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Highly Enantioselective Synthesis of β -Amino Alcohols

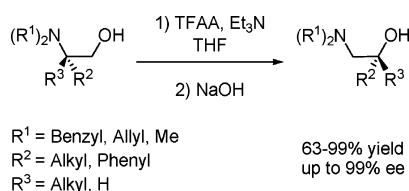
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ABSTRACT



N,N-Dialkyl- β -amino alcohols derived from α -amino acids can be rearranged enantiospecifically by using TFAA/Et₃N/NaOH to give 1,2-amino alcohols with enantiomeric excess up to 99%.

β -Amino alcohol moieties are present in a large variety of naturally occurring and pharmacologically active molecules.¹ The amino alcohol relative stereochemistry is highly important for the biological activity of these molecules. These entities can also be used as chiral auxiliaries in asymmetric synthesis.^{2,3}

Linear *N,N*-dialkyl- β -amino alcohols have been shown to rearrange, via an aziridinium ion, into β -halogenoamines (on treatment with SOCl₂,⁴ MsCl,⁵ TsCl,⁵ SOBr₂,⁶ CBr₄/PPh₃,⁷ DAST,⁸ or Deoxofluor⁹), into β -mesylamines (on treatment with Ms₂O^{10,11}), and into thiocyanates (on treatment with

KSCN¹²). Recently we have shown that prolinols can be rearranged enantiospecifically to give optically active piperidin-3-ols, via an aziridinium intermediate, by using TFAA/Et₃N/NaOH.^{13,14} In this Letter, we would like to report that these latter conditions can be applied to linear optically active β -amino alcohols of type **A** to produce 1,2-amino alcohols of type **B** in a very regio-, stereo-, and enantioselective process (Scheme 1).

N,N-Dibenzyl- β -amino alcohols **2a**,¹⁵ **2c**,⁵ **2e**,¹⁶ **2f**,¹⁷ **2g**, and **2h**¹⁸ were prepared from the commercially available amino alcohols by using benzyl bromide (2.2 equiv) in the

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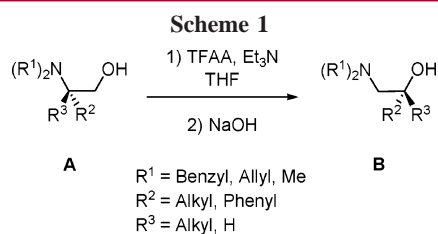
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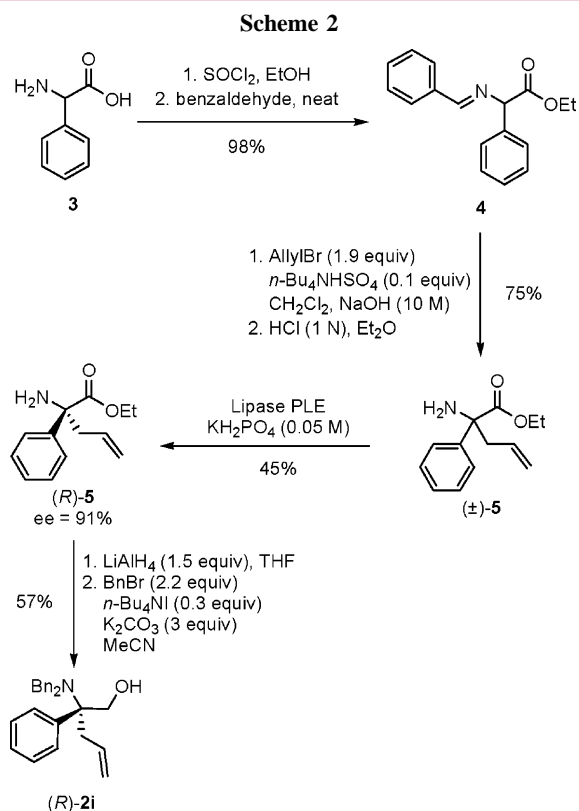
presence of K_2CO_3 (3 equiv) and *n*-tetrabutylammonium iodide (0.3 equiv) in refluxing acetonitrile (Table 1). *N,N*-Dibenzyl- β -amino alcohols **2b** and **2d** are commercially available.

Table 1. Synthesis of *N,N*-Dibenzylamino Alcohols

| entry | R | product (yield) |
|-------|--------------------|-----------------|
| 1 | Ph | 2a (79%) |
| 2 | BnOCH ₂ | 2c (76%) |
| 3 | <i>i</i> -Pr | 2e (81%) |
| 4 | <i>t</i> -Bu | 2f (75%) |
| 5 | | 2g (67%) |
| 6 | | 2h (96%) |

The optically active amino alcohol (*R*)-**2i** was synthesized from the racemic phenylglycine **3**. Esterification with SOCl_2 in ethanol followed by treatment with benzaldehyde furnished the corresponding imine **4**. After alkylation under catalytic phase transfer conditions (AllylBr, *n*- Bu_4NHSO_4 , NaOH, CH_2Cl_2) and hydrolysis of the imino group, the racemic amino ester **5** was obtained in 75% yield. The resulting α -allylphenylglycine ethyl ester **5** was subjected to a kinetic enzymatic resolution by using lipase PLE¹⁹ to provide the (*R*)-enantiomer of **5** in 45% yield and 91% enantiomeric excess.^{20,21} This latter compound was then converted to the corresponding amino alcohol (*R*)-**2i** in 57% yield by reduction with LiAlH_4 , followed by bis-*N*-benzylation with benzyl

bromide (K_2CO_3 , *n*- Bu_4NI , CH_3CN , microwaves irradiation, 120 °C, 3 h) (Scheme 2).



N,N-Dibenzylamino alcohols **2a–i** were treated with trifluoroacetic anhydride (TFAA, 1.5 equiv) and Et_3N (2 equiv) and heated at 100 °C under microwave (MW) irradiation. After 2 h, the reaction mixture was treated with NaOH (3.75 N) to provide the *N,N*-dibenzyl- β -amino alcohols **6a–i** in good yields and with excellent enantiomeric excess (Table 2).²² The (*S*)-absolute configuration of **6a**²³ was determined by comparison of the $[\alpha]_D$ of the (*S*)-*N,N*-2-dibenzylamino-1-phenylethanol synthesized from the commercially available (*S*)-2-amino-1-phenylethanol. The (*R*)-absolute configuration was established for compounds **6b**,²⁴ **6d**,²⁴ and **6e**²⁵ by comparison of the $[\alpha]_D$ reported in the literature. We have to point out that in the case of amino-1,3-diol **2h** the amino-1,2-diol **6h** was obtained in 66% yield indicating that the reaction is very regio- and diastereoselective. Furthermore, almost no loss of chirality was observed in the case of the amino alcohol **6i**, possessing a tertiary hydroxyl group, as it was obtained from **2i** with 63% yield

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(19) Lipase PLE was purchased from Sigma.

Table 2. Rearrangement of *N,N*-Dibenzylamino Alcohols

| entry | substrates | products | yield(ee) |
|-------|------------|----------|-------------------------------------|
| 1 | | | 93%(99%) ^a |
| 2 | | | 97%(95%) ^b |
| 3 | | | 76%(95%) ^b |
| 4 | | | 99% ^c (99%) ^a |
| 5 | | | 88% |
| 6 | | | 99% |
| 7 | | | 97% ^d |
| 8 | | | 66% ^e |
| 9 | | | 63% ^f (88%) ^a |

^a Determined by chiral HPLC (see the Supporting Information for details).^b Determined by application of the modified Mosher method.²⁶ ^c TFAA (4,5 equiv), Et₃N (9 equiv), reflux, 37 h. ^d TFAA (3 equiv), Et₃N (4 equiv). ^e TFAA (1,1 equiv), Et₃N (1,5 equiv). ^f TFAA (2 equiv), Et₃N (3 equiv), rt, 48 h.

and 88% ee [starting from ee (**2i**) 91%]. Even for amino alcohols of type **A** possessing a quaternary center, the rearrangement is enantiospecific as compounds of type **B** were obtained with good enantiomeric excess.

N-Alkyl groups have almost no influence on the rearrangement, as the *N,N*-diallylamino alcohol **7a**²⁷ and the *N,N*-

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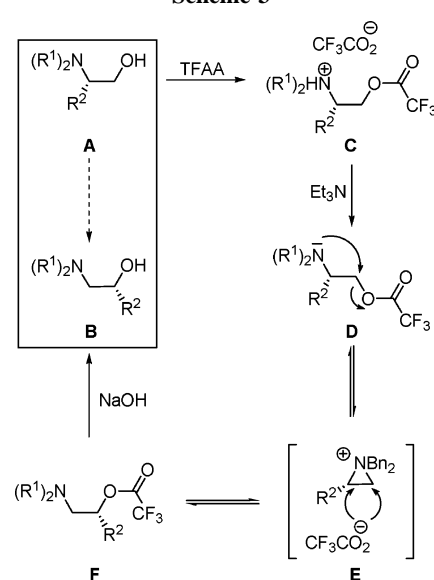
dimethylamino alcohol **7b**²⁸ led to the amino alcohols **8a**²⁹ and **8b**³⁰ in 85% and 72% yield, and in 99% and 95% enantiomeric excess, respectively (Table 3). The (*S*)-configuration of **8a** and **8b** were established by comparison with the [α]_D reported in the literature.^{29,30}

Table 3. Rearrangement of Diallyl- and Dimethylamino Alcohols

| entry | R | yield, % | ee, ^a % (configuration) |
|-------|---------------------|----------|---------------------------------------|
| 1 | allyl (8a) | 85 | 99 (<i>S</i>) |
| 2 | Me (8b) | 72 | 95 (<i>S</i>) |

^a Determined by chiral HPLC (see the Supporting Information for details).

The stereospecificity of this reaction can be rationalized by the intermediacy of an aziridinium ion of type **E**.¹³ This aziridinium is formed from the ammonium trifluoroacetate ester **C**, which is transformed to the aziridinium **E**, via the amino ester **D**, after treatment with Et₃N. As a trifluoroacetate anion is liberated into the reaction media, this anion can attack the more substituted carbon atom of the aziridinium **E**, producing the aminoester **F**. By analogy with the work of Gmeiner,¹⁰ we assume that compounds **D** and **F** are in equilibrium, and that the secondary trifluoroacetate ester **F** is the thermodynamic product. After saponification of **F**, amino alcohols of type **B** are liberated (Scheme 3). Due to the high ee observed in the rearrangement it is unlikely that the reaction proceeds via a planar carbocation intermediate.

Scheme 3

The treatment of 1,2-amino alcohols with TFAA/Et₃N/NaOH is a very powerful procedure that allows the synthesis of β -amino alcohols of type **B** with high yield and enantiomeric excess. Furthermore, the *N,N*-dibenzyl- β -amino alcohols of type **B** can be used to provide chiral 2-amino-1-alkylethanol by hydrogenolysis of benzyl groups.²⁵ Further

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studies with amino alcohols of type **B** as chiral auxiliaries, as well as in the synthesis of natural products, are currently underway.

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Supporting Information Available: General experimental procedure and characterization data of compounds **2a**, **2c**, **2e–i**, **6a–i**, **7a,b**, and **8a,b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.