# Conjugate Addition of Chloride to α,β-Unsaturated Chiral Imides Promoted by $BCl_3$-derivatives. A Synthesis of 3-Chlorobutanoic Acid

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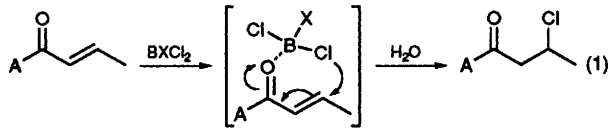
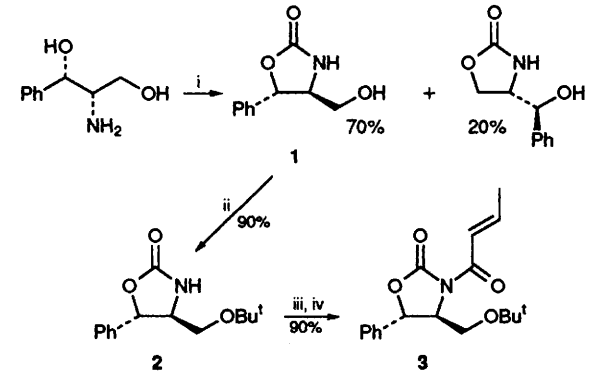
The conjugate addition of chloride to chiral but-2-enoic imides promoted by $BCl_3$-derivatives proceeds with diastereoisomeric ratios of up to 90:10 and affords the corresponding 3-chlorobutanoic imides from which, after mild hydrolysis, the 3-chlorobutanoic acid is obtained.

Conjugate addition to chiral α,β-unsaturated carboxylic acid derivatives is an efficient method to introduce a new asymmetric centre at the β position of a carboxylic acid.[1] Recent studies in this group[2] have shown that Lewis acids such as $TiCl_4$ and $AlMe_2Cl$[3] promoted the 1,4-addition of *O*-benzylhydroxylamine to (4*S*,5*R*)-1,5-dimethyl-3-alkenoyl-4-phenylimidazolidin-2-ones, affording in good yield and high diastereoselectivity the 4-*O*-benzylhydroxylamino derivatives which were then converted into the corresponding chiral β-amino acids.

When $BCl_3$-derivatives were used as Lewis acids on similar chiral unsaturated imides, a new reaction occurred, which exhibited an interesting behaviour. In fact the chloride is able to migrate from the four-co-ordinate boron to the 4 position of the unsaturated system[4] [eqn. (1), A = chiral auxiliary, X = $OPr^i$ or Cl].




A preliminary study of the reaction was made using as chiral auxiliary the oxazolidin-2-ones **1** and **2** prepared from the commercially available (1*S*,2*S*)-(+)-2-amino-1-phenylpropane-1,3-diol. The aminodiol was treated with an excess of diethyl carbonate according to the Evans procedure.[5] After flash chromatography, the oxazolidin-2-one **1** {$[\alpha]_D$ −43.3 (*c* 1.0, $CHCl_3$)} was separated from its regioisomer. The hydroxyl group of **1** was selectively protected with isobutene under acid catalysis affording **2** in good yield. By treatment with buten-2-oyl chloride, the magnesium salt of **2** was converted into the corresponding imide **3** {$[\alpha]_D$ +25.9 (*c* 1.02, $CHCl_3$)} (Scheme 1).



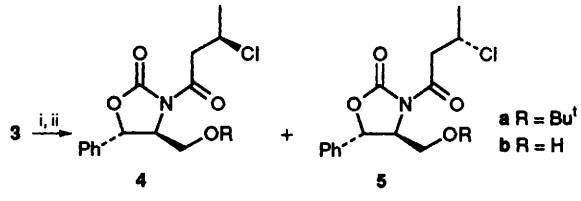

**Scheme 1** *Reagents and conditions*: i, $EtO_2CO$ (2 equiv.), $Na_2CO_3$ (0.1 equiv.), 150 °C, 2 h; ii, isobutene, Amberlyst H-15, dioxane, 0 °C, 12 h; iii, MeMgCl (1.2 equiv.), dry THF, 0 °C, 30 min; iv, ClCOCH=CHMe (1.2 equiv.), 2 h

By addition of $BCl_2OPr^i$ to **3** under argon atmosphere, a clean reaction took place and afforded essentially **4b** and **5b** (Scheme 2).

Following carefully the course of the reaction by $^1H$ NMR analysis, we could observe that the diastereoisomeric ratio† changed upon varying the reaction time and temperature, as shown in Table 1. After 7 h (Entry 1) the product **4a** was the major isomer and the *tert*-butyl protecting group was still present, while, after 24 h, the diastereoisomeric ratio changed and the hydroxyl group was completely deprotected.‡

In order to examine the influence of the free hydroxyl group of the chiral auxiliary on the diastereoisomeric ratio of the products, the imide **6** {$[\alpha]_D$ = +14.3 (*c* 1.3, $CHCl_3$)} was prepared starting from **1** through the simple steps reported in Scheme 3.

The reaction of **6** with $BCl_3$ at −78 °C (Entry 2), at −50 °C (Entry 3) and at room temperature (Entry 4), gave the chloro derivatives **4b** and **5b** in different diastereoisomeric ratios, with **5b** always the more abundant isomer (Scheme 3). On the basis of the results we presume that $BCl_3$ could interact with the free hydroxyl group before the addition took place, thus affording the reversed diastereoselectivity.




**Scheme 2** *Reagents and conditions*: i, $BCl_2(OPr^i)$ (2 equiv.), dry $CH_2Cl_2$; ii, $NaHCO_3$ (1 mol $dm^{-3}$)

**Table 1** Substrates, Lewis acid and conditions for formation of compounds **4** and **5**

| Entry | Substrate | Lewis acid (equiv.) | Reaction time/h | Conversion[a] (%) | *T*/°C | **4**:**5**[a] |
|---|---|---|---|---|---|---|
| 1 | **3** | $BCl_2(OPr^i)$ (2) | 7 | 58[b] | −78 | 66:34[b] |
| | | | 24 | 89[c] | r.t. | 57:43[c] |
| 2 | **6** | $BCl_3$ (1)[d] | 7 | 93 | −78 | 25:75 |
| 3 | **6** | $BCl_3$ (1)[d] | 4 | 98 | −50 | 32:68 |
| 4 | **6** | $BCl_3$ (1)[d] | 1 | 85 | r.t. | 45:55 |

r.t. = Room temperature. [a] Determined by 300 MHz $^1H$ NMR spectroscopy of the crude products. [b] Recovered with *tert*-butyl protection. [c] Recovered without *tert*-butyl protection. [d] Reaction carried out in the presence of 1 equivalent of $NaHCO_3$.

The absolute configuration of the newly formed stereogenic centre was assigned performing the hydrolysis of the mixture of **4b** and **5b** obtained from entry 3 under the reaction conditions reported by Evans (Scheme 4). The 3-chlorobutanoic acid was isolated after the usual work-up and a value of $[\alpha]_D$ −4.4 (*c* 1.8 in $Et_2O$) was measured, revealing the enantiomeric ratio (*S*)-(−)-**7**:(*R*)-(+)-**8** = 69:31, based on $[\alpha]_D$ −11.5 (*c* 10 in $Et_2O$) for (*S*)-(−)-3-chlorobutanoic acid.[8]

Although low diastereoisomeric ratios were obtained with both **3** and **6**, the reversed selectivity can be rationalised by assuming that the bulky *tert*-butyl group in **3** induces the preferential attack on the *re* face while the interaction between the hydroxyl group of **6** and the Lewis acid favours the attack on the *si* face.

Since the selectivity of this reaction strongly depends on the kind of chiral auxiliary utilised, to improve our results we tested the racemic indane derivative **9**[9] under the conditions reported in Scheme 5. Indeed the racemic derivative **10** was obtained in 90:10 diastereoisomeric ratio as shown by $^1H$ NMR analysis of the reaction mixture (Scheme 5).

This result fulfils our expectations and can be rationalised considering that the bicyclic chiral auxiliary is more rigid than the previous ones **1** and **2**, thus it more effectively hinders one face of the unsaturated system. On the basis of these encouraging results, further work with different chiral substrates is now in progress in order to improve the diastereoisomeric ratio and to clarify some aspects of the reaction mechanism.

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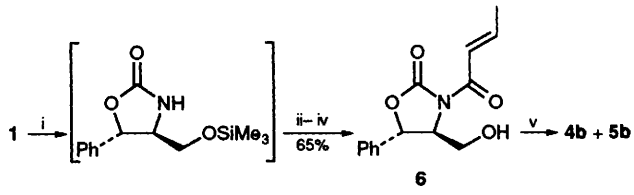
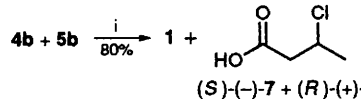
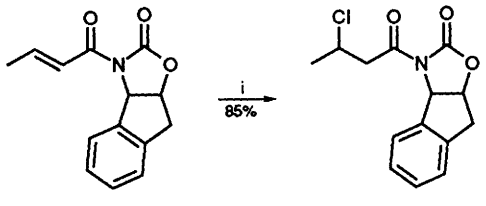



**Scheme 3** *Reagents and conditions*: i, $Me_3SiCl$ (1.5 equiv.), $NEt_3$ (1.5 equiv.), dry THF, 0 °C, 2 h; ii, MeMgCl, (1.2 equiv.), dry THF, 0 °C, 30 min; iii, ClCOCH=CHMe (1.2 equiv.), 2 h; iv, 1 mol $dm^{-3}$ HCl, 15 min; v, $BCl_3$ (1 equiv.), $NaHCO_3$ (1 equiv.), dry $CH_2Cl_2$




**Scheme 4** *Reagents and conditions*: i, LiOH (1.5 equiv.), $H_2O_2$ (5 equiv.), THF–$H_2O$ (4:1), 0 °C, 90 min




**Scheme 5** *Reagents and conditions*: i, $BCl_2(OPr^i)$ (2.5 equiv.), dry $CH_2Cl_2$, −78 °C, 6 h

## Footnotes

† The diastereoisomeric ratios of epimers **4** and **5** were determined on the basis of the integrals of the two non-equivalent hydrogens of the methylene group α to the stereogenic centre.

‡ The possibility of the occurrence of an equilibrium was taken into consideration but reactions of several mixtures of **4b** and **5b** with $BCl_3$ and $BCl_2(OPr^i)$ at different temperatures did not show any variation in the diastereoisomeric ratios.

## References

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