N-Substituent effects of camphor-derived β-amino alcohols on the stereoselectivity of the oxazaborolidine-catalyzed borane reduction of acetophenone

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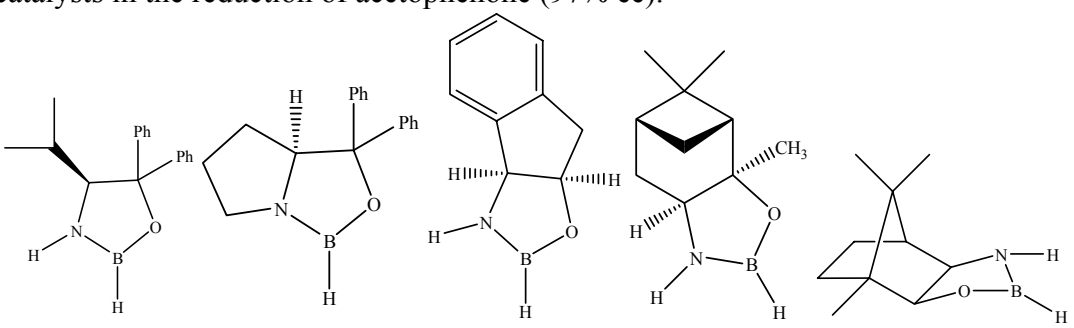
Abstract

Structure-stereoselectivity relationship in modifying chiral ligands usually sheds light on the ligand structure with better stereoselectivity. The camphor-derived β-amino alcohol **5a** with a primary amino group [R = H (84% ee)] carries out better ee in the oxazaborolidine-catalyzed borane reduction of acetophenone than the ones **5b**~**e** with secondary amino groups [R = *n*-Bu (11% ee), *i*-Bu (19% ee), *i*-Pr (13% ee), benzyl (9% ee)].

Keywords: Asymmetric synthesis, borane reduction, amino alcohol

Introduction

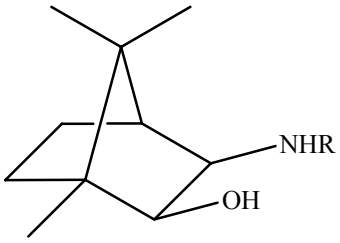
Enantioselective reduction of prochiral ketones to form chiral secondary alcohols is one of important issues in organic synthesis.[1] Oxazaborolidine-catalyzed asymmetric borane reduction of prochiral ketones has been one of important methods to carry out this transformation.[2-11] Among the oxazaborolidine catalysts, **1**[3], **2**[2a], **3**[2a], **4**[2a], and **5**[4] successfully reduced acetophenone in 95%, 97%, 86%, 94%, and 79% ee, respectively. It was found that bulky substituents on the carbinol carbon of these β-amino alcohols performed better enantioselective reduction of acetophenone[2a] and **2** with a secondary amine of β-amino alcohol is one of the most efficient chiral catalysts in the reduction of acetophenone (97% ee).[2a]



A chiral ligand provides chiral environment in the catalytic asymmetric synthesis, so studies concerning the relationship between the ligand structure and asymmetric induction can be used to develop more efficient catalysts. In this article, we use acetophenone as a model substrate of prochiral ketones and study *N*-substituent effects of camphor-derived β-amino alcohols on the stereoselectivity of the oxazaborolidine- catalyzed borane reduction.

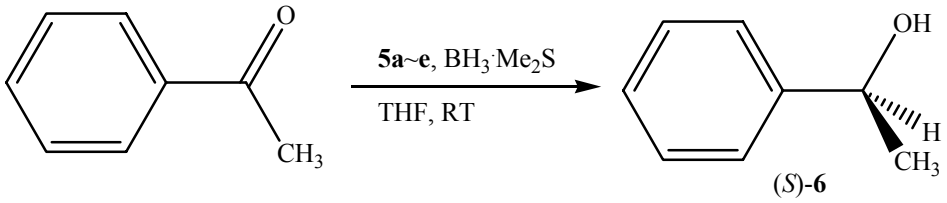
Results and Discussion

The oxazaborolidine-catalyzed borane reduction of acetophenone was carried out according to the known procedure,[4,5] whereas, 10% of oxazaborolidine catalyst was prepared *in situ* by mixing 1 equivalent of camphor-derived β-amino alcohol (**5a**, **5b**, **5c**, **5d**, or **5e**) with 8.5 equivalent of $BH_3 \cdot Me_2S$ at room temperature for one hour. The following oxazaborolidine-catalyzed borane reduction of acetophenone was carried out at room temperature for 3 hours. By following this method, the camphor-derived β-amino alcohol **5a**, which is a primary amine, led the reduction of acetophenone to (*S*)-**6** with 84% ee, which is consistent with the literature result of 79% ee.[4] When the camphor-derived β-amino alcohol (**5b**, **5c**, **5d**, or **5e**) with a secondary amine group was applied to the oxazaborolidine-catalyzed borane reduction of acetophenone, ee values of the product (*S*)-**6** dramatically decrease in spite of high yield. (Table 1)



5a : R = H
5b : R = *n*-Bu
5c : R = *i*-Bu
5d : R = *i*-Pr
5e : R = Benzyl

Table 1. Oxazaborolidine-catalyzed borane reduction of acetophenone



(*S*)-**6**

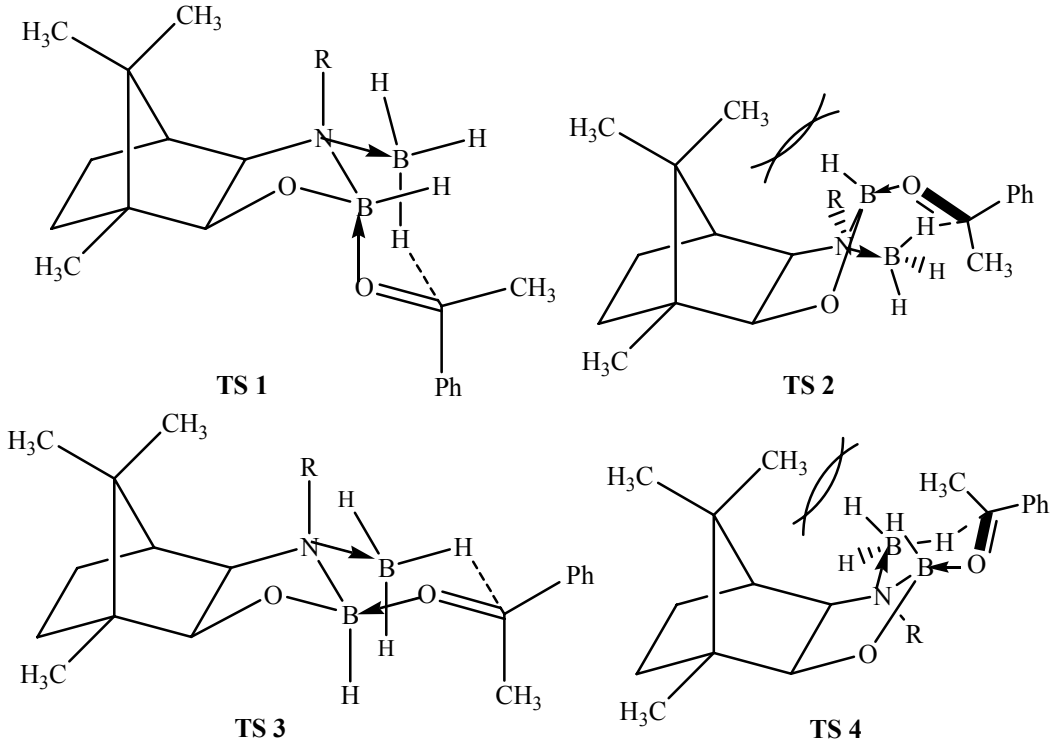
Chiral ligand	R on chiral ligand	Yield (%)	ee (%)[a] of product
5a	H	97	84
5b	*n*-Bu	90	11
5c	*i*-Bu	96	19
5d	*i*-Pr	97	13
5e	Benzyl	86	9

[a].The major product is (*S*)-**6**. The ee was determined by HPLC analysis with a Chiralcel OD-RH column and the configuration was assigned based on the result of the $BH_3 \cdot Me_2S$/**5a**-catalyzed borane reduction of acetophenone, HPLC analysis, and the literature.[4]

According to the Corey proposed mechanism,[2a] the oxazaborolidine-catalyzed borane reduction involving camphor-derived β-amino alcohol (**5a**~**e**) was expected to go through **TS1**, **TS2**, **TS3**, or **TS4**, where the first equivalent of BH_3 is consumed to produce the oxazaborolidine catalyst after reaction with the corresponding amino alcohol. This complex serves as a Lewis acid to activate acetophenone. The second equivalent of BH_3 works as a hydride donor to reduce acetophenone. The **TS1** and **TS2** have oxazaborolidine ring cis fusion with formation of six-member ring, while trans fusion was found in the **TS3** and **TS4**. Both **TS2** and **TS4** suffer from steric repulsion between B-H and methyl group on the camphor skeleton. However, cis fusion has less angle strain than trans fusion and thus, **TS1** is more stable than **TS3** and the product (*S*)-**6**, which results from **TS1**, is expected to be the major. That is consistent with the experimental results.

The presence of large R group in the camphor-derived β-amino alcohol results in more steric repulsion between the R group and the camphor skeleton in **TS1** and **TS3**. In addition, **TS3** and **TS4** suffer an additional trans-fusion angle strain and **TS4** is further destabilized by steric repulsion between B-H and methyl group of the camphor skeleton. Thus, **TS1** is expected to be the most stable among **TS1**, **TS3**, and **TS4**. Even though there is very little steric repulsion between the R group and the camphor skeleton in **TS2**, there is also a steric repulsion between B-H and methyl group on the camphor skeleton. According to the experimental results, when R group in the camphor-derived β-amino alcohol is larger, it is likely that the oxazaborolidine-catalyzed borane reduction follows the route via **TS1** only a little bit faster than other routes via **TS2**, **TS3**, and **TS4** because of increasing repulsive destabilization between the R group and the camphor skeleton in **TS1**, resulting in decrease of ee values.

Finally, based on our experiments and the above discussion we conclude that *N*-alkyl substituents in the camphor-derived β-amino alcohols decrease stereoselectivity of the oxazaborolidine-catalyzed borane reduction of acetophenone.



Experimental Section

General Procedures. Reagents were used as they were obtained from commercial sources. Chiral β-amino alcohols **5a**~**e** were prepared according to the literature.[12]

General procedure for the oxazaborolidine-catalyzed borane reduction of acetophenone
The camphor-derived β-amino alcohol **5** (0.2 mmol) was dissolved in 3 mL of dry THF in a two-necked flask fitted with a septum in a nitrogen atmosphere. The 0.3 mmol of 2 M BH_3 ·Me_2S in THF was added to this solution and the mixture was stirred for one hour at room temperature. Then another 1.4 mmol of 2 M BH_3 ·Me_2S in THF was added to this solution and the reaction mixture was stirred for another 10 minutes. Acetophenone (0.240 g, 2 mmol) in 4 mL THF was added dropwise to this solution. After 3 hours of reaction, the excess of borane was destroyed by dropwise addition of cold 0.1 M HCl(aq). The reaction mixture was extracted with ether. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography with silica gel using a mixture of hexane and ethyl acetate as the eluent to get alcohol (*S*)-**6**. The degree of conversion was determined by proton NMR

spectroscopy. The enantiomeric excesses was determined by HPLC analysis with a Chiralcel OD-RH column, mobile phase: 40% acetonitrile in H_2O, UV detector: 257 nm, and flow rate: 0.3 ml/min. The retention time for (*R*)-**6** and (*S*)-**6** are 11.67 and 12.55 min, respectively.

Acknowledgements

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