

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

Katsuyuki Inoue, Akemi Sawada, Ikuya Shibata, and Akio Baba\*

Department of Molecular Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamada-Oka, Suita, Osaka 565-0871, Japan

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Among radical reducing reagents, tributyltin hydride (Bu<sub>3</sub>SnH) 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.<sup>1</sup> Hence, the development of novel radical initiators such as Et<sub>3</sub>B for the generation of tributyltin radical under mild conditions has still been an important subject.<sup>2</sup> 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)3-SiH),<sup>3</sup> cyclohexadienyl-silane,<sup>4</sup> tri-2-furanylgermane,<sup>5</sup> and Schwartz reagents<sup>6</sup> 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<sub>2</sub>InH), generated by the transmetalation between Bu<sub>3</sub>SnH and indium(III) trichloride (InCl<sub>3</sub>), has a radical character to promote the reduction of organic halides.<sup>7</sup> Interestingly, even a catalytic amount of InCl<sub>3</sub> was also effective for the dehalogenation.8 For the InCl3-catalyzed reaction, it could be considered that in situ generated Cl<sub>2</sub>InH works as reactive species for the reduction of organic halides. However, we could not completely exclude the possibility that InCl<sub>3</sub> 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<sub>3</sub> (Scheme 2). In the context of our studies on the catalytic use of InCl<sub>3</sub>, we have found a simple, mild and nontoxic system NaBH4/InCl3/CH3CN 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<sub>3</sub>-SnH system.9

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<sub>3</sub>SnH (THF solvent, rt) (entry 1), all attempts using metal hydrides such as CaH<sub>2</sub>, LiH, and BH<sub>3</sub>—THF failed in the reduction (entries 2–4). The use of NaBH<sub>4</sub> afforded *n*-propylbenzene (**2a**) in 15% yield (entry 5). In this NaBH<sub>4</sub>/InCl<sub>3</sub> 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<sub>3</sub>SnH system (entry 8). Of course, this reaction also proceeded with an equimolar amount of InCl<sub>3</sub> (entry 9). InCl<sub>3</sub> particularly



Scheme 2

Table 1. Indium-Catalyzed Reduction of Alkyl Halide with Mt-Ha

	Br InCl <sub>3</sub> (cat.), <i>Mt</i> - H		Ļ
	Ph	nt, rt, 2 h	Ph 🔨
	1a		2a
entry	<i>Mt</i> -H	solvent	yield of 2a/%
1	Bu <sub>3</sub> SnH	THF	82
2	CaH <sub>2</sub>	THF	trace
3	LiH	THF	trace
4	BH <sub>3</sub> -THF	THF	trace
5	$NaBH_4$	THF	15
6	$NaBH_4$	toluene	0
7	$NaBH_4$	diglyme	62
8	$NaBH_4$	MeCN	78 (0) <sup>f</sup>
$9^b$	$NaBH_4$	MeCN	81 (0) <sup>f</sup>
$10^{c}$	$NaBH_4$	MeCN	5
$11^{d}$	$NaBH_4$	MeCN	0
$12^{e}$	$NaBH_4$	MeCN	90

<sup>*a*</sup> InCl<sub>3</sub> 0.1 mmol, *Mt*-H 1 mmol, **1a** 1 mmol, solvent 2 mL. <sup>*b*</sup> 1.0 mmol of InCl<sub>3</sub> was used. <sup>*c*</sup> Without InCl<sub>3</sub>. <sup>*d*</sup> AlCl<sub>3</sub> was used instead of InCl<sub>3</sub>. <sup>*e*</sup> 1.5 mmol of NaBH<sub>4</sub> was used. <sup>*f*</sup> 0.1 mmol of *p*-DNB was added.

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<sub>4</sub> acts as a reducing reagent. When a little excess (1.5 equiv) of NaBH<sub>4</sub> 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<sub>3</sub>SnH, NaBH<sub>4</sub> has no radical reactivity;<sup>10,11</sup> therefore, it could be concluded that indium hydride acts as a radical reducing reagent. Thus, novel reducing system NaBH<sub>4</sub>/InCl<sub>3</sub> could be found here to undergo the radical reduction of alkyl halides under very mild conditions such as ambient temperature.<sup>12</sup>

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





 $^a$  InCl<sub>3</sub> 0.1 mmol, NaBH<sub>4</sub> 1.5 mmol, RX 1 mmol, MeCN 2 mL, rt, 2 h.  $^b$  InCl<sub>3</sub> 0.1 mmol, NaBH<sub>4</sub> 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).



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).



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



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



 $(k_{\rm H} = 1.0 \times 10^9 \text{ M}^{-1} \text{ s}^{-1})$  was determined by the radical clock experiments using **3a**.<sup>13</sup> This value is very similar to that of the rate constant for Bu<sub>3</sub>SnH determined at 25 °C ( $k_{\rm H} = 8.4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ ).<sup>14</sup>

In conclusion, we found that the indium hydride generated from  $NaBH_4$  and  $InCl_3$ , is a promising candidate of an alternative to  $Bu_3$ -SnH. 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.

## References

- Reviews: (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987. (b) RajanBavu T. V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Willey: New York, 1995; Vol. 7; pp 5016–5023.
- (2) Bu<sub>3</sub>SnH-initiator systems. Bu<sub>3</sub>SnH-Et<sub>3</sub>B: (a) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. Bull. Chem. Soc. Jpn. **1989**, 62, 143-147. Bu<sub>3</sub>SnH-9BBN: (b) Perchyonok, V. T.; Schiesser, C. H. Tetrahedron Lett. **1998**, 39, 5437-5438. Bu<sub>3</sub>SnH-CuCl: (c) Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. Tetrahedron Lett. **1999**, 40, 2133-2136. Bu<sub>3</sub>SnH-ZnEt<sub>2</sub>: (d) Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. Tetrahedron Lett. **1998**, 39, 6335-6336.
- (3) Chatgilialoglu, C. Acc. Chem. Res. 1992, 25, 188–194.
- (4) Studer, A.; Amrein, S. Angew. Chem., Int. Ed. 2000, 39, 3080-3082.
  (5) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. Synlett 1999,
- 1415-1416 and references therein. (6) Eulita K · Nakamura T · Vorimiteu H · Oshima K / Am Cham Soc
- (6) Fujita, K.; Nakamura, T.; Yorimitsu, H.; Oshima, K. J. Am. Chem. Soc. 2001, 123, 3137–3138.
- (7) Miyai, T.; Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* 1998, *39*, 1929–1932.
- (8) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. Tetrahedron Lett. 2001, 42, 4661–4663.
- (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<sub>4</sub> (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<sub>2</sub>In•). Alternative possibility is that indium(I) chloride or In(0) metal generated by reduction of indium(III) trichloride with NaBH<sub>4</sub> act as a radical reducing reagent. However, when the reaction 1a of using InCl or In metal instead of InCl<sub>3</sub> 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<sub>3</sub>SnH was reported by Carden et al. (7.8 × 10<sup>8</sup> M<sup>-1</sup> s<sup>-1</sup>). 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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