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Allylation of methylenecyclopropanes with allylindium reagents

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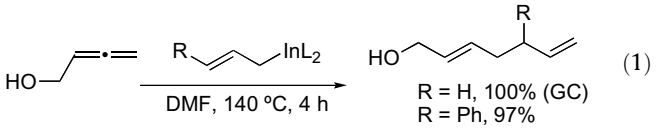
ABSTRACT

Methylenecyclopropanes carrying a hydroxymethyl group at the ring underwent stereoselective allylindation with allylindium sesquiiodide to afford the allylated products, in which the allyl group was delivered at the external sp^2 carbon via cyclopropylindium intermediates. The reaction of ethyl 2-cyclopropylideneacetate and triallylindium afforded the 1,4-adduct along with dimeric products.

Methylenecyclopropanes (MCPs) are attractive compounds from a viewpoint of physical and synthetic chemistry, because a reactive cyclopropane unit has an enormous potential for a broad range of chemical transformations.[1] A variety of reactions of MCPs in the presence of Lewis acids or transition metal catalysts has been reported; however, little attention has been paid for a reaction involving organo-main group metal compounds. We have explored allylindation of carbon-carbon multiple bonds: allylindation of alkynes,[2] cyclopropenes,[3] and norbornenes[4] proceeds with high stereoselectivity in cases where a hydroxy group is located adjacent to the multiple bonds. Allenols also undergo allylindation with high regio- and stereoselectivity via a hydroxyl-chelated bicyclic transition state giving 1,5-dienes in high yields (Eq. 1).[5]



(1)

We turned next our attention to MCP as an analogue of allene. Here, we disclose that MCPs undergo a smooth allylindation to afford the allylated products with high stereoselectivity.

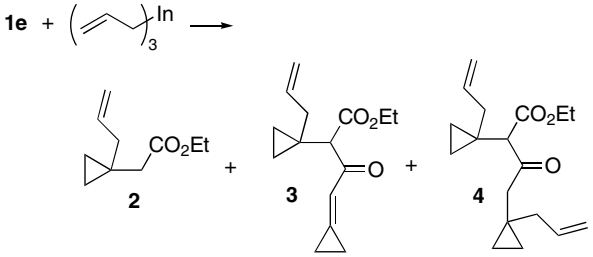
We first examined the reactions of MCPs **1a–e** with allylindium sesquiiodide[6] prepared from allyl iodide and metallic indium in THF under reflux conditions (Fig. 1). However, no allylation product was obtained. After screening the reaction conditions, triallylindium instead of allylindium sesquiiodide proved to be useful for the reaction of ethyl 2-cyclopropylideneacetate (**1e**), giving allylated product **2** and dimeric compounds **3** and **4** (Table 1, entry 1). The reaction at elevated temperature or with an increased amount of triallylindium gave better results (entries 2 and 3). Under reflux conditions, **1e** was consumed within 3 h, and products **2–4** were obtained in higher yields (entry 4). In the presence of water (1 equiv), **2** was selectively obtained in 65% yield (entry 5).

The most plausible reaction mechanism is depicted in Scheme 1. Triallylindium attacks MCP **1e** in a 1,4-addition mode to give an indium enolate **A**, which undergoes protonolysis to afford **2** or a Claisen condensation with another MCP **1e** leading to the formation of **3**. The second 1,4-addition of triallylindium onto **3** gave **4**. In contrast, allylmagnesium bromide, the precursor to triallylindium, when subjected to the reaction with **1e** afforded the corresponding

1a: R^1 = Ph, R^2 = H, **1b**: $R^1 = R^2$ = Ph
1c: R^1 = *p*-$CH_3C_6H_4$, R^2 = H, **1d**: R^1 = *p*-$NO_2C_6H_4$, R^2 = H
1e: R^1 = CO_2Et, R^2 = H

Figure 1. Structures of MCPs **1a–e**.

Table 1
Reactions of **1e** with triallylindium[a]



Entry	$(allyl)_3In$ (mol %)	Conditions	Yield (%)		
			2	**3**	**4**
1	100	0 °C, 15 h	16	8	0
2	100	rt, 15 h	23	Trace	14
3	200	rt, 15 h	0	Trace	41
4	200	rfx, 3 h	20	11	47
5	200	rfx, 5 h, H_2O (1 equiv)	65	0	0

[a] All reactions were performed with the ratio $(allyl)_3In$/**1e** = 2/1.

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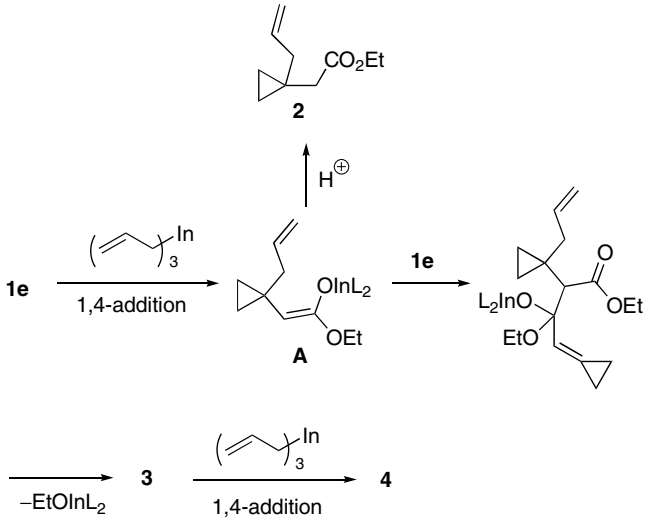
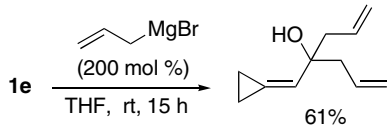


Scheme 1.

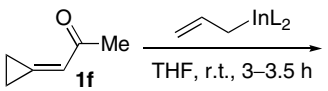
tertiary alcohol selectively in 61% yield (Eq. 2), which clearly shows the difference of the nature of the allylindium and magnesium reagents.

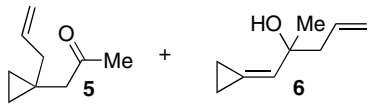


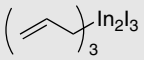
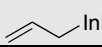
(2)

Normally, allylindium reagents are not capable of reacting with an ester group; however, a ketone functionality is easily converted into the corresponding tertiary alcohol. When MCP ketone **1f** is employed in the reaction, a selection of 1,2-/1,4-addition mode is a practical matter. The reaction of **1f** with triallylindium gave the 1,4-adduct **5** selectively (Table 2, entry 1). In contrast, allylindium sesquiiodide and allylindium diiodide underwent 1,2-addition to afford **6** exclusively (entries 2 and 3). This switching of the mode depending on allylindium species is consistent with the allylation of benzylidenmalononitrile.[7]

Table 2
Reactions of **1f** with allylindium reagents

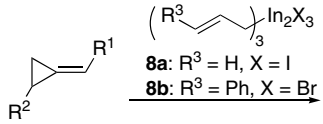




Entry	Allyindium	Yield (%)	
		5	**6**
1[a]		35	0
2[b]		0	46
3[c]		0	36

[a] Molar ratio **1f**/$InCl_3$/allylmagnesium bromide = 1/1/3.
[b] Molar ratio **1f**/In/allyl iodide = 1/1.2/1.8.
[c] Molar ratio **1f**/InI/allyl iodide = 1/1/1.

Table 3
Allylindation of MCPs **7**[a]



7a: R^1 = H, R^2 = CH_2OH
7b: R^1 = Ph, R^2 = CH_2OH
7c: R^1 = Ph, R^2 = CO_2H
7d: R^1 = Ph, R^2 = $(CH_2)_2OH$
7e: R^1 = Ph, R^2 = CMe_2OH
7f: R^1 = Ph, R^2 = CH_2OBn

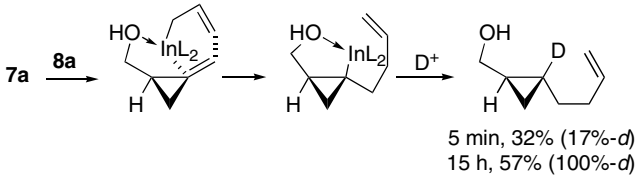
9a: R^1 = R^3 = H
9b: R^1 = H, R^3 = Ph
9c: R^1 = Ph, R^3 = H

Entry	7	8	Conditions	Isolated yield (GC yield)
1	**7a**	**8a**	THF, rfx, 3 h	**9a** 55% (25%)
2[b]	**7a**	**8a**	THF, rfx, 3 h	**9a** 89% (96%)
3	**7a**	**8b**	THF, rfx, 17 h	**9b** 19%
4	**7a**	**8b**	DMF, 140 °C, 4 h	**9b** 30%
5	**7b**	**8a**	THF, rfx, 17 h	**9c** 52%
6	**7b**	**8a**	H_2O–THF (3:1), rfx, 17 h	0
7	**7b**	**8b**	THF, rfx, 17 h	0

[a] All reactions were performed with the ratio In/allylic halide/MCP = 2/3/1.
[b] Quenched with 1 M HCl for 17 h prior to extraction.

Next, we conducted an allylindation of MCPs bearing a hydroxymethyl group. In view of the results mentioned above, triallylindium was considered to be the best choice for the allylating agent. However, no coupling product was obtained with triallylindium. During tuning the reaction conditions again, allylindium sesquiiodide proved to be better for the allylindation of **7a**. Thus, allylindium sesquiiodide (**8a**), prepared from allyl iodide and indium powder in THF, was allowed to react with **7a** under reflux conditions. The introduction of the allyl group occurred selectively at the external sp^2 carbon giving **9a** in 55% yield (Table 3, entry 1). However, the GC yield showed a large gap compared to the isolated one: the GC analysis prior to chromatographic separation showed only 25% yield of **9a**. We envisaged that the intermediate cyclopropylindium still existed in the ethereal extracts even after quenching with diluted HCl, and that it was gradually transformed to **9a** by protonolysis during the chromatographic separation on silica gel. In order to confirm this possibility, the reaction mixture was treated with 1 M HCl for a longer time (17 h) prior to extraction. The GC and isolated yields were increased to 96% and 89%, respectively (entry 2). In addition, a deuterium labeling experiment was carried out: when the reaction mixture was exposed to 1 M DCl for 5 min, the incorporation of deuterium was only 17%, whereas **9a** with quantitative deuterium incorporation was obtained after 15 h (Scheme 2).

These phenomena can be explained by the stability of the cyclopropylindium intermediate supported by a chelating unit, such as hydroxy and carbonyl groups as reported.[3b] The reaction of **7a** with cinnamylindium sesquibromide (**6b**) gave **9b** in a lower yield (entry 3). When the reaction conditions that gave good results in the case of allenols were applied to **7a**, the yield was slightly improved (entry 4). MCP **7b** underwent the allylindation to provide **9c** in 52% yield (entry 5). The reaction in aqueous THF and the reaction with



Scheme 2.

8b gave no allylindation product (entries 6 and 7). Other MCPs **7c–f** resisted with the allylation by **8a**. MCP carboxylic acid **7c** was completely recovered, which is in sharp contrast to the case with a cyclopropene carboxylic acid.[3a] The longer methylene chain, the sterically encumbering methyl groups, and the protection of the hydroxy group presumably prevent the proper chelation promoting the allylation.

On the basis of a ^{13}C-NMR analysis, the allylated products **9a** and **9c** were found to be single isomers, and **9b** was a mixture of only two isomers. These facts show that the allylations of **7** proceed with high faceselectivity. The configurations of **9a** and **9c** were confirmed by lanthanoid-induced-shift (LIS) experiments. The results (Fig. 2) clearly demonstrate that the allyl group is introduced from the same face with respect to the hydroxymethyl group on the cyclopropane.

Finally, MCPs **10** and **11** having a hydroxy group at the external carbon were examined for the allylindation to compare with the case of **7** (Fig. 3). As shown in Table 3, a proper distance from the multiple bond to the hydroxy group is essential for promoting the allylindation of MCPs. MCPs **10** and **11** are therefore expected to form a favorable five- or six-membered chelating structure during their transition state of allylindation.

The reactions of **10** or **11** in THF under reflux conditions were carried out with allylindium sesquiiodide; however, no allylated product was observed. The results with MCPs **10** and **11** clearly demonstrated that not only the distance but also a proper special regulation are crucial for promoting the allylindation of MCPs.

Further applications of the stable cyclopropylindium intermediate are currently under study.

Preparation of starting materials: MCPs **1a**,[8] **1b**,[9] **1c**,[10] **1d**,[10] **1e**,[11] **1f**,[12] **7a**,[13] **10**,[14] and **11**[15] were obtained by the literature procedure. MCPs **7b**, **7c**, **7e**, and **7f** were prepared from the corresponding ethyl ester,[16] and **7d** was synthesized from **7b**.[17]

Typical reaction procedure (Table 2, entry 2): A mixture of indium (0.15 g, 1.3 mmol) and allyl iodide (0.18 mL, 1.9 mmol) was stirred for 1 h. To the resulting allylindium sesquiiodide, **7a** (57 mg, 0.68 mmol) in ether (0.27 mL) was added and the mixture was refluxed for 3 h. The reaction was quenched with 1 M HCl (10 mL), and the mixture was stirred at room temperature for 17 h. After the addition of dodecane (standard material, 57 μL, 0.25 mmol), the product was extracted with ether and washed with water, brine, and dried over Na_2SO_4. The ether solution was submitted to the GC analysis (96%). The product was purified by chromatography on silica gel (*n*-hexane–CH_2Cl_2 = 1:1) to give **9a** (72 mg, 89%).

trans-(2-But-3-enyl)cyclopropylmethanol (**9a**)[18] ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 0.29–0.43 (m, 2H,), 0.54–0.70 (m, 1H), 0.79–0.91 (m, 1H), 1.22–1.48 (m, 3H), 2.11–2.21 (m, 2H), 3.40–3.46 (m, 2H), 4.93–5.07 (m, 2H), 5.74–5.91 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 10.10, 16.91, 21.38, 32.92, 33.98, 67.05, 114.32, 138.57.

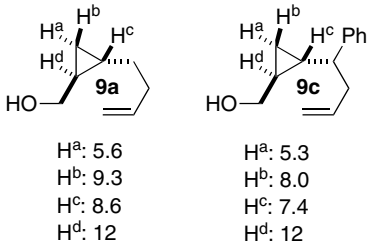


Figure 2. LIS experiments.

Figure 3. MCPs bearing a hydroxy group at the external carbon.

Acknowledgments

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