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Chelation-controlled regio- and stereoselective allylindation of norbornenols

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Abstract

The first allylindation of norbornenol derivatives has been realised highly regio- and stereoselectively. The reactions of allylindium sesquiiodide with *syn*-bicyclo[2.2.1]hept-2-en-7-ol and *endo*-bicyclo[2.2.1]hept-5-en-2-ol gave allylated products together with iodinated and oxygenated compounds. The product distribution could be controlled by changing the reaction solvent. In these reactions, the regio- and stereochemistry of the addition of the allylindium reagent is highly regulated via the chelation with the neighbouring hydroxyl group. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: allylation; chelation; indium; indium compounds; metalation.

Carbometalation of unsaturated compounds is an important procedure in organometallic chemistry. A variety of addition reactions of organometallics to carbon–carbon multiple bonds have been reported so far.[1] Recently, the use of organoindium reagents, particularly allylindium reagents, for carbon–carbon bond formation has been the subject of increasing interest.[2] The addition of allylindium reagents to alkynes,[3] allenes[4] and cyclopropenes[5] has been reported to proceed with high regio- and stereoselectivity. Thus, it has been shown that the carbon–carbon multiple bonds with enhanced s character undergo smooth allylindation, whereas ordinary carbon–carbon double bonds are inert.[6] Here we disclose that the first allylindation of non-activated carbon–carbon double bonds of norbornenols proceeds highly regio- and stereoselectively, where a proximal hydroxyl group exerts a significant effect on determining the selectivity based on the intramolecular chelation.

The reaction of allylindium sesquiiodide with *syn*-bicyclo[2.2.1]hept-2-en-7-ol (**1**)[7] in THF at reflux temperature gave three products **2**, **3** and **4** in moderate yields (Table 1, entries 1 and 2). The compound **2** is an expected allylindation product, whereas the compounds **3** and **4** are further iodinated and oxygenated, respectively. The stereoselectivity of the present allylindation is very high: the allylic group was introduced exclusively from the *exo* face. The *trans*-relationship of the allyl and iodo groups in

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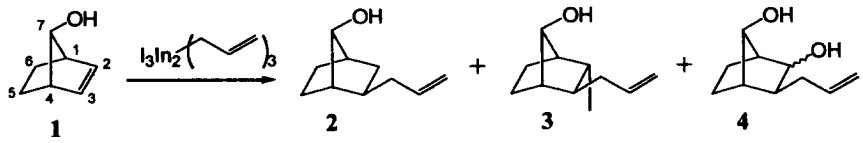
Table 1
Allylindation of *syn*-bicyclo[2.2.1]hept-2-en-7-ol



1 2 3 4

Entry	Molar Ratio[a]	Conditions	Yield (%)[b]		
			2	3	4[c]
1	A	THF, rfx, 1.5 h	26	6	32
2	B	THF, rfx, 19 h	15	14	22
3[d]	C	THF, rfx, 22 h	28	0	45
4	D	DMF, 110-140 °C, 18 h	37	<1	18
5	A	DMA, 150 °C, 17 h	47	0	0
6	A	NMP, 180 °C, 16 h	72	0	0

[a]Molar ratio A: In/allyl iodide/1 = 1.0:1.5:0.5, molar ratio B: In/allyl iodide/1 = 1.0:1.5:0.9, molar ratio C: In/allyl bromide/1 = 1.0:1.5:0.3, molar ratio D: In/allyl iodide/1 = 1.0:1.5:0.6. [b]Isolated yield. [c]Stereomixture. [d]Reaction with allylindium sesquibromide.

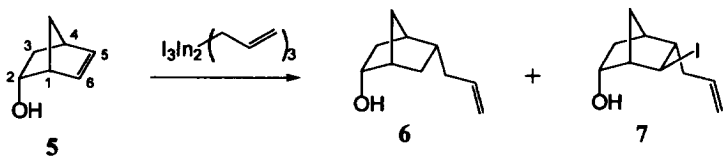
3 was confirmed by ^{1}H NMR analylsis, whereas diol **4** was a mixture of stereoisomers. Allylindium sesquibromide gave **2** and **4**, and the brominated product corresponding to **3** was not obtained (Table 1, Entry 3). In polar solvents, such as DMF, DMA and NMP, compound **2** was produced predominantly or exclusively (Table 1, entries 4–6). The importance of the C^7-hydroxyl group for the smooth allylindation is evident by the fact that norbornene itself is inert to allylindation under these conditions. γ-Substituted allylic indium reagents such as crotyl- and cinnamylindium did not give allylation products.

In a similar way, the reaction of *endo*-bicyclo[2.2.1]hept-5-en-2-ol (**5**)[8] with allylindium sesquiiodide gave products **6** and **7** (Table 2, entries 1 and 2). Again, the products **6** and **7** were formed in complete regio- and stereoselectivity: the allylic group was introduced exclusively to the C^5-carbon and the allylindium reagent added from the *endo* face (*cis* to the hydroxyl group). In polar solvents, **6** was formed preferentially; in particular, NMP gave the highest yield of **6** (Table 2, entries 4–7). When the allylindation mixture was treated with excess iodine, the iodinated product **7** was obtained exclusively in 59% yield (Table 2, entry 8). Recently, allylindium reagents have been developed for use in water.[9] The present allylindation, however, did not occur at all in aqueous media (Table 2, entries 9 and 10).

The observed high regio- and stereoselectivity in the allylindation of the hydroxyl-bearing norbornenes **1** and **5** can be best explained by intramolecular coordination of the hydroxyl oxygen to the indium atom. Scheme 1 depicts the most plausible reaction courses for **1** and **5**. The chelators direct the allylindium reagent stereoselectively, and the new carbon–carbon bonds are formed via the tetracyclic transition states. The norbornylindium intermediates were quenched with H^+, giving the protonated products **2** and **6**. The iodonorbornanes **3** and **7** are considered to be formed via back-side attack by the iodine formed during the reaction; thus, the S_E2 reaction occurred with inversion of the configuration in these cases. It is known that the S_E2 reaction proceeds generally with retention of the configuration.[10] However, it is also reported that in some cases such as norbornyllithium[11] and trinorbornylborane assisted by sodium methoxide,[12] the S_E2 reaction proceeds with inversion of the stereochemistry. The experimental findings described in this work add further examples in which the S_E2 replacement takes place with inversion, probably owing to the blocking of the front side by the large indium atom. The diol **4** is considered to be formed via the oxidation of the norbornylindium by residual oxygen in the reaction system.

In summary, smooth allylindation of non-activated carbon–carbon double bonds of norbornenols

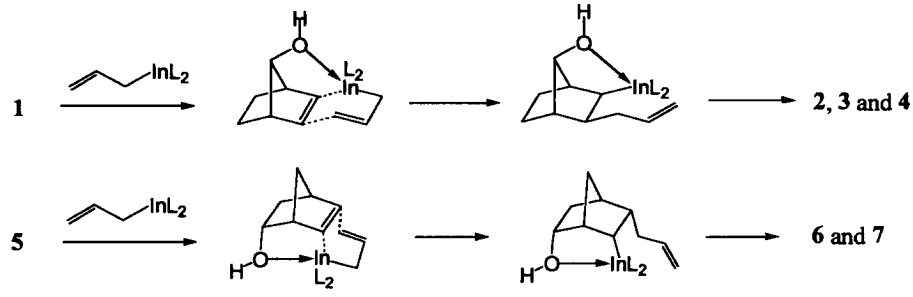
Table 2
Allylindation of *endo*-bicyclo[2.2.1]hept-5-en-2-ol



5 6 7

Entry	Molar Ratio[a]	Conditions	Yield (%)[b] 6	7
1	A	THF, rfx, 15 h	37	43
2	B	THF, rfx, 24 h	30	38
3	B	THF/DMF,[c] rfx, 24 h	55	5
4	B	DMF, 90 °C, 20 h	18	0
5	B	DMA, 100 °C, 24 h	56	0
6	C	DMA, 100 °C, 24 h	32	0
7	A	NMP, 150 °C, 15 h	65	0
8[d]	A	THF, rfx, 5 h, then I_2, 15 h	0	59
9	B	THF/H_2O,[e] rfx, 24 h	0	0
10	A	NMP/D_2O,[f] 150 °C, 18 h	0	0

[a] Molar ratio A: In/allyl iodide/5 = 1.5:2.25:0.78, molar ratio B: In/allyl iodide/5 = 1.0:1.5:0.78, molar ratio C: In/allyl iodide/5 = 2.0:3.0:0.78. [b] Determined by GLC. [c] THF/DMF = 1:1. [d] After refluxing for five hours, iodine (1.0 mmol) was added. [e] THF/H_2O = 5:1. [f] NMP/D_2O = 50:1.



Scheme 1.

has been achieved, where a proximal hydroxyl group plays an important role in determining the regio- and stereoselectivity. Similar acceleration and stereoselection based on hydroxyl-chelation have been observed in the allylindation of alkynols,[3] allenols[4] and hydroxyl-bearing cyclopropenes.[5] The iodinated and oxygenated products were also obtained in the allylindation of norbornenols depending on the reaction conditions. Although the scope of the present allylindation is rather limited and the reactions require forced conditions, the results provide rare examples of allylindation of non-activated carbon–carbon double bonds.

Typical experimental procedure (Table 1, entry 6): A mixture of indium powder (115 mg, 1.0 mmol) and allyl iodide (137 μL, 1.5 mmol) was stirred in NMP (2 mL) at room temperature for 0.5 h. *syn*-Bicyclo[2.2.1]hept-2-en-7-ol (55 mg, 0.5 mmol) in NMP (3 mL) was added. After being stirred at 180°C for 16 h, the reaction mixture was quenched with 1N hydrochloric acid and the product was extracted with ether. The combined organic layers were washed with water and brine, dried over anhydrous sodium

sulfate, and concentrated. The residue was purified by flash column chromatography on silica gel (elution with dichloromethane) to give 2-*exo*-allyl-*syn*-bicyclo[2.2.1]heptan-7-ol (**2**) (55 mg, 72%).

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