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Generation of Allylic Indium by Hydroindation of 1,3-Dienes and One-Pot Reaction with Carbonyl Compounds

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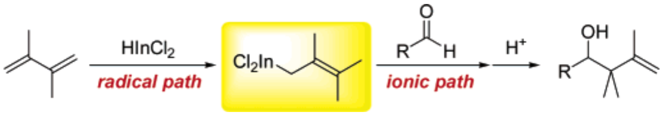
ABSTRACT



A hydroindation of 1,3-dienes by dichloroindium hydride ($HInCl_2$) generates allylic indiums that react with carbonyl or imine moieties in a one-pot treatment. The former reaction proceeds in a radical manner, and the latter is ionic allylation. Moreover, both reactions require no additives such as radical initiators, Lewis acids, or transition metal catalysts.

Much attention has been paid to the generation of characteristic allylic metals and their reactions with various electrophiles.[1] In particular, an important subject is the generation of multisubstituted active allylic metals, which can lead to tertiary or quaternary carbon centers by reactions with carbon electrophiles. One of the practical methods is a hydrometalation of 1,3-dienes. This method provides an atom-economical reaction system and can be applied to various substituted allylic species. A conventional method by transmetalation using allylic metals such as the Grignard reagent is not appropriate for this purpose.[1a,2] Although a number of reports have been presented for the hydrometalation of 1,3-dienes, most required the assistance of transition metal catalysts.[3] Moreover, there are a few methods that include subsequent one-pot allylations by the generated metal species without any additives.[3a,b] Borohydrides are plausibly the most versatile reagents, but control of the reactivity is not so easy.[3a] Recently, allylic indium reagents have been recognized because of their environmentally benign character that includes water tolerance.[4] However, there is no report about the generation of allylic indiums by the hydroindation of 1,3-dienes.

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(1) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2, Chapter 1.1, p 1.

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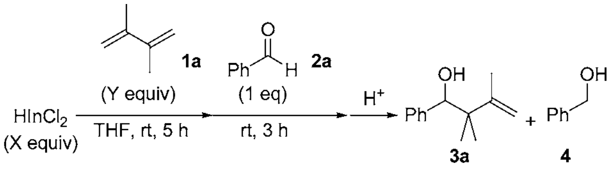
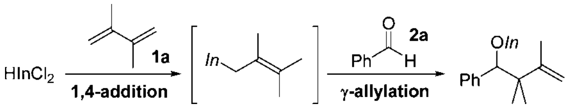
We have recently developed the generation and synthetic use of dihaloindium hydrides ($HInX_2$).[5] Indium hydride has effected not only some ionic reductions[6] of carbonyl compounds but also radical reactions such as dehalogenation and hydroindation of alkynes.[7,8] In the course of our investigation, dihaloindium hydrides were found to promote radical conjugate addition to 1,3-dienes. Herein we report the generation of allylic indium species and subsequent one-pot allylation of aldehydes, ketones, and imines to produce tertiary and quaternary carbon centers, in which both steps require no promoters. This is the first example of radical hydroindation of 1,3-dienes to furnish multisubstituted allylic indiums.

First, to optimize the reaction conditions, 2,3-dimethyl-1,3-butadiene (**1a**) was treated with $HInCl_2$ generated from the effective transmetalation between $InCl_3$ and Bu_3SnH,[9] and subsequently benzaldehyde (**2a**) was added to the resulting mixture under various conditions. In this system, the generation of a prenyl type of indium species is expected to produce the adduct **3a** possessing a quaternary carbon center. Under the optimized conditions, treating 2 equiv of $HInCl_2$ with an excess amount of the 1,3-diene at room temperature, a quantitative yield of **3a** was obtained (entry 3 in Table 1). The selective formation of **3a** plausibly suggests that 1,4-addition of indium hydride to the 1,3-diene **1a** took place and the subsequent allylation of aldehyde was promoted at the γ-position of the resulting allylic indium (eq 1). Internal dienes such as cyclohexadiene and 1,4-diphenyl-1,3-butadiene were found to be inert to the hydroindation because predominant reduction of aldehyde by $HInCl_2$ took place instead of allylation.

Table 1. Hydroindation of 1,3-Diene and One-Pot Allylation



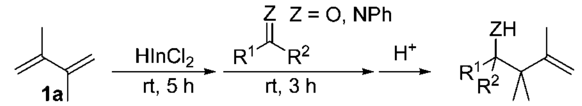
entry	X (equiv)	Y (equiv)	yield (%)	
			3a	**4**
1	1	1	49	5
2	2	2	69	24
3	2	4	94	0

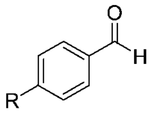
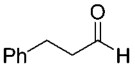
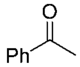
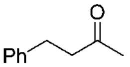
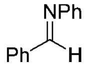


(1)

Next, we investigated the reactions of diene **1a** with various electrophiles under the optimized conditions. The reactions with benzaldehyde derivatives bearing either electron-donating or electron-withdrawing substituents gave the corresponding products in good yields (entries 2−6 in Table 2). The reducible functionalities such as Cl, NO_2, and methoxycarbonyl groups tolerated the conditions. Moreover, aliphatic aldehyde **2g** also afforded allylated product **3g** in 88% yield (entry 7). Although 3 equiv of $HInCl_2$ and a long reaction period were needed, aromatic ketone **2h** gave moderate yields (entries 8). Imine **2j** also reacted in moderate yield after a long reaction period (entry 10). Unfortunately, aliphatic ketone **2i** gave a low yield (entry 9). We speculated that these results depended on the low nucleophilicity of sterically demanding γ-disubstitued allylic indium species generated in situ.

Table 2. Allylation of Various Electrophiles[a]



entry	electrophile			product	yield (%)
1		R = H	**2a**	**3a**	94
2		Me	**2b**	**3b**	80
3		Cl	**2c**	**3c**	99
4		NO_2	**2d**	**3d**	69
5		OMe	**2e**	**3e**	93
6		COOMe	**2f**	**3f**	85
7			**2g**	**3g**	88
8[b]			**2h**	**3h**	50
9[c]			**2i**	**3i**	28
10[d]			**2j**	**3j**	42

[a] Diene (4 mmol), $HInCl_2$ (2 mmol), electrophile (1 mmol), THF solvent (2 mL). [b] $HInCl_2$ (3 mL) and THF solvent (3 mL) were used. The period of reaction between allylic indium and **2h** was 16 h. [c] The period of reaction between allylic indium and **2i** was 16 h. [d] The period of reaction between **1a** with $HInCl_2$ was 14 h.

In the next stage we examined the reactions of 1,3-butadiene (**1d**) in which the formation of less substituted crotyl indium was expected to lead to facile reaction

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(4) (a) Cintas, P. *Synlett* **1995**, 1087−1096. (b) Marshall, J. A. *Chemtracts: Org. Chem.* **1997**, *10*, 481−496. (c) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149−11176. (d) Araki, S.; Hirashita, T. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 323−386.

(5) Baba, A.; Shibata, I. *Chem. Rec.* **2005**, *5*, 323−335.

(6) (a) Miyai, T.; Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1998**, *39*, 1929−1932. (b) Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 711−713.

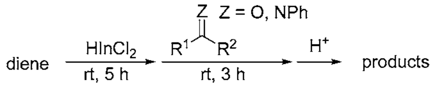
(7) (a) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2001**, *42*, 4661−4663. (b) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906−907. (c) Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4981−4983. (d) Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2005**, *7*, 3093−3096.

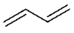
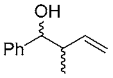
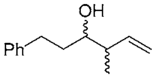
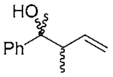
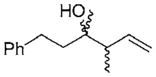
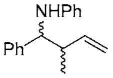
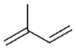
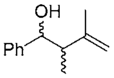
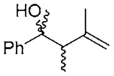
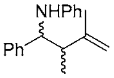
(8) Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993−2995.

(9) Here we selected the $InCl_3/Bu_3SnH$ system, which generates $HInCl_2$ effectively compared to other hydride sources such as $NaBH_4$ and Et_3SiH. In the case of other hidride sources, slow generation of $HInCl_2$ and side reactions became problematic.

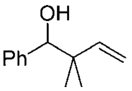
with ketones. As expected, the subsequent reactions with aromatic and aliphatic ketones and an imine proceeded smoothly to give the corresponding allylation products in good yields (entries 3−5 in Table 3). Even alkyl ketone **2i** gave a higher yield of 69%, whereas little allylation adduct was obtained from 2,3-dimethyl-1,3-butadiene (entry 9 in Table 2 vs entry 4 in Table 3). Unfortunately, the stereoselectivities are not high, furnishing mixtures of *anti* and *syn* isomers.

Table 3. Reaction with 1,3-Butadiene and Isoprene[a]

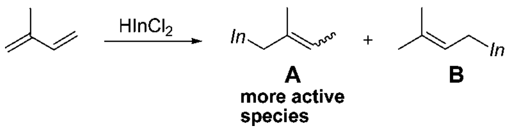


entry	diene	electrophile	product (*syn* : *anti*)	yield (%)
1	 **1d**	**2a**	 **3k** (45 : 55)	85
2		**2g**	 **3l** (47 : 53)	79
3[b]		**2h**	 **3m** (79 : 21)	87
4		**2i**	 **3n** (57 : 43)	69
5		**2j**	 **3o** (53 : 47)	52
6	 **1e**	**2a**	 **3p** (48 : 52)	75[c]
7		**2h**	 **3q** (*dr* = 72 : 28)	70
8		**2j**	 **3r** (*dr* = 57 : 43)	90

[a] Diene (4 mmol), HInCl$_2$ (2 mmol), electrophile (1 mmol), THF solvent (2 mL). [b] A excess amount of 1,3-butadiene was used. [c] Byproduct **3s** was obtained in 12% yield.


3s

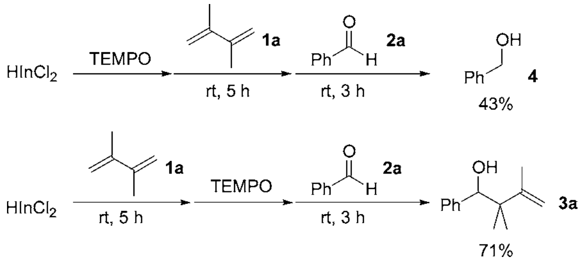
In the case of isoprene, the reaction with benzaldehyde (**2a**) gave a mixture of expected adduct **3p** (75%) along with 2,2-dimethylallylic alcohol **3s** (12%) (entry 6). On the other hand, when ketone **2h** and imine **2j** were treated, only the former type of adducts **3q** and **3r** were obtained (entries 7 and 8). These results indicate that two types of allylic indiums, **A** and **B**, were generated, and both reacted with aldehyde to give **3p** and **3s**, respectively, as a result of the high reactivity of aldehyde (eq 2). In contrast, less reactive ketone **2h** and imine **2j** reacted with only the less bulky species **A**. As far as we know, this is the first example of the direct reaction of imine with allylic metals generated by hydrometalation of 1,3-diene.



(2)

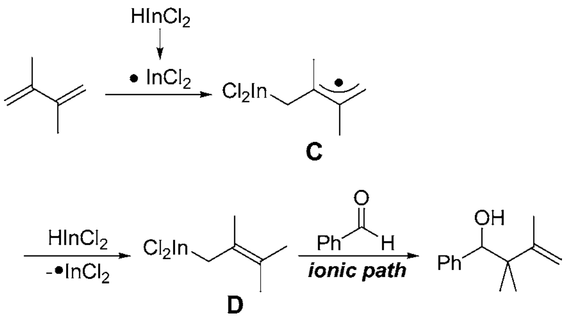
To confirm the reaction, the effect of radical inhibitor (TEMPO) was examined by changing the timing of the addition (Scheme 1). When TEMPO was added before the incorporation of 1,3-dienes, only the reduction of benzaldehyde (**2a**) to benzyl alcohol (**4**) was promoted without the formation of allylated products. Thus the hydroindation of the diene was apparently supressed by TEMPO. In contrast, when TEMPO was added after the completion of hydroindation, the allylated product **3a** was obtained effectively. No inhibition of allylation of aldehyde took place. These results indicate that the present system includes both radical hydroindation and ionic allylation steps. A plausible reaction course is shown in Scheme 2. Dichloroindium radical is generated by homolytic cleavage of the In−H bond.[7a] Next, the indium radical adds to the terminal position of 1,3-dienes to give allylic radical **C**, which is hydrogenated by HInCl$_2$ into allylic indium **D** along with regeneration of indium radical. The reaction between the resulting allylic indium and aldehydes proceeds in an ionic manner. Since the

Scheme 1[a]



[a] HInCl$_2$/TEMPO/diene/aldehyde = 2/0.1/4/1 (equiv), THF solvent.

Scheme 2



nucleophilic addition occurs at the γ-carbon in the allylic indium, the reactivity depends on the steric hindrance around the γ-carbon.

In conclusion, we have developed a novel one-pot reaction in which the generation of allylic indiums by hydroindation of 1,3-dienes was followed by successive allylation of electrophiles such as aldehydes, ketones, and imine. The former proceeds in a radical manner, and the latter includes an inonic process. Both the hydroindation and allylation steps required no assistance of either radical initiator, transition metal catalysts, or Lewis acids. Further applications of present reaction will be reported in the near term.

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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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