



Preparation of a Novel Indium Hydride and Application to Practical Organic Synthesis

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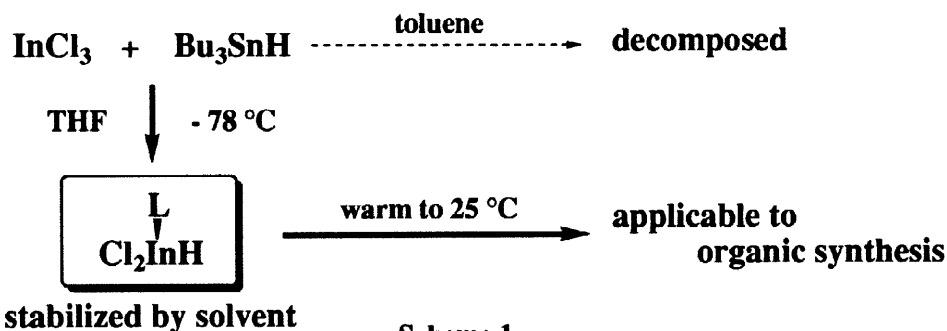
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Abstract: Dichloroindium hydride was first generated using the transmetalation between indium trichloride and tributylstannane at $-78\text{ }^{\circ}\text{C}$, and the generation was confirmed by IR and NMR measurements. The resulting hydride is considerably stable even at ambient temperature due to the coordination of THF, such that it is applicable to practical reduction of carbonyls and halides.

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Among the hydride derivatives of group 13 elements, various types of aluminum hydrides and boron hydrides have been employed as powerful reduction tools in complex organic syntheses. In addition, fundamental recent advances have been also made for the application of gallium hydride.¹ Although the synthesis of indium trihydride (InH_3) has been known for several decades,² hydroindium compounds have not received much attention because of their low reactivity and instability. There is no precedent for monometallic indium hydride having practical reactivity, while ate complex hydrides such as $\text{LiPh}_n\text{InH}_{4-n}$ ($n = 0-2$) were reported by Butsugan *et al.*³ to readily reduce carbonyl compounds. Quite recently, organoindium compounds like alkyl-,⁴ allyl-,^{5,6,7} alkynyl-⁶ derivatives have been used in organic synthesis. On the other hand, organotin compounds are known to be versatile reagents for the generation of reactive organometallic intermediates by transmetalation.⁸ The first example of high stereoselective allylation using the transmetalation between indium trichloride and allylic tins has been proposed by Marshall *et al.*^{5a-b} In previous papers, we also reported the indium-catalyzed allylation or alkynylation of carbonyl compounds *via* the transmetalation between indium trihalide and organotin compounds.^{5c,6} These results prompted us to prepare a novel monometallic indium hydride using the transmetalation between indium trichloride (InCl_3) and tributylstannane (Bu_3SnH). This may be the first generation of dichloroindium hydride (Cl_2InH) that is applicable to practical organic syntheses. In this study, we proved the generation of the indium hydride by IR and NMR measurements and demonstrated preliminary applications of the indium hydride to reduction of alkyl halides and carbonyls.



Scheme 1

The transmetalation between InCl_3 and Bu_3SnH occurred smoothly under the conditions of $-78\text{ }^\circ\text{C}$ and 10 min in THF. ^1H NMR indicated that the resulting indium hydride was stable in THF solution even at an ambient temperature, although during the generation the temperature had to be kept at $-78\text{ }^\circ\text{C}$. Therefore, at $25\text{ }^\circ\text{C}$ the generation of Cl_2InH was easily monitored by IR and ^1H NMR. The infrared spectrum showed a strong In-H absorption band at 1801 cm^{-1} . The complete disappearance of Bu_3SnH was confirmed by ^1H NMR (4.77 ppm) and ^{119}Sn NMR (-90 ppm), and a broad new peak appeared at around 6.5 ppm in ^1H NMR.⁹ In addition, one equivalent formation of free Bu_3SnCl (107 ppm) was observed by ^{119}Sn NMR even in the presence of an excess amount of Bu_3SnH . These results demonstrate the following facts; the displacement of only one In-Cl bond to In-H. On the other hand, very sluggish transmetalation proceeded in toluene at $-78\text{ }^\circ\text{C}$, and no formation of indium hydride was monitored at ambient temperature in spite of the almost consumption of tributylstannane. Consequently it is apparent that the coordination of THF effects both the generation and stabilization of Cl_2InH (Scheme 1). Although indium reagents such as allylindium are known to be stable in aqueous media,⁷ this indium hydride was decomposed by water.

Next, we examined the preliminary reduction ability of Cl_2InH . The results are summarized in Table 1. A general procedure was as follows; a mixture of InCl_3 (1.0 mmol) and Bu_3SnH (1.0 mmol) in dry THF (1 mL) was stirred for 10 min at $-78\text{ }^\circ\text{C}$ under nitrogen, and a substrate (1.0 mmol) was subsequently added. The reaction mixture was warmed to the appropriate temperature noted in Table 1. After 1 h the reaction was quenched with 1 N HCl. The reaction mixture was washed with aqueous NH_4F to remove Bu_3SnCl , and extracted with ether.

Dichloroindium hydride facilely reduced aromatic and alkyl aldehydes, an α,β -unsaturated aldehyde, and even sterically demanding one to give the corresponding alcohols **4a-d** (entries 1, 4-6 in Table 1). The reduction of benzaldehyde proceeded smoothly in THF, even after the THF solution including Cl_2InH was stirred for 1 h at $25\text{ }^\circ\text{C}$, whereas the decomposition of hydride species took place in toluene under similar conditions (entries 2 and 3). This hydride is a milder reagent, such that as shown in Table 1 formyl groups are predominantly reduced over such functional groups as nitro, cyano, halide, and ester groups **3e-h** (entries 7-10), whereas a nitro group is easily reduced by LiPhInH_3 .³ In contrast to the sluggish reduction of acetophenone **3i** (entries 11 and 12), activated ketones such as chalcone **3j** and benzoin methyl ether **3k** were reduced in good yields. In particular, the regioselective 1,4-reduction of **3j** (entry 13) is in contrast to the reported 1,2-reduction by hydroalumination.¹⁰ The more effective reduction of **3k** than that of acetophenone indicated the strong chelation between indium center and the methoxy oxygen where *anti*-2-methoxy-1,2-diphenylethanol **4k** was stereoselectively produced (82% yield, >99% d.e., entry 14). This indium hydride also showed high reducing ability toward alkyl bromides. Benzyl bromide **3l** and 1-bromo-3-phenylpropane **3m** were readily reduced to toluene **4l** and 1-phenylpropane **4m**, respectively in good yields (entries 15 and 16). Bromide **3m**, however, was completely recovered in toluene solvent. The results of the debromination and the 1,4-reduction indicated the radical characters of the indium hydride. Then radical inhibitors such as galvinoxyl and *p*-dinitrobenzene were added to the reduction of **3a**, **3j**, and **3m**. In the cases of benzaldehyde and chalcone, no effect was observed, whereas the reduction of 1-bromo-3-phenylpropane was completely suppressed. Thus Cl_2InH has apparently both radical and ionic characters.

Table 1. Reduction by Dichloroindium Hydride.

Entry	Substrate	Temp /°C	Product	Yield /% ^a
1		25		93
2 ^b	3a PhCHO	25	4a PhCH ₂ OH	86
3 ^c		25		0
4	3b <i>n</i> -C ₅ H ₁₁ CHO	0	4b <i>n</i> -C ₅ H ₁₁ CH ₂ OH	78
5	3c Bu ^t CHO	25	4c Bu ^t CH ₂ OH	84
6	3d Ph-CH=CH-CHO	0	4d Ph-CH=CH-CH ₂ OH	99
7	3e NO ₂ -C ₆ H ₄ -CHO	0	4e NO ₂ -C ₆ H ₄ -CH ₂ OH	75
8	3f N≡C-C ₆ H ₄ -CHO	0	4f N≡C-C ₆ H ₄ -CH ₂ OH	76
9	3g Cl-C ₆ H ₄ -CHO	25	4g Cl-C ₆ H ₄ -CH ₂ OH	93
10	3h MeOCO-C ₆ H ₄ -CHO	25	4h MeOCO-C ₆ H ₄ -CH ₂ OH	96
11	3i Ph-C(=O)-CH ₃	0	4i Ph-CH(OH)-CH ₃	2
12		25		23
13	3j Ph-CH=CH-C(=O)-Ph	25	4j Ph-CH ₂ -CH ₂ -C(=O)-Ph	93
14	3k Ph-C(=O)-CH(OMe)-Ph	0	4k Ph-CH(OH)-CH(OMe)-Ph	82 (>99%de) ^{d,e}
15	3l Ph-CH ₂ -Br	25	4l PhMe	99
16	3m Ph-CH ₂ -CH ₂ -CH ₂ -Br	25	4m Ph-CH ₂ -CH ₂ -CH ₂ -H	77

^a Yields were determined by GLC. ^b The THF solution including Cl₂InH was stirred for 1 h at 25 °C before the addition of substrate. ^c The toluene solution including Cl₂InH was stirred for 1 h at 25 °C before the addition of substrate. ^d *Anti*-2-methoxy-1,2-diphenylethanol was obtained (> 99% d.e.). ^e Yield and diastereoselectivity were determined by ¹H NMR.

In summary, we have prepared Cl_2InH which has interesting features such as the chemoselective reduction of functionalized benzaldehydes, chelation-controlled reduction of benzoin methyl ether, and selective 1,4-hydroindation of chalcone.

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9. **Preparation of ^1H NMR sample.**
A 5-mm NMR tube charged with InCl_3 (35.3 mg, 0.16 mmol) was heated (150 °C) in vacuo (0.1 mmHg) for 1 h and charged with nitrogen. Then the tube was charged with dry THF- d_8 (0.75 mL) and frozen by liquid nitrogen. Next, Bu_3SnH (21.2 mg, 0.073 mmol) was added onto the solidified THF. Then the mixture was frozen again and the tube was flame-sealed under vacuum. The ^1H NMR spectrum was measured after warming to 25 °C, and referenced to residual tetrahydrofuran (δ 3.58ppm, δ 1.73ppm).
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