2InH), generated by transmetalation of nBu$_3$SnH and In^{III} halides InX_3.[2] However, since indium hydrides should be generated prior to the addition of enones or aldehydes, equimolar amounts of InX_3 must be treated with nBu$_3$SnH before the reaction.[3,4] Here we report a superior method in which no presynthesis of indium hydrides is required and where nBu$_3$SnH is not used. In particular, the catalytic use of $InBr_3$ was acieved (Scheme 1).



Scheme 1. Reductive aldol reaction.

We focused on hydrosilanes as hydride sources instead of nBu$_3$SnH. Active metal hydrides such as $NaBH_4$ and $LiAlH_4$ are not appropriate as they readily reduce aldehydes in the absence of InX_3. Trialkyl silanes are stable liquids that are easy to handle and have low toxicity.[5] They have no reactivity towards carbonyl compounds in the absence of additives.[5b] When transmetalation with InX_3 occurs, only indium hydrides could act as reactive species in reactions with electrophiles.

Initially, we applied the $Et_3SiH/InCl_3$ 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 $InCl_3$ (1 mmol) and Et_3SiH (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 $InCl_3$.

For the nBu$_3$SnH/InX$_3$ system, we earlier reported the formation of thermodynamically stable *anti*-aldol adducts under aprotic conditions.[2] 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.

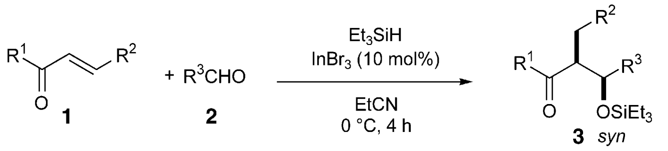
Next, we investigated the generation of indium hydride by transmetalation. $Et_3SiH/InCl_3$ was chosen for comparison with our previously reported generation of Cl_2InH from nBu$_3$SnH/InCl$_3$.[6] When $InCl_3$ and Et_3SiH were mixed in CD_3CN at −10°C for 5 min, ^{1}H NMR analysis showed a new peak at $\delta = 6.6$ ppm besides the Et_3SiH peak at $\delta = 3.6$ ppm.[6a] The peak at $\delta = 6.6$ ppm is consistent with our previously reported value for Cl_2InH generated from the nBu$_3$SnH/InCl$_3$ system, for which transmetalation occurred smoothly at −78°C in THF. After stirring the solution of $Et_3SiH/InCl_3$ at −10°C for 20 min, the peak of Cl_2InH gradually decreased because of its instability, while the peak of Et_3SiH still remained. When the ^{1}H NMR analysis was performed in [D$_8$]THF, no peaks other than that of Et_3SiH were observed. Although the transmetalation was slow compared with the nBu$_3$SnH/InCl$_3$ system, it was found that Cl_2InH was generated from $Et_3SiH/InCl_3$ in nitrile solvents.

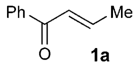
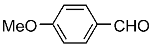
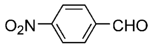
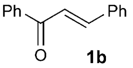
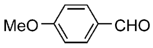
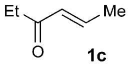
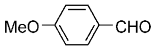
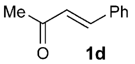
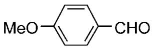
Thus, the effective reaction shown in Scheme 2 is explainable: Indium hydride generated in situ promotes 1,4-reduction of enone **1a** to the indium enolate, which gives aldolate **3** by reaction with aldehyde **2**. The formation of *syn*-aldolates **3a** indicates that immediate trapping of kinetically 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 $InCl_3$ (10 mol%) resulted in an unsatisfacory yield of silyl aldolate **3a** (entry 1). However, **3a** was obtained in 75% yield when $InBr_3$ 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$_3$SnH/InBr$_3$ system, which is seriously limited to the reaction with p-anisaldehyde 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 $InBr_3$ is shown in Scheme 3. Initially, Br_2InH is generated by the slow transmetalation of $InBr_3$ with Et_3SiH. The generated Br_2InH next undergoes 1,4-addition with enone **1** to give indium enolate A. In this step, Br_2InH does not reduce the coexistent aldehydes **2**. The absence of aldehyde reduction is due to the low concentration of Br_2InH from the slow transmetalation. In contrast, in the case of nBu$_3$SnH/InBr$_3$, Br_2InH is formed in high concentration because of the easy transmetalation of nBu$_3$SnH with $InBr_3$ 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**.[7] Indium enolate A reacts with **2** via a Zimmerman–

Table 1: Diastereoselective reductive aldol reactions.[a]

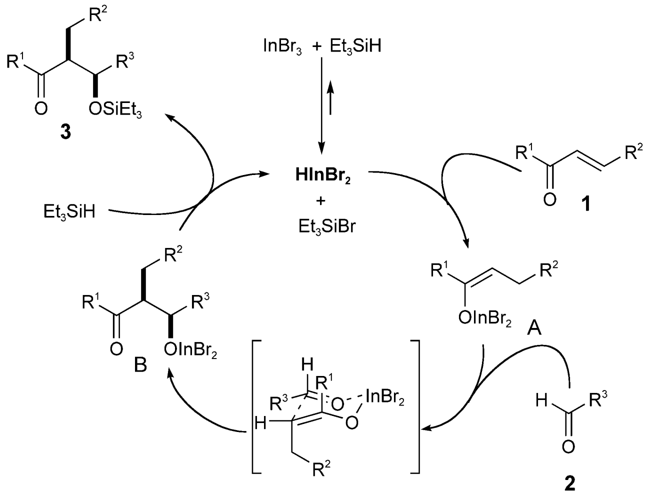


Entry	Enone **1**	Aldehyde **2**	Product	Yield [%]	*syn*:*anti*
1	 **1a**		**3a**	33[b]	>99:1
2			**3a**	75	90:10
3			**3b**	59	>99:1
4		PhCHO	**3c**	78	92:8
5		$PhCH_2CHO$	**3d**	40	>99:1
6		*t*BuCHO	**3e**	73	>99:1
7		Et_2CHO	**3f**	87	90:10
8	 **1b**		**3g**	82	>99:1
9		PhCHO	**3h**	65[c]	78:22
10	 **1c**		**3i**	61	>99:1
11		PhCHO	**3j**	40	>99:1
12	 **1d**		**3k**	46	>99:1

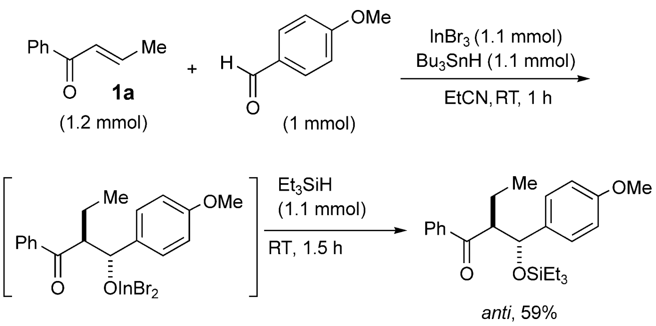
[a] Conditions: Et_3SiH (1.2 mmol), $InBr_3$ (0.1 mmol), enone **1** (1 mmol), EtCN (1 mL). [b] $InCl_3$ was used instead of $InBr_3$. [c] Product was isolated as desilylated aldol adduct.

Traxler six-membered cyclic transition state[8] to form *syn*-indium aldolate B, which is immediately trapped by Et_3SiH. Thus, *syn*-silyl aldolate **3** is obtained with regenation of Br_2InH. In this step, there is the possibility of trapping of indium aldolate B with Et_3SiBr to regenerate $InBr_3$, because Et_3SiBr is produced by the initial transmetalation step. However, we consider that the trapping of indium aldolate A by Et_3SiH is plausible considering the initial concentrations of Et_3SiH and Et_3SiBr. Moreover, it was confirmed that the Et_3SiBr-free indium aldolate generated by $n Bu_3SnH/InBr_3$[2] is easily trapped by Et_3SiH (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.



Scheme 3. Plausible catalytic cycle.



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

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Keywords: aldol reaction · diastereoselectivity · hydroxyketones · indium · silanes

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[1] a) I. Matsuda, K. Takahashi, S. Sato, *Tetrahedron Lett.* **1990**, *31*, 5331–5334; b) E. J. Enholm, Y. Xie, K. A. Abboud, *J. Org. Chem.* **1995**, *60*, 1112–1113; c) T. Kawakami, M. Miyatake, I. Shibata, A. Baba, *J. Org. Chem.* **1996**, *61*, 376–379; d) T. Ooi, K. Doda, D. Sakai, K. Maruoka, *Tetrahedron Lett.* **1999**, *40*, 2133–2136; e) S. J. Taylor, M. O. Duffey, J. P. Morken, *J. Am. Chem. Soc.* **2000**, *122*, 4528–4529.

[2] K. Inoue, T. Ishida, I. Shibata, A. Baba, *Adv. Synth. Catal.* **2002**, *344*, 283–287.

[3] The potential of indium compounds in the field of organic synthesis has been intensively studied. Barbier-type allylation: a) S. Araki, H. Ito, Y. Butsugan, *J. Org. Chem.* **1988**, *53*, 1831–1833; b) C. J. Li, T. H. Chan, *Tetrahedron Lett.* **1991**, *32*, 7017–7020; c) C. J. Li, T. H. Chan, *Tetrahedron* **1999**, *55*, 11149–11176; d) C. J. Li, *Tetrahedron Lett.* **1995**, *36*, 517–518; e) M. B. Isaac, T. H. Chan, *Tetrahedron Lett.* **1995**, *36*, 8957–8960; f) L. A. Paquette, T. M. Mitzel, *J. Org. Chem.* **1996**, *61*, 8799–8804; Pd-catalyzed allylation: g) S. Araki, T. Kamei, T. Hirashita, H. Yamamura, M. Kawai, *Org. Lett.* **2000**, *2*, 847–849. Pinacol coupling h) H. J. Lim, G. Keum, S. B. Kang, B. Y. Chung, Y. Kim, *Tetrahedron Lett.* **1998**, *39*, 4367–4368; Transmetalation: i) J. A. Marshall, K. W. Hinkle, *J. Org. Chem.* **1995**, *60*, 1920–1921; j) J. A. Marshall, K. W. Hinkle, *J. Org. Chem.* **1996**, *61*, 105–108; k) M. Yasuda, T. Miyai, I. Shibata, R. Nomura, H. Matsuda, A.

Baba, *Tetrahedron Lett.* **1995**, *36*, 9497–9500; l) T. Miyai, K. Inoue, M. Yasuda, A. Baba, *Synlett* **1997**, 699–700.

[4] Although several indium hydrides have been reported, they have scarcely been used in organic synthesis. $LiPh_nInH_{4-n}$ ($n = 0$–2): a) M. Yamada, K. Tanaka, S. Araki, Y. Butsugan, *Tetrahedron Lett.* **1995**, *36*, 3169–3172; b) M. Yamada, T. Horie, M. Kawai, H. Yamamura, S. Araki, *Tetrahedron* **1997**, *53*, 15685–15690; $InH_3[CN(Mes)C_2H_2N(Mes)]$ and $InH_3[P(C_6H_{11})_3]$: c) C. D. Abernethy, M. L. Cole, A. J. Davies, C. Jones, *Tetrahedron Lett.* **2000**, *41*, 7567–7570.

[5] a) N. Greeves in *Comprehensive Organic Synthesis*, *Vol. 8* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 1; b) L. Fry, M. Orfanopoulos, M. G. Adlington, W. R. Dittman, S. B. Silverman, *J. Org. Chem.* **1978**, *43*, 374–375.

[6] We reported the first generation of Cl_2InH, which showed a ^1H NMR peak at $\delta = 6.5$ ppm in THF. a) T. Miyai, K. Inoue, M. Yasuda, I. Shibata, A. Baba, *Tetrahedron Lett.* **1998**, *39*, 1929–1932; b) K. Inoue, M. Yasuda, I. Shibata, A. Baba, *Tetrahedron Lett.* **2000**, *41*, 113–116; c) K. Inoue, A. Sawada, I. Shibata, A. Baba, *Tetrahedron Lett.* **2001**, *42*, 4661–4663.

[7] a) G. P. Boldrini, F. Mancini, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Chem. Soc. Chem. Commun.* **1990**, 1680–1681; b) G. P. Boldrini, M. Bortolotti, F. Mancini, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Org. Chem.* **1991**, *56*, 5820–5826.

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