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Effect of Temperature on the Enantioselectivity in the Oxazaborolidine-Catalyzed Asymmetric Reduction of Ketones. Noncatalytic Borane Reduction, a Nonneglectable Factor in the Reduction System

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The effect of temperature on the enantioselectivity of the oxazaborolidine-catalyzed asymmetric borane reduction of ketones has been investigated carefully using alkyl aryl ketones with a variety of functional groups and a *B*-methoxyoxazaborolidine derived from trimethyl borate and (*S*)-α,α-diphenylprolinol as a catalyst. The reductions were carried out over a range of temperatures in THF and toluene with or without the catalyst. The reductive rates increase along with increasing reaction temperature with or without the catalyst by determining the conversion of the ketones to alcohols by GC analysis. However, the rates of the catalytic reductions increase faster than those without the catalyst. The results indicate that the noncatalytic borane reduction is an important factor to the enantioselectivity in the reduction. The highest enantioselectivities were usually obtained between 20 and 30 °C in the asymmetric reduction.

Introduction

Enantioselective 1,3,2-oxazaborolidine-catalyzed borane reduction of prochiral ketones to chiral secondary alcohols is an important reaction in asymmetric syntheses, which has attracted much attention and was widely used in the preparation of various secondary alcohols during the past decade.[1] Since it was pioneered by Itsuno et al.[2] and then developed by Corey's group and is well-known as the complete basis set reduction,[3] some of the best enantioselectivities have been achieved with chiral 1,3,2-oxazaborolidines derived from chiral vicinal amino alcohols. In comparison with the numerous attempts to search for new catalysts and to improve the enantioselectivity, few papers have concentrated on the mechanistic investigation of the catalytic reaction.[3,4] Although, many chemists have mentioned that the asymmetric reduction shows temperature-dependent enantioselectivity, and the enantioselectivity was improved with increasing temperature.[3a,b,5] It is well-known that the enantioselectivity generally decreases with increasing temperature in most asymmetrically catalytic reactions. Why does it show some differences in the asymmetric borane reduction of ketones? Herein, we attempt to give another rationale and experimental evidence for the temperature-dependent enantioselectivity in the oxazaborolidine-catalyzed asymmetric borane reduction of ketones. Noncatalytic borane reduction is a nonneglectable factor in the reduction system.

Results and Discussion

A lot of catalysts have been developed for the borane asymmetric reduction of ketones until now.[1,5] Among them, (*S*)-2-substituted 4,4-diphenyl-3,1,2-oxazaboro-[3.3.0]octanes **1** (Scheme 1), derived from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine, with several different substituents (such as H for **1a**, Me for **1b**, Bu for **1c**, MeO for **1d**, and Ph for **1e**) on the B atom, have been proven to be a series of effective catalysts in the asymmetric reduction with excellent yields and enantioselectivities for a wide variety of ketones. However, **1a**−**1c** have not

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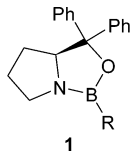
SCHEME 1



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been entirely satisfactory, particularly for large-scale productions, owing to the necessity of relatively expensive reagents, such as trimethylboroxin, methylboronic acid, or *n*-butylboronic acid, for their preparation,[3] and the necessity of 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.[6] The advantage of the catalyst **1d** is that it can be prepared from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine and inexpensive trimethyl borate and used directly without any further separation and purification.

On the basis of the published results,[1,6] borane asymmetric reduction of ketones catalyzed by (*S*)-2-substituted 4,4-diphenyl-3,1,2-oxazaboro[3.3.0]octanes **1** in THF or toluene is the best reaction condition in most cases. However, for the reduction temperature, different research groups gave different suggestions. To develop a practical and efficient method for the preparation of various chiral secondary alcohols with excellent yields and enantioselectivity, it is better to understand this reaction and to investigate in detail the optimal reaction conditions. In previous papers,[6a,7,8] it was found that the heteroatoms (O, S, and N) in ketones show an obvious effect on the enantioselectivity in the asymmetric reduction. For comparison, we selected four ketones, one without a heteroatom and others containing a heteroatom, O, S, or N, to investigate the effect of temperature on enantioselectivity in the asymmetric reduction. We also found that the enantioselectivity of acetophenone is too high in the reduction and that the enantioselectivities of alkyl aryl ketones decrease with increasing lengths of both the alkyl chain and the alkyl substituent on the aryl group.[7] To observe an obvious effect, we designed four ketones with some long-chained alkyl group and the substituent of the aryl group to determine the effect. In our asymmetric reduction, the catalyst **1d** was prepared in situ by the addition of trimethyl borate into a solution of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine in toluene (or THF). After the resulting mixture was stirred for 2 h and borane was added, a ketone was added dropwise for 1 h at the desired reduction temperature. After the reaction mixture was quenched with methanol and the usual workup, the ee value was determined using a chiral column on HPLC. The results are shown in Figure 1. From Figure 1, a remarkable effect of the reaction temperature on the enantioselectivity was found, and turnovers of enantioselectivities are from 20 to 30 °C for all of these four ketones. Nonheteroatom-containing ketone **2c** shows a lesser effect of temperature on the

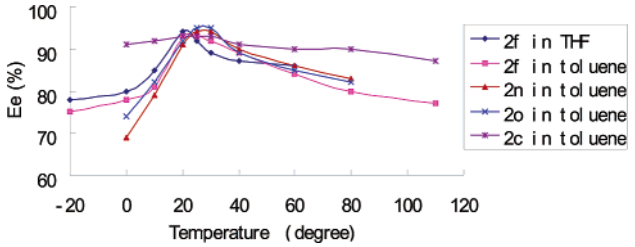

FIGURE 1. Effect of temperature on the enantioselectivity in the oxazaborolidine-catalyzed borane reduction of ketones.

enantioselectivity, while heteroatom-containing ketones **2f**, **2n**, and **2o** show a significant effect of temperature on the enantioselectivities under our reaction conditions.

Reduction of nitrogen, oxygen, and sulfur heteroatom-containing ketones provided relatively low enantioselectivity at low temperatures (below 20 °C) and at high temperatures (over 30 °C) because the noncatalyzed reduction can also occur by hydrogen transfer from the borane coordinated to these three heteroatoms. The noncatalyzed reaction pathways were added because of the existence of the heteroatoms.[6a,7]

When we optimized the reduction temperature for obtaining the highest enantioselectivity, we found that the reduction time became shorter with increasing temperature. We rationalized that the enantioselectivity increases with the increasing reduction temperature, in most cases below 20−30 °C, partly because of the increase of the catalytic reduction rate; as Prasad et al. said, the faster the rate of the catalyzed reduction, the better the selectivity.[9] As the catalytic reduction became faster with the increasing temperature, the enantioselectivity became more highly improved. However, when the reduction temperature was increased over 30 °C, generally, the free borane (including other noncatalyst-coordinated borane, such as coordinated complexes of BH_3 with Me_2S, THF, etc., with the same meaning in the following) reduction became an important factor to the enantioselectivity. The rate of the free borane reduction increases more heavily with increasing reduction temperature over 30 °C. Thus, the enantioselectivity decreases somewhat with increasing temperature, in most cases, over 30 °C.

To confirm our rationalization, we determined the conversion rates of the two ketones, one with a heteroatom O [BuOPhCOEt (**2f**)] and the other without a heteroatom [AmPhCOEt (**2c**)], in both free borane reduction and 1,3,2-oxazaborolidine (**1d**)-catalyzed borane reduction conditions at different temperatures by GC analyses. The results are shown in Figures 2−7.

To investigate the effect of the solvent, we chose two widely used solvents, THF and toluene, for the asymmetric reduction to tracing the reduction conversion. The results indicate that the conversion rates of ketone **2f** to the corresponding alcohol under catalytic conditions increase faster than those under noncatalytic conditions at each of the same temperatures, and the catalytic rates in toluene increase more obviously than those in THF because THF as a Lewis basic solvent can coordinate with borane. The coordinated borane can cause noncatalytic reduction (Figures 2, 4 and 3, 5).[5e] For nonheteroatom-

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(9) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, *61*, 3888−3889.

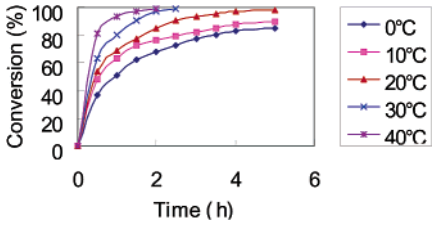

FIGURE 2. Free borane reduction of 1-(4-butoxyphenyl)-ethanone **2f** in THF.

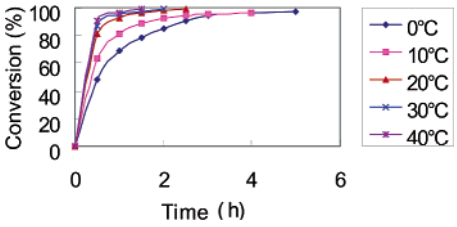

FIGURE 3. Oxazaborolidine-catalyzed borane reduction of 1-(4-butoxyphenyl)ethanone **2f** in THF.

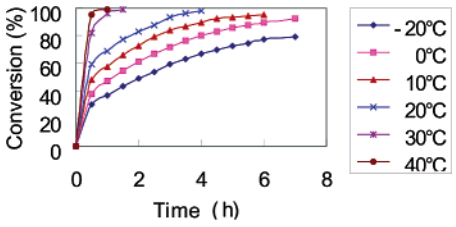

FIGURE 4. Free borane reduction of 1-(4-butoxyphenyl)-ethanone **2f** in toluene.

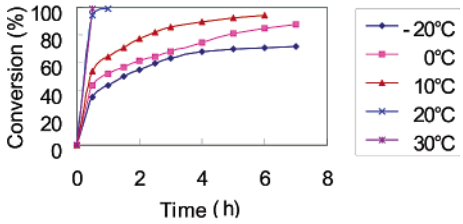

FIGURE 5. Oxazaborolidine-catalyzed borane reduction of 1-(4-butoxyphenyl)ethanone **2f** in toluene.

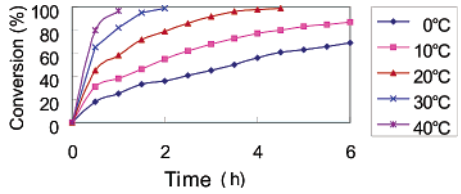

FIGURE 6. Free borane reduction of 1-(4-pentylphenyl)-ethanone **2c** in toluene.

containing ketone **2c**, only the conversion in toluene was determined, and the same results were observed (Figures 6 and 7). Because reductions are almost completed after the addition of the ketone to borane over 40 °C, the tracing results are not shown in the figures. On the basis of our observations (Figures 2−7), it seems that free borane reduction is an important factor to the enantioselectivity in the borane asymmetric reduction of ketones. Corey et al. mentioned previously that the enantioselectivity of the reduction often decreases somewhat

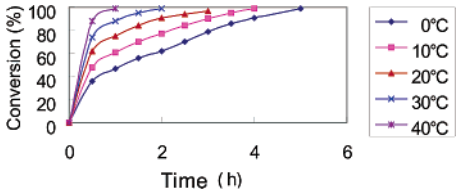

FIGURE 7. Oxazaborolidine-catalyzed borane reduction of 1-(4-pentylphenyl)ethanone **2c** in toluene.

with the increasing amount of BH_3·THF above 0.6 equiv.[3a] The enantioselectivity decreases because the free borane reduction increases with the increasing amount of BH_3·THF. This is in accordance with our observations.

Previously, several groups paid some attention to studying the abnormal temperature-dependent enantioselectivity in the oxazoborolidine-catalyzed borane asymmetric reduction of ketones. Most of researchers searched for the optimal reduction temperature for gaining the highest enantioselectivity. Some of them presumed that the enantioselectivity decreases with increasing temperature because of the stability and dimerization of the catalyst 1,3,2-oxazaborolidine[3a,b,5a−c] and the effect of different solvents.[5b,h] Much effort has been made to investigate the stability and dimerization of the catalysts.[5a] After a survey of the investigation on the stability and dimerization of the catalysts, we found that they are not the major reason for the abnormal effect of the temperature-dependent enantioselectivity above 0 °C or at least above room temperature, based on our results, and they may be the reason for the abnormal effect below room temperature. Alternatively, Cai, Douglas, and their coworkers investigated secondary reduction of the resulting first intermediate monoalkoxyborane, which was ignored in previous investigations, and found that it produced relatively low enantioselectivity in the reduction system.[10] Less attention has been paid to free borane reduction in the asymmetric reduction systems even though borane reduction of aldehydes and ketones was investigated,[11] and some researchers mentioned it as a possible reason for the abnormal effect of the temperature-dependent enantioselectivity.[3b] However, no experimental evidence has been provided. The relation between the free borane reduction and temperature has not yet been taken into consideration.

To further confirm the conclusion, a set of experiments reducing ketone **2f** as a model substrate in toluene was designed and carried out. The results are tabulated in Table 1. From Table 1, one can find that the addition time (namely, the addition rate) has just a very slight effect on the enantioselectivity when it is longer than 0.5 h (Table 1, entries 2 and 3 for 0 °C; entries 8−11 for 25 °C; and entries 18 and 19 for 80 °C), while it has a greater effect when it is less than 0.5 h (Table 1, entries 1 and 2 for 0 °C; entries 6−8 for 25 °C; and entries 17 and 18 for 80 °C). However, the enantioselectivity is decreased significantly with the increasing amount of borane (Table

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TABLE 1. Oxazaborolidine-Catalyzed Asymmetric Borane Reduction of Ketones under Different Conditions

entry	ketone	temp (°C)	catalyst loading (equiv[a])	borane (equiv[a])	add. time (h)	yield (%)	ee (%)
1	**2f**	0	0.1	1.0	0	88	75
2	**2f**	0	0.1	1.0	1	89	78
3	**2f**	0	0.1	1.0	10	85	80
4	**2f**	0	0.5	1.0	1	97	89
5	**2f**	0	1.0	1.0	1	92	98
6	**2f**	25	0.1	1.0	0	98	86
7	**2f**	25	0.1	1.0	0.25	97	89
8	**2f**	25	0.1	1.0	0.5	96	93
9	**2f**	25	0.1	1.0	1	97	93
10	**2f**	25	0.1	1.0	2	96	94
11	**2f**	25	0.1	1.0	10	97	94
12	**2f**	25	0.1	0.5	1	80	92
13	**2f**	25	0.1	2.0	1	96	91
14	**2f**	25	0.1	4.0	1	97	85
15	**2f**	25	0.1	8.0	1	98	70
16	**2f**	25	1.0	1.0	1	98	98
17	**2f**	80	0.1	1.0	0	95	78
18	**2f**	80	0.1	1.0	1	96	80
19	**2f**	80	0.1	1.0	10	95	81
20	**2f**	80	1.0	1.0	1	96	96
21	**2f**	40	1.0	1.0	1	96	98
22	**2f**	60	1.0	1.0	1	95	97
23	**2c**	25	1.0	1.0	1	96	98
24	**2n**	25	1.0	1.0	1	98	99
25	**2o**	25	1.0	1.0	1	92	99

[a] Equiv of ketone.

1, entries 12−15), and it is improved obviously with the increasing loading amount of the catalyst (Table 1, entries 2, 4, and 5 for 0 °C; entries 9 and 16 for 25 °C; and entries 18 and 20 for 80 °C). A total of 98% of the ee values was obtained using the stoichiometric catalyst−borane complex reduction from 0 to 40 °C (Table 1, entries 5, 16, and 21), and 97% and 96% of the ee values were obtained under the same conditions at 60 and 80 °C, respectively (Table 1, entries 22 and 20). To figure out the generality, a series of ketones **2c**, **2n**, and **2o** with different substituents were also reduced using the stoichiometric catalyst−borane complex, and 98−99% of the ee values were also obtained (Table 1, entries 23−25). According to our results, it is obvious that free borane reduction is an important factor for the temperature-dependent enantioselectivity in the oxazoborolidine-catalyzed asymmetric borane reduction.

There are three possible reasons for the low enantioselectivity at high temperature in the asymmetric reduction. They include free borane reduction, secondary reduction of the resulting first intermediate monoalkoxyborane, and high temperatures provided by high energy, which is higher than the energy barriers of the transition states (both **A** and **B**) for the formation of (*S*)- and (*R*)-alcohols, respectively. The energy barrier of transition state **A** is higher than that of **B** in this asymmetric reduction (shown in Figure 8). According to our results, good enantioselectivities were also obtained at high temperatures, even in refluxing toluene. The catalyst should be stable and can still keep its enantioselective ability at high temperatures, even in refluxing toluene. High energy provided by high temperatures does not seem to be a major reason for the decreasing enantioselectivity. Secondary reduction is the main reason for the decreasing enantioselectivity in some cases.[10] However, it does not seem to be a major reason in the current

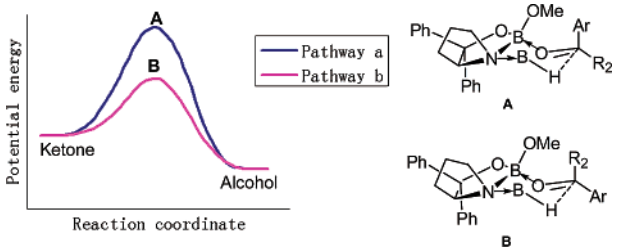


FIGURE 8. Potential energy diagram for the enantioselective oxazaborolidine-catalyzed borane reduction of a ketone.

case because 96−98% of the ee values were obtained without free borane in the reduction system at different temperatures. Now we can conclude that free borane reduction is an important factor for the temperature-dependent enantioselectivity in the asymmetric borane reduction. The highest enantioselectivity is usually reached at 20−30 °C for longer than the 1 h addition of the ketone.

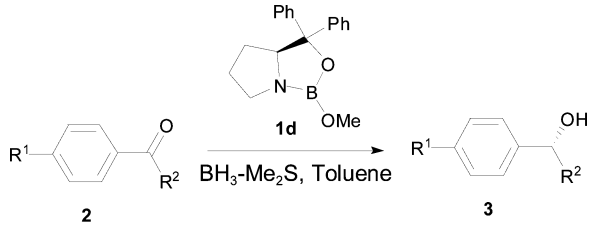
Rao et al. reported that good enantioselectivity was obtained only at room temperature and the reaction led to low enantioselectivity at −78 and +65 °C. They assumed that the catalyst may not be stable at 65 °C and the catalyst formation may be slow at −78 °C. In both cases, free borane reduction may occur at a faster rate, leading to low enantioselectivity of the product.[5i] Corey et al. observed by ^{11}B NMR analysis that the proportion of the catalyst dimer increases with decreasing temperatures.[3a,b] Mathre et al. isolated the dimer of the catalyst **1a** by adding excess BH_3·SMe_2 to a solution of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine in toluene at room temperature and found it to be not so unstable.[12]

Stone studied this effect in detail using catalysts **1b**, **1c**, and **1e** and ketones, acetophenone and cyclohexyl methyl ketone, as models used previously.[5b] Corey et al. summarized this effect in their recent comprehensive review and stated that the coordination of Me_2S, THF, etc., to borane generally did not affect the enantioselective level except at temperatures below −40 °C, while free borane reduction affects the enantioselectivity.[1d] These elucidations may be reasonable, but there are still no definite conclusions and convincing experimental proofs. Here we investigate the abnormal temperature-dependent enantioselectivity again with a practical and efficient catalyst **1d** and a variety of ketones as model substrates in the hope of gaining insight into the effect on different ketones, and we give some useful information on this effect.

Buono and his colleagues found that their catalyst (*S*)-3,1,2-oxazaboro[3.3.0]octane, derived from prolinol and borane, showed higher enantioselectivity with increasing reaction temperatures and the highest enantioselectivity in refluxing toluene.[5a] After isolation and NMR studies of the dimer of the catalyst, they rationalized that the catalyst favored dimerizing at low temperatures because of the less steric hindrance on the C4 position, compared with the catalysts of Corey et al., (*S*)-2-substituted 4,4-diphenyl-3,1,2-oxazaboro[3.3.0]octanes **1a**−**c**. The dimer

(12) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880−2888. (b) Tlahuext, H.; Contreras, R. *Tetraherdon: Asymmetry* **1992**, *3*, 1145−1148.

TABLE 2. Oxazaborolidine-Catalyzed Asymmetric Borane Reduction of Ketones



entry	ketone	R^1	R^2	yield (%)[a]	ee (%)[b]	$[\alpha]^{20}_D$	config.
1	**2a**	*n*-Bu	Me	99	98[c]	+34.2 (1.6, MeOH)	*R*[h]
2	**2b**	*n*-Am	Me	99	97[c]	+30.8 (1.5, MeOH)	*R*[h]
3	**2c**	*n*-Am	Et	98	93[c]	+28.7 (1.8, MeOH)	*R*[h]
4	**2d**	*n*-BuO	Me	99	98[d]	+37.3 (0.80, $CHCl_3$)	*R*[i]
5	**2e**	*n*-AmO	Me	99	97[d]	+35.1 (1.3, $CHCl_3$)	*R*[h]
6	**2f**	*n*-BuO	Et	97	93[e]	+31.3 (2.1, MeOH)	*R*[h]
7	**2g**	*n*-AmO	Et	95	92[e]	+29.0 (1.7, MeOH)	*R*[h]
8	**2h**	*n*-HexO	Et	97	93[e]	+27.2 (1.8, MeOH)	*R*[h]
9	**2i**	*n*-BuO	Bu	95	92[e]	+28.6 (2.0, MeOH)	*R*[h]
10	**2j**	*n*-AmO	*n*-Bu	98	94[e]	+28.4 (2.2, MeOH)	*R*[h]
11	**2k**	*n*-HexO	*n*-Bu	96	93[e]	+23.9 (2.0, MeOH)	*R*[h]
12	**2l**	*n*-BuS	Me	99	99[f]	+28.3 (1.2, $CHCl_3$)	*R*[i]
13	**2m**	*n*-AmS	Me	99	>99[f]	+24.9 (1.2, $CHCl_3$)	*R*[i]
14	**2n**	*n*-BuS	Et	99	94[g]	+19.7 (0.90, $CHCl_3$)	*R*[h]
15	**2o**	Et_2N	Me	95	95[c]	+46.6 (0.64, $CHCl_3$)	*R*[i]

[a] Isolated yields after column chromatography. [b] ee values were determined by HPLC analysis using AS, OD, or OJ chiral columns (Chiralcel) and a mixture of *n*-hexane and 2-propanol as an eluent. [c] OD column, *n*-hexane/2-propanol (95:5, v/v). [d] AS column, *n*-hexane/2-propanol (90:10, v/v). [e] OJ column, *n*-hexane/2-propanol (99:1, v/v). [f] AS column, *n*-hexane/2-propanol (95:5, v/v). [g] OD column, *n*-hexane/2-propanol (99:1, v/v). [h] 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 the reported work (ref 7, 15, and 16). [i] Configuration was tentatively assumed according to the mechanism and their rotation signs.

catalyst is inactive toward asymmetric reduction because the Lewis acid character of the boron atom is decreased by the strong oxygen and nitrogen donors, while when the reaction temperature was increased, the dimer showed a tendency to transfer predominately into the active monomer catalyst, which is responsible for the high enantioselectivity encountered as the major form in refluxing toluene.[5a] The same temperature-dependent enantioselectivity was also observed in borane (catecholborane) asymmetric reduction of an oxygen-containing imine, 3,3,3-trifluoro-2-(4-methoxyphenylimino)propionate, in dichloromethane.[13]

For the difference between the results of Buono et al.[5a] and our results (including Stone's[5b] results) on the temperature-dependent enantioselectivity, Martens et al. argued against the results of Buono et al. 1 year later. They could not repeat the results of Buono et al. under refluxing conditions.[14] Thus, there is doubt that the highest enantioselectivity was obtained under refluxing toluene. The enantioselctivity shows a turnover between 20 and 40 °C in Stone's[5b] and our reduction system. We rationalized that the difference was caused by the structure of the catalysts. The catalyst of Buono et al. is B-unsubstituted and favors dimerizing at low temperatures. For their case, the dimerization of the catalyst is an important factor in temperature-dependent enantioselectivity. While for Stone's and our case, free borane reduction is important to the enantioselectivity at high temperatures. According to the literature and our results, a conclusion may be drawn that the enantioselectivity of oxazaborolidine-catalyzed borane reduction is dependent on both the catalyst structure and the temperature under the same reduction conditions. For B-unsubstituted oxazaborolidine catalysts, the enantioselectivity increases generally with increasing reduction temperatures. While for B-substituted catalysts, the highest enantioselectivity generally appears between 20 and 30 °C.

A series of ketones with a variety of functional groups were reduced in high yields along with enantioselectivities utilizing our optimal catalytic asymmetric reduction conditions. The results are summarized in Table 2.

Although the effect of temperature on the enantioselectivity has been described many times in the literature,[5] no complete explanation has been reported. It is difficult to provide a straightforward explanation, because the enantioselectivity of this asymmetric reduction is likely to be a result of many complex factors, such as the structure and loading amount of the catalyst, the borane source and amount, the order and rate of the addition, the reduction temperature, the solvent, and the additive, etc. Very recently, Matos et al. found that $NaBH_4$ stabilizer in BH_3·THF can affect enantioselectivity in the oxazaborolidine-catalyzed asymmetric reduction of ketones with BH_3·THF as a reductant.[17] Our observations just add another aspect of the reaction and hope in

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gaining insight into the origin of the temperature effects on the borane reduction catalyzed by chiral oxazaborolidines.

A survey of the literature reveals that a variety of conditions have been recommended for the asymmetric reduction. We hope that the present study has addressed an important issue regarding the experimental aspects of the oxazaborolidine-catalyzed asymmetric reduction of ketones. We recommend that the present optimized protocol should be valuable for organic chemists interested in the methodology, especially for chemists working in the industry of large-scale production of chiral secondary alcohols from ketones.

Conclusion

The effect of temperature on the enantioselectivity of the oxazaborolidine-catalyzed asymmetric borane reduction of ketones has been investigated using alkyl aryl ketones with a variety of functional groups and (*S*)-2-methoxy-4,4-diphenyl-3,1,2-oxazaboro[3.3.0]octane as a catalyst. The results indicate that the noncatalytic borane reduction is an important and nonneglectable factor to the enantioselectivity in the reduction. The highest enantioselectivities were obtained usually between 20 and 30 °C in the asymmetric reduction.

Experimental Section

General Procedure for the Asymmetric Reduction of Ketones. 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 a 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 (25 min for the tracing conversion). The mixture was stirred at 25−30 °C (at the desired temperature for the tracing conversion) until the ketone disappeared on GC 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.

(*R*)-1-(4-Butoxyphenyl)ethanol (3d): colorless liquid; $[\alpha]^{20}_D = +37.3$ (*c* 0.80, $CHCl_3$), 98% ee value; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, $J = 7.5$ Hz, 3H, CH_3), 1.47 (d, $J = 6.3$ Hz, 3H, CH_3), 1.49 (sextet, $J = 7.5$ Hz, 2H, CH_2), 1.76 (quintet, $J = 7.5$ Hz, 2H, CH_2), 1.84 (s, br, 1H, OH), 3.95 (t, $J = 6.6$ Hz, 2H, OCH_2), 4.84 (t, $J = 6.3$ Hz, 1H, CH), 6.87 (d, $J = 8.4$ Hz, 2H, ArH), 7.28 (d, $J = 8.4$ Hz, 2H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.85, 19.21, 24.95, 31.29, 67.69, 69.99, 114.39, 126.59, 137.73, 158.54; MS (EI) *m*/*z* 194 (M^+, 29), 179 (62), 151 (6), 137 (4), 123 (100), 95 (28), 77 (14), 43 (22); IR ν (cm^{-1}) 3379 (OH), 2961, 2933, 1512, 1244. Anal. Calcd for $C_{12}H_{18}O_2$ (194.27): C, 74.19; H, 9.34. Found: C, 73.86; H, 9.18.

(*R*)-1-(4-Butylthiophenyl)ethanol (3l): colorless liquid; $[\alpha]^{20}_D = +28.3$ (*c* 1.2, $CHCl_3$), 99% ee value; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (t, $J = 7.2$ Hz, 3H), 1.46 (d, $J = 6.0$ Hz, 3H), 1.21−1.66 (m, 4H), 2.90 (t, $J = 7.2$ Hz, 2H), 4.83 (q, $J = 6.0$ Hz, 1H), 7.18−7.28 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 21.9, 25.0, 31.2, 33.4, 69.9, 125.9, 129.1, 143.4, 155.0; MS (EI) *m*/*z* 210 (M^+, 63), 195 (100), 167 (10), 139 (28), 123 (9), 111 (21), 77 (16), 43 (32); IR ν (cm^{-1}) 3373 (OH), 2958, 2928, 1493, 1450, 1094. Anal. Calcd for $C_{12}H_{18}OS$ (210.34): C, 68.52; H, 8.63. Found: C, 68.39; H, 8.60.

(*R*)-1-(4-Pentylthiophenyl)ethanol (3m): colorless liquid; $[\alpha]^{20}_D = +24.9$ (*c* 1.2, $CHCl_3$), 99% ee value; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J = 7.2$ Hz, 3H), 1.22−1.46 (m, 4H), 1.45 (d, $J = 6.3$ Hz, 3H), 1.59−1.69 (m, 2H), 2.89 (t, $J = 7.2$ Hz, 2H), 4.82 (q, $J = 6.3$ Hz, 1H), 7.24−7.30 (m, 4H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 22.2, 25.0, 28.8, 30.9, 33.6, 69.9, 125.9, 128.9, 135.9, 143.3; MS (EI) *m*/*z* 224 (M^+, 65), 209 (100), 181 (9), 139 (33), 111 (18), 77 (16), 43 (42); IR ν (cm^{-1}) 3357 (OH), 2958, 2928, 1599, 1494, 1094. Anal. Calcd for $C_{13}H_{20}OS$ (224.36): C, 69.59; H, 8.98. Found: C, 69.60; H, 9.16.

(*R*)-1-(4-*N*,*N*-Diethylaminophenyl)ethanol (3o): colorless liquid; $[\alpha]^{20}_D = +46.6$ (*c* 0.64, $CHCl_3$), 95% ee value; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, $J = 6.9$ Hz, 6H, $2CH_3$), 1.45 (d, $J = 6.3$ Hz, 3H, CH_3), 2.02 (s, br, OH), 3.33 (q, $J = 6.9$ Hz, 4H, $2CH_2$), 4.75 (t, $J = 6.3$ Hz, 1H, CH), 6.64 (d, $J = 8.7$ Hz, 2H, ArH), 7.20 (d, $J = 8.7$ Hz, 2H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 24.5, 44.3, 69.96, 111.6, 126.6, 132.4, 147.2; MS (EI) *m*/*z* 193 (M^+, 31), 178 (100), 160 (28), 150 (6), 134 (7), 132 (7), 77 (10), 43 (5); IR ν (cm^{-1}) 3389 (OH), 2970, 1614, 1521, 1265. Anal. Calcd for $C_{12}H_{19}NO$ (193.29): C, 74.57; H, 9.91; N, 7.25. Found: C, 74.33; H, 9.60; N, 7.17.

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Supporting Information Available: The chromatograms for the determination of ee of the unknown chiral alcohols **3d**, **3l**, **3m**, and **3o** and their ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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