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Triethylsilane–Indium(III) Chloride System as a Radical Reagent

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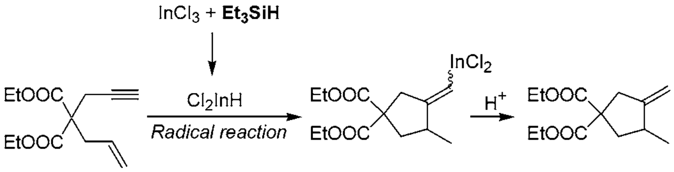
ABSTRACT



A novel generation method of indium hydride (Cl_2InH) was found by the transmetalation of $InCl_3$ with Et_3SiH. In the intramolecular cyclization of enynes, the previously reported system ($NaBH_4$–$InCl_3$) has a problem of side reactions with the coexistent borane. In contrast, the problem was solved by the presented system, which affords effective hydroindation of alkynes.

The use of radical reactions in modern organic synthesis is now well-established.[1] Despite the many well-documented advantages of free-radical chain reactions in organic chemistry, the majority of examples still rely on the use of tri-*n*-butyltin hydrides.[2,3] Hence, a major area of current research is the development of processes that seek to either alleviate the problems associated with toxic tin residues or remove the need for tin completely.[4] With a potential similar to that of Bu_3SnH, dihalogenoindium hydrides (X_2InH) have been recently found by us and other groups to be novel reagents that were generated by the transmetalation of indium(III) trihalides ($InCl_3$ or $InBr_3$) with metal hydrides.[5−7] At first, Bu_3SnH was employed as a hydride source,[5] and then it was replaced by $NaBH_4$[6] and DIBAL-H.[7] While the advances have been significant, all suffer from the strong reducing ability of the hydride sources themselves. All the hydrides employed could reduce a variety of functionalities without any assistance of Lewis acids or catalysts. In the case of $NaBH_4$−$InCl_3$, although we could achieve intramolecular cyclization and intermolecular coupling reactions initiated by dehalogenation,[6] the generation of BH_3 during transmetalation becomes a serious problem. Therefore, an alternative hydride source that causes no side reactions should be developed. Considering this background, Et_3SiH is a good candidate, and we already found weak ionic interactions

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[1] (a) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2. (b) Samir, Z. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: Oxford, 2003.

[2] For tin hydride reviews, see: (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987. (b) RajanBabu T. V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: New York, 1995; Vol. 7, p 5016.

[3] For examples of Bu_3SnH-initiator systems (Bu_3SnH−Et_3B, Bu_3SnH−9BBN, Bu_3SnH−CuCl, and Bu_3SnH−$ZnEt_2$), see: (a) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143−147. (b) Perchyonok, V. T.; Schiesser, C. H. *Tetrahedron Lett.* **1998**, *39*, 5437−5438. (c) Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2133−2136. (d) Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335−6336.

[4] For reviews see: (a) Studer, A.; Amrein, S. *Synthesis* **2002**, 835−849. ($(TMS)_3SiH$): (b) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194. Cyclohexadienyl-silane: (c) Studer, A.; Amrein, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080−3082. Tri-2-furanylgermane: (d) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **1999**, 1415−1416. Gallium hydride: (e) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2003**, *59*, 6627−6635. Schwartz reagents: (f) Fujita, K.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 3137−3138.

[5] We have already reported that indium hydrides act as both radical and ionic reagents in the reaction with a variety of halides, carbonyls, imines, and carbon−carbon multiple bonds. (a) Miyai, T.; Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 1929−1932. (b) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2001**, *42*, 4661−4663.

[6] Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906−907.

[7] Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993−2995.

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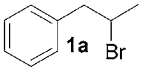
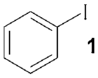
between $Et_3SiH-InCl_3$.[8] Herein we report the first application of Et_3SiH in a radical reaction via the generation of an indium hydride.

Initially, we performed the reduction of alkyl halide **1a** by $Et_3SiH-InCl_3$ in optimized conditions of our previous systems such as $Bu_3SnH-InCl_3$[5] and $NaBH_4-InCl_3$[6] (Table 1, entries 1 and 2). The reduction proceeded in moderate yield at room temperature in MeCN to afford **2a** (entry 3). In the presence of Et_3B as a radical initiator, the yield of **2a** was slightly increased (entry 4), while in CH_2Cl_2, Et_3B was essential for the reaction (entries 5 and 6). When 2 mmol Et_3SiH was used, **2a** was obtained in good yield (entry 7). In the reaction of the less reactive aryl iodide **1b**, a catalytic amount of $InCl_3$ was less effective (entry 8), but the use of equimolar $InCl_3$ afforded dehalogenation to give benzene (**2b**) in 67% (entry 9). The use of $InCl_3$ catalyst is essential because no reduction took place in the absence of $InCl_3$. As Et_3SiH has no radical reactivity,[9] indium hydride is a plausibly reactive species. In our $Bu_3SnH-InCl_3$ and $NaBH_4-InCl_3$ systems, various alkyl halides were reduced with a catalytic amount of $InCl_3$ without any initiators.[5,6] Although the exact reason Et_3B and equimolar $InCl_3$ are necessary in the $Et_3SiH-InCl_3$ system is not clear yet, this may be due to the low concentration of indium hydride because the transmetalation of $Et_3SiH-InCl_3$ is slow,[8] especially in CH_2Cl_2.

Table 1. Reduction of Halides by a *Mt*-H$-InCl_3$ System

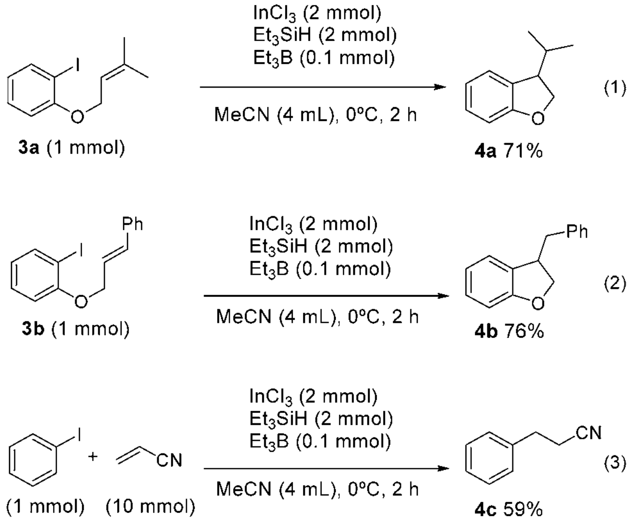
$$\underset{\mathbf{1}}{\text{RX}} \xrightarrow[\text{Solvent (2 mL), rt, 2 h}]{\text{InCl}_3\text{ (0.1 mmol)} \quad Mt\text{-H (1 mmol)}} \underset{\mathbf{2}}{\text{RH}}$$

entry	RX	*Mt*-H	solvent	product	yield (%)
1		Bu_3SnH	THF	**2a**	82
2	**1a**	$NaBH_4$	MeCN	**2a**	78
3	**1a**	Et_3SiH	MeCN	**2a**	32
4[a]	**1a**	Et_3SiH	MeCN	**2a**	39
5	**1a**	Et_3SiH	CH_2Cl_2	**2a**	9
6[a]	**1a**	Et_3SiH	CH_2Cl_2	**2a**	49
7[a]	**1a**	Et_3SiH[c]	CH_2Cl_2	**2a**	83
8[a]	 **1b**	Et_3SiH[c]	MeCN	**2b**	20
9[a,b]	**1b**	Et_3SiH[c]	MeCN	**2b**	67

[a] Et_3B (0.1 mmol) was added. [b] $InCl_3$ (1 mmol) was used. [c] Et_3SiH (2 mmol) was used.

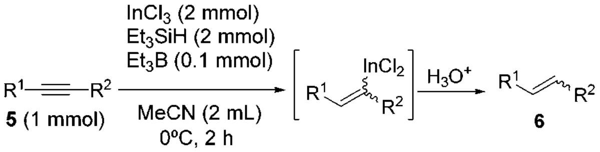
Under the optimized conditions, radical cyclizations from haloalkenes were performed effectively (Scheme 1, eqs 1 and 2). Intermolecular radical addition could be accomplished effectively to give **4c** (eq 3).

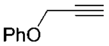
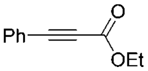
Scheme 1



In the next stage, we performed the reaction with alkynes. For example, hydrostannation of alkynes is often accelerated by radical initiators such as UV irradiation, AIBN, Et_3B, and ultrasound.[10] An indium hydride is also expected to perform hydroindation of alkynes due to its radical reactivity. When $NaBH_4-InCl_3$[6] was allowed to react with alkynes, not only hydroindation but also side reactions occurred by BH_3 generated in situ.[11] In contrast, Et_3SiH, an alternative hydride source that causes no side reactions, was used in the reactions with alkynes (Table 2). In the reduction of **5a**, product **6a** was obtained in 90% yield in MeCN (entry 1). Under the

Table 2. Reduction of Alkynes by a $Et_3SiH-InCl_3-Et_3B$ System



entry	alkyne **5**		product	yield (%)
1	Ph—≡	**5a**	**6a**	90
2	n-$C_{10}H_{21}$—≡	**5b**	**6b**	59
3		**5c**	**6c**	70
4	Ph—≡—Ph	**5d**	**6d**	77 (E : Z = 86 : 14)
5		**5e**	**6e**	68 (E : Z = 96 : 4)

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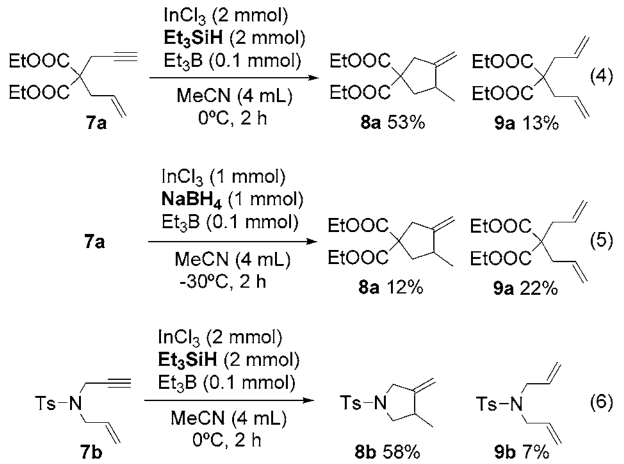
[8] We have recently developed a $Et_3SiH-InBr_3$ system that alternatively afforded ionic reactions such as reductive aldol reaction of enones. Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 711−713.

[9] Banfi, L.; Narisano, E.; Riva, R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: New York, 1995; Vol. 7, pp 4522.

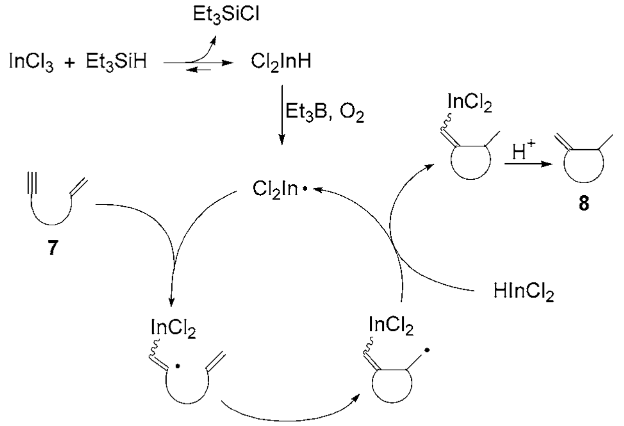
Scheme 2



same conditions, aliphatic alkyne **5b** was reduced to alkene **6b** in 59% yield (entry 2). Propargylic ether and internal alkynes **5c** and **5d** were effectively reduced to **6c** and **6d**, respectively (entries 3 and 4). $Et_3SiH-InCl_3$ also reduced alkynyl ester **5e** to **6e** without affecting the ester moiety (entry 5).

We next performed representative cyclization of enynes. Allylpropargylmalonate (**7a**) underwent cyclization to give *exo*-methylene compound (**8a**) in 53% yield at 0 °C for 2 h (Scheme 2, eq 4).[12] This reaction involves the cyclization of the generated vinyl radical to the remaining alkene (Scheme 3). The $Et_3SiH-InCl_3$ system is superior to $NaBH_4-InCl_3$ in which linear compound **9a** was obtained as a major product (eq 5). This would be because of $NaBH_4-InCl_3$, which resulted in the occurrence of hydroboration. In

Scheme 3



contrast, as shown Scheme 3, the transmetalation of $Et_3SiH-InCl_3$ gives Et_3SiCl as a byproduct, which has no reducing ability to alkynes. The reaction of *N*-tosyl allylpropargylamine (**7b**) gave nitrogen heterocycle **8b** in 58% yield (eq 6).

In conclusion, the indium hydride generated from Et_3SiH and $InCl_3$ is a promising alternative to the Bu_3SnH system. The reducing system has several advantages in terms of convenience, low toxicity, and mild conditions, and $InCl_3$ and Et_3SiH in particular are readily available and easy to handle.

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

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(10) (a) Leusink, A. J.; Budding, H. A. *J. Organomet. Chem.* **1968**, *11*, 533−539. (b) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3465−3467. (c) Nakamura, E.; Machii, D.; Inubishi, T. *J. Am. Chem. Soc.* **1989**, *111*, 6849−6850.

(11) When $NaBH_4-InCl_3$[6] was allowed to react with phenylacetylene (**5a**), styrene (**6a**) was obtained in 68% yield in MeCN at −30 °C in the presence of a radical initiator, Et_3B. The reduction scarcely proceeded in the absence of Et_3B under the same conditions. One of the serious problems of $NaBH_4-InCl_3$ system is the generation of BH_3 in the transmetalation, which was found to promote hydroboration. Indeed, even in the conditions promoting no hydroindation, namely, in the presence of a radical scavenger (*p*-dinitrobenzene) and in the absence of Et_3B, 23% of the product **6a** was still obtained by the hydroboration of **5a** at room temperature. This result suggests that the $NaBH_4-InCl_3$-promoted reaction at room temperature includes hydroboration besides the Cl_2InH-promoted radical hydroindation. From these reasons, the $NaBH_4-InCl_3$ must be carried out below −30 °C to effect hydroindation as the sole reaction.

(12) **Typical Experimental Procedure of the Reduction of Enyne.** The 10 mL round-bottom flask charged with $InCl_3$ (0.442 g, 2.0 mmol) was heated at 110 °C under reduced pressure for 1 h. After the system was filled with nitrogen, MeCN (4 mL) and Et_3SiH (2.0 mmol) were added and the mixture was stirred at 0 °C for 5 min. Then enyne **7a** (1.0 mmol) and 1 M Et_3B in hexane (0.1 mL) were added, and the resulting mixture was stirred at 0 °C for 2 h. After deionized water was added, the reaction mixture was extracted with ether (10 mL x 3). The combined organic layer was dried over $MgSO_4$ and concentrated. The crude mixture was purified by column chromatography to give cyclization product **8a** (0.127 g, 53%).