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Efficient and Highly Selective Synthesis of Enantiopure *cis*- or *trans*-3,4-Disubstituted 1,2,3,4-Tetrahydroisoquinolines

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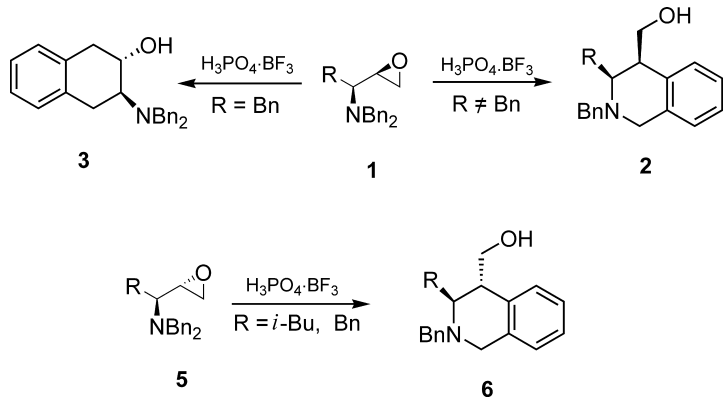
ABSTRACT



An efficient synthesis of enantiopure 3,4-disubstituted 1,2,3,4-tetrahydroisoquinolines, by treatment of readily available (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides with $H_3PO_4{\cdot}BF_3$ complex, under mild reaction conditions, is reported. Both enantiopure diastereoisomers (3*S*,4*S*)- and (3*S*,4*R*)-3-alkyl-4-hydroxymethyl-1,2,3,4-tetrahydroisoquinolines were available starting from the suitable *syn*- or *anti*-aminoepoxide, respectively. A mechanism based on an intramolecular Friedel−Crafts-type reaction has been proposed to explain these results.

Tetrahydroisoquinolines (THIQs) are important organic compounds due to their widespread occurrence in nature[1] and pharmacological applications.[2] Indeed, the use of THIQs as calcium antagonists,[3] antibacterial[4] and antitumor antibiotics,[5] or in cardiovascular diseases[6] has been described. A typical example of a THIQ with therapeutic properties is 1-methyltetrahydroisoquinoline, a simple compound with activity against endogenous Parkinson's disease.[7] Consequently, much attention has been focused toward the

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development of efficient syntheses of a range of substituted tetrahydroisoquinolines.

Traditionally, tetrahydroisoquinolines were synthesized using the ring closure of iminium intermediates via the Pictet−Spengler[8] or Bischler−Napieralski reactions.[9] Other methods are also known for the synthesis of 1-substituted 1,2,3,4-tetrahydroisoquinolines in racemic and enantiopure forms. However, although enantiopure 3- and/or 4-substituted tetrahydroisoquinolines are of considerable interest due to their biological activity and as naturally occurring alkaloids,[10] the reported methods for the synthesis of enantiopure 3,4-disubstituted tetrahydroisoquinolines with high diastereoselectivity are scarce.[11] In addition the reported syntheses present some drawbacks, such as the high number of reaction steps required,[11a,d] the production of some intermediate compound as mixture of diastereoisomers[11d] or the poor generality of the THIQs prepared.[11b,c,e] Taking into account these previously described syntheses, development of new methods for the synthesis of enantiopure 3,4-disubstituted 1,2,3,4-tetrahydroisoquinolines from readily available starting compounds is of considerable interest.

Previously, we reported the synthesis of both enantiopure (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl) epoxides by the total stereoselective reduction of enantiopure α-amino-α′-chloro ketones with $LiAlH_4$ or by a highly stereoselective addition reaction of iodomethyllithium to chiral 2-amino aldehydes, respectively.[12] More recently, we have developed various transformations of the former aminoepoxides to obtain several enantiopure compounds with total or high selectivity.[13] As part of our interest in the development of new synthetic applications of the these enantiopure amino epoxides, our objective in this paper is to describe a novel and efficient transformation of (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl) epoxides into enantiopure *cis*- and *trans*-3,4-disubstituted 1,2,3,4-tetrahydroisoquinolines, respectively. These transformations were promoted by boron trifluoride phosphoric acid complex ($H_3PO_4.BF_3$).

Our first attempt to obtain THIQs were performed using the *syn*-aminoepoxide derived from alanine [(2*R*,1′*S*)-2-(1-dibenzylaminoethyl)epoxide] **1a** as the starting material model. The treatment of **1a** was performed under the reaction conditions shown in Table 1. While no THIQ **2a** was obtained with BF_3·OEt_2, the use of H_3PO_4·BF_3 complex allowed access to **2a** in all cases. Analysis of results shown in Table 1, indicates that the best result was obtained by treatment of a solution of **1a** in CH_2Cl_2 with 3 equivalents of H_3PO_4·BF_3 at room temperature for 6 h. After usual workup, (3*S*,4*S*)-2-benzyl-3-methyl-4-hydroxymethyl 1,2,3,4-tetrahydroiso-quinoline **2a** was obtained with complete selectivity (only one isomer was detected in the crude reaction products) and in high yield (92%).

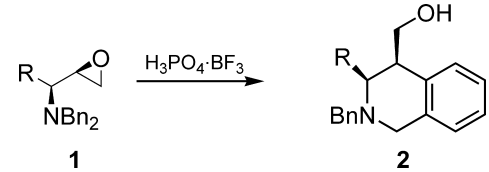
Table 1. Reaction Conditions Tested to Transform the Aminoepoxide **1a** into the Tetrahydroisoquinoline **2a**

entry	solvent	Lewis acid	T (°C)	reaction time (h)	yield (%)[a]
1	CH_2Cl_2	BF_3·OEt_2	rt	6	–
2	CH_2Cl_2	H_3PO_4·BF_3	rt	2	50
3	CH_2Cl_2	H_3PO_4·BF_3	rt	4	78
4	CH_2Cl_2	H_3PO_4·BF_3	rt	6	92
5	CH_2Cl_2	H_3PO_4·BF_3	0	8	77
6	CH_2Cl_2	H_3PO_4·BF_3	reflux	4	80[b]
7	PhMe	H_3PO_4·BF_3	rt	6	81

[a] Isolated yield after column chromatography based on the starting amino epoxide **1a**. [b] Mixture of *cis/trans* diastereoisomers (8.1) was obtained.

To establish the generality and limitations of this transformation, the reaction was also performed utilizing other *syn*-amino epoxides **1b**-**d**. Thus, under the same reaction conditions, enantiopure *cis*-3,4-substituted tetrahydroisoquinolines **2b** and **2c** were obtained from aminoepoxides **1b** and **1c**. In both cases the transformation took place with total regio- and stereoselectivity, as is shown in Scheme 1 and

Scheme 1. Synthesis of Enantiopure *cis*-3,4-Disubstituted 1,2,3,4-Tetrahydroisoquinolines **2**



1 **2**

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Table 2. Synthesis of Enantiopure 3,4-Disubstituted 1,2,3,4-Tetrahydroisoquinolines **2** or **6** and Tetrahydronaphthalene **3**

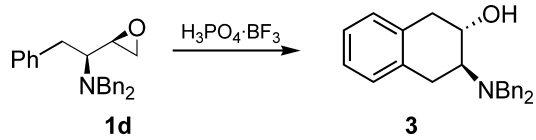
entry	starting compound	R	product	dr[a]	yield (%)[b]
1	**1a**	Me	**2a**	>98:2	90
2	**1b**	*i*-Bu	**2b**	>98:2	96
3	**1c**	$HOCH_2$	**2c**[c]	>98:2	98
4	**1d**	Bn	**3**	>98:2	87
5	**5b**	*i*-Bu	**6b**	90:10 (91:9)	82
6	**5d**	Bn	**6d**	90:10 (92:8)	90

[a] Relation determined by ^{1}H NMR analysis of the crude products; dr of the starting aminoepoxides **5** is given in parentheses. [b] Isolated yield after column chromatography based on the starting amino epoxide **1** or **5**. [c] Compound **2c** was obtained as its *O*-debenzylated derivative.

Table 2. In the case of reaction of **1c**, *O*-deprotection took place under the reaction conditions and the *O*-debenzylated THIQ **2c** was obtained. Remarkably, this Friedel−Crafts-type reaction was mediated by H_3PO_4·BF_3 complex under very mild conditions. To the best of our knowledge, applications in organic synthesis of this complex have scarcely been reported to date. Thus, this transformation is the first example reported, in which H_3PO_4·BF_3 promotes the synthesis of an enantiopure organic compound.

However, when the reaction was performed on the *syn*-aminoepoxide, derived from phenylalanine **1d**, a chiral tetrahydronaphthalene **3** (Scheme 2 and Table 2) instead of

Scheme 2. Synthesis of Enantiopure Tetrahydronaphthalene **3**



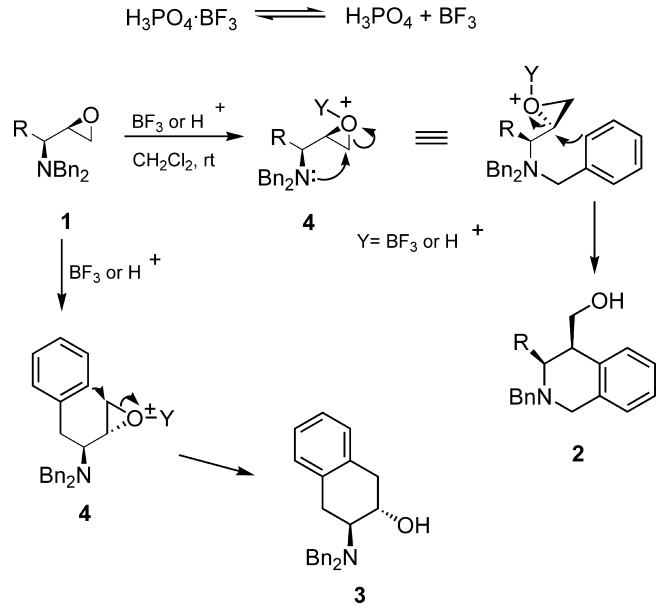
1d **3**

the expected tetrahydroisoquinoline was obtained. The structure and absolute configuration of compound **3** (as depicted in Scheme 2) were established unambiguously by single-crystal X-ray analysis.[14]

The synthesis of products **2** and **3** can be explained by assuming that in both cases an intramolecular Friedel−Crafts-type reaction took place (Scheme 3). Initially, H_3PO_4 and BF_3 were released from the complex. Then, the coordination of the oxygen with the BF_3 or a proton (released in turn from H_3PO_4) weakened the C−O bond generating electrophilic species **4**. The electrophilic aromatic substitution reaction took place by reaction of the more substituted carbon atom of the oxirane ring and the *ortho*-carbon of a phenyl of the dibenzylamino group affording a six-membered

(14) CCDC 732703 contains the supplementary crystallographic data for compound **3**. These data can be obtained free of charge via: www.ccdc.cam.ac.uk/conts/retrieving.html (or the Cambridge Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax (+44)1223−336−033, or e-mail deposit@ccdc.cam.ac.uk).

Scheme 3. Proposed Mechanism to Obtain THIQs **2** or Tetrahydronaphthalene **3**

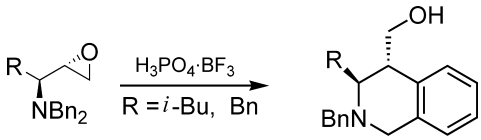


heterocycle. Thus, the regiochemistry of the ring-opening of oxirane could be governed by the size of the generated heterocycle, the formation of six-membered ring being favored over a seven membered-ring. The ring-opening took place with complete inversion of its absolute configuration. After the final hydrolysis of the reaction mixture, the THIQ **2** was obtained with complete selectivity and in nearly quantitative yield (Scheme 3). This proposed stereochemical course is supported by the absolute configuration of the C-4 atom of the obtained THIQ (see below). When the reaction was performed from **1d**, a different intramolecular Friedel−Crafts-type reaction took place. In this case, the electrophilic substitution took place on the ω-phenyl group of the aminoepoxide **1d**, instead of the phenyl group of the dibenzylamino group. In addition, the regiochemistry of the ring-opening of the oxirane also changed and the reaction took place on the less substituted carbon atom instead of the most substituted, since the formation of a six membered-ring (instead of five) could be favored (Scheme 3).

To test this hypothesis and to prove the utility of the method to obtain the other *trans*-diastereoisomer with high enantiomeric purity, we synthesized the *anti*-aminoepoxides **5c** and **5d**, which were subsequently treated with H_3PO_4·BF_3 under the same reaction conditions (CH_2Cl_2, room temperature, 6 h). Thus, from **5d** the corresponding enantiopure tetrahydroisoquinoline **6d** was obtained in high yield and with complete selectivity (Scheme 4 and Table 2). Therefore, the synthesis of THIQ instead of the tetrahydronaphthalene, could demonstrate that the electrophilic substitution reaction took place on the phenyl group closer to the oxirane ring, which in turn depended on the relative configuration of the aminoepoxide derived from phenylalanine.

As was expected, the reaction from *anti*-aminoepoxide **5b**, with only one type of phenyl group, afforded the corre-

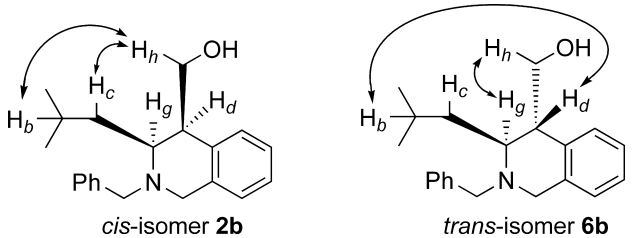
Scheme 4. Synthesis of Enantiopure *trans*-3,4-Disubstituted 1,2,3,4-Tetrahydroisoquinolines **6**



5 **6**

sponding THIQ **6b**, in an enantiopure manner (Scheme 4 and Table 2). Therefore, the two diastereoisomers (*cis* and *trans*) were available in enantiopure form by this method. In addition, no important differences were observed in the yields of THIQ **6b** and in the course of reaction from **5b** in comparison with that described from *syn*-aminoepoxide **1b**.

The total regio- and stereoselectivity of the ring-opening of epoxides was established by ^{1}H and ^{13}C NMR analyses (300 MHz) of the crude reaction products, showing the presence of a single isomer in the crude reaction from amino epoxides **1**. In contrast, starting from amino epoxides **5b** or **5d**, the THIQs **6** were obtained as a diastereoisomeric mixture in the same relationship to that of the starting amino epoxides **5**.[9] Thus, these results constitute indirect evidence of the stereospecificity of the ring-opening of amino epoxides **1** or **5** by the phenyl group being promoted by H_3PO_4•BF_3. In addition the absence of diastereoisomers in the crude reaction constituted evidence of the enantiomeric purity of THIQs **2** and **6** (Figure 1).



cis-isomer **2b** *trans*-isomer **6b**

Figure 1. NOE Effect observed on compounds **2b** and **6b**.

The structures of THIQs **2** and **6** shown in Schemes 1, 3, and 4 were assigned on the basis of the corresponding data of ^{1}H and ^{13}C NMR data and HMBC and HSQC experiments on compounds **2** and **6**. The absolute configurations were established on the basis of NOESY experiments of compounds **2b** and **6b**.[15] NOESY experiments on compound **2b** shown a *cis* arrangement of $H_{b,c}$ and H_h protons. Moreover, the NOE interactions of H_g with H_h, and H_b with H_d, in the case of the *trans*-isomer **6b** would also support the configuration of compound **2b** due to the absence of NOE interactions between $H_{b,c}$ and H_h in compound **6b**. The absolute configuration of the other compounds **2** and **6** was established based on their corresponding spectral data and by analogy to the results of the NOESY experiments of THIQs **2b** and **6b**.

In conclusion, a H_3PO_4•BF_3-mediated synthesis of enantiopure *cis*- or *trans*-3,4-disubstituted 1,2,3,4-tetrahydroisoquinolines, under mild reaction conditions from the readily available (2*R*,1′*S*)- and (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **1** or **5** is reported. This protocol constitutes the first example in which H_3PO_4•BF_3 is reported to promote the synthesis of enantiopure compounds. A mechanism, via an intramolecular Friedel−Crafts type reaction, is proposed to explain the synthesis of enantiopure 3,4-disubstituted THIQ, which are not trivial to access in enantiopure form. Studies directed toward fully delineating the factors involved in these transformations, the generality of the reaction and the development of other synthetic applications of the H_3PO_4•BF_3 complex are currently under investigation in our laboratory.

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Supporting Information Available: General procedure, CIF for compound **3**, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for THIQs **2** and **6**, and tetrahydronaphthalene **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Since the stereochemistry of the *CHN* carbon is fixed in the starting material, the determination of relative congifuration by nOe effect has also been utilised as a proof for the elucidation of the absolute stereochemistry of compounds **2** and **6**.