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Inter- and Intramolecular Radical Couplings of Ene-ynes or Halo-alkenes Promoted by an $InCl_3/MeONa/Ph_2SiH_2$ System

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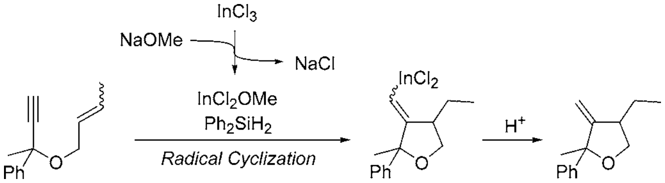
ABSTRACT



An effective generation of indium hydride ($HInCl_2$) under nonacidic conditions is achieved by transmetalation between Ph_2SiH_2 and $InCl_2OMe$. The presented system achieves the titled coupling reactions in a radical manner. In particular, the nonacidic character enables the applications to acid-sensitive inter- and intramolecular ene-yne couplings.

The use of radical reactions in modern organic synthesis is now well-established.[1] Despite the disadvantages of toxicity and difficulty in the removal of tin residues,[2] the majority of examples still rely on the use of tri-*n*-butyltin hydride because of its high versatility.[3,4] An alternative promising radical reagent, dihalogenoindium hydride ($HInX_2$), has been recently found by us and other groups and can be generated from indium(III) trihalides ($InCl_3$ or $InBr_3$) and metal hydrides.[5−8] At first, Bu_3SnH had to be employed as a hydride source,[5] and then it was replaced by $NaBH_4$,[6] DIBAL-H,[7] and then Et_3SiH.[8] While the advances have been

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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 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.

[3] 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.

[4] 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.

[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.

[8] Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4981−4983.

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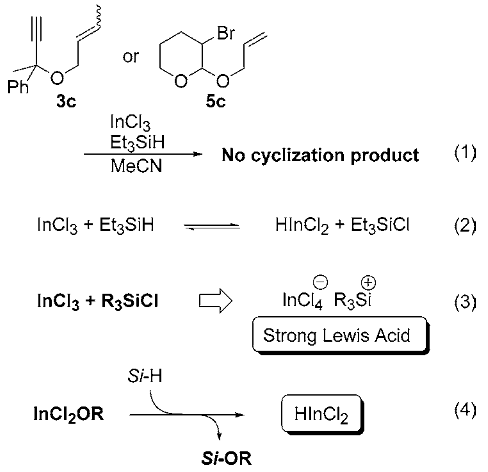
Scheme 1

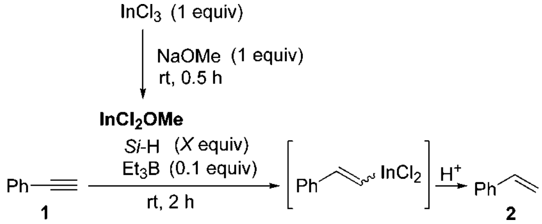


significant, all suffer from the strong reducing ability of the hydride sources themselves and from the actions of byproducts. In the case of $NaBH_4$, the generation of BH_3 during transmetalation becomes a serious problem in the reaction with alkynes. We have recently developed an $InCl_3/Et_3SiH$ system that can achieve intramolecular cyclization of enynes. This result strongly indicates the higher potentiality of indium hydride over tributyltin hydride because such cyclization has usually required transition metal catalysts under harsh conditions. However, in the course of expanding the application to various substrates, we met with serious problems since enyne **3c** and halo-alkene **5c** gave no desired products, although all starting substrates were consumed (Scheme 1, eq 1). This is because Et_3SiCl is the byproduct in transmetalation of $InCl_3$ with Et_3SiH (eq 2). We have already reported that enhanced Lewis acidity can be achieved by the combination of silyl chloride and $InCl_3$ (eq 3),[9] which may work to decompose substrates **3c** and **5c** or their products. To overcome this serious problem we made an attempt using an alkoxyindium that is generated in situ (eq 4). If the alkoxyindium were transmetalated to dichloroindium hydride, alkoxy silanes (*Si*-OR) would be the byproduct instead of Et_3SiCl. Thus, the formation of a strong acid system, $InCl_3/Et_3SiCl$, can be avoided.

Herein we report a new method for generation of indium hydride from alkoxy indium and expand the scope of application to acid-sensitive reactions. In addition, the first examples of intermolecular radical reaction between alkynes and alkenes are presented.

Initially, we investigated the optimized conditions for the radical reduction of ethynylbenzene (**1**) using $InCl_3$/NaOMe/hydrosilane system as summarized in Table 1. A mixture of $InCl_3$ (1 equiv) and NaOMe (1 equiv) was stirred in THF at room temperature for 0.5 h to generate indium alkoxides. To the resulting mixture were sequentially added Ph_2SiH_2 (1 equiv), the alkyne, and Et_3B (0.1 equiv), and the mixture was stirred at room temperature for 2 h to give the reduction product, styrene, in 66% yield after the usual workup (Table 1, entry 1).[10]

Table 1. Effects of Solvents and Silanes



entry	*X*	solvent	*Si*-H	yield (%)
1	1	THF	Ph_2SiH_2	66
2	1	MeCN	Et_3SiH	0
3	1	MeCN	Ph_2SiH_2	8
4	1	hexane	Ph_2SiH_2	0
5	1	CH_2Cl_2	Ph_2SiH_2	0
6[a]	1	THF	Ph_2SiH_2	0
7[b]	1	THF	Ph_2SiH_2	0
8[c]	1	THF	Ph_2SiH_2	0
9[d]	1	THF	Ph_2SiH_2	0
10	2	THF	Ph_2SiH_2	95
11[e]	2	THF	Ph_2SiH_2	79

[a] Without NaOMe. [b] $AlCl_3$ was used instead of $InCl_3$. [c] BF_3 was used instead of $InCl_3$. [d] Without $InCl_3$. [e] Without Et_3B.

The solvent and hydrosilane used were THF and Ph_2SiH_2, respectively. Other solvents such as acetonitrile and hexane promoted the reaction in low yields (entries 2−5), while acetonitrile was the most effective solvent in the case of the transmetalation between $InCl_3$ and Et_3SiH to give $HInCl_2$ and Et_3SiCl.[8] Other hydrosilanes (Ph_3SiH, $PhSiH_3$) gave lower yields than Ph_2SiH_2 in THF. No reaction occurred without the addition of NaOMe in THF (entry 6) perhaps because of the sluggish transmetalation between $InCl_3$ and Ph_2SiH_2. Other metal alkoxides such as NaO^{t}Bu, KO^{t}Bu, and NaOAc were less effective. Using typical Lewis acids such as $AlCl_3$ or BF_3 instead of $InCl_3$ also gave no product (entries 7 and 8). Of course, no reduction took place without $InCl_3$ (entry 9). These results indicate that the transmetalation between the In−OR bond and the Si−H bond takes place under the optimized conditions. When 2 equiv of Ph_2SiH_2 was used, product **2** was obtained in a higher yield (entry 10). In addition, although the yield was slightly lower, this reaction proceeded well without Et_3B (entry 11).[11]

In the next stage, we carried out intramolecular radical cyclizations of enynes under the optimized conditions (Scheme 2, eqs 5−7). Heterocycles including oxygen or nitrogen were obtained in good yields. Particularly, enyne

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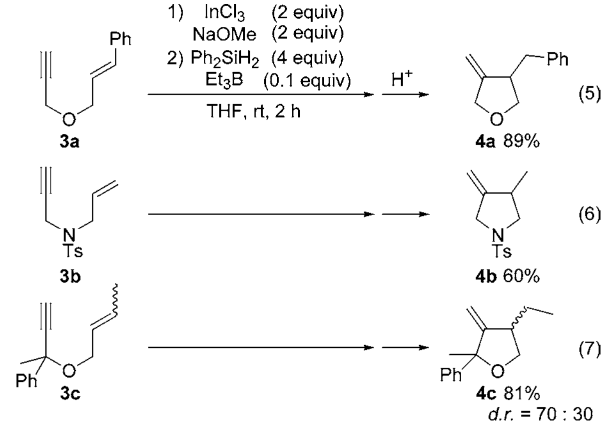
(9) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227−8235.

(10) For the generation of the In−C bond after the hydroindation, we can detect β-iodostyrene by quenching with I_2.

(11) We have already reported that the radical reaction of $HInCl_2$ from $InCl_3/Bu_3SnH$ proceeded without any initiators because homolytic cleavage of the In−H bond takes place easily. Hence, the $InCl_3$/NaOMe/hydrosilane system caused effective transmetalation to give $HInCl_2$. On the contrary, the previously reported system $InCl_3/Et_3SiH$ required Et_3B because of the low concentration of indium hydride due to the slow transmetalation between $InCl_3$ and Et_3SiH.

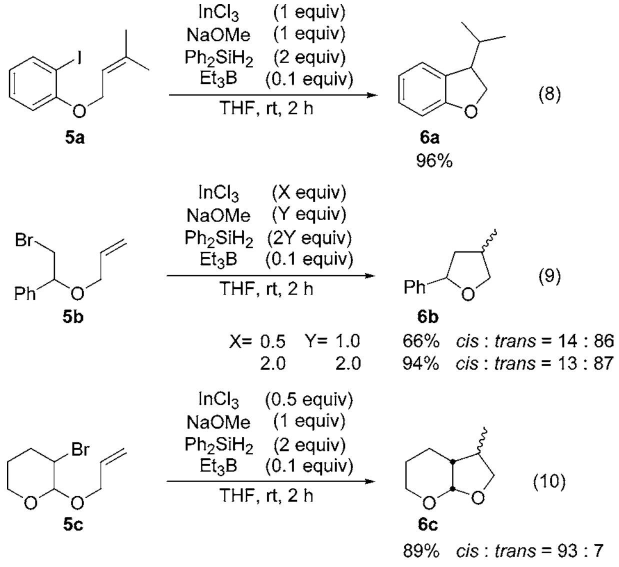
Scheme 2. Cyclization of Enynes



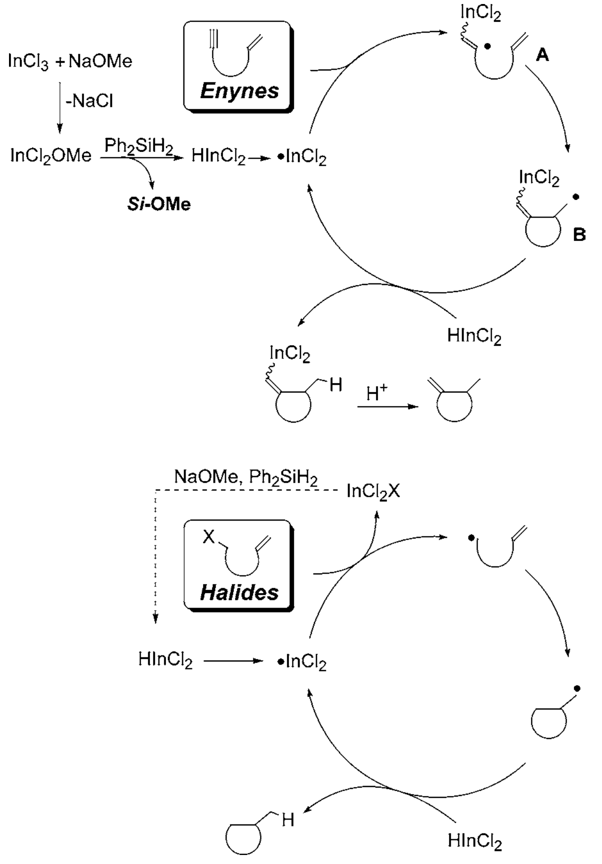
3c, which had afforded no cyclization product by the InCl$_3$/Et$_3$SiH system, gave **4c** in 81% yield (eq 7). Even in the case of **3b** bearing terminal alkene and alkyne moieties, a similar cyclization took place in an acceptable yield. These results indicate the low acidity of this system and the characteristic interaction between the alkyne moiety with an indium species.[12]

This low-acid system was found to be applicable to a radical dehalogenation as effectively as already reported indium hydride systems.[6,8] Among the dehalogenation reactions, Scheme 3 exemplifies intramolecular cyclizations of halo-alkenes bearing acid-sensitive moieties. It is particularly notable that the adduct **6c** was obtained in 89% yield from **5c**, which had been decomposed by the system of InCl$_3$/Et$_3$SiH in acetonitrile (eq 10). That the use of 50 mol % InCl$_3$ was sufficient for this high yield suggests the possibility of a catalytic reaction, although it is not completely achieved in this stage.

Scheme 3. Cyclization of Halo-alkenes



Scheme 4. Plausible Cyclization Mechanisms



Plausible cyclization mechanisms are illustrated in Scheme 4. The in situ-formed InCl$_2$OMe is transmetalated with Ph$_2$SiH$_2$ to give HInCl$_2$, which affords an indium radical ($^{\bullet}$InCl$_2$) by the easy cleavage of the In−H bond. No direct reaction between InCl$_3$ and Ph$_2$SiH$_2$ is taking place, and also the participation of the transmetalation of InCl$_2$OMe with Ph$_2$SiH$_2$ could be plausibly proposed on the basis of the fact that no reaction proceeds without NaOMe. The choice of solvent is important for the control of the reaction. In THF, the formation of InCl$_2$OMe and/or the transmetalation between In−OMe and Si−H bonds may be promoted effectively. Even if a small amount of silyl chloride is generated, the strong coordination ability of THF disturbs the interaction between the silyl chloride and indium species to depress the formation of a strong Lewis acid. The resulting indium radical ($^{\bullet}$InCl$_2$) adds to the C−C triple bond to give vinyl radical **A**, which reacts with the remaining alkene moiety to give cyclized radical **B**. Finally, the radical **B** is hydrogenated by HInCl$_2$.

In the reaction with organic halides, a similar radical chain mechanism is plausible. When the reaction of the resulting InCl$_2$X and NaOMe is effectively achieved in situ, a catalytic cycle is completed.

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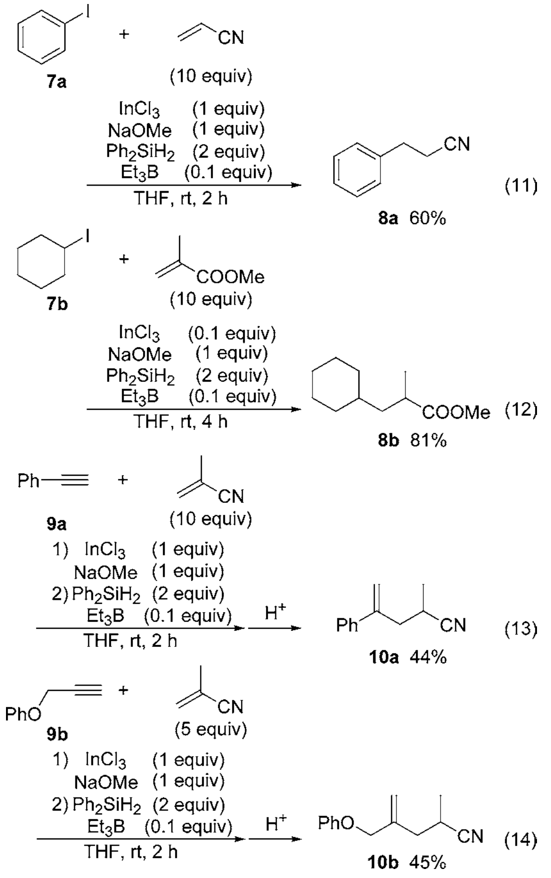
(12) Tin hydride is more reactive toward alkene than indium hydride. Leusink, A. J.; Noltes, J. G. *Tetrahedron Lett.* **1966**, *7*, 335−340.

Scheme 5. Intermolecular Radical Reactions



Next, intermolecular radical reactions were carried out. In the reaction of phenyl iodide (**7a**) with acrylonitrile, the desired product **8a** was obtained in a moderate yield by using excess alkene (Scheme 5, eq 11). More active secondary alkyl iodide **7b** reacted with methyl methacrylate to give **8b** in the presence of a catalytic amount (10 mol %) of $InCl_3$ (eq 12). The intermolecular radical reaction of alkyne with alkene was also enabled by detailed investigations to give products **10a** and **10b** in 44 and 45% yields, respectively (eqs 13 and 14). To the best of our knowledge, this is the first example of intermolecular radical coupling between alkynes and alkenes. When Bu_3SnH was used instead of our system, no intermolecular coupling product was obtained. This failure may result from the higher reactivity of tin hydride toward alkene because the hydrostannation product of alkene was obtained in the intermolecular coupling of alkyne with alkene.

In conclusion, we developed an effective method for the generation of indium hydride by using alkoxyindium formed in situ. This system was able to prevent decomposition of acid-sensitive substrates to achieve intermolecular ene−yne couplings. The detailed mechanism is under investigation.

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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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