SYNTHESIS OF CHIRAL AMINES USING TERPENYL SPIROBORATE ESTERS AS CATALYSTS

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Abstract: Spiroborate ester received from (1*R*,2*S*,3*R*,5*R*)-(–)-3-amino-6,6-dimethyl-2-hydroxybicyclo[3.1.1.]heptane and ethylene glycol was employed as catalysts in borane reduction of acetophenone and dihydroisoquinoline derived imines giving the corresponding amines in high yields and good enantioselectivity (up to 93% ee). The results were compared with corresponding oxazaborolidines. The influence of the substituent size on nitrogen atom in imine molecule on enantioselectivity of its reduction was examined.

Keywords: spiroborate ester, imine, amine, borane, asymmetric reduction

Introduction

Pure chiral amines play recently a key role in many branches of human life, because they are widely applied as starting materials for the total syntheses of natural products or drugs. Moreover, a large number of them exhibit a wide range of bioactivities by acting on the central nervous system, decreasing a blood pressure, and smooth muscle relaxation (e.g. salsolidine [1]). On the other hand, optically active amines and their derivatives have been utilized successfully in a widespread modern asymmetric syntheses as chiral catalysts and building blocks.

Several strategies for the synthesis of optically active amines have been reported in the literature. The most popular are: the asymmetric reduction of imines via enantioselective hydrogenation in the presence of metal complexes [2], hydrosilylation [3], borane reduction catalyzed with chiral oxazaborolidines [4]. The asymmetric reduction of oxime ethers gives also quite good results [5]. However, there is still a wide requirement to expand a better approaches. In this work, we present an alternative method based on the enantioselective

borane reduction of cyclic and acyclic imines using chiral terpenyl spiroborate esters as catalysts. Our earlier studies showed that spiroborate esters can be successfully utilized as catalysts in enantioselective borane reduction of ketones and their derivatives [6] giving the corresponding alcohols with very good yields and enantiomeric excesses. On the other hand, this class of compounds is much more stable towards moisture and air than other boron catalysts because of the unique structure containing a characteristic O_3BN framework, where B-N bond is a coordinate bond.

In this presentation, we show optically active spiroborate ester (**1**) (Figure 1.) derived from (1*R*,2*S*,3*R*,5*R*)-(–)-3-amino-6,6-dimethyl-2-hydroxybicyclo[3.1.1.]heptane and ethylene glycol used as catalyst in borane reduction of acyclic and cyclic prochiral imines in comparison with the corresponding oxazaborolidines.

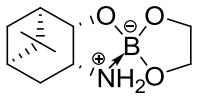

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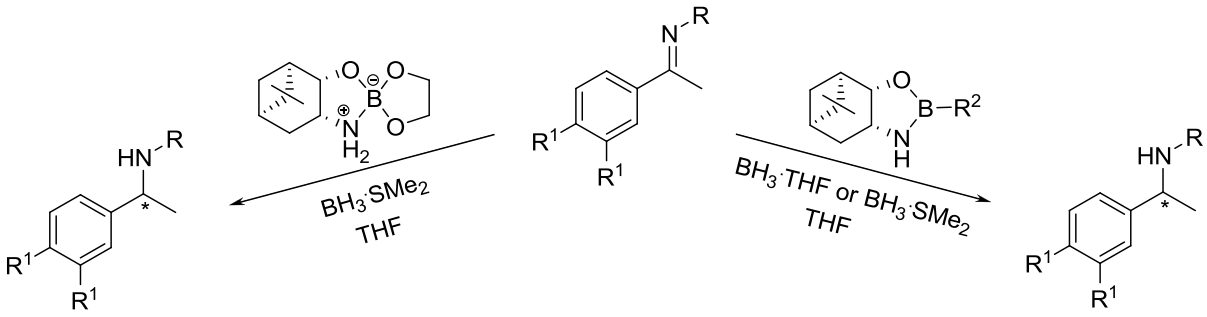
Figure 1.

Results and discussion

It is well-known that the enantioselectivity in the reduction of C=N bonds depends not only on the chirality's transfer agent but also on the *E*/*Z* isomeric purity. Therefore imines applied in our further studies must have been obtained as a single stereoisomer. To show the catalytic ability of our spiroborate ester **1**, we synthesized (*E*)-*N*-(1-phenyl-ethylidene)methanamine (**2**), (*E*)-*N*-(1-phenylethylidene)aniline (**3**), 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**4**), and 1-phenylethanimine (**5**). *N*-(1-phenylethylidene)-methanamine (**2**) and *N*-(1-phenylethylidene)aniline (**3**) were prepared from acetophenone in the reaction with appropriate amines (methylamine and aniline, respectively) in the presence of titanium(IV) chloride for **2** [7] and molecular sieves for **3** [8]. Isomeric purity was carefully assessed by NMR analysis and afforded 93% and >99% of (*E*)-isomer for **2** and **3** respectively. 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**4**) was obtained from 2-(3,4-dimethoxyphenyl)ethanamine in two-steps reaction [9]. Firstly, amine was converted into acetic amide, and then undergone cyclodehydration in Bischler-Napieralski reaction giving **4**.

The last imine **5** was generated in situ from 1,1,1-trimethyl-*N*-(1-phenylethylidene)silanamine in the presence of trialkyl borane as complexing agent to keep only one isomer of **5**. To obtain 1,1,1-trimethyl-*N*-(1-phenylethylidene)silanamine benzonitrile was transformed in reaction with methyllithium and then chlorotrimethylsilane [10].

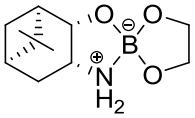
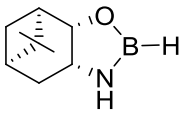
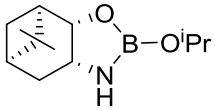
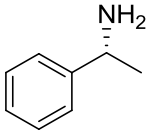
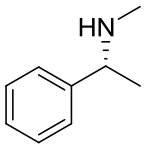
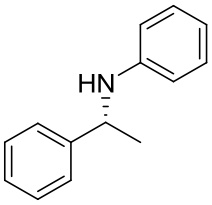
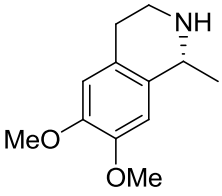
Imines **2-5** were reduced with borane in the presence of spiroborate ester **1** (Scheme 1). The reaction run in tetrahydrofuran at room temperature afforded mixtures of the corresponding amines of 11 – 93% ee in 71 – 90% yield (Table 1). The products were readily separated by flash chromatography. Several types of borane source were examined, but the best results were achieved in case of using borane dimethyl sulfide adduct. The catalytic amount of **1** also didn't give the satisfactory result, therefore all reductions were carried out with 1 molar equivalent of **1**.



Scheme 1.

Imines **3-5** were also reduced in the presence of 1 molar equivalent of oxazaborolidines derived from (1*R*,2*S*,3*R*,5*R*)-(–)-3-amino-6,6-dimethyl-2-hydroxy-bicyclo[3.1.1.]heptane to compare the results with spiroborate ester **1** (Scheme 1., Table 1.). It is noticeable that in all cases spiroborate ester **1** gave significantly better results in enantioselectivity of the imine reductions than oxazaborolidines. Only for (*R*)-*N*-methyl-1-phenylethanamine obtained enantiomeric excess was identical (50 %). The configuration of final amines is determined by chiral amino alcohol moiety in catalyst, thus both spiroborate ester **1** and oxazaborolidines gave (*R*)-amines. The influence of the substituent size on nitrogen atom in imine molecule on enantioselectivity of studied reduction was also noticeable. Except cyclic **4** that gave the best results (by using spiroborate ester **1)** from all imines (71 % of yield and 93 % ee), we observed that the smaller substituent occured the better results in enantioselectivity were received.

Table 1. Obtained amines in borane reduction of imines **2**-**5** catalyzed by spiroborate ester **1** and the corresponding oxazaborolidines.

Catalyst						
Amine	**Yield, %**	**Ee, %[a)]**	**Yield, %**	**Ee, %[a)]**	**Yield, %**	**Ee, %[a)]**
 **(5)[b)]**	71	73	---	---	---	---
 **(2)[b)]**	84	50	77	50	---	---
 **(3)[b)]**	90	11	29	3.1	93	2.2
 **(4)[b)]**	71	93	---	---	56	0

[a)] Determined by HPLC analysis of TFA derivatives on a chiral column, Daicel Chiralcel OD-H, 250 × 4.6 mm, 5 μm. [b)] The starting imine.

Conclusions

Spiroborate ester **1** was tested in borane reduction of prochiral cyclic and acyclic imines, and in all cases exhibited better catalytic ability than the corresponding oxazaborolidines. The best results were obtained for (*R*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (71 % of yield and 93 % ee). For the reduction of acetophenone derived imines, the substituent size on nitrogen atom in imine molecule was the dominant factor affecting the enantioselective reduction by the spiroborate catalyst.

The described spiroborate ester **1** is a highly efficient and stable catalyst for the asymmetric reduction of various prochiral imines and represents an interesting alternative to currently used methods for the preparation of optically active amines.

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