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8. Spectroscopic data are as follows. **3a**: colorless oil; IR (neat) 1707 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.88 (s, 3H), 4.20 (d, J=14.4 Hz, 1H), 5.18 (d, J=14.4 Hz, 1H), 5.71 (s, 1H), 7.26-7.39 (m, 5H), 7.46-7.57 (m, 3H), 7.86-7.88 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 43.1, 49.4, 85.6, 123.5, 123.7, 127.6, 128.6, 128.7, 130.0, 132.1, 133.0, 136.8, 140.4, 167.5; MS m/z (relative intensity) 253 (M^+, 29), 222 (23), 194 (6), 133 (36), 91 (100), 77 (12). **4a**: colorless oil; IR (neat) 1734 (C=O), 1697 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 4.29 (d, J=14.4 Hz, 1H), 4.93 (s, 1H), 5.47 (d, J=14.4 Hz, 1H), 7.24-7.36 (m, 5H), 7.51-7.57 (m, 3H), 7.88-7.91 (m, 1H); MS m/z (relative intensity) 281 (M^+, 18), 222 (68), 133 (6), 91 (100).
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Catalytic Enantioselctive Reactions. Part 10. Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Chiral Oxazaborolidines

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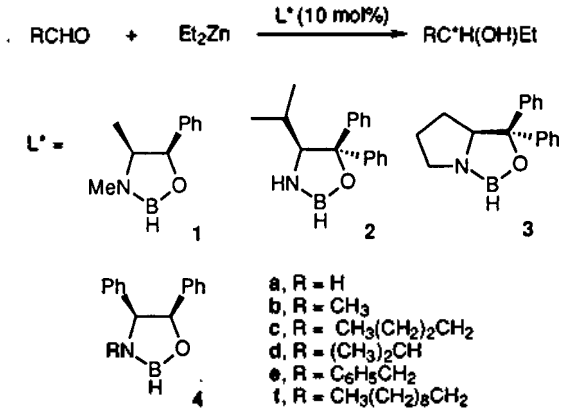
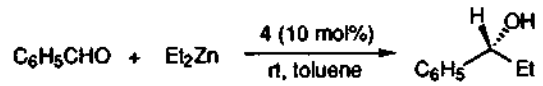
Catalytic enantioselective addition of diethylzinc to aldehydes has attracted much attention for the asymmetric synthesis of optically active secondary alcohols.[1] Accordingly, a wide range of catalysts for such reaction has been extensively developed.[1a] Among them, most of highly effective chiral catalysts for the reaction are both natural and synthetic β or γ-amino alcohols[2] (or thiols).[3] In 1989, Brown *et al.* repoted that a chiral oxazaborolidine, (4*S*,5*R*)-3,4-dimethyl-5-phenyl-1,3,2-oxazaborolidine (**1**), prepared from (1*R*,2*S*)-ephedrine with borane dimethyl sulfide provided 95% *ee* for the ethylation of benzaldehyde (Scheme 1). This value is superior to 66% ee obtained by the ephedrine itself.[4] They explained that the higher enantioselectivity of **1** might be attributable to more rigid structure of the catalyst by the formation of shorter B-O and B-N bonds than those of zinc metal. Recently, a number of chiral oxazaborolidines used as chiral catalysts for asymmetric borane reduction of ketones has been reported.[5] However, to the best of our knowledge, the use of other chiral oxazaborolidines with the exception of **1** for the ethylation to aldehydes has not been reported in literatures. Therefore, it appeared desirable to examine the catalytic asymmetric ethylation using other chiral oxazaborolidines. We chose first geminal diphenyl substituted oxazaborolidines, such as Itsuno's reagent (**2**)[6] and Corey's reagent (**3**),[7] which provided high enantioselctivities for borane reduction of ketones and tested the asymmetric ethylation using these reagents for benzaldehyde chosen as a model substrate. Thus, the reaction was carried out with addition of 2 equiv of diethylzinc to benzaldehyde in the presence of 10 mol% of **2** or **3** in toluene at room temperature (*ca.* 25 ℃). Unfortunately, the reaction provided the product alcohol of 62% *ee* and 16% *ee*, respectively. During this study, we found that an *erythro* diphenyl oxazaborolidine, (4*S*,5*R*)-3-isopropyl-4,5-diphenyl-1,3,2-oxazaborolidine (**4d**) generated from (1*R*,2*S*)-2-*N*-monoisopropylamino-1,2-diphenylaminoethanol (**5d**)[8] and borane dimethyl sulfide by literature procedure,[9] afforded 80% ee for benzaldehyde under the same reaction conditions. In this reaction, we observed that decrease of steric size of R in **4** diminished asymmetric inductions dramatically (entries 1, 2 and 3 in Table 1). At 0 ℃, the reaction proceeded much slowly with somewhat lower enantioselectivity (entry 5). Using **4d** as a chiral catalyst, substituted aryl aldehydes, such as *o*-, *p*-tolualdehyde and *p*-chlorobenzaldehyde, were alkylated to the corresponding alcohols with 69-77% *ee* (entries 1, 2, and 4 in Table 2). However, only low enantiomeric excesses (21-47% *ee*) were achieved for an unhindered aliphatic aldehyde, heptanal (entries 5-8). Addition to relatively hindered aliphatic aldehyde, such as 2,2-dimethylpropanal



Scheme 1.

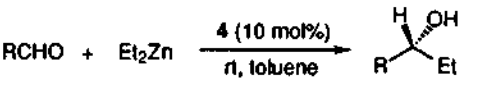
Table 1. Enantioselective Addition of Diethylzinc to Benzaldehyde[a]



Entry	Catalyst	Yield (%)[b]	% ee[c]
1	**4a**	83	8.3
2	**4b**	78	40
3	**4c**	82	64
4	**4d**	86	80
5	**4d**	43[d]	71
6	**4e**	86	60
7	**4f**	82	73

[a]Reactions were carried out in toluene at room temperature (*ca.* 25 ℃) in the presence of 10 mol% of **4**, unless otherwise indicated. [b]GC yields after 18 h. [c]Determined by capillary GC analyses using a Chiraldex GTA column (0.25 mm×20 m, Astec Inc.). [d]GC yield after 26 h at 0 ℃.

Table 2. Enantioselctive Addition of Diethylzinc to Aldehydes[a]



Entry	Aldehydes	Catalyst	Yield (%)[b]	% ee
1	*o*-$CH_3C_6H_4CHO$	**4d**	80	69[c]
2	*o*-$CH_3C_6H_4CHO$	**4f**	89	57[c]
3	*p*-$CH_3C_6H_4CHO$	**4d**	74	70[d]
4	*p*-ClC_6H_4CHO	**4d**	82	77[c]
5	$CH_3(CH_2)_5CHO$	**4a**	79	21[d]
6	$CH_3(CH_2)_5CHO$	**4c**	69	34[d]
7	$CH_3(CH_2)_5CHO$	**4d**	72	40[d]
8	$CH_3(CH_2)_5CHO$	**4f**	78	47[d]
9	$(CH_3)_3CCHO$	**4d**	69	72[d]
10	$(CH_3)_3CCHO$	**4f**	76	79[d]
11	*c*-$C_6H_{11}CHO$	**4d**	89	77[c]

[a,b]See the corresponding footnotes in Table 1. [c]Determined by capillary GC analyses of their (−)-menthyl carbonates.[10] [d]Determined by capillary GC analyses of their (*R*)-(+)-MTPA esters.[11] [e]Determined by capillary GC analysis of its trifluoroacetate using a Chiraldex GTA column (0.25 mm×20 m, Astec Inc.)

and cyclohexanecaboxaldehyde showed moderate enantioselectivity of 72% ee and 79% *ee*, respectively (entries 9 and 11). All the product alcohols obtained are consistently enriched with *R*-configurations. Other examples with **4** are summarized in Table 2.

Typical procedure: Addition of diethylzinc to benzaldehyde is representative. Diethylzinc (1 M in toluene, 2.0 mmol) was added to **4d** (0.5 M in toluene, 0.2 mmol) at 0 ℃ and stirred at room temperature (*ca.* 25 ℃) for 0.5 h. To this, benzaldehyde (1.0 M in toluene, 1 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. Finally, the excess diethylzinc was destroyed by addition of 1 N HCl at 0 ℃. The aqueous phase was extracted with ether, and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. GC analysis indicated the formation of 1-phenyl-1-propanol in a 86% yield. The product alcohol was isolated by bulb-to-bulb distillation and further purified with silica gel column chromatography. Capillary GC analysis using a Chiraldex GTA column (0.25 mm×20 m, Astec. Inc.) showed a composition of 90 (*R*) and 10 (*S*) (*i.e.*, 80% *ee*).

In conclusion, catalytic enantioselective additions of diethylzinc to aldehydes using chiral oxazaborolidines including geminal diphenyl oxazaborolidines, such as Itsuno's reagent (**2**) and Corey's reagent (**3**) were examined. Among them, **4d**, an *erythro* diphenyl oxazaborolidine, provided the best results to give the corresponding alcohols with moderate enantioselectivities of up to 80% *ee*.

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8. **4d** was obtained by reductive amination of (1*R*,2*S*)-2-amino-1,2-diphenylaminoethanol with acetone and cyanoborohydride in a 54% yield. Data for **4d**: mp 130-131 ℃; $[\alpha]_D^{22}$ 33.07 (*c* 1.0, $CHCl_3$); IR (KBr) 3305, 3187, 2912, 1467, 1373, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, 3H, *J*=2.4 Hz), 1.02 (d, 3H, *J*=2.4 Hz), 2.69 (m, 1H), 4.08 (d, 1H, *J*=5.4 Hz), 4.83 (d, 1H, *J*=5.2 Hz), 7.00-7.26 (m, 10H); Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49, found: C, 80.08; H, 8.36; N, 5.58.

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Catalytic Enantioselctive Reactions. Part 11. Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by A New Chiral Oxazaborolidine Derived from D-Mannitol

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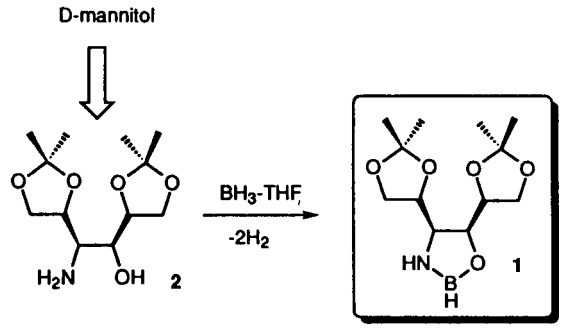
Chiral oxazaborolidine-borane adducts have been shown to be highly effective for the catalytic asymmetric reduction of prochiral ketones.[1] Although a number of chiral oxazaborolidines to provide high enantioselectivites for the reduction have been extensively developed, most of them are derived from β-amino alcohols bearing geminal diphenyl substituents obtained from natural α-amino acids.[2] Recently, it has been reported that chiral erythro β-amino alcohols which can block one face of the oxazaborolidines are also highly effective for such reduction as chiral sources, such as (1*S*,2*S*,3*R*,5*S*)-3-amino-2-hydroxy-pinane,[3a] (1*R*,2*S*)-2-amino-1-acenaphthenol,[3b] (1*R*,2*S*)-2-amino-1,2-diphenylethanol,[3c] (1*R*,2*S*)-1-amino-2-indanol,[3d,e] *endo* (or *exo*)-3-amino-2-hydroxybornanes derived from D-camphor,[3f] and (1*R*,2*S*)-ephedrine.[3g] However, to the best of our knowledge, the use of chiral oxazaborolidines derived from monosaccharides for the reduction has not been reported. In this communication, we describe the catalytic enantioselective borane reduction of ketones using a new class of chiral oxazaborolidine (**1**)[4] generated from an erythro β-amino alcohol, 3-amino-3-deoxyl-1,2;5,6-di-*O*-isopropylidene-D-altritol (**2**),[5] derived from D-mannitol (Scheme 1).

We examined asymmetric induction of the new oxazaborolidine **1** for borane reduction of acetophenone chosen as representative. The reduction was performed by dropping the ketone slowly over a period of 1 h to a solution of 0.6 equiv of borane-THF in the presence of 10 mol% of **1** in THF at room temperature (*ca.* 25 °C). The reaction proceeded rapidly to give (R)-1-phenylethanol of 81% ee in a 98% yield within 10 min (entry 3). We then extended our investigation to several kinds of ketones under the same reaction conditions. The results are summarized in Table 1. When steric size of R in aromatic ketones, PhCOR, was varied from Me → Et → *n*-Bu → *i*-Pr, optical yields of product alcohols obtained decreased, such as 81% *ee* for acetophenone, 77% *ee* for propiophenone, 75% *ee* for butyrophenone and 12% *ee* for isobutyrophenone (entries 1, 6, 7 and 8). Absolute configurations of all the product alcohols obtained were in good agreement with the expectation based on a proposed transition models[8] to give (*R*)-enantiomers except for that of isobutyrophenone. The reason for providing opposite absolute configuration ((*S*)-isomer) in the reduction of isobutyrophenone is not fully understood. For aliphatic ketones, increase of steric size of R in MeCOR resulted in increase of enantioselectivities of product alcohols, such as 40% *ee* for 2-heptanone, 52% *ee* for cyclohexyl methyl ketone, 53% ee for 4-



Scheme 1.

Table 1. Catalytic Asymmetric Borane Reduction of Various Ketones in the Presence of 1 in THF at Room Temperature[a]

Entry	Ketones	1 (mol%)	Product alcohols[b] % eec	Config.[d]
1	$PhCOCH_3$	2	71	*R*
2	$PhCOCH_3$	5	73	*R*
3	$PhCOCH_3$	10	81	*R*
4	$PhCOCH_3$	10	42[e]	*R*
5	$PhCOCH_3$	10	33[f]	*R*
6	$PhCOCH_2CH_3$	10	77	*R*
7	$PhCOCH_2CH_2CH_3$	10	75	*R*
8	$PhCOCH(CH_3)_2$	10	12	*S*
9	$PhCOCH_2Cl$	10	70	*S*
10	$PhCOCO_2CH_3$	10	58	*S*
11	$n\text{-}C_5H_{11}COCH_3$	10	40	*R*
12	$(CH_3)_2CHCH_2COCH_3$	10	53	*R*
13	$c\text{-}C_6H_{11}COCH_3$	10	52	*R*
14	$(CH_3)_3CCOCH_3$	10	80	*R*
15	2,2-Dimethylcyclopentanone	10	51[g]	*R*
16	$(CH_3O)_2CHCOCH_3$	10	68[g]	*S*

[a]The reactions were carried out with slow addition of ketones over a period of 1 h to mixture of 10 mol% of 1 and 0.6 eq of BH_3-THF in THF at room temperature (*ca.* 25 °C), unless otherwise indicated. [b]The reduction proceeded rapidly to give the corresponding alcohols in >98% yields within 10 min. [c]Determined by capillary GC analyses of their (*R*)-MTPA esters,[9] unless otherwise indicated. [d]By the comparison of elution orders of (*R*)-MTPA esters of the authentic optically active alcohols. [e]% Ee of the alcohol obtained at 0 °C. [f]% Ee of the alcohol obtained by rapid mixing of all the reagents followed by quenching and workup after 10 min. [g]Determined by capillary GC anaylses of their (−)-menthyl carbonates.[10]