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Synthesis of Enantiopure Allylamines by Reductive Alkylation of Amino Epoxides with Organolithium Reagents

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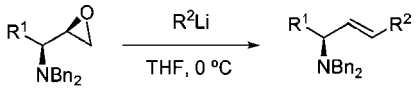
ABSTRACT



Transformation of enantiopure (2*R*,1′*S*)-2-(1-aminoalkyl)epoxides 1 into the corresponding allylamines 2 is described. The opening of the epoxide ring with different organolithium compounds takes place with total selectivity and in high yields.

Chiral allylamines are important building blocks and have been used as synthetic precursors to prepare a number of important classes of compounds, such as α- and *β*-amino acids,[1] alkaloids,[2] carbohydrate derivatives,[3] and other compounds.[4]

In addition, allylamines are also of industrial interest.[5] For these reasons, many efficient methods for the racemic synthesis of allylamines have been reported.[6] However, the asymmetric synthesis of allylamines has not been so well developed in comparison with the racemic synthesis. The synthesis of chiral allylamines is generally achieved by (a) amination of enantiopure allyl alcohols or their derivatives,[7] (b) asymmetric amination of nonfunctional alkenes,[8] or (c) from α-amino aldehydes.[9] However, general methods to prepare allylamines with an enantiomeric excess (ee) > 99%, in which only one regioisomer is obtained and the double

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bond is generated with total stereoselectivity by using method (a) or (b) are very scarce. In addition, syntheses of enantiopure allylamines involving the Wittig olefination reaction of α-amino aldehydes[10] are limited by the possibility that racemization may occur during the Wittig reaction.[4b]

For this reason, a general synthesis of enantiopure allylamines with complete regio- and stereoselectivity would be still desirable.

Previously, the olefin formation with alkylation of epoxides using organolithiums has been described by Crandall and Lin,[11] and a number of research groups have subsequently made contributions to this field.[12]

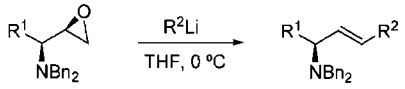
In the past, we have reported the synthesis of enantiopure allylamines by successive reaction of α-amino aldehydes with chloromethyllithium generated in situ and further lithiation with lithium powder.[13] However, by using this method, it is possible to prepare only allylamines with the C═C double bond in the terminal position.

Previously, we reported an efficient synthesis of enantiopure (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides by total stereoselective reduction of the easily available, from natural α-amino acids, α-amino-α′-chloroketones with $LiAlH_4$, or by highly stereoselective addition of in situ generated iodomethyllithium (from diiodomethane and methyllithium) to α-aminoaldehydes.[14]

As part of a program concerned with the development of a new synthesis of enantiopure compounds, we wish to report herein a new easy and general access to enantiopure allylamines by treatment of enantiopure (2*R*,1′*S*)-(1-aminoalkyl)epoxides with alkyllithium which takes place in high yield, with complete *E*-stereoselectivity.

The reaction of different (2*R*,1′*S*)-(1-aminoalkyl)epoxides **1** with various organolithium compounds at 0 °C during 30 min afforded the corresponding enantiopure allylamine in high yields (>74%) with complete *E*-stereoselectivity (Scheme 1 and Table 1).[15]

Scheme 1. Synthesis of Allylamines **2**



1 **2**

As is shown in Table 1, transformation of amino epoxides **1** into allylamines **2**, seems to be general. Therefore, the reaction was performed with different amino epoxides, derived from alanine (Table 1, entries 1−6), leucine (entries 7−12), and phenylalanine (entries 13−18) and various primary, secondary, and tertiary alkyllithium and aryllithium compounds.

Table 1. Synthesis of (2*R*,3*S*)-1,3-Diaminoalkan-2-ols **3**

entry	**2**	R^1	R^2	*T* (h)	yield[a] (%)
1	**2a**	Me	Me	6	81
2	**2b**	Me	*i*-Pr	0.5	79
3	**2c**	Me	*n*-Bu	0.5	95
4	**2d**	Me	*s*-Bu	0.5	75[b]
5	**2e**	Me	*t*-Bu	0.5	84
6	**2f**	Me	Ph	6	75
7	**2g**	*i*-Bu	Me	6	79
8	**2h**	*i*-Bu	*i*-Pr	0.5	77
9	**2i**	*i*-Bu	*n*-Bu	0.5	86
10	**2j**	*i*-Bu	*s*-Bu	0.5	76[b]
11	**2k**	*i*-Bu	*t*-Bu	0.5	78
12	**2l**	*i*-Bu	Ph	6	89
13	**2m**	Ph	Me	6	75
14	**2n**	Ph	*i*-Pr	0.5	88
15	**2o**	Ph	*n*-Bu	0.5	91
16	**2p**	Ph	*s*-Bu	0.5	85[b]
17	**2q**	Ph	*t*-Bu	0.5	89
18	**2r**	Ph	Ph	6	93

[a] Isolated yield after column chromatography based on the starting amino epoxide **1**. [b] A mixture of two diastereoisomers in a 1:1 relationship was obtained when *s*-BuLi was used.

When less reactive organolithium compounds, such as methyllithium or phenyllithium, were used, longer reaction times were necessary to obtain the corresponding allylamine **2** in high yield (Table 1, entries 1, 6, 7, 12, 13, and 18).

The complete stereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy (300 MHz) of the crude reaction, showing the presence of a single diastereoisomer.

The *E*-stereochemistry of the double C═C bond of allylamines **2** was assigned on the basis of the value of the ^{1}H NMR coupling constant of olefinic protons (ranging between 15.4 and 16.1 Hz according to the average literature values).[16]

The enantiomeric purity of **2h** was determined by chiral HPLC analysis, showing an ee < 99%. To exclude the possibility of coelution of both enantiomers, a racemic mixture of **2h** was prepared and analyzed by HPLC.[17]

(10) α-Amino aldehydes are often susceptible to racemization: (a) Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676−678. (b) Rettle, K. E.; Hommick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016−3018. (c) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1988**, *110*, 7447−7455.

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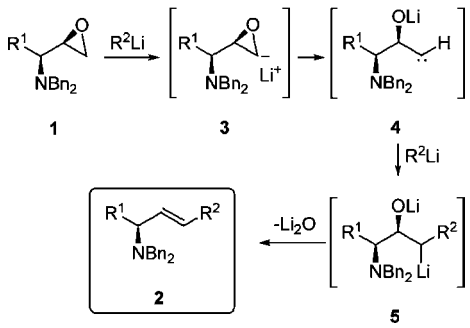
(15) **Representative Experimental Procedure.** To a stirred solution of the corresponding amino epoxide **1** (0.2 mmol), in THF (1 mL), was added the corresponding alkyllithium (3 equiv) at 0 °C. After the solution was stirred at this temperature until the reaction finished (see Table 1), an aqueous saturated solution of NH_4Cl (5 mL) was added, and the mixture was stirred at room temperature for 5 min. Then, the aqueous phase was extracted with diethyl ether (3 × 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (hexane/EtOAc 10:1) provided pure compounds **2**.

(16) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley and Sons: New York, 1991; Chapter 4, Appendix F, p 221.

This transformation and the observed stereochemistry of the products **2** may be explained by assuming that after lithiation of epoxide ring, at the less hindered side, would produce the oxiranyl anion intermediate **3**. This anion **3** could suffers an α-elimination affording an α-alkoxycarbenoid intermediate **4**, which could react with a second equivalent of the organometallic compounds to give the dianion **5**. Finally, lithium oxide is then eliminated to afford allylamines **2** (Scheme 2).

Scheme 2. Proposed Mechanism

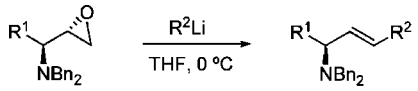


An indirect support for this proposed mechanism is provided by the isolation of a 1:1 mixture of the starting amino epoxide and the corresponding allylamine when the reaction was carried out by using only 1 equiv of organolithium compound.

We here also performed the reaction starting from the *anti*-amino epoxide **6** with *n*-BuLi and *t*-BuLi under the same reaction conditions (Scheme 3).

(17) Chiracel OD, UV detector 210 nm, 0.5 mL/min, hexane, rt: **2h** 18.826 min; rt: enantiomer of **2h** 13.737 min.

Scheme 3. Reaction with the Anti Amino Epoxide **6**



6

2c R^2 = *n*-Bu 78%
2e R^2 = *t*-Bu 76%

In both cases, the corresponding allylamines**2** were obtained with total *E*-selectivity in yields (78 and 76%, respectively) similar to those obtained from the *syn*-amino epoxide (Table 1, entries 3 and 5, respectively). Then, the described transformation was not affected by the stereochemistry of the starting amino epoxide.

In conclusion, in this paper, we have presented an easy, simple, general, and efficient preparation of enantiopure allylamines by reaction of (2*R*,1′*S*)-2-(1-aminoalkyl)epoxides **1** with different organolithium compounds. This transformation takes place in high yield, with complete *E*-stereoselectivity of the double C=C bond formation.

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Supporting Information Available: General methods, spectroscopic data of **2**, and ^{13}C NMR spectra of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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