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Structural Effects of the Oxazaborolidine Derived from L-Threonine in the Reduction of (Trifluoroacetyl)biphenyl Derivatives with Catecholborane

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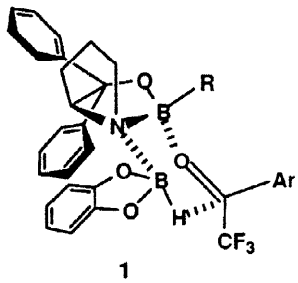
Abstract

The reduction of (trifluoroacetyl)biphenyl derivatives with catecholborane as a stoichiometric reductant in the presence of the oxazaborolidine catalyst derived from L-threonine in dichloromethane-toluene at -90 °C proceeds to give the corresponding alcohols in high yields with high enantioselectivity. The distinctive feature of this oxazaborolidine exists in the five-membered ring covered with the *t*-butyldimethylsiloxy group.

Keywords: reduction; oxazaborolidine; L-threonine; (trifluoroacetyl)biphenyl derivatives

The reduction of prochiral ketones to chiral secondary alcohols using a catalytic amount of oxazaborolidine and borane as a stoichiometric reductant [1] provides a practical route to many useful chiral synthons for asymmetric organic synthesis. The methods developed by Itsuno et al., [2] and by Corey et al., [3] of oxazaborolidine-catalyzed reduction have been studied extensively [4]. Fluorine-containing optically active alcohols are recently studied in connection with ferroelectric liquid crystals [5] and tools for metabolic studies [6]. However, it is difficult to produce optically active alcohols with satisfactory enantiomeric purity by reduction of trifluoromethyl ketone using oxazaborolidine due to the electronic factor of fluorines. Using oxazaborolidine **4** derived from L-proline the reduction of trifluoroacetylmesitylene or 9-anthryl trifluoromethyl ketone possessing respectively a mesityl or an anthryl group, a sterically bulky substituent, was reported to give the corresponding chiral alcohol in high enantioselectivity [7]. We have previously reported that the reductions of 1,2-diimine [8], and α-imino ketone [9] using oxazaborolidine **5**



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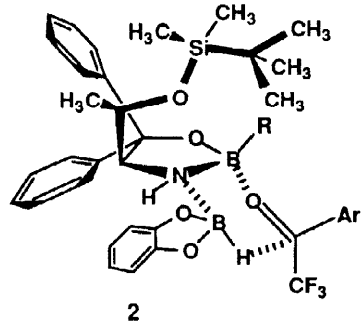

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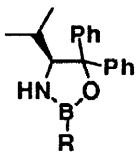
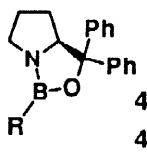
derived from L-threonine provide chiral 1,2-diphenylethylendiamine and 2-amino-1,2-diarylethanol in high enantioselectivity. By the MM2 calculation, the distinctive feature of oxazaborolidine **5** is considered to exist in the *t*-butyldimethylsiloxy group covering the oxazaborolidine ring as a roof, and this group was found to have marked influence on the enantioselectivity of the present reduction as shown in the transition state **2**, which should be compared with that of **1**. In this paper the oxazaborolidine **5** derived from L-threonine is reported to be superior to oxazaborolidines **3** and **4** in terms of the enantioselectivity in the reduction of (trifluoroacetyl)biphenyl derivatives **6a~6e** which are potentially good precursors for the preparation of ferroelectric liquid crystals [5].

Initial examination into the reduction of simple acetophenone using the oxazaborolodine **5** (R = H) and BH_3•THF indicated that the reduced (*R*)-1-phenylethanol was obtained with 98% ee (with 100 mol% of **5**) to 95% ee (with 10 mol% of **5**), which is comparable to those obtained by Itsuno [2] and Corey [3]. Encouraged with these observations, enantioselective reduction of 4-methoxy-4'-(trifluoroacetyl)biphenyl **6b** with catecholborane using the oxazaborolidines **3**, **4** and **5** was examined, and the results are shown in Table 1.



3a R = Me
3b R = ^{n}Bu



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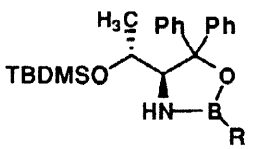
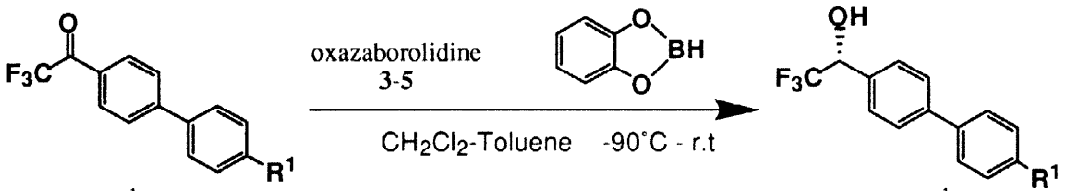


5a R = Me
5b R = ^{n}Bu
5c R = ^{i}Bu

Table 1
Oxazaborolidine catalyzed reduction of 4-methoxy-4'-(trifluoroacetyl)biphenyl **6b**.

Entry	Oxazaborolidine	R	Mol%	Time (h)[a]	Yield (%)[b]	% ee[c,d]
1	**3a**	Me	100	24	95	80
2	**3b**	^{n}Bu	100	24	93	72
3	**4a**	Me	100	24	87	80
4	**4b**	^{n}Bu	100	24	93	84
5	**5a**	Me	100	18	95	90
6	**5b**	^{n}Bu	100	18	81	90
7	**5c**	^{i}Bu	100	18	81	72
8	**3a**	Me	10	24	73	72
9	**3b**	^{n}Bu	10	24	90	70
10	**4a**	Me	10	24	84	76
11	**4b**	^{n}Bu	10	24	70	86
12	**5a**	Me	10	24	73	86
13	**5b**	^{n}Bu	10	24	78	80

a) Reaction time is disappearance of starting material. b) Isolated by preparative TLC. c) The enantiomeric excess of the products was determined by HPLC using a chiral stationary column (Daicel OJ). d) The absolute configuration of optically active alcohol **7b** obtained by the present reduction was *R*.



6a R^1 = OH
6b R^1 = OMe
6c R^1 = OTs
6d R^1 = OTBDMS
6e R^1 = Br

7a R^1 = OH
7b R^1 = OMe
7c R^1 = OTs
7d R^1 = OTBDMS
7e R^1 = Br

The reduction of trifluoromethyl ketone **6b** with 2 eq. of catecholborane in the presence of stoichiometric amounts of the oxazoborolidines **3a** and **3b** showed moderate enantiomeric discrimination (entries 1, 2), because the *iso*-propyl group on the five-membered ring is less effective in terms of steric bulk than the *t*-butyldimethylsiloxyethyl counterpart in the oxazaborolidine **5**. The reduction with oxazaborolidines **4a and 4b** using a similar procedure gave the alcohol **7b** with slightly improved enantiomeric purity (entries 3, 4). On the other hand, the reduction of **6b** with 2 eq. of catecholborane in the presence of the catalysts **5a** and **5b** (1 eq.) showed the best discrimination,[1] in which the reduction proceeded faster than in the cases with **3a**, **3b**, **4c** and **4b** (entries 5, 6). However, the increase in bulkiness of the substituent on boron was seen to decrease enantioselectivity; *e. g.*, in the case of the oxazaborolidine **5c**, low enantioselectivity may be due to the repulsion between the *t*-butyldimethylsiloxy group and the *iso*-butyl group on boron (entry 7). Similarly, in the presence of a catalytic amount (10 mol%) of oxazaborolidine **5**, the reduction of 4-methoxy-4'-(trifluoroacetyl)biphenyl **6b** showed higher enantioselectivity than those attained using **3** and **4** (entries 8, 10, 12).

The reduction of (trifluoroacetyl)biphenyl derivatives **6a~6e** with various *para*-substituents in the presence of oxazaborolidine **5a** was next investigated as shown in Table 2. (Trifluoroacetyl)biphenyl derivative **6a** possessing a hydroxy group gave the corresponding alcohols **7a** in 90% yield with 90% ee (entry 1). The bulkiness of the *para*-substituent showed no influence on the enantioselectivity (entries 1~4). Even bulky substituents such as the *t*-butyldimethylsiloxy group did not show any change in the enantiomeric excess (entries 3, 7). The reduction of (trifluoroacetyl)biphenyl derivatives proceeded to give the corresponding alcohols with moderate discrimination in the presence of a catalytic amount of the oxazaborolidine **5a** (entries 5~8). Furthermore, for the preparation of enantiomerically pure alcohols, a single recrystallization increased the enantiomeric purity up to 100% ee. The absolute configurations of all optically active alcohols were determined to be *R* by comparison with the authentic samples [10].

Table 2
Reduction of various (trifluoroacetyl)biphenyl derivatives in the presence of oxazaborolidine 5a.

Entry	R^1	Mol%	Time (h)	Yield (%)[a]	% ee[b]
1	OH	100	24	90	90
2	OTs	100	20	88	88
3	OTBDMS	100	18	90	90[c]
4	Br	100	20	82	90
5	OH	10	38	83	86
6	OTs	10	24	86	86
7	OTBDMS	10	38	80	86
8	Br	10	35	82	84

a) Isolated on preparative TLC. b) Determined by HPLC (Merck Hibar column) analysis of the corresponding (*R*)-MTPA esters.
c) Determined by HPLC using a chiral stationary column (Daicel OJ).

The increased enantioselectivity of the present reduction is most reasonably explained in terms of the transition state **2**, in which the *tert*-butyldimethylsiloxy group occupies the top

[1]A typical experimental procedure using oxazaborolidine **5**: To a solution of the (trifluoroacetyl)biphenyl derivative **6b** (28 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) was added a solution of the catalyst **5a** (R^1 = Me, 100 mol%) in CH_2Cl_2 (1 mL) under an argon atmosphere, and the resulting solution was cooled to -90 °C. To it was added a solution of catecholborane (1.11 ml, 0.20 mmol, 0.18 *N* in toluene) dropwise at -90 °C for 2 h. After being stirred at -90 °C~r.t for 24 h, the reaction mixture was quenched with aq. $NaHCO_3$. Extraction of the entire mixture with ethyl acetate (10 ml x 3) followed by drying with Na_2SO_4 and concentration of the combined extracts gave an oil, which was purified on preparative TLC to give 2,2,2-trifluoro-1-(4-methoxy-4'-biphenylyl)ethanol **7b** (95%). The ratio of the enantiomers was determined to be *R* : *S* = 95 : 5 (retention time : 44 min, 60 min, flow 0.5 ml / min) by HPLC (eluent: nC_6H_{14} : *i*PrOH = 2 : 1) using a chiral stationary column (Daicel OJ).

side of the oxazaborolidine to make the reduction from the *si*-face of the carbonyl highly favorable due to the steric repulsion between the trifluoromethyl and the TBDMSO groups. Such a subtle discrimination between the trifluoromethyl and aryl groups has a good precedent in the (-)-DIP-chloride mediated reduction of 2,2,2-trifluoroacetophenone [11], in which the trifluoromethyl group behaves as a bulkier substituent than the benzene ring. Moreover, the coordination of an oxazaborolidine to the carbonyl oxygen of a trifluoromethyl ketone is reported to take place from the *anti*-side of the trifluoromethyl group due to the electronic repulsion [7]. The ability of the TBDMSO group of the present oxazaborolidine **5** to shield the top face of the oxazaborolidine ring is to be compared with that of the *iso*-propyl group of **3** or the proline ring of **4**, reflecting the increased enantiofacial discrimination.

In conclusion, (trifluoroacetyl)biphenyl derivatives were reduced with catecholborane as a stoichiometric reductant in the presence of the oxazaborolidine **5** derived from L-threonine to give chiral trifluoromethyl carbinols with high enantioselectivity, where the oxazaborolidine **5** was found to be superior to **3** and **4**.

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