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Indium-mediated consecutive 1,2-shift reaction and regioselective allylation of vinyl epoxides

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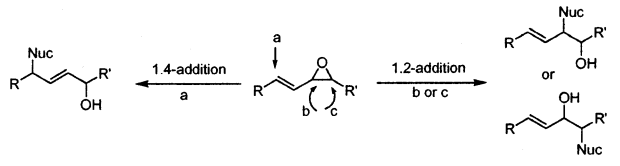
Abstract—Allyl indium, prepared from allyl bromide and indium metal in aprotic solvent, reacts with terminal vinyl epoxides at room temperature to afford various bishomoallyl alcohols in moderate to high yields via consecutive 1,2-shift reaction and regioselective allylation.

The use of organometallic reagents for organic synthetic purpose has been growing in scope and in importance.[1] In particular, organoindium reagents have attracted much attention due to their compatibility with many common organic functional groups and stability under aqueous conditions. Allyl indium reagents, generated in situ from indium metal with activated halide (e.g. allyl halide, α-halo ester) in organic solvent is known to be sesquihalide,[2] $(allyl)_3In_2X_2$ that reacts with various electrophiles, such as carbonyl compounds to give homoallyl alcohols. Epoxides are good electrophiles capable of reacting with organometallic reagents, such as allyl magnesium, allyl zinc and allylsilane.[3–5] However, most of these reagents are sensitive to air or moisture in contrast with allyl indium. Vinyl epoxides are commonly used starting materials in organic synthesis. Ring opening reaction of vinyl epoxides nucleophile goes to two pathways which are 1,4-nucleophilic addition and 1,2-nucleophilic addition[6] (Scheme 1).

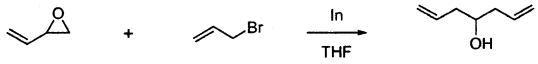


Scheme 1.

We attempted indium mediated regioselective allylation with vinyl epoxides with various allylbromides via ring opening reaction. Unexpectedly, we could obtain the consecutive 1,2-shift reaction to generate terminal aldehyde and then allylation products instead of 1,2-addition or 1,4-addition product (Scheme 2). We extended this result to the reactions using several kinds of vinyl epoxides and various allyl bromides.

The 1,2-shift reaction of epoxides to give aldehydes using indium(III) chloride has been reported.[7] The terminal epoxides undergo allylation reaction at less hindered position using indium and allyl bromides without 1,2-shift reaction.[8] In the case of vinyl epoxides, alkenyl group could stabilize the generated carbocation in migrating intermediate without Lewis acid. Herein we report a facile and high regioselective method for 1,2-shift and allylation reaction of vinyl epoxides using indium.

Firstly, we carried out the reaction of vinyl epoxide and methyl vinyl epoxide with various allyl bromides in THF at room temperature (Table 1). We applied two reaction methods, Grignard type (method a)[9] and Barbier type (method b).[10] Grignard type reaction is generally called a method for the generation of allyl indium before addition of substrates. For the Barbier type, generation of allyl indium and the allylation reaction



Scheme 2.

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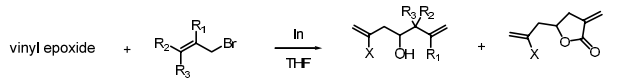
Table 1. Tandem 1,2-shift reaction and allylation of vinyloxirane and methyl vinyloxirane



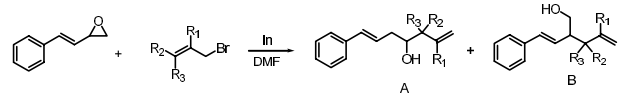
Entry	Vinyl epoxide	Allyl bromide R_1	R_2	R_3	time(h)	Product	Yield(%)
1	X=H	H	H	H	1	A	**87**
2		CH_3	H	H	1	A	**58**
3		H	CH_3	H	4	A	**61**
4		H	CH_3	CH_3	4	A	**81**
5		CO_2CH_3	H	H	3	B	**91**
6	X=CH_3	H	H	H	1	A	**71**
7		CH_3	H	H	1	A	**65**
8		H	CH_3	H	2	A	**75**
9		H	CH_3	CH_3	2.5	A	**75**
10		CO_2CH_3	H	H	1	B	**84**

a. Grignard type reaction

occurred in situ. In this case (Table 1), all the reactions were accomplished by Grignard type and we could get single bishomoallyl alcohols (A) in high yield (61–91%). Exceptionally, 2-bromomethyl acrylate led to homoallylic alcohol which underwent further cyclization to give lactone (B). We further studied the reactions of conjugated aromatic vinyl epoxide (Table 2) and cyclohexenyloxirane system (Table 3).

When *trans*-cinnamyloxirane was treated with allyl indium in DMF, it also produced 1,2-addition reaction product (B) via inside attack of epoxide as well as tandem 1,2-shift reaction and allylation product (A) in ratio of 1.4–8.5 to 1 (A/B). In the case of 2-bromomethyl acrylate, no reaction occurred.

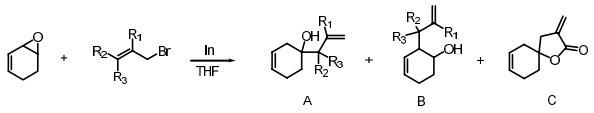
Table 2. Tandem 1,2-shift reaction and allylation of *trans*-cinnamyloxirane



Entry	Allyl bromide R_1	R_2	R_3	time(h)	Regioselectivity (A/B)	Yield(%)
11	H	H	H	1.5	8.5/1	**70**
12	CH_3	H	H	0.25	3.6/1	**75**
13	H	CH_3	H	3.5	7.37/1	**85**
14	H	CH_3	CH_3	6	2.4/1	**84**

Grignard type reaction

Table 3. Tandem 1,2-shift reaction and allylation of cyclohexenyloxirane



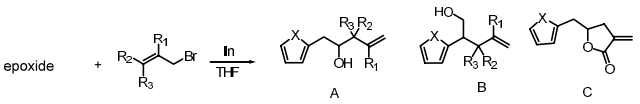
Entry	Allyl bromide R_1	R_2	R_3	time(h)	Product (Regioselectivity)	Yield(%)
15	H	H	H	0.5	A/B(1.1/1)	**82**
16	CH_3	H	H	0.5	A/B(1/4,7)	**85**
17	H	CH_3	H	0.5	A/B(1/8.7)	**88**
18	H	CH_3	CH_3	0.5	B	**86**
19	CO_2CH_3	H	H	0.5	C	**78**

Grignard type reaction

The reactions of cyclohexenyloxirane were accomplished in THF to give two products A and B in high yield (78–88%) shown in Table 3. In this cyclic alkenyl system, 1,2-addition reaction was more favorable than 1,2-shift reaction and allylation in ratio of 1–8.7 to 1 (B/A).

Instead of terminal vinyl epoxides, we have tried with epoxides having heterocyclic ring (Table 4). These reactions gave same products as other vinyl epoxide reactions, 1,2-addition reaction product and tandem 1,2-shift and allylation product. Thiophenyl epoxides

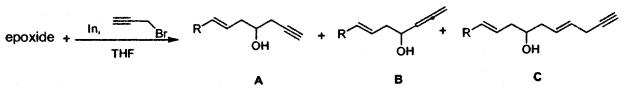
Table 4. Tandem 1,2-shift reaction and allylation of conjugated heterocyclic epoxides



Entry	epoxide	Allyl bromide R_1	R_2	R_3	time(h)	Product (Regioselectivity)	Yield(%)
20	X=O	H	H	H	1	A/B(1.1/1)[a]	**92**
						A/B(1.1/1)[a]	**85**
21		CH_3	H	H	1	A/B(1.1/1)[a]	**88**
22		H	CH_3	H	0.5	A/B(1.3/1)[a]	**90**
23		H	CH_3	CH_3	2	B[b]	**92**
					0.5	A[a]	**88**
24		CO_2CH_3	H	H	1.5	C[a]	**78**
25	X=S	H	H	H	1	A/B(6.3/1)[a]	**90**
26		CH_3	H	H	0.75	A/B(4.3/1)[a]	**95**
27		H	CH_3	H	1	A/B(6.0/1)[a]	**90**
28		H	CH_3	CH_3	2	A/B(4.4/1)[a]	**92**
29		CO_2CH_3	H	H	3	C[b]	**87**

a. Grignard type reaction
b. Barbier type reaction

Table 5. Tandem 1,2-shift reaction and propargylation of various epoxides



Entry	Epoxide	Reaction time(hr)	Product (Regioselectivity)	Yield(%)
30		2	A/B/C(3/1.8/1)[a]	**87**
31		3	A/B(1/1)[a]	**92**
32		1	A[b]	**90**
33		1	A[b]	**90**
34		0.5	A/B(1.05/1)[a]	**85**

a. Grignard type reaction
b. Barbier type reaction

gave higher ratio of 1,2-shift and allylation than furanyl epoxides, it might be due to the electron rich sulfur stabilizing carbocation intermediate.

Propargylation of several vinyl epoxides were performed with propargyl bromide (Table 5). In these reactions, we could only obtain tandem 1,2-shift reaction and propargylation or allenylation reaction. In the case of entry 30, we also obtained a small amount of further propagylation product C of product A.[11]

In summary, we have described a facile and highly efficient consecutive 1,2-shift reaction and allylation of vinyl epoxides using indium metal and allylbromide or propagyl bromide to afford bishomoallyl alcohols in high yields.

Acknowledgements

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9. *(a) Grignard type reaction (typical procedure, entry 11)*: A suspension of indium powder (157.1 mg, 1.36 mmol) and allyl bromide (248.0 mg, 2.05 mmol) in 2 mL of DMF was stirred until the metal dissolved completly. To the allyl indium reagent generated as above, a solution of 2-styryloxirane (100 mg, 0.68 mmol) was added and stirred for 1.5 h. After completion of the reaction, the reaction mixture was quenched with 1N HCl and extracted with methylene chloride. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography (ethyl acetate:hexane = 1:6) to afford the products (80.6 mg; **11A**, 9.5 mg; **11B**, 70%).
Compound **11A**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 5H), 6.51 (d, J = 15.9 Hz, 1H), 6.27 (m, 1H), 5.87 (m, 1H), 5.19 (m, 2H), 3.18 (m, 1H), 2.42 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.7, 135.0, 133.5, 128.9, 127.7, 126.6, 126.5, 118.5, 70.7, 41.7, 40.8; IR (KBr): 3501, 2940, 1655, 1477 cm^{-1}; HRMS (CI, M–H$^+$) calcd for $C_{13}H_{15}O$: 187.1123; found: 187.1122.
Compound **11B**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (m, 5H), 6.43 (d, J = 15.9 Hz, 1H), 6.00 (dd, J = 15.9, 8.5 Hz, 1H), 5.74 (m, 1H), 5.01 (m, 2H), 3.62 (m, 1H), 3.49 (m, 1H), 2.43 (m, 1H), 2.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 136.5, 132.7, 131.1, 128.9, 127.8, 126.6, 116.9, 66.0, 46.14, 13.6; IR (KBr): 2943, 2904, 2301, 1588, 1480 cm^{-1}; HRMS (CI, M–H$^+$) calcd for $C_{13}H_{15}O$: 187.1123; found: 187.1119.
10. *(b) Barbier type reaction (typical procedure, entry 20)*: 2-Oxiranylfuran (100 mg, 0.91 mmol) is added to the solution of indium powder (208.5 mg, 1.82 mmol) and allyl bromide (351.4 mg, 2.72 mmol) in 2 mL of THF and stirred for 1 h. After completion of the reaction, the reaction mixture was quenched with 1N HCl and extracted with methylene chloride. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography (ethyl acetate:hexane = 1:7) to afford products (70.6 mg; **20A**, 46.8 mg; **20B**, 85%).
Compound **20A**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (t, J = 1.0 Hz, 1H), 6.24 (t, J = 2.6 Hz, 1H), 6.04 (d, J = 3.1 Hz, 1H), 5.70 (m, 1H), 5.09 (m, 2H), 3.90 (m, 1H), 2.76 (m, 2H), 2.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.0, 142.0, 134.8, 118.5, 110.7, 107.4, 69.9, 41.5, 35.8; IR (KBr): 3450, 2940, 2804, 1588 cm^{-1}; HRMS (CI, M–H$^+$) calcd for $C_9H_{11}O_2$: 151.0759; found: 151.0758.
Compound **20B**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (t, J = 1.0 Hz, 1H), 6.24 (t, J = 2.9 Hz, 1H), 6.05 (dd, J = 3.2, 0.5 Hz, 1H), 5.68 (m, 1H), 4.98 (m, 2H), 3.70 (m, 2H), 2.93 (m, 1H), 2.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 141.9, 136.1, 117.4, 110.4, 106.7, 65.0, 42.0, 34.8; IR (KBr): 3454, 2840, 2804, 1608 cm^{-1}; HRMS (CI, M–H$^+$) calcd for $C_9H_{11}O_2$: 151.0759; found: 151.0755.
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