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Influences of Electronic Effects and Anions on the Enantioselectivity in the Oxazaborolidine-Catalyzed Asymmetric Borane Reduction of Ketones

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The influence of electronic effects on the enantioselectivity of the oxazaborolidine-catalyzed asymmetric borane reduction of ketones has been observed and investigated with use of para-substituted acetophenones and propiophenones with a variety of functional groups and *B*-unsubstituted and *B*-methoxyoxazaborolidines derived from (*S*)-2-(diphenylhydroxymethyl)-pyrrolidine with borane and trimethyl borate as catalysts in toluene and THF. The results indicate that Hammett linear free energy electronic effects on the enantioselectivity in the asymmetric reduction were observed and rationalized. Tuning electronic effects of the catalyst can improve the enantioselectivity in the reduction. Another interesting finding to be noted is that anions heavily affect the enantioselectivity, especially for the *B*-methoxy catalyst, because of their coordination with the boron atom in the catalysts.

Introduction

Since Itsuno et al. discovered that the reduction of ketones by borane is strongly catalyzed by a chiral oxazaborolidine,[1] the enantioselective 1,3,2-oxazaborolidine-catalyzed borane reduction of prochiral ketones to chiral secondary alcohols has become an important reaction in asymmetric syntheses, which has been widely used in the preparation of various secondary alcohols during the past decade.[2] Numerous new efficient oxazaborolidines as catalysts have been reported and a plethora of applications have appeared until now. In comparison with the numerous attempts to search for new catalysts and to improve the enantioselectivity, several papers have concentrated on the mechanistic investigation of the catalytic asymmetric reduction reaction,[3,4] and some papers have paid attention to the factors which affect the enantioselectivity in the asymmetric reduction, such as the structure,[2,3,5] stability [3a,6] (including dimerization) and the amount of the catalyst,[3a,6a,7] the borane source[8] and the borane amount,[3a,7c] the order and rate of the addition of a ketone or borane into the reductive system,[2d,7c] the reduction temperature,[7c,9] solvent,[6a,7c,8c] additive,[9g,10] secondary reduction,[10a,11] and stabilizer in borane,[12] etc. Although a few papers have considered the influence of

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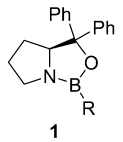
SCHEME 1



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a: R = H, **b**: R = Me, **c**: R=Ph, **d**: R = MeO

the electronic effects of ketones and catalysts on the enantioselectivity, all of the results indicated that no obvious influence has been observed in the asymmetric reduction[5a,6a,13] except for the observation of Corey et al.[13c] Very recently we investigated the temperature-dependent enantioselectivity of the asymmetric reduction and found that the noncatalytic reduction is an important factor for the enantioselectivity in asymmetric reductions.[7c] We also observed obvious influences of electronic effects and anions on the enantioselectivity in the asymmetric reduction. Herein, we wish to report our observations and rationales on these influences.

The factors governing enantioselectivity in the catalytic asymmetric reaction are usually interpreted in steric terms,[14] affected by the temperature and solvent, etc.[6a,7c,8c,9] Electronic effects have been reported to control the enantioselectivity recently. In reported studies on the electronic effects on the enantioselectivity,[15,16] the underlying reasons are poorly understood in most of the cases. It should be very useful to understand all factors that affect the enantioselectivity in this asymmetric reduction in detail. And it will be helpful to apply the reduction effectively in the preparation of secondary alcohols with a variety of functional groups.

Results and Discussion

Many chiral 1,3,2-oxazaborolidines derived from chiral vicinal amino alcohols have been prepared and evaluated in the asymmetric borane reduction of ketones, and some of the best enantioselectivities have been achieved with them.[2] Among them, (*S*)-2-substituted 4,4-diphenyl-3,1,2-oxazaboro[3.3.0]octanes **1**, derived from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine, with several different substituents (such as H for **1a**, Me for **1b**, Ph for **1c**, and MeO for **1d**, as representatives, Scheme 1) on the B atom, have been proven to be effective catalysts in the asymmetric reduction with excellent yields and enantioselectivities for a wide variety of ketones.[2,3,7] However, **1a** and **1b** are not entirely satisfactory, particularly for large-scale productions, owing to the necessity of relatively expensive reagents, such as trimethyl boroxin or methylboronic acid, for their preparation[3] and the necessity of the preparation before catalytic reactions in order to get excellent and stable enantioselectivity. Furthermore, the catalyst **1a** is air and moisture sensitive.[3] The catalyst **1d**, modified by the catalyst **1b**, was developed and applied successfully in the enantioselective reduction.[7] The advantage of the catalyst **1d** is that it can be prepared from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine and inexpensive trimethyl borate in situ, and used directly without any further separation and purification.[7]

After the investigation on the effect of the temperature on the enantioselectivity, it seems that the catalyst **1d** is an effective, convenient, and practical catalyst for the asymmetric borane reduction of ketones. We wish to extend the utility of the robust catalyst **1d** for the preparation of secondary alcohols with a variety of functional groups. However, when we reduced the acetophenones with electron-withdrawing groups in the para position under our optimal reductive conditions, lower enantioselectivities were obtained. The results prompt us to consider the influence of the electronic effects of the substituents in the ketones on the enantioselectivity in the asymmetric reaction. To investigate the influence, two series of ketones, para-substituted acetophenones and propiophenones, were purchased or prepared. The steric surroundings of the carbonyl groups of the ketones had to be kept as constant as possible to obtain reliable data concerning the electronic effect. Acetophenones and propiophenones have been electronically modified simply by variation of the substituent attached to the phenyl moiety on their para positions. So that changes in the steric situation at the carbonyl group are negligible, they were reduced by using the same reductive conditions, our optimal standard conditions, with the oxazaborolidine **1d** as a catalyst first. In our asymmetric reduction, the catalyst **1d** was prepared in situ through addition of trimethyl borate into a solution of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine in toluene. After the resulting mixture was stirred for 2 h and borane was added, a ketone was added dropwise at 25 °C. After the reaction mixture was quenched with methanol and the usual workup, the enantiomeric excess value was determined by using a chiral column on HPLC. The results are presented in Table 1, columns 5 and 6. Obvious electronic effects on the enantioselectivity were observed.

To further observe the generality of the influence of the electronic effects on the enantioselectivity in the asymmetric borane reduction, both of these series of ketones were further reduced with catalyst **1a** under the same conditions. In our asymmetric reduction, catalyst **1a** (0.1 equiv to ketone) was prepared first through addition of borane−dimethyl sulfide complexes (1.5 equiv) into a solution of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine in toluene or THF. After the resulting mixture was stirred for 14 h at 45 °C, the mixture was cooled to 25 °C and to the borane−dimethyl sulfide complexes (1.0 equiv to ketone) was added a ketone dropwise over 1 h at 25

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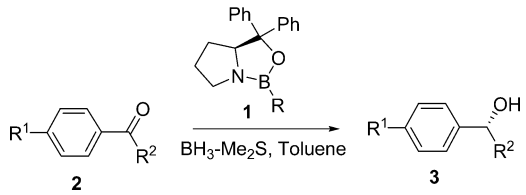
TABLE 1. Oxazaborolidine-Catalyzed Asymmetric Borane Reduction of Ketones



				cat. **1d** in PhMe		cat. **1a** in PhMe		cat. **1a** in THF	
entry	ketone	R^1	R^2	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
1	**2a**	Me_2N	Me	95	86.5[c]				
2	**2b**	MeS	Me	98	99.2[d]	96	99.9		
3	**2c**	MeO	Me	99	99.1[e]	98	99.3		
4	**2d**	Me	Me	97	98.7[e]	98	98.5		
5	**2e**	H	Me	99	98.9[f]	97	99.1		
6	**2f**	Br	Me	92	0.5[g]	91	90.1		
				93	90.9[h]	93	89.9[h]		
7	**2g**	Cl	Me	91	1.2[g]	95	90.4		
				95	95.2[h]	94	90.1[h]		
8	**2h**	F	Me	92	−0.8[i]	93	87.5		
				94	92.1[h]	95	88.1[h]		
9	**2i**	O_2N	Me	96	66.7[j]	94	73.8		
10	**2j**	Me_2N	Et	95	64.7[c]				
11	**2k**	MeS	Et	96	97.5[d]	95	94.9	96	96.3
12	**2l**	MeO	Et	97	94.2[e]	97	93.6	98	91.4
13	**2m**	Me	Et	99	93.4[e]	98	91.5	98	87.7
14	**2n**	H	Et	96	93.0[f]	98	88.9	97	87.5
15	**2o**	Br	Et	94	−1.7[g]	94	81.3	95	65.8
				95	89.0[h]	96	80.7[h]		
16	**2p**	Cl	Et	94	−0.4[g]	92	79.5	93	59.2
				96	87.8[h]	95	79.4[h]		
17	**2q**	F	Et	91	1.4[i]	95	79.7	93	47.2
				93	90.5[h]	96	79.2[h]		
18	**2r**	O_2N	Et	96	52.4[j,k]	95	63.5	94	56.7

[a] Isolated yields after the column chromatography. [b] Ee values were the average values of twice parallel experiments with less than 1% ee difference and each of the ee values was determined by HPLC analysis, using AS, OD, or OJ chiral columns (4.6 × 250 mm, Chiralcel) and a mixture of *n*-hexane and 2-propanol as an eluent at an eluent rate of 0.5 to 0.8 mL/min at monitoring wave 228 nm. Configuration was assigned according to the rotation value. In each case a positive rotation was obtained, indicating that the selectivity was for the (*R*)-enantiomer in agreement with reported work (refs 6a, 7d, 21, and 22). [c] OD column, *n*-hexane:2-propanol (96:4, v/v). [d] AS column, *n*-hexane:2-propanol (95:5, v/v). [e] OD column, *n*-hexane:2-propanol (95:5, v/v). [f] OJ column, *n*-hexane:2-propanol (90:10, v/v). [g] OD column, *n*-hexane:2-propanol (97:3, v/v). Minus ee values indicate that the (*S*)-enantiomer predominated. [h] Ee value for $AgNO_3$-washed ketone. [i] OD column, *n*-hexane:2-propanol (99:1, v/v). [j] OD column, *n*-hexane:2-propanol (90:10, v/v). [k] Configuration was tentatively assumed according to the mechanism and its rotation sign.

°C. After the reaction mixture was quenched with methanol and the usual workup, the enantiomeric excess value was determined by using a chiral column on HPLC. The results are summarized in Table 1, columns 7 and 8 in toluene, and columns 9 and 10 in THF. From Table 1, an obvious influence of the electronic effects on the enantioselectivity was observed for both of these series of ketones in toluene and in THF. Now a conclusion may be drawn that the enantioselective 1,3,2-oxazaborolidine-catalyzed borane reduction of prochiral ketones to chiral secondary alcohols shows an obvious influence of electronic effects on the enantioselectivity.

On the basis of our results, the influence of the electronic effects on the enantioselectivity is obvious. The enantioselectivity of the reduction is subjected to a

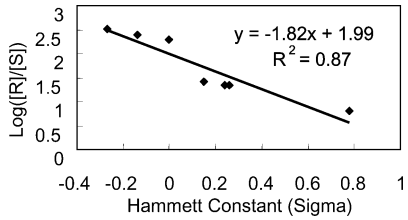


FIGURE 1. Hammett plot of the catalyst **1a**-catalyzed borane reduction of acetophenones in toluene (log([R]/[S]) vs Hammett constant σ_p: MeO, −0.27; Me, −0.14; H, 0; F, 0.15; Cl, 0.24; Br, 0.26; O_2N, 0.78, the same as in Figures 2−4.

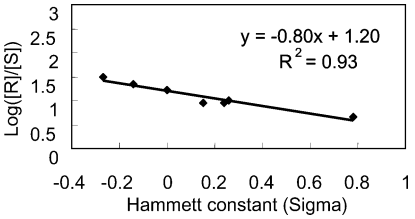


FIGURE 2. Hammett plot of the catalyst **1a**-catalyzed borane reduction of propiophenones in toluene.

remote electronic effect to the substrate ketones. Thus, ketones with electron-donating groups in the para-position of acetophenones and propiophenones afforded higher enantioselectivity than those bearing electron-withdrawing groups. To investigate the influence of the solvent, we chose two widely used solvents, toluene and THF, to run the asymmetric reduction of propiophenones, which show a more obvious influence than acetophenones, under the same conditions. The results indicate that the same tendency of the influence of the electronic effects on the enantioselectivity was observed. From the Hammett plots of log ([R]/[S]) versus Hammett constants σ_p,[19] a straight line for each of the asymmetric reductions catalyzed by catalysts **1a** and **1d** was obtained,[20] with $R^2 = 0.87$ for acetophenones in toluene catalyzed by **1a** (Figure 1), $R^2 = 0.93$ for propiophenones in toluene catalyzed by **1a** (Figure 2), $R^2 = 0.90$ for acetophenones in toluene catalyzed by **1d** (Figure 3); and $R^2 = 0.93$ for propiophenones in toluene catalyzed by **1d** (Figure 4). The reduction of propiophenones in THF catalyzed by **1a** did not show a good linearity because THF as a Lewis basic solvent can coordinate with the boron atom in the catalyst as a competing coordinating reaction in the reduction system. Its Hammett plot is not shown. On the basis of our observations (Figures 1-4), we conclude that the electron-donating substituents in ketones increase the enantioselectivity and the electron-withdrawing substituents in ketones decrease the enantioselectivity in the

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(20) The data for dimethylamino- and methylthio-substituted ketones were not used in Hammett plots because dimethylamino ketones show strong amine−boron coordination, and methylthio is a seldom used substituent in the Hammett linear free energy investigation. If the data of methylthio-substituted ketones were used, R^2 will become lower. Reference 19 gives 0.06 of the σ value for the MeS group. However, on the basis of our experimental results, the σ value of the MeS group should be suggested as −0.51, which is an average of the σ values calculated from Figures 2 and 4 because substituted propiophenones show good linearities in the Hammett plots.

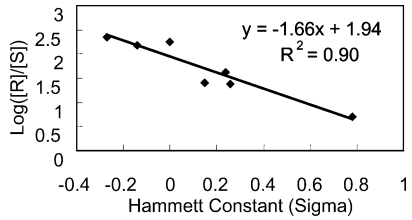


FIGURE 3. Hammett plot of the catalyst **1d**-catalyzed borane reduction of acetophenones in toluene.

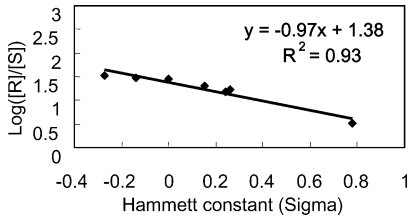
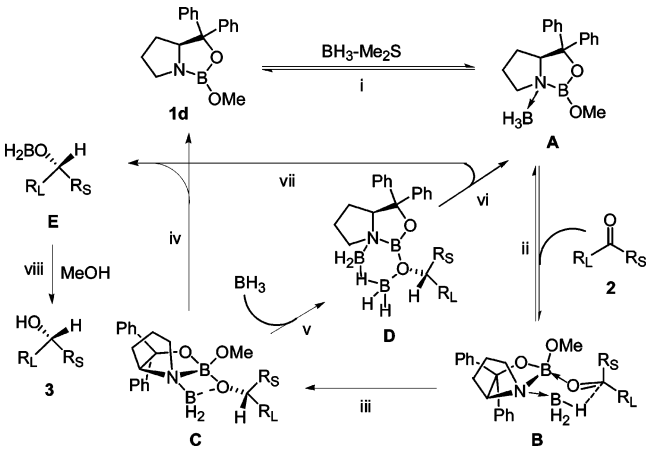


FIGURE 4. Hammett plot of the catalyst **1d**-catalyzed borane reduction of propiophenones in toluene.

SCHEME 2. Proposed Mechanism for the Oxazaborolidine-Catalyzed Asymmetric Borane Reduction of Ketones by Corey et al.[2d]



asymmetric borane reduction. The conclusion is in accordance with the observation of Corey et al.[13c] A similar electronic effect was also observed in the chiral bisoxazoline−Cu-catalyzed asymmetric aziridination of chalcones, α,*β*-unsaturated ketones, recently.[23] Another important evidence is that diborane reduces trimethylacetaldehyde readily, but fails to react with chloral under the usual mild conditions.[24] The inertness of chloral toward diborane is attributed to the decreased basic property of the oxygen atom of the carbonyl group resulting from the powerful inductive effects of the halogen substituents. The enantioselectivity is an electronic effect dependent in the reductions. It was rationalized that the oxyatom of the carbonyl group in the ketones with electron-withdrawing groups show weaker basicity than that of the ketones with electron-donating groups. The oxyatom shows weaker coordination with the boron atom in the catalysts than that of the ketones with electron-donating groups. This suggests that larger amounts of the ketones with electron-withdrawing groups were reduced by noncatalytic borane to produce racemic alcohols. Thus, their ee values are lower than those of the ketones with electron-donating groups. The results should also indicate that the coordination step in the catalytic cycle is a key step for the enantioselectivity in the reductions (Scheme 2). This should be an ee-determining step in the reduction cycle.

Although the mechanism of the oxazaborolidine-catalyzed asymmetric borane reduction of ketones is probably very complicated as shown in Scheme 2 suggested by Corey et al.,[2d] most of the experimental results indicated that the catalytic cycle involving steps i−iv is a major pathway in the reduction[3a] because high enantioselectivity was obtained in most cases, especially for catalyst oxazaborolidines derived from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine. And the oxazaborolidine-catalyzed reduction rate is very fast in most cases.[1,2,3a] Thus, the intermediates **C** and **D** are very short-life and low-concentration intermediates in the reduction system. Intermediate **E** seems to be a long-life species.[25] However, as an alkoxyborane, its reductive activity is weaker than that of intermediate **A** and borane in the reduction conditions because no dialkoxyborane was observed in the borane reduction of acetone.[25]

The influence of electronic effects on the enantioselectivity in the asymmetric borane reduction of ketones has been considered several times in the literature.[5a,6a,13] However, no obvious influence has been observed when the *B*-alkyl- and aryl-substituted oxazaborolidines **1b** and **1c** were used as catalysts, and different alkyl para-substituted aryl ketones were used as substrates except for the report of Corey et al.[13c] Mathre et al. investigated the influence of para-substituted acetophenones using oxazaborolidine **1b** as the catalyst under *stoichiometric* reduction conditions in most cases.[6a] Jones, Blacklock, and their co-workers paid much attention to the influence using the oxazaborolidine **1b** itself and its derivatives with different para substituents on the phenyl ring of the diphenylprolinol, the oxazaborolidine **1c** itself, and its derivatives with different para substituents on the phenyl ring attached to the boron atom in the asymmetric reduction.[5a] Unfortunately, no significant electronic effect was observed with acetophenones with a variety of substituents and with both the substitution on the phenyl groups in the diphenylprolinol and that on the boron-bearing phenyl group. Here, we investigated the influence using para-substituted acetophenones and propiophenones as substrates and the other two widely used chiral oxazaborolidines **1a** and **1d** as catalysts. An obvious influence was observed for both of these catalysts. Both of them show a Hammett linear free energy electronic effect on the enantioselectivity in asymmetric reductions.

p-Dimethylaminoacetophenone **2a** and *p*-dimethylaminopropiophenone **2j** with an electron-donating group gave relative lower ee values (86.2% and 64.7%, respectively, Table 1, entries 1 and 10). The reason is that noncatalytic reduction is increased because the nitrogen atom in the amino group shows a strong coordination with borane

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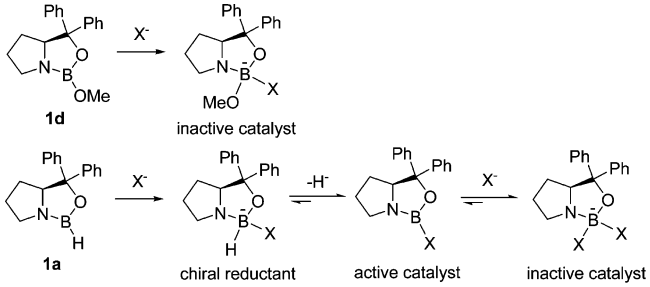
SCHEME 3. Effects of Anions on the Enantioselctivity in the Oxazaborolidine-Catalyzed Asymmetric Borane Reduction

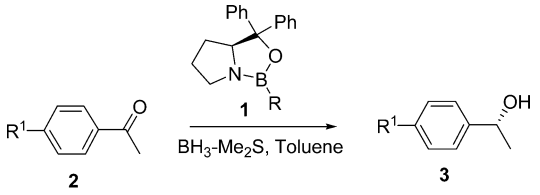


and the coordinated borane can reduce the ketone to give a racemic alcohol. Thus, these two ketones were not used in further experiments to avoid other effects. *p*-Methylsulfonyl- and *p*-methylsulfinyl-substituted acetophenones and propiophenones were also prepared by oxidation of methylthioacetophenone **2b** and methylthiopropiophenone **2k** with peroxy acetic acid and freshly made manganese dioxide, respectively.[17,18] However, unfortunately, all of them yielded the corresponding 1-(4-methylthiophenyl)ethanol **3b** and 1-(4-methylthiophenyl)-1-propanol **3k**, respectively, under our reduction conditions. Thus, both sulfinyl and sulfonyl groups were reduced to sulfide (data were not shown in Table 1). Although sulfone-containing ketones were reduced successfully to chiral sulfone-containing alcohols previously,[13a] our ketones which contain a sulfone or sulfoxide group adjacent to phenyl groups were reduced to chiral sulfide-containing alcohols under the current reduction conditions.

Another interesting observation is that it is obviously different to reduce halogenated ketones in the reductions. The catalyst **1a** gave enantioselective products, while the catalyst **1d** produced racemic products with commercial available and self-prepared halogenated ketones. Why did they generate different results? Considering the structures of the catalysts, the reason may be caused by the halide anion coordination to the boron atom in the catalysts (as shown in Scheme 3). The halogenated ketones contain some halide anions which can coordinate with the boron atom in the catalysts. When they coordinate with the boron atom in catalyst **1d**, the halide-coordinated catalyst **1d** cannot further coordinate with the carbonyl group of ketones. Thus, it is an inactive catalyst. The halogenated ketones were reduced only by the noncatalytic borane to yield racemic alcohols. However, for the catalyst **1a**, the halide-coordinated catalyst **1a** is a chiral reductant, which reduces halogenated ketones to produce chiral alcohols. Moreover, the halide-coordinated catalyst **1a** can lose a hydrogen anion to form *B*-halogenated catalysts, which are also chiral catalysts in the borane reduction of ketones. This is the reason these two catalysts show different effects in the presence of halide anions in the reduction system.

To further verify this rationale, acetophenone was reduced by using catalysts **1a** and **1d** in the presence of different halide anions and different amounts of chloride anion (Table 2, entries 1−10) with tetrabutylammonium fluoride (TBAF) for fluoride anion, lithium chloride and benzyltriethylammonium chloride (TEBA) for chloride

TABLE 2. Oxazaborolidine-Catalyzed Asymmetric Borane Reduction of Acetophenones (with Different Additives)



1a: R = H; **1d**: R = MeO; **1e**: R = F; **1f**: R = Cl

entry	ketone (R)	catalyst	catalyst loading (equiv[a])	additive (equiv[b])	yield (%)	ee[c] (%)
1	**2d** (H)	**1d**	0.1	LiCl (1.0)[d]	95	37.2
2	**2d** (H)	**1d**	0.1	TBAF (1.0)	96	0.7
3	**2d** (H)	**1d**	0.1	TEBA (1.0)	94	0.2
4	**2d** (H)	**1d**	0.1	HTMAB (1.0)	96	0.8
5	**2d** (H)	**1d**	0.1	TBAI (1.0)	94	0.5
6	**2d** (H)	**1a**	0.1	TEBA (0.5)	95	98.6
7	**2d** (H)	**1a**	0.1	TEBA (1.0)	95	98.3
8	**2d** (H)	**1a**	0.1	TEBA (1.5)	96	95.2
9	**2d** (H)	**1a**	0.1	TEBA (2.0)	97	51.7
10	**2d** (H)	**1a**	0.1	TEBA (2.5)	95	23.1
11	**2d** (H)	**1a**	0.1	$PhCO_2Na$ (1.0)[d]	96	96.2
12	**2d** (H)	**1d**	0.1	$PhCO_2Na$ (1.0)[d]	95	96.9
13	**2i** (ON_2)	**1d**	0.1		96	66.7
14	**2i** (ON_2)	**1a**	0.1		94	73.8
15	**2i** (ON_2)	**1e**[e]	0.1		97	76.6
16	**2i** (ON_2)	**1f**[f]	0.1		96	76.9
17	**2d** (H)	**1d**	0.05		97	98.0
18	**2d** (H)	**1d**	0.01		98	94.4
19	**2d** (H)	**1d**	0.005		95	93.5
20	**2d** (H)	**1d**	0.001		98	88.9

[a] Equiv to ketone. [b] Equiv to the catalyst. [c] Ee values were determined by HPLC analysis. Analytic conditions are provided in the footnotes of Table 1. [d] Actually only saturated solution due to poor solubilities of LiCl and $PhCO_2Na$ in toluene. [e] **1e** was prepared in situ via the exchange reaction of **1a** and TEBA as shown in Scheme 3. [f] **1f** was prepared in situ via the exchange reaction of **1a** and TBAF as shown in Scheme 3.

anion, hexadecyltrimethylammonium bromide (HTMAB) for bromide anion, and tetrabutylammonium iodide (TBAI) for iodide anion. The results indicate that halide anions can decrease the enantioselectivity of the borane reduction of kenones. For catalyst **1d**, addition of an equivalent of halide anion to the catalyst can completely inactive catalyst **1d**. However, for catalyst **1a**, it is obviously inactive with more than 2 equiv of chloride anion. Its activity is not affected when the amount of chloride is less than equivalent to the catalyst **1a**. These results support our rationale. The benzoate ion, a bidentate anion, was also evaluated in the asymmetric reduction of acetophenone, and the results indicate that it just shows a slight effect due to its very poor solubility in toluene (Table 2, entries 11 and 12). This implies that soluble and coordinate-able anions can affect the enantioselectivity in the reduction.

Because the halides can affect the enantioselectivity in the asymmetric reduction, all of halogenated ketones were washed twice with aqueous silver nitrate, dried over anhydrous sodium sulfate, and asymmetrically reduced again to give chiral alcohols. The results are listed in the Table 1. It was found that no obviously difference was observed for the results catalyzed by catalyst **1a** before and after washing with aqueous silver nitrate.

It was reported previously that the electronic tuning of asymmetric catalysts can change the stereoselectivity in catalytic asymmetric reactions.[15a,b,d] Regulation of electronic effects of catalysts is another important pathway to find effective catalysts. Regulation of the electronic effects of catalysts to match with substrates should be important especially for asymmetric transformations where stereoselectivity relies purely on nonbonded interactions. The interaction performs stereochemical communication between a chiral catalyst and a substrate. The regulation should be a very useful tool to determine reaction mechanisms, especially to identify the ee-determining step in the catalytic cycle.

For the *p*-nitro ketones **2i** and **2r**, it was found that they showed higher enantioselectivities with catalysis of **1a** than those with catalysis of **1d**. It was rationalized that the difference was caused by the different substituents on the boron atom of catalysts **1a** and **1d**. The electron-donating group methoxy attached to the boron atom in the catalyst of **1d** decreases the Lewis acidity of the boron atom in catalyst **1d** so that the boron atom shows a weaker coordination with the oxyatom of the carbonyl group in the ketones with an electron-withdrawing nitro group because the oxyatom of the carbonyl group is a weaker Lewis base than that in the ketones with electron-donating groups owing to the existence of the electron-withdrawing nitro substituent. Larger amounts of the nitro ketones were reduced by the noncatalytic borane to produce racemic alcohols under the catalysis of **1d**. Thus, the ee values are lower than those under the catalysis of **1a**.

On the basis of the above analysis, we rationalized that a catalyst with an electron-withdrawing group, such as fluoro or chloro substituents, attached to the boron atom should be a suitable catalyst for the asymmetric reduction of the ketones with electron-withdrawing groups. The boron atom in the catalysts with an electron-withdrawing group attached to the boron atom should show a stronger Lewis acidity than that in the *B*-unsubstituted catalyst **1a** and that in the catalysts **1b**−**d** with electron-donating groups attached to the boron atom. It should show a stronger coordination with the oxyatom of the carbonyl group in the ketones with electron-withdrawing groups, such as nitro and halo groups. Thus, if the ketones with electron-withdrawing groups were reduced by using the catalyst with an electron-withdrawing group, their enantioselectivity may be improved. The *B*-fluoro- and *B*-chloro-substituted catalysts **1e** and **1f** may be prepared by the exchange reaction with halide anions in the reduction system as shown in Scheme 3. First, the *B*-unsubstituted catalyst **1a** was prepared and then was converted into the *B*-fluoro- and *B*-chloro-substituted catalysts **1e** and **1f** by in situ exchange reactions with TBAF and TEBA, respectively, as shown in Scheme 3. The freshly prepared catalysts **1e** and **1f** were tested in the asymmetric reduction of *p*-nitroacetophenone, which gave lower enantioselectivity under the reductions catalyzed by catalysts **1a** and **1d**. The results indicated that the enantioselectivity of *p*-nitroacetophenone was slightly improved (Table 2, entries 15 and 16). The current studies indicate that tuning the electron effects of a catalyst can improve its enantioselectivity in the asymmetric borane reduction (Table 2, entries 13−16).

One can find that catalyst **1d** always shows excellent enantioselectivities to the ketones with electron-donating substituents or without substituent (see Table 1). It was assumed that the Lewis acidity of the boron atom in catalyst **1d** is decreased because of its bearing an electron-donating methoxy group. The coordination between the oxyatom of the carbonyl group of ketones and the boron atom of catalyst **1d** is diminished. The interaction between the oxyatom of alkoxy and the boron atom of catalyst **1d** (Scheme 2, **C** and **D**) is also weaker. In the catalytic reduction cycle, reduced product, alkoxyborane **E**, could be released more easily (Scheme 2, steps iv and vii). Thus, catalyst **1d** undergoes the catalytic reduction cycle at a faster speed than catalysts **1a**−**c**, and shows a higher catalytic efficiency for the ketones with electron-donating groups. To further confirm the assumption, acetophenone was reduced with the decreasing amount of catalyst loading (Table 2, entries 17−20). It was found that the catalytic efficiency of catalyst **1d** is obviously higher than that of catalyst **1a**.[3a] Catalyst **1a** gave an enantioselectivity of 80% when it was used in the reduction of acetophenone with 0.5% equiv of catalyst,[3a] while catalyst **1d** yielded an enantioselectivity of 88.9% with 0.1% equiv of the catalyst loading in the same reduction reaction. This supports our assumption and seems to indicate that the releasing steps (Scheme 2, steps iv and vii) are rate-determining steps in the catalytic cycle.

The present investigation indicates that the electronic tuning of catalysts **1** can improve their enantioselectivity and efficiency in the asymmetric borane reduction and the electronic tuning of catalysts and ketones can identify that the ketone and catalyst coordinating step (Scheme 2, step ii) is a key step for the enantioselectivity in the catalytic cycle.

On the basis of investigation, one can select a suitable catalyst for the borane asymmetric reduction of ketones. We hope that the present study has addressed an important issue: the regulation of electronic effects of catalysts to match with substrates should be important in asymmetric catalytic reactions. It should be an important way to improve the enantioselectivity for some substrates. We hope that the present study has also addressed an important issue regarding the catalyst selection in the oxazaborolidine-catalyzed asymmetric reduction of ketones. We recommend oxazaborolidine **1d** as the most suitable catalyst for ketones with electron-donating groups because of its convenient preparation, economic starting materials, high efficiency, and excellent yields and enantioselectivity, and the oxazaborolidines **1b** and **1c** as good choices for all ketones with either electron-donating groups or electron-withdrawing groups, but especially for ketones with electron-withdrawing groups. Although oxazaborolidine **1d** as the most suitable catalyst is limited to ketones with electron-donating groups, it is convenient and practical in the preparation and application, especially for large-scale preparation in industry due to low catalyst loading in the asymmetric reduction.

Conclusion

The influence of the electronic effects on the enantioselectivity of the oxazaborolidine-catalyzed asymmetric

borane reduction of ketones has been observed and investigated with use of para-substituted acetophenones and propiophenones with various functional groups and *B*-unsubstituted and *B*-methoxyoxazaborolidines derived from (*S*)-diphenylprolinol with borane and trimethyl borate as catalysts in toluene and THF. The results indicate that they show Hammett linear free energy electronic effects on the enantioselectivity in the asymmetric reduction. Tuning the electronic effect of the catalyst can extend its utility effectively and improve the enantioselectivity for some substrates in the reduction. Another interesting finding is that soluble and coordinateable anions in the reductive system heavily affect the enantioselectivity, especially for the *B*-methoxy catalyst, because of their coordination with the boron atom in the catalysts.

Experimental Section

General Procedure for the Asymmetric Reduction of Ketones with Catalyst 1d. To a solution of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (12.5 mg, 0.05 mmol) in dry toluene (2.5 mL) was added trimethyl borate (6.0 mg, 0.06 mmol), and the mixture was stirred under a nitrogen atmosphere at room temperature for 2 h. After 2 M borane−dimethyl sulfide complex in THF (0.25 mL, 0.5 mmol) was added, a solution of ketone (0.5 mmol) in dry toluene (2.5 mL) was added dropwise over 1 h. The mixture was stirred at 25 °C until the ketone disappeared by gas chromatographic monitoring. The resulting mixture was quenched with methanol in an ice bath and concentrated under reduced pressure. The residue was purified on a silica gel column with a mixture of petroleum ether (60−90 °C) and ethyl acetate (5:1, v/v) as an eluent to give a colorless oil chiral secondary alcohol. The spectral and analytical data of all obtained alcohols are in agreement with those reported in the literature.[6a,7d,19,20]

General Procedure for the Asymmetric Reduction of Ketones with Catalyst 1a. To a solution of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (12.5 mg, 0.05 mmol) in dry toluene (2.5 mL) was added 2 M borane−dimethyl sulfide complexes in THF (0.038 mL, 0.075 mmol), and the mixture was stirred under nitrogen at 45 °C for 14 h. After the mixture was cooled to 25 °C, 2 M borane−dimethyl sulfide complex in THF (0.25 mL, 0.5 mmol) was added, then a solution of ketone (0.5 mmol) in dry toluene (2.5 mL) was added dropwise over 1 h. The mixture was stirred at 25 °C until the ketone disappeared on gas chromatographic monitoring. The resulting mixture was quenched with methanol in an ice bath and concentrated under reduced pressure. The residue was purified on a silica gel column with a mixture of petroleum ether (60−90 °C) and ethyl acetate (5:1, v/v) as an eluent to give the chiral secondary alcohol as a colorless oil.

(*R*)-1-(4-Nitrophenyl)-1-propanol (3r). Colorless liquid; $[\alpha]^{25}_{D}$ +20.4 (*c* 1.20, $CHCl_3$), ee 63.3%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H, CH_3), 1.78 (dq, J = 6.4, 7.2 Hz, 2H, CH_2), 2.80 (s, br, 1H, OH), 4.74 (t, J = 6.4 Hz, 1H, CH), 7.51 (d, J = 9.0 Hz, 2H, ArH), 8.16 (d, J = 9.0 Hz, 2H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.6, 31.9, 74.6, 123.4, 126.6, 146.9, 152.1; MS (EI) *m*/*z*:181 (M^+, 1.2), 163 ($M^+ - H_2O$, 1.4), 152 ($M^+ - Et$, 100), 122 (O_2NPh^+, 28); IR ν (cm^{-1}) 3220 (OH), 2966, 2928, 1604, 1519, 1346. Anal. Calcd for $C_9H_{11}NO_3$ (181.19): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.53; H, 6.32; N, 7.57.

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Supporting Information Available: The chromatogram for the determination of enantiomeric excess of the unknown chiral alcohol **3r** and its ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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