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Stereoselective allylation of azirines with allylindium reagents

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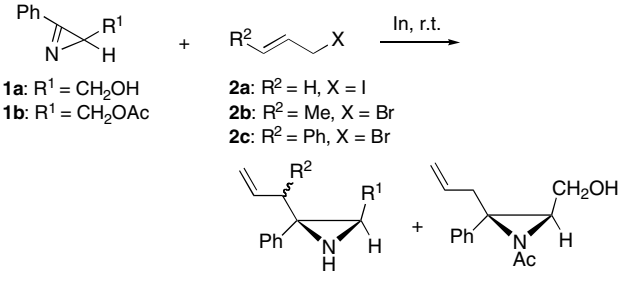
Abstract—Allylindium reagents allylated azirines to give allylaziridines in good yields. The delivery of the allyl group was well regulated by the substituents at the C^3-carbon of azirines. The cis-allylation with respect to the substituent was realized with azirines bearing a hydroxylmethyl or an acetoxymethyl group due to the chelation with allylindium reagents, whereas the trans-allylation was achieved with azirines substituted by a methyl, phenyl, or ester group owing to the steric repulsion.

The addition of organometallic compounds to an unsaturated bond (carbometallation) is one of the most fundamental reactions in organic synthesis, which provides not only a new carbon–carbon bond but also another organometallic compound.[1] A broad range of organometallics has hitherto been utilized for this purpose. In the course of our systematic study of organoindium chemistry, we have explored allylindation to unsaturated carbon–carbon bonds such as alkynes,[2] alkenes,[3] allenes,[4] and cyclopropenes,[5] where a hydroxyl group introduced at a proper position of the substrates dominates the direction of the allyl group to the substrates. Azirines are known to have a highly strained ring similar to cyclopropenes and are expected to be more reactive than cyclopropenes due to the polarization of the C=N bond. However, few reactions of azirines with organometallic compounds have been documented.[6] We first describe here addition of allylindium to azirines, which gives a distinct outcome in comparison with the case of cyclopropenes; in cooperation with the chelation of the azirine nitrogen, the substituent on azirines regulates the direction of the allylation more efficiently than the case of cyclopropenes.

The reaction of 3-phenyl-2*H*-azirine-2-methanol (**1a**) with allylindium sesquiiodide[7] gave the corresponding allylaziridine **3aa** in 71% yield as a single isomer (Table 1, entry 1). The stereochemistry observed in the allylindation toward cyclopropenes led us to speculate that

Table 1. Cis-selective allylation of azirines with allylindium[a]



Entry	1	2	Conditions	Product	Yield (%)
1	**1a**	**2a**	THF, 2 h	**3aa**	71
2	**1a**	**2a**	DMF, 2 h	**3aa**	79
3	**1a**	**2b**	THF, 1 h	**3ab**	95 (56:44)[b,c]
4	**1a**	**2c**	THF, 2 h	**3ac**	85 (59:41)[b,c]
5	**1b**	**2a**	THF, 2 h	**3ba**	73 [36:64][d]
6	**1b**	**2a**	DMF, 2 h	**3ba**	67 [67:33][d]
7	**1b**	**2a**	DMI, 3 h	**3ba**	60 [78:22][d,e]

[a] All reactions were performed with **1**/**2**/In = 1/3/2 at room temperature.
[b] The numbers in parentheses refer to diastereomeric ratio.
[c] Determined by ^{13}C NMR.
[d] The numbers in square brackets refer to the ratio of **3ba**:**3ba′**.
[e] N-Allylated product, (1,3-diallyl-3-phenylaziridin-2-yl)methyl acetate, was also obtained in 6% yield.

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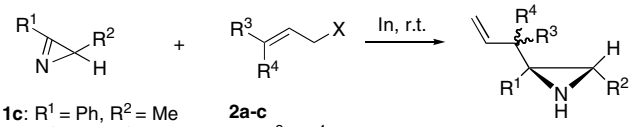
the allylation of the azirine with chelating substituent **1a** gives the cis-allylated products.[5a] This assumption was reinforced by comparison of the NOE experiment between the internal vinylic –C*H*═ and the C*H* on the aziridine ring in a series of the allylated product **3**.[8] In DMF, similar results were obtained (entry 2). The crotylation and cinnamylation of **1a** also proceeded with cis-selectivity to afford **3ab** and **3ac**, respectively, as mixtures of two diastereomers (entries 3 and 4). The reaction of 3-acetoxymethyl-2-phenyl-2*H*-azirine (**1b**) yielded the cis-allylated product **3ba** and its acetyl-migrated product **3ba′** (entries 5–7). The cis-stereochemistry of **3ba** was determined by comparison of the ^{1}H NMR spectra of the acetylation products from **3aa** and **3ba**; the two products were found to be identical. It is worthy of note that, in the allylindation of 3-acetoxymethyl-2-hexylcyclopropene, the allyl group was delivered from an opposite direction with respect to the acetoxymethyl group (trans-allylindation).[5a] This difference shows that the interaction between the indium atom and both the azirine nitrogen and the carbonyl oxygen of the acetoxy group operates significantly during the allylation of **1b**.

The reaction of 3-methyl-2-phenyl-2*H*-azirine (**1c**) with the allylindium reagent gave **3ca** in high yield (Table 2, entry 1). As was seen in the allylindation of cyclopropenes, a nonchelating group on the C-3 is expected to prevent the attack of the allylindium reagent from the cis-direction. The NOE experiment of **3ca** demonstrated that the allyl group was introduced from the trans-face with respect to the methyl group.[8] The yields were lower, when DMF and DMI were employed as a solvent (entries 2–4). The reaction with crotylindium sesquibromide afforded **3cb** as a mixture of two diastereomers similar to the case of **1a** in Table 1 (entry 5). With cinnamylindium sesquibromide, all four possible diastereomers were detected, indicating that the cinnamyl group was delivered from both the cis- and trans-faces (entry 6). Prenylindium reacted with **1c** at the substituted carbon selectively to afford **3cd** as a single isomer (entry 7). Azirine **1d** underwent allylation in both organic and aqueous media with trans-selectivity (entries 8 and 9).

The crotylation and cinnamylation of **1d** produced **3db** and **3dc**, in both of which only two diastereomers were found, suggesting that addition of the crotyl and cinnamyl groups proceeded with exclusive face-selectivity (entries 10 and 11). The stereochemistry of **3da**, **3db**, and **3dc** is not assigned, but is assumed to be the trans-adducts considering the similarity in the non-coordinative nature of methyl and phenyl group. Ethyl 2-methyl-2*H*-azirine-3-carboxylate (**1e**), though less reactive than **1a**–**d**, also underwent allylation (entries 12–16). As the NOE experiment of **3ea** showed results similar to those observed in **3ca**,[8] we concluded that azirine **1e** underwent the trans-allylation selectively. When an ester group was involved, the face-selectivity proved to be markedly different in cyclopropenes and azirines as mentioned above for **1b**. The allylindation of the cyclopropene bearing an ester group gave both cis- and trans-adducts.[5a]

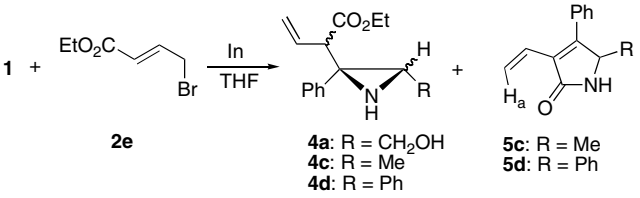
Table 2. Trans-selective allylation of azirines with allylindium[a]



Entry	1	2	Conditions	Product	Yield (%)
1	**1c**	**2a**	THF, rt, 3 h	**3ca**	98
2	**1c**	**2a**	DMF, rt, 4 h	**3ca**	51
3	**1c**	**2a**	DMF, 110 °C, 1 h	**3ca**	51
4	**1c**	**2a**	DMI, rt, 3 h	**3ca**	48[b]
5	**1c**	**2b**	THF, rt, 2 h	**3cb**	84 (56:44)[c,d]
6	**1c**	**2c**	THF, rt, 3 h	**3cc**	66 (51:34:7:8)[c,e]
7	**1c**	**2d**	THF, rt, 2 h	**3cd**	70
8[f]	**1d**	**2a**	THF, rt, 1 h	**3da**	95
9	**1d**	**2a**	H_2O, rt, 5 h	**3da**	71[g]
10	**1d**	**2b**	THF, rt, 5 h	**3db**	77 (62:38)[c,h]
11	**1d**	**2c**	THF, rt, 2 h	**3dc**	84 (51:49)[b,c]
12	**1e**	**2a**	THF, rt, 2 h	**3ea**	50
13	**1e**	**2a**	DMF, rt, 4 h	**3ea**	43
14	**1e**	**2a**	DMI, rt, 2 h	**3ea**	53
15	**1e**	**2b**	THF, rt, 2 h	**3eb**	91 (51:49)[b,c]
16	**1e**	**2c**	THF, rt, 2 h	**3ec**	68 (55:45)[b,c]

[a] All reactions were performed with **1**/**2**/In = 1/3/2.
[b] Determined by ^{1}H NMR.
[c] The numbers in parentheses refer to diastereomeric ratio.
[d] Determined by ^{13}C NMR.
[e] Determined by GC analysis.
[f] This reaction was conducted in a Barbier-type manner.
[g] N-Allyllated product, 1,2-diallyl-2,3-diphenylaziridine, was also obtained in 16% yield.
[h] The diastereomers were separated by column chromatography.

Table 3. Reaction of azirines with ester-bearing allylindium[a]



Entry	1	Time (h)	Yield (%)	
			4	**5**
1	**1a**	2	61[b]	0
2	**1c**	2	0	54
3	**1d**	4	40[b]	45

[a] All reactions were performed in THF with **1**/**2e**/In = 1/3/2.
[b] A mixture of diastereomers. The ratio was not determined.

Finally, the allylindium reagent possessing an ester group at the γ-position was employed in the allylation of **1** (Table 3). The reaction of **1a** gave the expected allylaziridine **4a** in 61% yield (entry 1). However, **1c** afforded not the corresponding aziridine **4c**, but the unexpected α,β-unsaturated lactam **5c** in 54% yield (entry 2). The ^{1}H NMR analysis of **5c** in $CDCl_3$ showed that one of the terminal vinylic protons (H_a) resonates in downfield (6.5 ppm) due to the anisotropic effect of the adjacent carbonyl group. Compound **5c** was fully identified by an X-ray crystallographic analysis

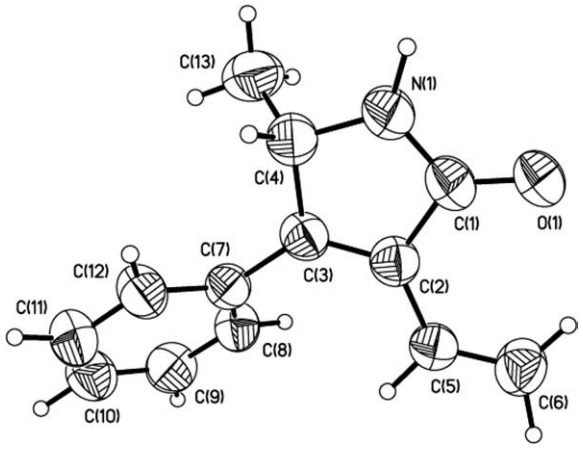
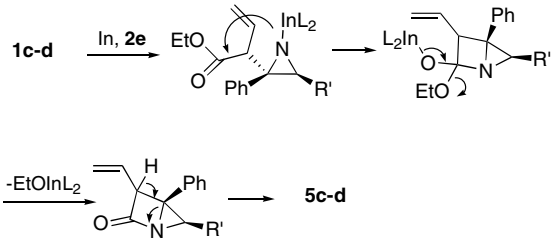


Figure 1. X-ray crystal structure of **5c**.



Scheme 1. A plausible mechanism for **5c** and **5d**.

(Fig. 1).[9] The diphenyl azirine **1d** gave both **4d** and **5d** (entry 3). A plausible mechanism for the formation of **5c** and **5d** is depicted in Scheme 1. The transient indium amide attacks the internal ester group, followed by successive elimination of the ethoxy group and opening of the annulated β-lactam leading to **5c** and **5d**.

In summary, the delivery of an allyl group to azirine was well regulated by the substituents on the C^3-carbon: The cis-allylation was realized with azirines bearing a hydroxylmethyl or an acetoxymethyl group due to the intermolecular chelation with allylindium reagents, whereas the trans-allylation occurred in azirines substituted by a methyl, phenyl, or ester group owing to the steric reason. α,β-Unsaturated lactam can be obtained with the γ-ethoxycarbonyl substituted allylindium reagent, followed by the spontaneous intramolecular nucleophilic cyclization. Aziridines are useful precursors for further transformations, such as stereospecific ring-opening reaction to amines and their derivatives.[10] The present allylation permits an access to both cis- and trans-stereodefined allylaziridines. Further applications for the allylindation of related compounds are currently under study.[11]

Acknowledgements

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References and notes

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5. The terms cis and trans mean the stereochemical relationship between the allyl group introduced and the substituent at the C^3-carbon of cyclopropanes and aziridines (a) Araki, S.; Nakano, H.; Subburaj, K.; Hirashita, T.; Shibutani, K.; Yamamura, H.; Kawai, M.; Butsugan, Y. *Tetrahedron Lett.* **1998**, *39*, 6327–6330; (b) Araki, S.; Shiraki, F.; Tanaka, T.; Nakano, H.; Subburaj, K.; Hirashita, T.; Yamamura, H.; Kawai, M. *Chem. Eur. J.* **2001**, *7*, 2784–2790.
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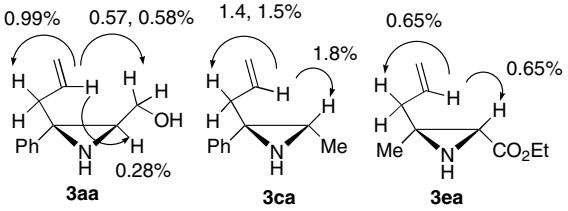
8. The NOE experiment of **3aa**, **3ca** and **3ea** exhibited the following results.



9. Crystal data for **5c**: $C_{13}H_{12}NO$, $M = 198.24$, monoclinic, space group $P2(1)/c$, $a = 5.7867(18)$, $b = 16.885(5)$, $c = 22.550(7)$ Å, $\beta = 89.993(6)$, $V = 2203.2(11)$ Å^3, $Z = 8$, $D_{calcd} = 1.195$ Mg/m^3, μ(Mo-Kα) $= 2.190$ mm^{-1}, $T = 300(2)$ K, crystal size $0.3 \times 0.1 \times 0.1$ mm, A total of 4446 unique reflections ($R_{int} = 0.0925$) were collected ($3.0 < 2\theta < 54.6°$) and 354 parameters were refined after structure solution by direct methods (SHELXTL). $R_1 = 0.1093$, $wR_2 = 0.2232$ for 1637 reflections with $I > 2\sigma(I)$ and $R_1 = 0.2346$, $wR_2 = 0.2901$ for all data. GOF on $F^2 = 1.037$. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 288700.
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11. The following reaction (Table 1, entry 1) represents a general procedure: a mixture of **2a** (0.25 g, 1.5 mmol) and indium powder (0.12 g, 1.0 mmol) in THF (2 mL) was stirred at room temperature for 1 h. To the resulting solution, **1a** (74 mg, 0.50 mmol) was added and the

mixture was stirred at room temperature for another 2 h. The reaction was quenched with water (10 mL) and the product was extracted with ether. The extracts were washed successively with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (elution with EtOAc–hexane = 1:10, then acetone) to give 2-allyl-2-phenylaziridine-3-methanol (**3aa**) (67 mg, 71%). Mp 74.0–75.0 °C (Et_2O). ^1H NMR (200 MHz, $CDCl_3$, δ ppm) 1.69 (s, 1H, –OH or –NH–), 2.73–2.88 (m, 2H, allyl–CH_2–, –CH–), 2.80 (dd, 1H, $J = 7.3$, 14.3 Hz, allyl–CH_2–), 3.12 (dd, 1H, $J = 6.9$, 11.7 Hz, –CH_2OH), 3.14 (dd, 1H, $J = 5.4$, 11.7 Hz, –CH_2OH), 5.01–5.14 (m, 2H, =CH_2), 5.60–5.80 (m, 1H, CH=), 7.18–7.41 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm) 42.2, 44.2, 46.2, 62.3, 119.1, 126.8, 127.8, 128.0, 132.1, 139.0. Calcd for $C_{12}H_{15}NO{\cdot}1/2H_2O$: C, 74.39; H, 7.80; N, 7.23. Found: C, 74.28; H, 8.14; N, 7.16.