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# Synthesis of enantiopure (*S*)-(*E*)-1-haloalk-1-ene-3-amines with total or very high diastereoselectivity by halomethylenation of α-amino aldehydes promoted by $CrCl_2$

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**Abstract**—Highly diastereoselective synthesis of enantiopure (*S*)-(*E*)-1-haloalk-1-ene-3-amines was achieved by reaction of α-amino aldehydes with trihalomethane promoted by chromium dichloride. The absence of racemization in the halomethylenation reaction was checked by chiral HPLC. A mechanism to explain this transformation is proposed.


Chiral α-amino acids are employed as starting materials to prepare a variety of chiral building blocks and, in this sense, α-amino aldehydes are important compounds widely used in organic synthesis owing to their ready availability from α-amino acids and pronounced versatility. In recent years, an important number of basic organic reactions using α-amino aldehydes have been described to prepare a range of enantiomerically pure compounds.[1]

Allylic amines are the focus of numerous studies due to the presence of the allylic amine moiety in many natural and bioactive compounds.[2] In addition, allyl amines offer important synthetic applications and a range of useful products, such as α- and β-amino acids,[3] various alkaloids,[4] and carbohydrate derivatives[5] which can be readily prepared by functionalization of their double bonds. For these reasons, synthesis of enantiopure building blocks containing the allyl amine moiety is desirable. In this sense, several methods to transform α-amino aldehydes into enantiopure 1-haloalk-1-ene-3-amines have been described, such as hydrozirconation of propargylic amines and further treatment with $I_2$,[6] reaction of α-vinyl amino esters with phenylselenyl bromide or chloride followed by oxidation and pyrolysis,[7] and treatment of amino vinyltributylstannanes with $I_2$.[8] However, some of these methodologies are tedious and involve multi-step transformations from α-amino aldehydes[7,8] other methods suffer from such limitations as poor selectivity,[7] and in other syntheses poor yields are observed.[6]

Previously, the transformation of aldehydes into vinyl halides through a $CrCl_2$-promoted reaction with haloform was described[9]. To the best of our knowledge, only one example of the stereoselective version of this methodology (iodomethylenation) was described to prepare the protein phosphatase inhibitor (−)-motuporin.[10] In these papers, no methodical study of iodo-, chloro- or bromomethylenation, of enantiopure *N*,*N*-dibenzyl α-amino aldehydes, including the determination of enantiomeric purity of the obtained vinyl halides, has been reported. For these reasons, a systematic study of halomethylenation of *N*,*N*-dibenzyl α-amino aldehydes with determination of the enantiomeric purity of the halogenated allyl amines would be of interest.

Recently, we described the synthesis of α,β-unsaturated esters from α-chloro-β-hydroxyesters promoted by $CrCl_2$.[11] Here we describe an efficient preparation of enantiopure (*E*)-1-haloalk-1-ene-3-amines, by reaction of chiral α-amino aldehydes with iodoform, chloroform or bromoform, promoted by $CrCl_2$ or $CrBr_2$ in which the C–C double bond is generated with total or very high diastereoselectivity. Halomethylenation of amino aldehydes **1** proceeds with no detectable racemization.

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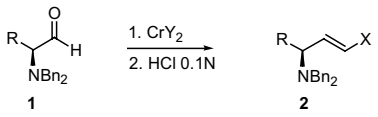



**Scheme 1.** Synthesis of (*S*)-(*E*)-1-haloalk-1-ene-3-amines **2** from α-amino aldehydes **1**.

Reaction of several α-amino aldehydes **1** with iodoform in the presence of $CrCl_2$ at room temperature afforded the corresponding (*S*)-(*E*)-1-iodoalk-1-ene-3-amines **2**[12] in high yield and with total or very high *E*-diastereoselectivity (Scheme 1 and Table 1). This β-elimination reaction was general such that elimination is observed in linear or branched aliphatic, aromatic and functionalized vinyl iodides **2**.

The starting α-amino aldehydes **1** used as starting compounds were easily prepared by reduction of ethyl α-amino esters with $LiAlH_4$, and further Swern oxidation of the **2**-aminoalcohol using standard methods.[13]

The diastereoisomeric excess of the newly generated C–C double bond was determined on the crude reaction products by GC–MS and $^1H$ NMR spectroscopy. The *E* stereochemistry of the C–C double bond of compounds **2** was assigned on the basis of the value of $^1H$ NMR coupling constant between the olefinic protons of compounds **2**[14] and by NOESY experiments of compounds **2f**, **2g** and **2i**.

The high proclivity of the N-protected aldehyde derived from phenylalanine to racemize has been carefully documented.[15] Under these reaction conditions, iodomethylenation of **1b** proceeds with no detectable racemization.

**Table 1.** Synthesis of (*S*)-(*E*)-1-haloalk-1-ene-3-amines **2**

| 2 | X | Y | R | Yield[a] (%) | de[b] (%) |
|---|---|---|---|---|---|
| **a** | I[c] | Cl | Me | 73 | 95 |
| **b** | I[c] | Cl | Bn[d] | 64 | 98 |
| **c** | I[c] | Cl | *i*-Bu | 66 | >98 |
| **d** | I[c] | Cl | $BnO–CH_2$ | 62 | >98 |
| **e** | Cl[e] | Cl | Me | 64 | 90 |
| **f** | Cl[e] | Cl | Bn[f] | 55 | >98 |
| **g** | Cl[e] | Cl | *i*-Bu | 75 | >98 |
| **h** | Br[g] | Br | Me | 50 | 97 |
| **i** | Br[g] | Br | Bn[h] | 58 | >98 |
| **j** | Br[g] | Br | *i*-Bu | 55 | >98 |

[a] Isolated yield after flash column chromatography based on starting α-amino aldehyde.
[b] Diastereoisomeric excess determinated by $^1H$ NMR analysis of the crude products **2** or by GC–MS.
[c] The reaction was carried out with 6 equiv of $CrCl_2$ at room temperature during 2 h.
[d] ee = 98% HPLC (Chiracel ODH, UV detector 210 nm, 0.8 mL/min, 99:1 hexane–propan-2-ol, tr: **2b** 5.597, enantiomer of **2b** 8.077).
[e] The reaction was carried out with 6 equiv of $CrCl_2$ at 50 °C during 3 h.
[f] ee > 98% HPLC (Chiracel ODH, UV detector 210 nm, 0.8 mL/min, 97:3 hexane–propan-2-ol, tr: **2f** 6.252, enantiomer of **2f** 8.901).
[g] A combination of $CrBr_3$ and $LiAlH_4$ (1:0.5 molar ratio) at 50 °C was employed instead of $CrCl_2$.
[h] ee > 98% HPLC (Chiracel ODH, UV detector 210 nm, 0.8 mL/min, 97:3 hexane: propan-2-ol, tr: **2i** 7.450, enantiomer of **2i** 10.012).

The enantiomeric purity of compound **2b** was determined by chiral HPLC analysis (Chiracel OD-H) showing an enantiomeric excess (ee) >99% (authentic samples of the racemate were analysed by HPLC to confirm the retention times of both enantiomers).

This method has been generalized to obtain 3-chloro- or 3-bromoallylamines **2**. Thus treatment of α-amino aldehydes in THF with chloroform in the presence of $CrCl_2$ at 50 °C, afforded the corresponding vinyl chloride **2** in high yield and with total or high diastereoselectivity (Table 1). No differences in yield or de were detected in the synthesis of vinyl chlorides with respect to iodides.

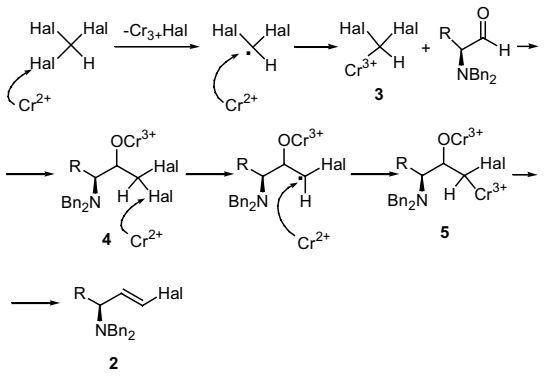
However, when α-amino aldehydes were treated with bromoform and chromium chloride, a mixture of the corresponding brominated and chlorinated derivatives **2**, in a 1:1 relationship were obtained. Increasing the amount of bromoform enhanced the yield of the brominated derivatives, although the vinylchloride derivatives were still present. To overcome this problem, the bromomethylenation was carried out with the $CrBr_2$ generated in situ from treatment of $CrBr_3$ with $LiAlH_4$. Previously $CrBr_3$ was obtained by heating of commercial $CrBr_3{\cdot}6H_2O$ under vacuum.[16] Thus, the reaction of α-amino aldehydes with bromoform and chromium bromide at 50 °C, afforded the corresponding vinyl bromide in high yield and with total de as a single product (Table 1).

All reactions took place with total diastereoselectivity, except from alaninal **1a**. In these cases the de was 95% or 90% from chloroform or iodoform, respectively.

The enantiomeric purity of compounds **2f** and **2i** (derived from phenylalaninal) was also checked by chiral HPLC analyses (Chiracel OD-H), again relying on authentic racemic samples of **2f** and **2i** to determine their retention times. The determinated enantiomeric excess (ee) >99% shows an absence of racemization.

The synthesis of enantiopure compounds **2** may be explained by assuming a sequential reaction where a C–C bond formation reaction in the first step is followed by β-elimination reaction. Thus, a double consecutive single electron transfers from the $CrCl_2$ produces the dihalogenated anion **3**, which is added to the starting α-amino aldehyde affording a dihalogenated alcoholate **4**.[17] The metalation of the C–halogen bond of **4** by 2 equiv of $CrCl_2$ gives the β-functionalized organochromiun intermediate **5**, which suffers a spontaneous β-elimination generating the final product **2** (Scheme 2).

Tentatively, we propose an *anti* elimination process, with transition states **A** and **B** being probable (Fig. 1). Due to the lack of steric hindrance between the Hal and $RCHNBn_2$ groups in **A**, and combined with the fact that elimination from **A** affords the (*E*)-alkene[18] it is reasoned that this is the most likely transition state. This model may also explain the lower diastereoselectivity observed from alaninal: when R is smaller, steric hindrance between Hal and $RCHNBn_2$ is diminished, and



**Scheme 2.** Mechanistic proposal for the synthesis of enantiopure (*E*)-1-haloalk-1-ene-3-amines.

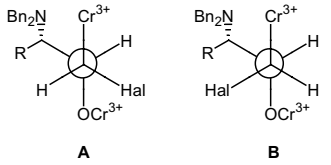


**Figure 1.** Proposed transition states.

consequently part of intermediate **5** eliminates through transition state **B**.

In conclusion, an easy, general and efficient methodology has been developed to obtain enantiopure (*S*)-(*E*)-1-haloalk-1-ene-3-amines with total or very high *E*-diastereoselectivity by reaction of easily available chiral α-amino aldehydes with iodoform, chloroform or bromoform promoted by $CrCl_2$ or $CrBr_2$. The enantiomeric purity of the prepared halogenated allylamines was determined by chiral HPLC analysis, showing no detectable racemization in any case.

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12. General procedure for the synthesis of (*S*)-(*E*)-1-haloalk-1-ene-3-amines. Anhydrous $CrCl_2$ (6.0 mmol) is suspended THF (10 mL) under a nitrogen atmosphere. A solution of the corresponding aldehyde (1 mmol) and iodoform or chloroform (2 mmol) was added dropwise to this suspension at room temperature ($CHI_3$) or 50 °C ($CHCl_3$). After strirring for 2 h, the reaction mixture was hydrolyzed with HCl 0.1 N and extracted with chloroform ($3 \times 10$ mL). The combined extracts are dried over $Na_2SO_4$ and concentrated. Then the organic layer was filtered through a pad of Celite® and the solvents were removed in vacuo. Purification by column chromatography on silica gel (hexane) afforded the 1-haloalk-1-ene-3-amines **2**. In the case of bromomethylenation, the reaction was carried out at 50 °C during 2 h by using anhydrous $CrBr_2$ generated in situ by reaction of $LiAlH_4$ (3 mmol) with $CrBr_3$ (6 mmol), obtained by heating of commercial $CrBr_3 \cdot 6H_2O$ under vacuum obtained.[16]
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