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Indium(III) Chloride−Sodium Borohydride System: A Convenient Radical Reagent for an Alternative to Tributyltin Hydride System

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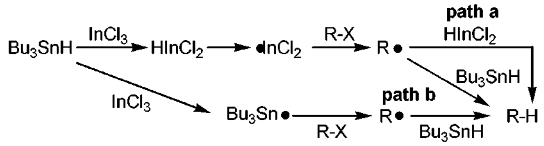
Among radical reducing reagents, tributyltin hydride (Bu_3SnH) is the most useful one in intermolecular radical additions using alkyl halides and unsaturated compounds such as alkenes and alkynes because of the high kinetic balance of the steps of dehalogenation by tributyltin radical, addition of the resulting alkyl radical to unsaturated bond and hydrogen donation of tributyltin hydride.[1] Hence, the development of novel radical initiators such as Et_3B for the generation of tributyltin radical under mild conditions has still been an important subject.[2] On the other hand, because the toxicity of tributyltin compounds has become a serious problem, an alternative hydride reagent has been strongly required. Although some promising reagents such as tris(trimethylsilyl)silane ($(TMS)_3SiH$),[3] cyclohexadienyl-silane,[4] tri-2-furanylgermane,[5] and Schwartz reagents[6] systems have been reported to promote intermolecular addition reactions, their applicability has not extended over that of tributyltin hydride. More convenient and useful radical reducing systems including no tin species have to be developed.

We have already demonstrated that an indium hydride (Cl_2InH), generated by the transmetalation between Bu_3SnH and indium(III) trichloride ($InCl_3$), has a radical character to promote the reduction of organic halides.[7] Interestingly, even a catalytic amount of $InCl_3$ was also effective for the dehalogenation.[8] For the $InCl_3$-catalyzed reaction, it could be considered that in situ generated Cl_2InH works as reactive species for the reduction of organic halides. However, we could not completely exclude the possibility that $InCl_3$ simply assists the radical reduction promoted by tributyltin hydride (Scheme 1 path b). To exclude the latter possibility, we have to develop other hydride sources (*Mt*-H) than tin hydrides, which should have no ability for the reduction of organic halide, but should promote the transmetalation with $InCl_3$ (Scheme 2). In the context of our studies on the catalytic use of $InCl_3$, we have found a simple, mild and nontoxic system $NaBH_4/InCl_3/CH_3CN$ in which indium hydride apparently works as a radical reducing reagent at ambient temperature without any initiators in which dehalogenation, intramolecular cyclization, and intermolecular coupling reactions have been effected in the manner similar to the reaction using the usual Bu_3SnH system.[9]

Scheme 1



Scheme 2

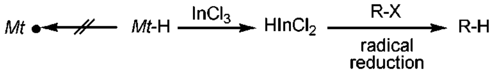
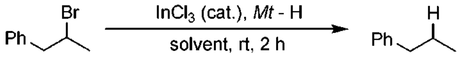


Table 1. Indium-Catalyzed Reduction of Alkyl Halide with *Mt*-H[a]



1a **2a**

entry	*Mt*-H	solvent	yield of **2a**/%
1	Bu_3SnH	THF	82
2	CaH_2	THF	trace
3	LiH	THF	trace
4	BH_3-THF	THF	trace
5	$NaBH_4$	THF	15
6	$NaBH_4$	toluene	0
7	$NaBH_4$	diglyme	62
8	$NaBH_4$	MeCN	78 (0)[f]
9[b]	$NaBH_4$	MeCN	81 (0)[f]
10[c]	$NaBH_4$	MeCN	5
11[d]	$NaBH_4$	MeCN	0
12[e]	$NaBH_4$	MeCN	90

[a] $InCl_3$ 0.1 mmol, *Mt*-H 1 mmol, **1a** 1 mmol, solvent 2 mL. [b] 1.0 mmol of $InCl_3$ was used. [c] Without $InCl_3$. [d] $AlCl_3$ was used instead of $InCl_3$. [e] 1.5 mmol of $NaBH_4$ was used. [f] 0.1 mmol of *p*-DNB was added.

Table 1 shows the results of using various hydride sources in the presence of a catalytic amount of $InCl_3$ for carrying out the reduction of 2-bromopropylbenzene (**1a**). Under the same conditions as using Bu_3SnH (THF solvent, rt) (entry 1), all attempts using metal hydrides such as CaH_2, LiH, and BH_3−THF failed in the reduction (entries 2−4). The use of $NaBH_4$ afforded *n*-propylbenzene (**2a**) in 15% yield (entry 5). In this $NaBH_4/InCl_3$ system, no product was obtained in toluene (entry 6), whereas, the reduction proceeded in diglyme solution to give 62% yield (entry 7). Furthermore, MeCN was found to be the choice of solvents examined, giving the yield of 78% which is comparable with the Bu_3SnH system (entry 8). Of course, this reaction also proceeded with an equimolar amount of $InCl_3$ (entry 9). $InCl_3$ particularly played an important role because little reduction took place in the absence of $InCl_3$ (entry 10). Use of another group-13 element such as $AlCl_3$ was not effective at all (entry 11). These results indicate that indium hydride generated by transmetalation between $InCl_3$ and $NaBH_4$ acts as a reducing reagent. When a little excess (1.5 equiv) of $NaBH_4$ was used, the yield increased to 90% (entry 12). It can be proved that a radical process is involved in this reduction because the addition of a radical scavenger, *p*-dinitrobenzene (*p*-DNB) completely suppressed the formation of **2a**. In contrast to Bu_3SnH, $NaBH_4$ has no radical reactivity;[10,11] therefore, it could be concluded that indium hydride acts as a radical reducing reagent. Thus, novel reducing system $NaBH_4/InCl_3$ could be found here to undergo the radical reduction of alkyl halides under very mild conditions such as ambient temperature.[12]

Table 2 shows the results of reduction of representative alkyl and aryl halides with this novel system. Secondary and primary alkyl bromides, **1a** and **1b** were reduced at room temperature to the corresponding alkanes in 90 and 95% yields, respectively (entries 1 and 2). A tertiary bromide, 1-bromoadamantane (**1c**), was readily reduced (83% yield, entry 3). Alkyl iodide **1d** was also

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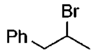
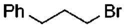
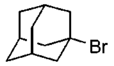
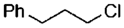
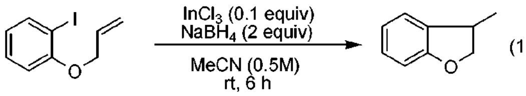
Table 2. $InCl_3$-Promoted Reduction of Various Halides[a]

Entry	R-X		Yield of R-H/ %
1		**1a**	90
2		**1b**	95
3		**1c**	83
4	1-iododecane	**1d**	93
5[b]		**1e**	0
6[b]	bromobenzene	**1f**	1

[a] $InCl_3$ 0.1 mmol, $NaBH_4$ 1.5 mmol, RX 1 mmol, MeCN 2 mL, rt, 2 h. [b] $InCl_3$ 0.1 mmol, $NaBH_4$ 1 mmol, RX 1 mmol, MeCN 2 mL, rt, 2 h.

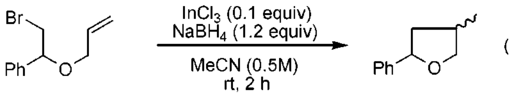
reduced to the corresponding alkane in 93% yield (entry 4). Alkyl chloride **1e** and aryl bromide **1f** were both hardly reduced under similar conditions (entries 5 and 6).

Next, we attempted some representative cyclizations and intermolecular addition reactions as a radical prove of this procedure. Aryl iodide such as 1-allyloxy-2-iodobenzene (**3a**) underwent cyclization to give 3-methyl-2,3-dihydrobenzofuran (**4a**) in 62% yield (eq 1).



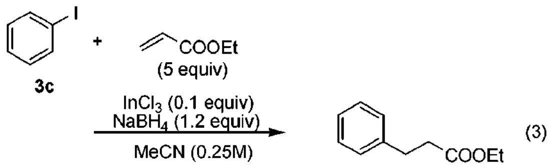
3a **4a** (62%) (1)

The reaction of alkyl bromide such as 3-(2-bromo-1-phenylethoxy)-propene (**3b**) gave 4-methyl-2-phenyl tetrahydrofuran (**4b**) in 50% yield (cis:trans = 15:85) (eq 2).

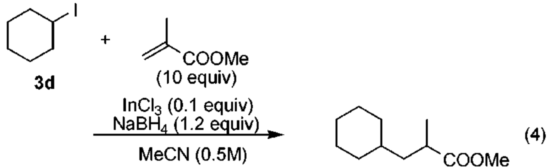


3b **4b** (50%) (*cis* :*trans* = 15:85) (2)

Intermolecular radical addition could be also accomplished with a $InCl_3$-catalyst loading of 10 mol %. For example, iodobenzene or cyclohexyl iodide added to electron-deficient olefins, effectively (eqs 3 and 4).

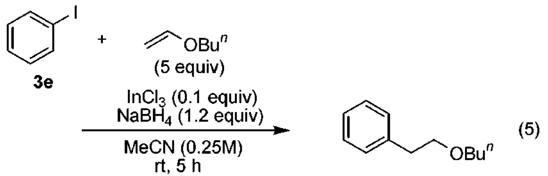


3c **4c** (57%) (3)



3d **4d** (62%) (4)

An electron-rich olefin was also applicable to the coupling reaction (eq 5).



3e **4e** (45%) (5)

These results proved that indium hydride becomes an efficient alternative to tributyltin hydride as a radical chain carrier. The rate constant for the reaction of aryl radical with Cl_2InH at 25 °C ($k_H = 1.0 \times 10^9$ M^{-1} s^{-1}) was determined by the radical clock experiments using **3a**.[13] This value is very similar to that of the rate constant for Bu_3SnH determined at 25 °C ($k_H = 8.4 \times 10^8$ M^{-1} s^{-1}).[14]

In conclusion, we found that the indium hydride generated from $NaBH_4$ and $InCl_3$, is a promising candidate of an alternative to Bu_3SnH. In particular, the catalytic performance of $InCl_3$ in the dehalogenation is noteworthy. The reducing system has several advantages in terms of convenience, economical reagents, mild conditions, and particularly both $InCl_3$ and $NaBH_4$ are stable and readily available in comparison to the reported alternatives.

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Supporting Information Available: Experimental details and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Quite recently Oshima's group reported the dehalogenation and the intramolecular cyclization of halo acetals by gallium hydride reagent induced by triethylborane, where in the application to catalytic use of gallium(III) chloride Red-Al was slowly added over 2 h as a hydride source. Mikami, S.; Fujioka, K.; Nakamura, T.; Yorimitsu H.; Shinokubo, Y.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1853−1855.

(10) Banfi, L.; Narisano, E.; Riva, R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Willey: New York, 1995; Vol. 7; pp 4522−4528.

(11) 2-Bromopropylbenzene (**1a**) was scarcely reduced (6%) with $NaBH_4$ (1 equiv) and AIBN (0.1 equiv) in diglyme at reflux.

(12) Although the mechanism of initiation is unclear as yet, it is considered that the In−H bond is cleaved homolytically to generate indium radical (Cl_2In•). Alternative possibility is that indium(I) chloride or In(0) metal generated by reduction of indium(III) trichloride with $NaBH_4$ act as a radical reducing reagent. However, when the reaction **1a** of using InCl or In metal instead of $InCl_3$ were performed under the conditions noted in Table 1, product **2a** was scarcely obtained (5% and 1%, respectively).

(13) The experimental details are provided in the Supporting Information. For the radical clocks studies, Newcomb, N. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds; Willey-VCH: New York, 2001; Vol. 1; pp 317−336.

(14) Recently, the similar rate constant for the reaction with Bu_3SnH was reported by Carden et al. (7.8×10^8 M^{-1} s^{-1}). Garden, S. J.; Avila, D. V.; Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 805−809.

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