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# Stereodivergent Allylindation of Cyclopropenes. Remarkable Stereodirection and Acceleration by Neighbouring Carboxyl and Hydroxyl Groups

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**Abstract**: Stereodivergent allylindation of cyclopropene derivatives has been realised regio- and stereoselectively. The coupling occurs exclusively at the γ-carbon of allylic indium reagents and the more substituted carbon of the cyclopropene double bond. The carboxyl and hydroxymethyl groups on the cyclopropene $C^3$-carbon exert significant effects in *cis*-direction and acceleration of the allylindation based on the intramolecular chelation, whereas the ester group directs a *trans*-addition owing to the steric interaction with incoming allylindium reagents.

Carbometalation of unsaturated compounds has long been the subject of great concern.[1] Of a variety of main group metals as well as transition metals, indium has recently received increasing interest as a versatile metal for carbometalation. Regioselective carboindation was first reported on alkynes with allylindium reagents.[2] Allenes were also found to undergo a clean regio- and stereoselective allylindation.[3] Thus, it has been shown that the carbon-carbon multiple bonds with enhanced s character, such as those of alkynes and allenes, undergo a smooth allylindation, whereas ordinary carbon-carbon double bonds are inert. Here we disclose that the first allylindation of cyclopropenes,[4] which possess an s character rich double bond ($sp^{1.19}$),[5] proceeds regio- and stereoselectively, where proximal carboxyl as well as hydroxyl groups exert significant effects in *cis*-direction and acceleration of the addition of allylindium reagents based on the intramolecular chelation.

3-(Hydroxymethyl)-1-hexylcyclopropene (**1a**) gave the allylindation product in high yields (Table, entries 1-4) (eq. 1). The reaction proceeded both in organic and aqueous media, but the yield and the selectivity in THF were higher than those in DMF and in water. γ-Substituted allylic indium reagents reacted at the γ-carbon (entries 5 and 6). The regio- and stereoselectivities of the present allylindation are high: the allylic group was introduced exclusively to the substituted carbon of the cyclopropene double bond, and the allylindium reagents added preferentially from the *cis* face of the hydroxymethyl group (confirmed by Lanthanide-induced-shift experiments on the products), though the *cis*-selectivity decreased in DMF and in water. Surprisingly, the corresponding carboxylic acid **1b**, though less reactive than **1a**, also underwent the clean allylindation at elevated temperature with high regio- and stereoselectivities (entries 7 and 8).

The complete regioselectivity (allylation of the substituted carbon of cyclopropene) was again attained with the acetate **1c** (entries 9-11). Quenching the reaction with trifluoroacetic acid-*d* resulted in **6**-*d*, in which the deuterium atom was introduced exclusively *syn* to the allyl group, thus confirming a *syn*-addition mode of

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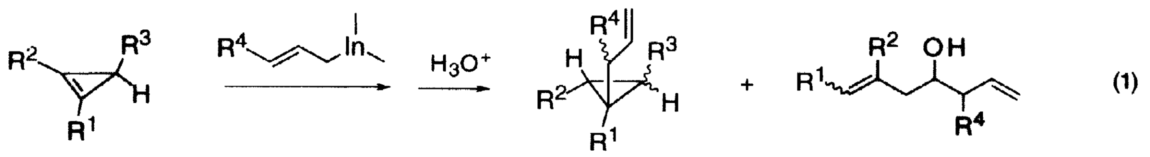
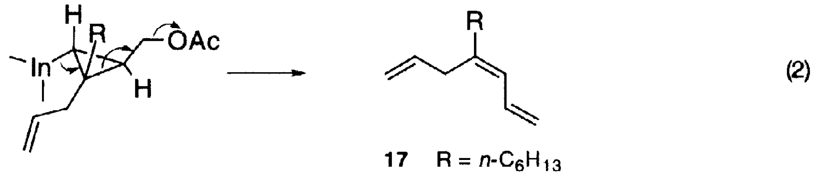


| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **1a** | $n$-$C_6H_{13}$ | H | $CH_2OH$ |
| **b** | $n$-$C_6H_{13}$ | H | $CO_2H$ |
| **c** | $n$-$C_6H_{13}$ | H | $CH_2OAc$ |
| **d** | $n$-$C_6H_{13}$ | H | $CO_2Et$ |
| **e** | Me | Me | $CH_2OH$ |
| **f** | Et | Et | $CH_2OH$ |

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **2** | $n$-$C_6H_{13}$ | H | $CH_2OH$ | H |
| **3** | $n$-$C_6H_{13}$ | H | $CH_2OH$ | Me |
| **4** | $n$-$C_6H_{13}$ | H | $CH_2OH$ | Ph |
| **5** | $n$-$C_6H_{13}$ | H | $CO_2H$ | H |
| **6** | $n$-$C_6H_{13}$ | H | $CH_2OAc$ | H |
| **7** | $n$-$C_6H_{13}$ | H | $CO_2Et$ | H |
| **8** | Me | Me | $CH_2OH$ | H |
| **9** | Me | Me | $CH_2OH$ | Me |
| **10** | Et | Et | $CH_2OH$ | H |

| | $R^1$ | $R^2$ | $R^4$ |
|---|---|---|---|
| **11** | H | $n$-$C_6H_{13}$ | Me |
| **12** | H | $n$-$C_6H_{13}$ | Ph |
| **13** | Me | Me | H |
| **14** | Me | Me | Me |
| **15** | Et | Et | H |
| **16** | Et | Et | Ph |

the allylindium derivative. Interestingly, the stereoselectivity was dramatically reversed to that of the alcoholic **1a** and carboxylic substrates **1b**; allylindium added *trans* with respect to the acetoxymethyl group. At elevated temperature, a ring-opening of the resulting cyclopropylindium species took place with an elimination of the acetoxy group to yield (*Z*)-hepta-1,3,6-triene (**17**) (eq. 2). The *Z*-geometry of **17**, confirmed by NOE experiments, supports again a *syn*-addition mode of the allylindium. The *trans*-selectivity was also observed for cyclopropenecarboxylate **1d**, and the selectivity increased with increasing the solvent polarity and the reaction temperature (entries 12 and 13). 1,2-Disubstituted cyclopropenes **1e** and **1f** resisted to allylindation, giving poor yields (20-27%) of the cyclopropane products **8** - **10** together with considerable amounts of the ring-opening products **13** - **16** (entries 14-18).[6] Nevertheless, a complete *syn*-addition mode regarding the allylic group and indium as well as a *cis*-addition to the hydroxymethyl group were again confirmed.



**17** R = $n$-$C_6H_{13}$

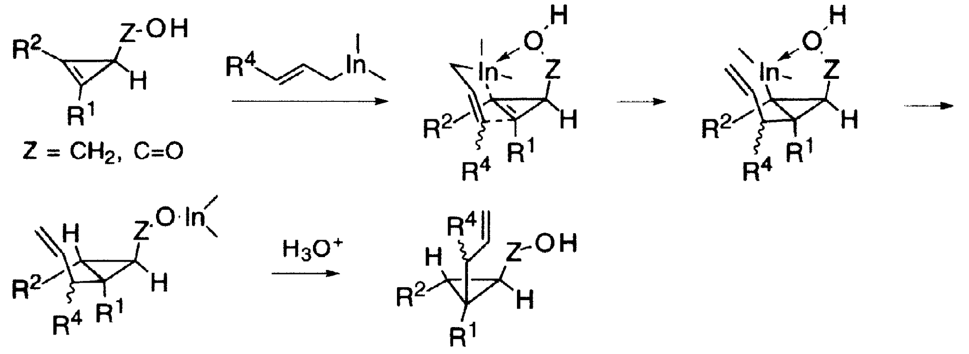
The relative reactivities of **1a** and **1c** were compared by a competition experiment. An equimolar mixture of **1a** and **1c** was subjected to allylindation in THF with a limited amount of allylindium sesquiiodide. The product mixture was found to contain **2** (64% yield) and unreacted **1c** (73% recovery), and **6** was not formed at all, thus demonstrating the highly enhanced reactivity of **1a**.

The observed high *cis*-stereoselectivity in the allylindation of the carboxyl- and hydroxymethyl-bearing cyclopropenes can be best explained by the intramolecular coordination of the hydroxyl oxygen to the indium atom (eq. 3). By the chelation with the allylic indium reagent, the chelators direct the reagent stereoselectively *cis*. Steric interaction is considered to be an important factor to determine the regioselectivity. The sterically demanding indium atom is expected to couple with the less substituted carbon atom of the two alkenic carbons and the γ-terminus of the allyl group is extruded to the other carbon, thus a new carbon-carbon bond is formed regioselectively at the more substituted double bond carbon via the tricyclic transition state. The enhanced reactivity of **1a** compared with **1c** is consistent with the fact that the involvement of a chelated intermediate lowers the transition state energy, consequently resulting in rapid conversion to the product.[7] More coordinative solvents such as water and DMF are considered to compete with the intramolecular chelation, accord-

Table. Allylindation of Cyclopropenes$^a$

| Entry | Cyclopropene | $R^4$ | Conditions | Product(s) (Yield/%) | *cis*:*trans*$^b$ |
|---|---|---|---|---|---|
| 1 | **1a** | H | THF, 0-5 °C | **2** (85) | 95:5 |
| 2 | | H | THF, r.t. | **2** (95) | 93:7 |
| 3 | | H | DMF, r.t. | **2** (74) | 85:15 |
| 4$^c$ | | H | $H_2O$, r.t. | **2** (30), (25)$^d$ | 45:55 |
| 5 | | Me | THF, r.t. | **3**$^e$ (63), **11** (5) | 92:8 |
| 6 | | Ph | DMF, 100 °C | **4**$^f$ (59), **12** (5) | 78:22 |
| 7 | **1b** | H | THF, rfx. | **5** (81) | 100:0 |
| 8$^c$ | | H | DMF, 100 °C | **5** (70) | 89:11 |
| 9 | **1c** | H | THF, r.t. | **6** (66) | 0:100 |
| 10 | | H | DMF, r.t. | **6** (42) (10)$^d$ | 0:100 |
| 11 | | H | DMF, 100 °C | **6** (25), **2** (16), **17** (36) | 0:100$^g$ |
| 12 | **1d** | H | THF, rfx. | **7** (63) | 26:74 |
| 13 | | H | DMF, 100 °C | **7** (50) (19)$^d$ | 3:97 |
| 14 | **1e** | H | THF, r.t. | **8** (21), **13** (49) | 100:0 |
| 15 | | Me | THF, r.t. | **9**$^h$ (22), **14** (27) | 100:0 |
| 16 | **1f** | H | THF, r.t. | **10** (20), **15** (42) | 100:0 |
| 17 | | H | DMF, 100 °C | **10** (27), **15** (28) | 100:0 |
| 18 | | Ph | DMF, 90 °C | **16** (43) | ---- |

[a] All reactions were carried out for 3-4 h unless otherwise noted. [b] *Cis*:*trans* refers to the relation between $R^3$ and the allyl group introduced in the cyclopropane product. [c] Reaction time ca. 20 h. [d] Recovery of the starting substrate. [e] Diastereomeric ratios 91:9 (*cis*-isomers) and 71:29 (*trans*-isomers). [f] Diastereomeric ratios 76:24 (*cis*-isomers) and 68:32 (*trans*-isomers). [g] Ratio of compound **6**. [h] Diastereomeric ratio 89:11.



(3)

ingly decreasing the reaction rate and the *cis*-selectivity of the allylindation. Although similar acceleration and stereoselection based on a hydroxyl-chelation were observed in the allylindation of alkynols[2] and allenols[3] as well as the allylation of hydroxyaldehydes,[8] examples based on the chelation of a carboxylic acid group are quite limited.[9]

In summary, it has been shown that the substituent on the cyclopropene $C^3$-carbon plays an important role in determining the stereoselectivity of allylindation: the carboxyl and hydroxymethyl groups facilitate a high *cis*-addition based on the chelation, whereas the ester group directs a *trans*-addition owing to the steric interaction with incoming allylindium reagents. The starting cyclopropene derivatives used in this work are easily accessible via the transition metal catalysed reaction of diazoacetates with alkynes.[10] Therefore, the present allylindation of cyclopropenes provides a convenient method for the stereodivergent synthesis of substituted cyclopropanes.[11]

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6. At present, the definitive mechanism for the formation of these ring-opening products is unknown. The physical data of **13** are shown as a representative: colourless oil, IR (neat): 3420, 3090, 3000, 2950, 1644, 1438, 1382, 1052, 1000, 918, 816 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 1.62 (d, *J* = 6.4 Hz, 3 H), 1.64 (s, 4 H), 2.05 (dd, *J* = 13.3, 9.0 Hz, 1 H), 2.16 - 2.28 (m, 3 H), 3.69 - 3.82 (m, 1 H), 5.11 (d, *J* = 11.3 Hz, 1 H), 5.12 (d, *J* = 16.4 Hz, 1 H), 5.27 - 5.39 (m, 1 H), 5.76 - 5.96 (m, 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 13.5, 15.7, 41.4, 47.3, 68.0, 117.5, 122.4, 132.6, 135.0. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.93; H, 11.69.
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11. The following reaction (entry 7, Table) represents a general procedure: To a solution of allylindium sesquiiodide, prepared from indium powder (172 mg, 1.5 mmol) and allyl iodide (0.20 mL, 2.3 mmol) in THF (3.0 mL), was added 1-hexylcyclopropene-3-carboxylic acid (**1b**) (168 mg, 1.0 mmol), and the mixture was heated under reflux for 4 h. The reaction mixture was allowed to cool down to room temperature and quenched by the addition of diluted hydrochloric acid. The product was extracted with dichloromethane and the extracts were washed with brine and then dried ($Na_2SO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel using $CH_2Cl_2$-hexane (1:1) as eluent to give **5** (169 mg, 81%): colourless oil; IR (neat): 3050, 2900, 2850, 1685, 1630, 1442, 1420, 1280, 1218, 982, 904 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 5.3 Hz, 3 H), 0.96 (dd, *J* = 7.9, 4.5 Hz, 1 H), 1.13 - 1.37 (m, 11 H), 1.52 (dd, *J* = 7.9, 5.5 Hz, 1 H), 2.08-2.37 (m, 2 H), 5.00 - 5.09 (m, 2 H), 5.64 - 5.84 (m, 1 H), 11.5 - 12.0 (bs, 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 14.0, 21.3, 22.6, 25.5, 26.0, 29.3 (overlapped two peaks), 31.8, 33.5, 37.0, 116.5, 135.7, 179.4. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.29; H, 10.48. Found: C, 74.16; H, 10.40.