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# New Access to Chiral *syn*-α-Chlorohydrins and *cis*-Vinyloxiranes through Chloroallylboration[1]

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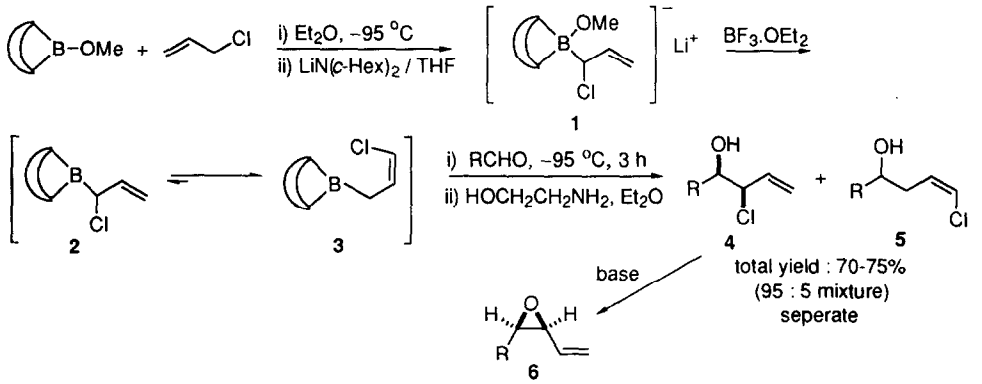
***Abstract:*** A new method to generate chiral *cis*-vinyloxiranes from readily available starting materials is reported. (α-Chloroallyl)lithium, generated *in situ* from LiN(*c*-Hex)$_2$ and allyl chloride at -95°C, reacts with (-)-*B*-methoxydiisopinocampheylborane, $^d$Ipc$_2$BOMe, to give an ate complex. Treatment of this with $BF_3{\cdot}OEt_2$ leads to the reagent, [(*Z*)-γ-chloroallyl]BIpc$_2$. Chloroallylboration of aldehydes using the latter reagent followed by elimination of chiral auxiliary provides *syn*-α-chlorohydrins in high de (≥94%) and ee (90-99%). Base-induced cyclization of chlorohydrins furnishes chiral *cis*-vinyloxiranes.

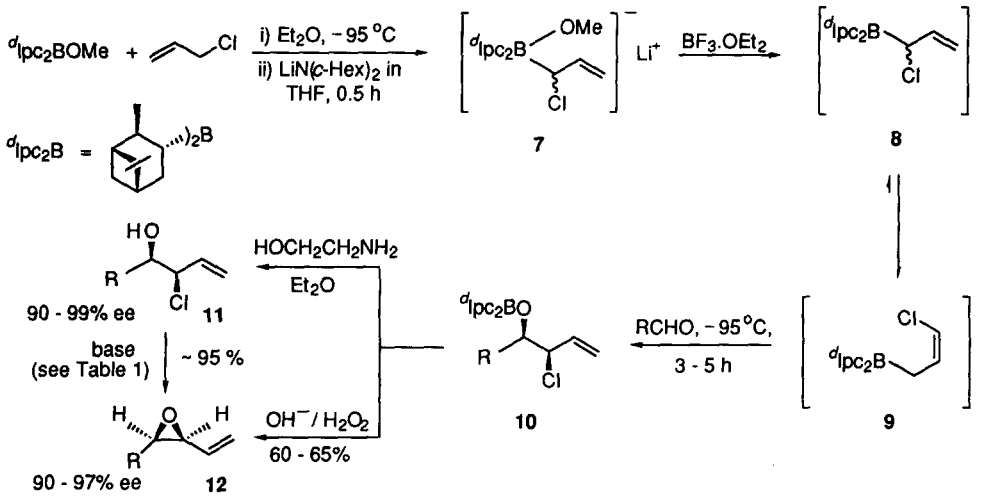
Racemic vinyloxiranes are easily prepared via reaction of carbonyl compounds with allyl organometallic reagents[2] or ylids.[3] The most common strategy for preparation of chiral vinyloxiranes is the Sharpless asymmetric epoxidation,[4] but for *Z*-allylic alcohols these epoxidations are slow and give variable enantioselectivities. The generation of chiral *syn*-α-chlorohydrins[5] from reactions of allyl organometallics with aldehydes followed by ring closure is an obvious strategy for the preparation of chiral *cis*-oxiranes[6] which should complement the Sharpless process. Allyl- and crotylboron reagents are readily available, undergo facile [1,3]-rearrangement and are easily delivered enantioselectively.[7] Herein we report a simple conversion of aldehydes to chiral *syn*-α–chlorohydrins and *cis*-vinyloxiranes through chloroallylboration.

It has been reported[8a] that 9-MeO-9-BBN reacts with chloroallyllithium[8b] to give α-product, **1**. This ate complex, upon reaction with $BF_3{\cdot}OEt_2$ furnished the less sterically hindered γ-chloroallylborane **3**, presumably *via* α-chloroborane **2**. Addition of aldehyde followed by elimination of 9-BBN moiety[9] afforded the (±) *syn*-α-chlorohydrin and γ-chlorohydrin in a ratio of ~95 : 5. The former could be converted to the (±) *cis*-vinyloxirane on treatment with a base (Scheme 1).




**Scheme 1**

It was expected that a bulkier group, such as Ipc, would favor the presumptive equilibrium more toward γ-chloroborane, **9**, which would enhance the α- vs γ-ratio. Extension of the above protocol using Brown's chiral auxiliary, *B*-methoxydiisopinocampheylborane,[10] led to *syn*-α-chlorohydrins **11** in high de (≥ 94%) and ee (90-99%) with a minimum (<1%) of γ-chlorohydrin. Base-induced cyclization of **11** furnished *cis*-vinyloxiranes **12** with no detrimental effect on ee (Scheme 2). Oxidation of **10** using alkaline $H_2O_2$ led directly to the desired oxiranes in 60-65% yield (Table 1).




**Scheme 2**

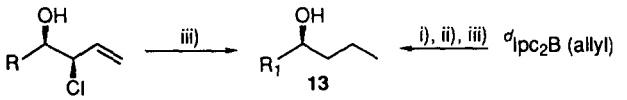
**Table 1. Chloroallylboration of Aldehydes using Reagent 9**

| entry | RCHO R= | *syn*-chlorohydrin, **11** yield, %[a] | ee, %[b] | *cis*-vinyloxirane, **12**[c] yield, %[a] | ee, %[b] | *cis*/ *trans*[h] |
|---|---|---|---|---|---|---|
| 1 | *n*-$C_8H_{17}$ | 70 | 98 | 95 | 98[d] | 99:1 |
| 2 | *i*-Pr | 68 | 95 | 99 | 95[d] | 98:2 |
| 3 | Ph | 78 | 99 | 96 | 97 | 98:2 |
| 4 | *c*-Hex | 72 | 93 | 94[f] | 93 | 98:2 |
| 5 | $PhCH_2$ | 85 | 90 | 97 | 90 | 99:1 |
| 6 | (*E*)-EtCH=CH | 78 | 99 | 95 | 97 | 97:3 |
| 7 | (*E*)-PhCH=CH | 75 | 92[e] | 85[g] | 92[d] | 98:2 |

[a] Isolated yields. [b] Ee's were determined by GC (J & W Cyclodex B fused silica column, 30 m x 0.25 mm; carrier gas He at 15 psi, temperature between 100 °C and 200 °C, isothermal; injector port and detector temperatures were 260 °C and 275 °C, respectively), unless otherwise noted. The racemic compounds were prepared using 9-methoxy-9-BBN. [c] Obtained by cyclization of chlorohydrins using $K_2CO_3$ / MeOH, unless otherwise noted. If the oxiranes are insensitive to base (except entries 3, 6 and 7), they could be obtained by oxidation of **10** (NaOH / $H_2O_2$), without isolation of the chlorohydrin. [d] Ee determined by $^1H$ NMR analysis (400 MHz) using Eu(hfc)$_3$ as chiral shift reagent. [e] Determined by $^1H$ NMR analysis of the MTPA ester. [f] Cyclized using NaOH / $H_2O_2$. [g] Cyclized using KO-*t*-Bu / THF. [h] Determined by $^1H$ NMR and capillary GC analysis. The ratio *syn*/*anti* of chlorohydrins is the same by both procedures.

Brown and Kramer[11] have demonstrated by variable temperature NMR that the α-methylallydialkylboranes rearrange spontaneously to the less sterically hindered crotyl isomers at low temperatures. In the present case, we believe that the conversion of **2** and **8** to γ-chloroallylborane, **3** and **9** respectively, is facilitated both by steric factors and the presence of excess of $BF_3{\cdot}OEt_2$.[12] However, direct formation of **3** and **9** from the ate complex containing *Z*-γ-chloroallyl moiety cannot be ruled out.

The absolute configuration of chlorohydrins, **11** [R=(*E*)-PhCH=CH, *c*-Hex] was elucidated by hydrogenolysis to alcohols, **13**, of known configuration[13] (Scheme 3). The configuration of the hydrogenation product, **13** ($R_1$=*c*-Hex) was further established by synthesis from $^{d}Ipc_2B$(allyl). The stereochemical preference of the γ-chloroallylborations is in agreement with that predicted for allylboration reagents derived from (+)-α-pinene.[14]




R = *c*-Hex, (*E*)-PhCH=CH $R_1$ = *c*-Hex, $PhCH_2CH_2$

i) $Et_2O$, *c*-HexCHO, –78 °C; ii) $NH_2CH_2CH_2OH$, $Et_2O$; iii) 5% Pd-C / $H_2$, MeOH

**Scheme 3**

In summary, (α-chloroallyl)lithium generated *in situ* is trapped by 9-MeO-9-BBN. Subsequent treatment with $BF_3{\cdot}OEt_2$ leads to the isomerically enriched product,[15] [(*Z*)-γ-chloroallyl]dialkylborane, **3**. Chloroallylboration of aldehydes using the latter followed by further transformations yield (±) *syn*-α-chlorohydrins and (±) *cis*-vinyloxiranes. Use of $^{d}Ipc_2BOMe$ in this process leads to chiral products in high de and ee. We are currently exploring this methodology for pheromone synthesis.[16]

**Experimental:** A representative procedure is as follows (R=*c*-Hex): To a stirred and cooled (–95 °C; liq. $N_2$-toluene bath) mixture of $^{d}Ipc_2BOMe$ (11.5 mmol) and allyl chloride (15 mmol) in ether (freshly distilled over benzophenone ketyl; 50 mL) was added a solution of $LiN(c\text{-Hex})_2$ (15 mmol) in THF (25 mL) through a cannula. After stirring for 0.5 h, $BF_3{\cdot}OEt_2$ (30 mmol) was added through a syringe, followed by cyclohexanecarboxaldehyde (11.5 mmol). Stirring was continued for additional 4 h and the temperature was maintained at –95 °C. The reaction mixture was allowed to attain r.t and the solvents were removed *in vacuo* (15 mm). The solid mass was then triturated with n-pentane (60 mL) and allowed to settle (12 h). The supernatant was transferred through a cannula to another flask. The residue was further treated with pentane (2 × 30 mL) and the pentane extracts were combined. Removal of pentane *in vacuo* furnished a semi-solid. This was dissolved in ether and treated with ethanolamine following a reported procedure.[9] Work-up gave a liquid which was purified by flash chromatography to yield **11** (R=*c*-Hex) as a colorless liquid (yield: 72%); bp 75 - 77 °C / 0.25 mm. This was converted to epoxide **12** (bp 110 °C / 14 mm) using NaOH / $H_2O_2$ (1 equiv.) in THF. Alternatively, compound **10** (R=*c*-Hex), obtained after extraction, was oxidized using NaOH / $H_2O_2$ (4 equiv.) in THF, to furnish epoxide **12** in 62% yield. All new compounds reported in this manuscript gave satisfactory spectral and analytical / HRMS data.

## References and Notes

1. Part of this work was presented at the 10th International Conference on Organic Synthesis at Bangalore, India, December 11-16, 1994.

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