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Stereoselective synthesis of halocyclopropanes via halogenation of cyclopropylindium reagents

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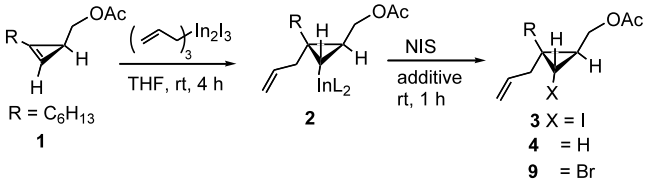
Abstract—A stereoselective synthesis of halocyclopropanes has been achieved via halogenation of the cyclopropylindium reagents prepared from allylindation of cyclopropenes.

Development of synthetic methods for halocyclopropanes with desired stereochemistry is important from a synthetic point of view, because stereo-defined halocyclopropanes are useful intermediates for polysubstituted cyclopropanes. However, direct halogenation of cyclopropanes or their precursors and halocyclopropanation of acyclic substrates often suffer from poor stereoselectivity.[1] We recently reported that the stereoselectivity of allylindation of cyclopropenes can easily be switched by changing the substituents on the cyclopropene ring, reaction solvents, and allylindium reagents.[2] The resulting allylindation products, cyclopropylindium, which can be isolated as stable crystals in some cases, are considered to be versatile precursors to halocyclopropanes. Here we describe a stereoselective halogenation of the cyclopropylindium compounds, which provides an easy access to stereo-defined halocyclopropanes.

First, we studied the iodination of cyclopropylindium **2**, synthesized in situ by the allylindation of cyclopropene **1** with allylindium sesquiiodide (Scheme 1). It is known that this allylindation proceeds in THF highly regio- and stereoselectively to give **2**.[2] The iodination of **2** was examined with *N*-iodosuccinimide (NIS) under various conditions. The results are summarized in Table 1. Without additives, the iodination is sluggish to give a mixture of iodocyclopropane **3** and cyclopropane **4** after aqueous work-up (entry 1). The addition of lithium chloride accelerated effectively the iodination, and high yield of **3** was attained with 2 equiv. of NIS in the presence of 3 equiv. of LiCl (entries 2–4). As additives, sodium hydroxide and sodium chloride are equally effective (entries 5 and 6). The role of the additives is considered that chloride and hydroxide anion coordinates to the indium atom of **2** to form indium ate complexes (indates), whose In–C bond is expected to be much more reactive than that of **2**.[3] The stereochemistry of **3** was easily deduced by the typical *trans* coupling constant ($J=5.0$ Hz) of the cyclopropane ring proton geminal of the iodine atom,[4] which indicates that the iodination of **2** proceeded with complete stereo-retention.[5] It is interesting to note that the iodination of norbornylindium compounds occurs with inversion of the configuration.[6]



Scheme 1.

Table 1. Iodination of cyclopropylindium **2** with NIS[a]

Entry	NIS (equiv.)	Additive (equiv.)	Yield (%)	
			3	**4**
1	2	None	22	57
2	2	LiCl (3)	83	0
3	1.5	LiCl (3)	23	50
4	1	LiCl (3)	4	86
5	2	NaOH (3)	79	0
6	2	NaCl (3)	78	0

[a] The iodination was carried out in THF at room temperature for 1 h with in situ prepared cyclopropylindium **2**.

Keywords: cyclopropanes; cyclopropenes; halogenation; indium and compounds.

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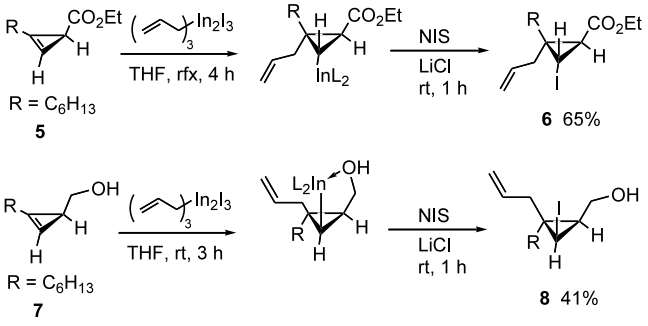
Table 2. Iodination of cyclopropylindium **2** with various oxidants[a]

Entry	Oxidant (equiv.)	Conditions	Yield (%)	
			3	**4**
1	I_2 (2)	rt, 1 h	36	0
2	$CuCl_2$ (4)	rt, 15 h	49	18
3	$FeCl_3$ (4.5)	rt, 90 h	22	0
4	$K_3Fe(CN)_6$ (4)	rt, 90 h	74	0
5	NCS (2)	rt, 1 h	56	0

[a] The iodination was carried out in THF with cyclopropylindium **2**, prepared from **1** (1 equiv.) and allylindium sesquiiodide (1.5 equiv.), in the presence of lithium chloride (3 equiv.).

Table 2 shows the results of the iodination of **2** with various oxidants. Iodine gave a complex mixture of products, in which low yield of **3** was found (entry 1). Interestingly, the iodination of **2** proceeded with high-valent metallic salts, such as Cu(II) and Fe(III) compounds, though longer reaction time was needed (entries 2–4). This fact means that the iodine atom on the indium of **2** was transferred to **3**. Indeed, the reaction with *N*-chlorosuccinimide (NCS) gave iodocyclopropane **3**, and the corresponding chlorocyclopropane was not formed (entry 5).

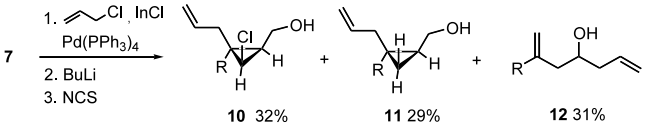


Scheme 2.

Table 3. Bromination of cyclopropylindium **2** with various oxidants[a]

Entry	Oxidant (equiv.)	Conditions	Yield (%)	
			9	**4**
1	NBS (2)	rt, 1 h	60	22
2	NBS (2)	rt, 2 h	82	0
3	Br_2 (2)	rt, 2 h	32	55
4	Br_2 (3)	rt, 12 h	66	0
5	NCS (2)	rt, 4 h	59	0

[a] The bromination was carried out in THF with cyclopropylindium **2**, prepared from **1** (1 equiv.) and allylindium sesquibromide (1.5 equiv.), in the presence of lithium chloride (3 equiv.).



Scheme 3.

The same allylindation–iodination procedure could be successfully applied to other cyclopropenes under similar conditions (Scheme 2). Cyclopropenecarboxylate **5** gave *trans*-iodocyclopropane **6** stereoselectively, whereas hydroxymethylcyclopropene **7** afforded *cis*-product **8** via chelation-assisted *cis*-allylindation.[2] Again, the stereochemistry of **6** and **8** was deduced by the ^1H NMR coupling constants ($J=5.3$ Hz for **6** and 8.0 Hz for **8**) of the cyclopropane ring protons (CH-I).

Allylbromination of **1** was also achieved after allylindation with allylindium sesquibromide (Table 3). With *N*-bromosuccinimide (NBS) or bromine, high yields of **9** were obtained. As expected, NCS gave the bromide **9** selectively (entry 5). In turn, iodocyclopropane **3** was obtained in 62% yield with NIS as the oxidant and LiCl as the additive.

The above iodination/bromination results imply that for chlorination allylindium sesquichloride has to be used for allylindation and then NCS or chlorine as the oxidant. However, allyl chloride is inert to a direct oxidative addition of indium metal. Alternatively, we turned to a new preparative method of allylindium dichloride via transient π-allylpalladium intermediates.[7] Thus, cyclopropene **1** was treated with allyl chloride and indium(I) chloride in the presence of the $Pd(PPh_3)_4$ catalyst, followed by the reaction with NCS. This reaction, however, gave only **4** in 45% yield after hydrolysis, and the expected chlorocyclopropane was not formed at all. Next, the reactivity of the intermediate cyclopropylindium reagents was tried to be enhanced by the formation of the indates with butyllithium.[3] As illustrated in Scheme 3, allylindation of **7** with allylindium dichloride (from allyl chloride/InCl/$Pd(PPh_3)_4$), addition of butyllithium, and oxidation with NCS gave chlorocyclopropane **10**, together with the by-products **11** and **12**. The yield of **10** was only modest (32%); nevertheless, the stereoselectivity was found to be 100% *cis*.

Although the halogenation of vinylindium compounds prepared by the allylindation of alkynes is known to give vinyl halides,[8] no chemical transformations of cyclopropylindium reagents have hitherto been reported. Here, a new route for the stereoselective synthesis of halocyclopropanes has been developed via allylindation of cyclopropenes followed by the halogenation of the resulting cyclopropylindium compounds. The complete stereoselectivity makes the present method synthetically valuable and attractive.

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