

Indium(III) Acetate-Catalyzed Intermolecular Radical Addition of Organic Iodides to Electron-Deficient Alkenes

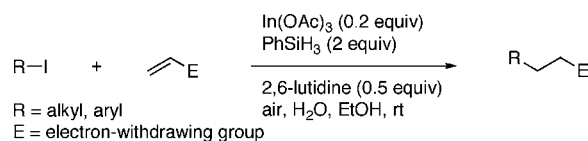
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Received November 8, 2007

ABSTRACT



In the presence of phenylsilane and a catalytic amount of indium(III) acetate, organic iodides added to electron-deficient alkenes in ethanol at room temperature. Both simple and functionalized organic iodides were applicable to this reaction. A plausible reaction mechanism involves the formation of indium hydride species by hydride transfer from silicon to indium and an indium hydride-mediated radical chain process.

Synthetic radical reactions directed toward fine organic synthesis have rapidly been developed in the last three decades.¹ At present carbon radicals are recognized as reactive, but controllable carbon species valuable for highly selective, efficient bond formation. Triorganotin hydrides such as Bu₃SnH have frequently been used as efficient radical mediators, which serve for generation of carbon radicals and radical quenching by hydrogen-donation.¹ Unfortunately, their use has two critical drawbacks, that is, the toxicity of organostannanes and the difficulty of product purification.^{2,3} A number of hydride-based radical mediators have been developed as substitutes for triorganotin hydrides.^{4–7} Additionally, the catalytic use of radical mediators in the presence of stoichiometric hydride sources has received much attention from the viewpoint of environmentally friendly and

economical synthesis.^{5c,6,8} Such catalytic reactions are very effective in radical reduction and intramolecular radical addition of organic halides and pseudohalides. However, intermolecular addition of these radical precursors (R–X) to alkenes (CH₂=CHE) using catalytic mediators (M–H) shows much room for improvement (Scheme 1).^{6b,8b}

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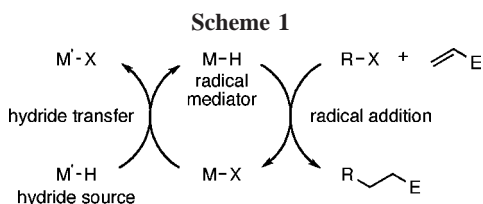
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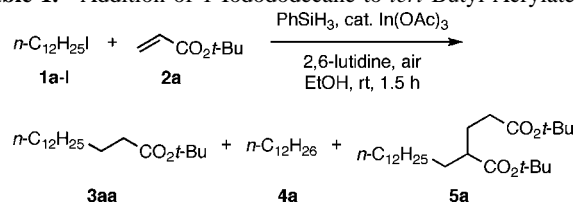


We have recently developed the $\text{In}(\text{OAc})_3$ -catalyzed radical reduction of organic halides with PhSiH_3 . With the aid of 2,6-lutidine and dry air, the catalytic system enables an efficient reduction of various iodoalkanes in EtOH at room temperature.⁹ We herein report that the reaction system using $\text{In}(\text{OAc})_3$, PhSiH_3 , 2,6-lutidine, and dry air is valuable also for catalytic radical addition of organic iodides to electron-deficient alkenes ($\text{M} = \text{X}_2\text{In}$, $\text{M}' = \text{PhH}_2\text{Si}$ in Scheme 1). In this context, Baba and Shibata have reported that similar reaction systems using $\text{In}(\text{III})$ catalysts and stoichiometric hydride sources are usable for intermolecular radical addition.^{6a,b} However, the limited examples were not enough to demonstrate the applicability and synthetic utility of these systems. The reaction efficiency was not necessarily good even with a large excess (5–10 equiv) of alkenes. This paper reveals that the $\text{In}(\text{OAc})_3$ -catalyzed system using PhSiH_3 as hydride source can be applied to a variety of organic iodides, and that it realizes moderate to good yield of desired adducts with 2–3 equiv of alkenes under mild, environmentally friendly conditions.

1-Iodododecane (**1a-I**) and *tert*-butyl acrylate (**2a**) were initially selected as substrates to optimize the reaction conditions. On the basis of the conditions used for the $\text{In}(\text{OAc})_3$ -catalyzed reduction of organic halides,⁹ the reaction of **1a-I** (1 equiv) with **2a** (3 equiv) was carried out with PhSiH_3 (1 equiv), $\text{In}(\text{OAc})_3$ (0.2 equiv), 2,6-lutidine (0.5 equiv), and dry air in EtOH at room temperature (entry 1 in Table 1). The reaction under these conditions gave the desired adduct **3aa** in 50% yield with a 10% recovery of **1a-I**. Dodecane (**4a**) and adduct **5a** were also formed as byproducts. The latter byproduct **5a** consists of one molecule of **1a-I** and two molecules of **2a**. With an increased amount of PhSiH_3 (2 equiv), the yield of **3aa** was improved to 60–67% (entry 2). The control experiment without 2,6-lutidine resulted in a lower yield of **3aa** (entry 3). Reproducible results were not obtained in the absence of air. Addition of H_2O did not affect the yield of **3aa**; however, it decreased unidentified byproducts to facilitate the isolation of **3aa** by silica gel column chromatography (entry 4). Use of 1 or 2 equiv of **2a** still led to a similar yield of **3aa** (entries 5–7). As expected, the equimolar reaction of **1a-I** with **2a** increased the amount of **4a** and suppressed the formation of **5a**.

Under the conditions of entry 4 in Table 1, the reaction of iodocyclododecane (**1b-I**) with **2a** resulted in low yield of the desired adduct **3ba** and recovery of **1b-I** (Scheme 2). In this protocol, 2,6-lutidine was introduced into the reaction

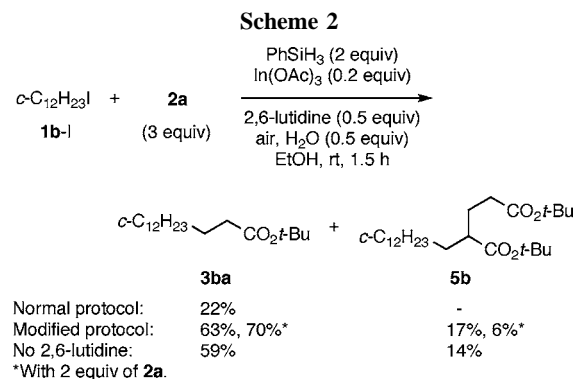
Table 1. Addition of 1-Iodododecane to *tert*-Butyl Acrylate^a



entry	2a /equiv	PhSiH_3 /equiv	GC yield/%		
			3aa	4a	5a
1 ^b	3	1	50	11	8
2	3	2	60–67 ^c	7–10 ^c	12
3 ^d	3	2	53	9	
4 ^e	3	2	67 (64) ^f	14	
5	2	2	64	6	12
6 ^e	2	2	65 (56) ^f	11	10
7 ^e	1	2	(63) ^f	22	5

^a Unless otherwise noted, all reactions were carried out with **1a** (0.50 mmol), **2a** (1.50, 1.00, or 0.50 mmol), PhSiH_3 (0.50 or 1.00 mmol), $\text{In}(\text{OAc})_3$ (0.10 mmol), 2,6-lutidine (0.25 mmol), dry air (4.8 mL), and EtOH (1.0 mL) under N_2 (2 L balloon) at room temperature for 1.5 h. ^b **1a** was recovered in 10% GC yield. ^c The results of three runs. ^d Without 2,6-lutidine. ^e H_2O (0.25 mmol) was used as an additive. ^f The isolated yield is shown in parentheses.

flask last of all at a 20–30 s interval after the addition of PhSiH_3 (see the Supporting Information). We found that the addition of 2,6-lutidine after an interval of 10 min was



effective in the intermolecular reaction. With the modified protocol, the reaction using 2 equiv of **2a** afforded **3ba** in 70% isolated yield. In the absence of 2,6-lutidine, **3ba** was obtained in slightly lower yield.

The scope and limitations of the $\text{In}(\text{OAc})_3$ -catalyzed intermolecular addition are summarized in Table 2. The addition of **1a-I** and **1b-I** to ethyl acrylate (**2b**) and acrylonitrile (**2c**) proceeded in moderate to good yields (entries 1–3 and 5). 1-Iodoadamantane (**1c-I**), a tertiary-alkyl iodide, smoothly added to **2a** (entry 7). The reactions without 2,6-lutidine showed lower efficiency, proving its effectiveness in the present reaction system (entries 4, 6, and 8). 1-Bromododecane (**1a-Br**) was quite unreactive to **2a** irrespective of the presence of 2,6-lutidine (entries 9 and 10).

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Table 2. Addition of Haloalkanes to Electron-Deficient Alkenes^a

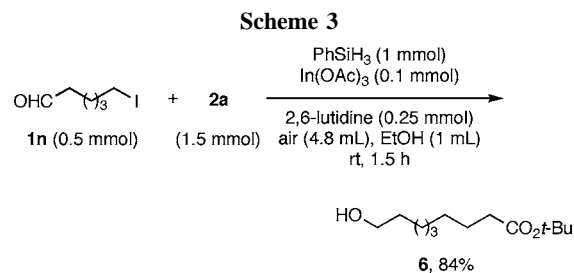
entry	R-X	2	method ^b	product, isolated yield/%
1	<i>n</i> -C ₁₂ H ₂₅ I (1a-I)	2b	A	3ab , 61 ^c
2	1a-I	2c	A	3ac , 76 ^c
3	<i>c</i> -C ₁₂ H ₂₃ I (1b-I)	2b	A ^d	3bb , 65
4	1b-I	2b	B	3bb , 59
5	1b-I	2c	A ^d	3bc , 74
6	1b-I	2c	B	3bc , 55
7	1-Ad-I (1c-I)	2a	A	3c , 63
8	1c-I	2a	B	3c , 55
9	<i>n</i> -C ₁₂ H ₂₅ Br (1a-Br)	2a	A	3aa , 0
10	1a-Br	2a	B	3aa , 0
11	<i>c</i> -C ₁₂ H ₂₃ Br (1b-Br)	2a	A	3ba , 71
12	1b-Br	2a	B	3ba , 35
13	1-Ad-Br (1c-Br)	2a	A	3c , 30
14	1c-Br	2a	B	3c , <5
15	PhCO ₂ (CH ₂) ₃ I (1d)	2a	A	3d , 61, 56 ^e
16	MeC(O)(CH ₂) ₃ I (1e)	2a	A	3e , 56
17	TBSO(CH ₂) ₃ I (1f)	2a	A	3f , 50
18	<i>n</i> -C ₈ H ₁₇ O(CH ₂) ₃ I (1g)	2a	A	3g , 55
19	HO(CH ₂) ₃ I (1h)	2a	A ^e	3d , 69
20	1h	2c	A	3hc , 75
21	MeCH(OH)(CH ₂) ₁₁ I (1i)	2a	A	3ia , 63
22	1i	2c	A	3ic , 83
23	PhI (1j)	2a	A ^f	3j , 75, 71 ^g
24	1j	2a	B ^f	3j , 23 ^g
25	1j	2a	A ^h	3j , <5 ^g
26	4-MeC ₆ H ₄ I (1k)	2a	A ^f	3k , 52, 55 ^g
27	4-MeOC ₆ H ₄ I (1l)	2a	A ^f	3l , 54
28	4-HOC ₆ H ₄ I (1m)	2a	A ^f	3m , 65 ^g

^a Unless otherwise noted, all reactions were carried out with **1** (0.50 mmol), **2** (1.50 mmol), PhSiH₃ (1.00 mmol), In(OAc)₃ (0.10 mmol), dry air (4.8 mL), H₂O (0.25 mmol), and EtOH (1.0 mL) under N₂ (2 L balloon) at room temperature for 1.5 h. ^b In method A, 2,6-lutidine (0.25 mmol) was used as an additive. In method B, 2,6-lutidine (0.25 mmol) was not used. ^c The result with 1.00 mmol of **2**. ^d 2,6-Lutidine was added at an interval of 10 min after the addition of PhSiH₃. ^e To ease the isolation of the product **3ha**, it was converted into **3d** by treatment with benzoyl chloride and pyridine. ^f An increased amount of dry air (9.6 mL) was used. ^g The result without water. ^h Without dry air.

In contrast, bromocyclododecane (**1b-Br**), a secondary bromide, was reactive enough for the addition to **2a**, and the corresponding adduct **3ba** was obtained in good yield (entry 11). Without 2,6-lutidine, the yield of **3ba** dropped remarkably (entry 12). The difference between **1a-Br** and **1b-Br** in reactivity is consistent with the previous result of the reduction of these bromides by a similar reaction system.⁹ 1-Bromoadamantane (**1c-Br**) was not as reactive as **1b-Br** (entry 13).

The In(OAc)₃-catalyzed addition was applicable to functionalized iodoalkanes as well as simple iodoalkanes (entries 15–22). The mild reaction conditions bring about high

compatibility with oxygen functional groups such as ester, ketone, ether, and alcohol. Particularly, iodo ketone **1e** added to **2a** without carbonyl reduction (entry 16). The tolerance of the carbonyl group is attributable to the low reactivities of PhSiH₃ and indium hydride species as hydride nucleophiles.^{9,10} The addition of iodo alcohols **1h** and **1i** proceeded efficiently without degradation of the hydroxy group (entries 19–22). Our attempts at the reaction of 1-iodohexanal (**1n**) with **2a** were not successful. In this case, hydroxyester **6** was formed in high yield by reduction of the formyl group simultaneously with the carbon–carbon bond formation (Scheme 3).¹⁰



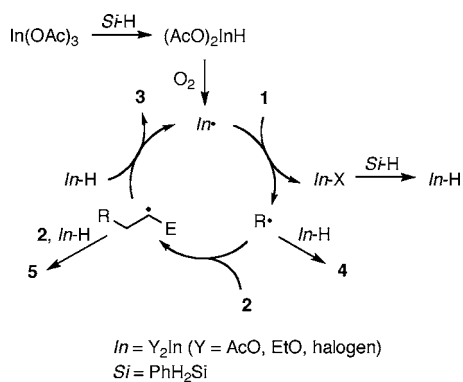
Iodoarenes also underwent the In(OAc)₃-catalyzed intermolecular addition to electron-deficient alkenes (entries 23 and 26–28). Oxygen functional groups on the benzene ring remained intact under these conditions. 2,6-Lutidine and air played critical roles also in the reaction of iodoarenes. For example, the addition of iodobenzene (**1j**) to **2a** using both additives gave **3j** in 71% yield. In the absence of 2,6-lutidine or air, the yield dropped to 23% or <5%, respectively (entries 24 and 25). H₂O was not effective in acceleration of the reaction (entries 23 and 26), but helpful for reduction of byproducts as in the reaction of **1a-I**.

A plausible mechanism for the present reaction is shown in Scheme 4.^{6a,b} The first step is the formation of (AcO)₂InH by hydride transfer from PhSiH₃ to In(OAc)₃. The indium hydride undergo H-abstraction by O₂ in air to give (AcO)₂In• (i.e., (AcO)₂In(II)). The active species abstracts halogen from a halide **1** (R–X) to generate the corresponding carbon radical R• and (AcO)₂InX. The addition of R• to an alkene **2** followed by H-abstraction from indium hydrides (In–H) gives the corresponding adduct **3** with regeneration of indium radicals (In•). The indium salt formed, (AcO)₂InX, is converted into In–H by the reaction with PhSiH₃ in EtOH. The formation of **4** is the result of direct H-abstraction of R• from In–H. The successive addition of R• to two molecules of **2** forms the adduct **5**. The present system enables proper control of the concentration of In–H to avoid these side reactions.

The effect of 2,6-lutidine on reaction efficiency was remarkable in the reaction of less reactive substrates such

(10) We have previously reported that the In(OAc)₃-catalyzed reaction of α-enones with PhSiH₃ in EtOH gives ketones by 1,4-reduction without overreduction leading to alcohols, and that the reduction system is effective in the conversion of aldehydes into alcohols. Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985.

Scheme 4



as bromoalkanes and iodoarenes. As reported previously, 2,6-lutidine would serve for neutralization of the reaction system, which prevents the solvolysis of $PhSiH_3$ with EtOH. The diminished effectiveness of 2,6-lutidine in the reaction of iodoalkanes is attributable to their fast reaction prior to the solvolysis.

In conclusion, we have developed a new method for tin-free radical addition of organic iodides to electron-deficient alkenes, which realizes high compatibility to functional groups as well as mild, environmentally sound reaction conditions. The present study has demonstrated that indium catalysis is valuable not only for radical reduction and radical cyclization but also for intermolecular radical addition. On the basis of the indium catalysis, more cost-effective methods for radical reactions using inexpensive hydride sources and bases are now under investigation.

Acknowledgment. This work was partly supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Government of Japan and by Banyu Pharmaceutical Co. Ltd.

Supporting Information Available: Procedure for the synthesis of functionalized iodoalkanes and the $In(OAc)_3$ -catalyzed intermolecular addition, as well as analytical and spectral characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL702712D