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Synthesis of allylamines in enantiomerically pure form

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Abstract

Enantiopure allylamines are obtained without racemization by reaction of α-amino aldehydes with chloromethyllithium followed by lithiation.

Keywords: amines; elimination reactions; enantiomeric purity; lithiation.

Chiral allylamines are synthetic precursors to a number of important classes of compounds, such as 4-aminoallylsilanes,[1] aminoepoxides,[2] iodocyclocarbamates[3] and isoxazolines.[4] One general method[3] for the synthesis of allylic amines involves the Wittig olefination reaction with amino aldehydes.[5] However, α-amino aldehydes are often susceptible to racemization[6] and there is a possibility that racemization may also occur during the Wittig reaction.[2a]

Previously, we have reported the synthesis of chiral *erythro* or *threo* aminoepoxides by epoxidation of *erythro* or *threo* 3-amino-1-haloalkan-2-ols. These enantiopure halohydrins can be obtained by reaction of halomethyllithium (generated in situ) with α-amino aldehydes or by reduction of chiral α′-amino α-chloro ketones, respectively.[7] Herein we wish to report a general one-pot synthesis of enantiopure allylamines by lithiation of chiral 3-amino-1-haloalkan-2-ols, which can be prepared by reaction of chloromethyllithium with chiral α-amino aldehydes.

The reaction of amino aldehyde **1** with chloromethyllithium (generated in situ from chloroiodomethane and methyllithium) at –78°C led to the expected chlorinated lithium alcoholate **2**; this intermediate was in situ lithiated with lithium powder at –45°C affording a β-functionalized organolithium intermediate **3**, which undergoes spontaneous β-elimination yielding, after hydrolysis, the corresponding allylamine **4** (Scheme 1).

Under these reaction conditions, the allylic amines **4** were obtained with no detectable racemization. The enantiomeric purity of product **4b** was determined by chiral HPLC (Chiracel OD-H) analysis,[8] showing an enantiomeric excess (ee) >99%. Previously, other chiral HPLC analysis was carried out, using a racemic mixture of **4b** to exclude the possibility of co-elution of both enantiomers.

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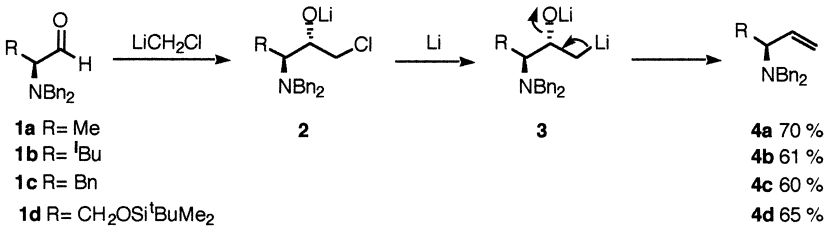

Scheme 1. Synthesis of enantiopure allylamines

The described transformation can also be carried out with functionalized amino aldehydes such as *O*-silylated serinal **1d** and it is noteworthy that this methodology provides directly enantiopure allylamines, from α-amino aldehydes, without isolating the intermediate **2**.

A typical procedure for the synthesis of allylamines **4** is as follows: to a –78°C solution of the corresponding aldehyde **1** (3 mmol) and chloroiodomethane (0.436 mL, 6 mmol) in THF (10 mL) was added methyllithium (4 mL of 1.5 M solution in diethyl ether, 6 mmol) dropwise over 5 min and under nitrogen. After stirring at –78°C for 30 min, lithium powder (0.216 g, 30 mmol) was added at –45°C, and the mixture was stirred for 8 h at the same temperature. The resulting mixture was treated with ice and after the usual work-up, crude allylamine **4** was obtained. Column flash chromatography over silica gel (15:1 hexane:ethyl acetate) provided the corresponding pure allylamine **4**.

In conclusion, we have described a direct, easy and simple transformation without racemization, of α-amino aldehydes into enantiopure allylamines.

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8. UV detector 325 nm, 0.8 mL/min, 400:1 hexane:isopropanol; t_R: 6.38 min.