Pinane-Type Tridentate Reagents for Enantioselective Reactions: Reduction of Ketones and Addition of Diethylzinc to Aldehydes

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The reduction of aryl and alkenyl methyl ketones using lithium aluminum hydride modified with (1*R*,2*S*,3*S*,5*R*)-(+)-10-anilino-3-ethoxy-2-hydroxypinane (**10b**) afforded chiral secondary alcohols in 83−96% chemical yields and 50−91% ee with dominance of *R* enantiomers. The reduction of acetophenone in the presence of lithium iodide gave the alcohol product with higher ee. On the other hand, the addition reaction of diethylzinc to benzaldehyde using the pinane-based diols **5**−**9** as promoters gave 1-phenylpropanol in favor of the *S* enantiomer up to 88% ee. Using the pinane-based alcohols **10a**−**e** as promoters, the *R* enantiomer was obtained as the major product. The addition reactions of diethylzinc to various substituted benzaldehydes, employing the diol ligands **5c** and **8e**, afforded predominantly the corresponding (*S*)-alcohols. The chiral modifiers **5**−**10** were prepared from (1*R*)-(−)-myrtenol and were readily recovered (>90%) after the asymmetric reactions. In this study, LAH reduction and Et_2Zn addition are complementary methods for the preparation of optically active secondary alcohols. The ligand 10-butylanilino-2,3-dihydroxypinane **5c** promoted the Et_2Zn additions effectively, whereas the modifier 10-anilino-3-ethoxy-2-hydroxypinane **10b** induced the LAH reductions in a highly enantioselective manner.

Introduction

Enantiomerically pure chiral secondary alcohols are important starting materials for the total synthesis of natural products.[1] Asymmetric reduction of ketones[2] and nucleophilic addition to aldehydes[3] are two general methods for the preparation of optically active secondary alcohols. In this paper, we report the use of pinane-type tridentates **5**−**12** (Figure 1) as the chiral modifiers of lithium aluminumhydride (LAH) reductions and diethylzinc additions. Asymmetric LAH reduction[2] and Et_2Zn addition[3] have been advanced to achieve high efficiency and remarkable enantioselectivity. Pinanes and their derivatives are economic and readily available compounds; pinane-derived boranes,[4] such as Alpine-Borane and $(Ipc)_2BCl$, have been successfully utilized in asymmetric reduction of ketones. Unlike bidentate chiral ligands, the tridentate chiral ligands are not extensively studied. We envisaged that LAH and Et_2Zn can be modified by the tridentate ligands **5**−**12** to form chiral reagents with rigid structure, which may exert distinct stereochemical bias to convey asymmetric induction. We report herein the study in this aspect.[5]

Results and Discussion

Preparation of pinane-type tridentates **5**−**12** was straightforward (Scheme 1). (1*R*)-(−)-Myrtenol (**1**) was reacted with PBr_3 to give (1*R*)-(−)-myrtenyl bromide (**2**) in 85% yield. The substitution reaction of **2** was easily carried out by treatment with a series of amines and alcohols, giving **3** and **4**, which were subsequently converted to diols **5**−**9** by the known procedure using OsO_4−Me_3NO as the oxidizing agents. Alternatively, compounds **4** could be prepared by alkylation of (1*R*)-(−)-myrtenol with alkyl bromides. Selective alkylation of the secondary hydroxyl group of the diols **5**−**9** furnished the desired modifiers **10**−**12** in respectable yields.

To determine the optical purity of the prepared ligands, a 3,5-dinitrobenzoate derivative **13** was synthesized from **10b** for HPLC analysis (Scheme 2). A racemic mixture of *β*-pinene underwent photooxidation, followed by $NaBH_4$ reduction of the resulting hydroperoxide, to afford (±)-myrtenol. By a procedure similar to that described in Scheme 1, (±)-myrtenol was transformed into (±)-**10b** via dihydroxylation and selective ethylation of the resulting diol. Treatment of (±)-**10b** with 3,5-dinitrobenzoyl chloride in the presence of Et_3N yielded a racemic ester (±)-**13**, of which two enantiomers were separable on a

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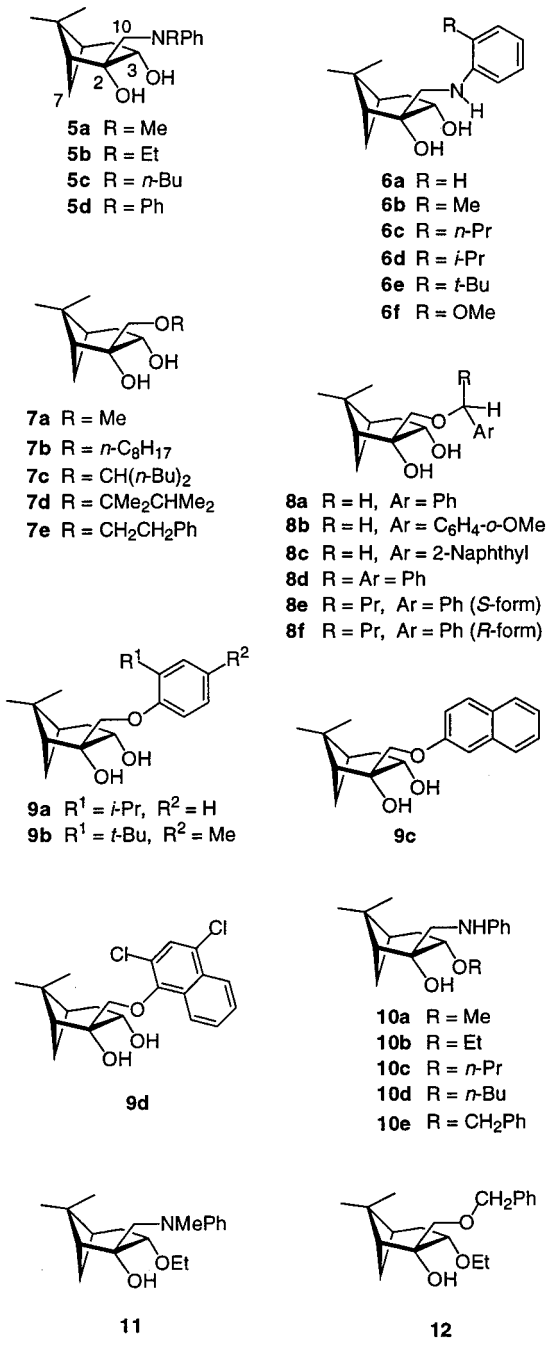
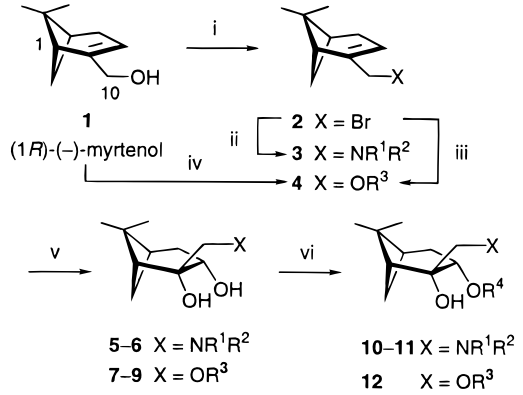


Figure 1. Pinane-type tridentates used in this study.

Chiralcel OD column. An optically enriched sample **10b**, $[\alpha]^{25}_D$ +11.5 ($CHCl_3$, *c* 1.04) was similarly prepared from (1*R*)-(−)-myrtenol and converted to the ester **13**, which consisted of two enantiomers in a ratio of 96.9:3.1 as determined by the HPLC analysis. The original sample of (1*R*)-(−)-myrtenol and the ligand (+)-**10b** therefrom were thus deduced to have 93.8% enantiomeric excess (ee).

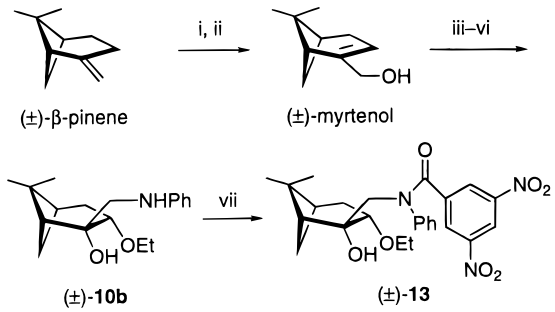
LAH Reductions. Our preliminary study[5a,b] indicated that secondary alcohols can be obtained in moderate optical yields (up to 52%) in the reduction of prochiral ketones by LAH using pinane-based diol modifiers **5**−**9**. After examination of the Dreiding molecular models of putative transition structures (see Figure 3)[6] in an attempt to develop more effective modifiers, we envisaged that a C-3 alkoxy group is sterically more demanding than a hydroxyl group and therefore can better differentiate the two reaction faces of the reactant. Thus, rationally designed pinane-based modifiers **10**−**12**, possessing a rigid bicyclic pinane skeleton and an ethoxy substituent at C-3, were prepared.[5c] The LAH reduction of acetophenone using modifiers **11** or **12**, having benzyloxy or *N*-methylanilino groups at C-10, still resulted in low enantioselectivity (up to 26% ee). However, remarkable enantioselectivity was procured by using the modifier **10** containing an anilino group at C-10. Table 1 lists the results of asymmetric LAH reductions of acetophenone and 1-acetylnaphthalene using modifiers **10a**−**e** with different alkoxy groups at C-3. The reactions were carried out in Et_2O/THF (1:10) solution with a ratio of LAH/modifier/ketone = 2.0:2.2:1.0. The best ee values, 62% and 80% for the reactions of acetophenone and 1-acetylnaphthalene, were obtained by using the modifier **10b** having an ethoxy group at C-3. Use of **10e** having a benzyloxy group at C-3 resulted in an opposite enantiotopic selection, though the ee values were low (15% and 3%).

Scheme 1[a]



[a] Reagents and conditions: (i) PBr_3, pyridine, PhH, rt, 1 h, 85%; (ii) KH, R^1R^2NH, THF, rt, 3 h, 74−85%; (iii) R^3OH, KH, THF, rt, 6 h, 65−81%; (iv) NaH or KH, R^3Br, rt, 6 h, 80−98%; (v) OsO_4, Me_3NO, THF/Me_2CO/H_2O, reflux, 4 days, 50−81%; (vi) NaH, R^4Br, rt, 24 h, 76−92%.

Scheme 2[a]



[a] Reagents and conditions: (i) O_2, TPP, *hν*, $CHCl_3$; (ii) $NaBH_4$, MeOH; (iii) PBr_3, pyridine, PhH, rt, 85%; (iv) KH, R^1R^2NH, THF, rt, 85%; (v) OsO_4, Me_3NO, THF/Me_2CO/H_2O, reflux, 50%; (vi) NaH, EtBr, 83%; (vii) 3,5-$(NO_2)_2C_6H_3COCl$, Et_3N.

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Table 1. LAH Reduction of Acetophenone and 1-Acetylnaphthalene Using Modifiers 10a−e[a]

entry	ketone	modifier, R =	product (yield/%)[b]	ee[c]/ %	config[d]
1	acetophenone	**10a**, Me	**14a** (83)	48	*R*
2	acetophenone	**10b**, Et	**14a** (85)	62	*R*
3	acetophenone	**10c**, Pr	**14a** (85)	47	*R*
4	acetophenone	**10d**, Bu	**14a** (86)	46	*R*
5	acetophenone	**10e**, $PhCH_2$	**14a** (84)	14	*S*
6	2-acetylnaphthalene	**10a**, Me	**14i** (84)	55	*R*
7	2-acetylnaphthalene	**10b**, Et	**14i** (93)	80	*R*
8	2-acetylnaphthalene	**10c**, Pr	**14i** (87)	62	*R*
9	2-acetylnaphthalene	**10d**, Bu	**14i** (86)	66	*R*
10	2-acetylnaphthalene	**10e**, $PhCH_2$	**14i** (90)	3	*S*

[a] The reaction was conducted in Et_2O/THF (1:10) solution at −78 °C for 1 h with a molar ratio of LAH/modifier/ketone = 2.0: 2.2:1.0. [b] Isolated yields. [c] The ee value was determined by HPLC analysis. [d] The configuration of the major enantiomer was assigned by comparison of the optical rotation with the reported value.

Table 2. Reduction of Methyl Ketones $RCOCH_3$ with $LiAlH_4$ and Chiral Modifier 10b[a]

entry	$RCOCH_3$, R =	additive (equiv)[b]	product (yield/%)	ee (%)	config
1	Ph		**14a** (85)	62	*R*
2	Ph	LiI (1)	**14a** (91)	83	*R*
3	*o*-tolyl		**14b** (86)	79[c]	*R*
4	2-bromophenyl		**14c** (86)	78	*R*
5	2-chlorophenyl		**14d** (86)	78	*R*
6	2-methoxyphenyl		**14e** (86)	91	*R*
7	2-nitrophenyl		**14f** (85)	72[d]	*R*
8	2,4-dimethylphenyl		**14g** (87)	74	*R*
9	2,5-dimethoxyphenyl		**14h** (91)	91	R
10	1-naphthyl		**14i** (93)	80	*R*
11	1-naphthyl	LiI (1)	**14i** (92)	84	*R*
12	1-naphthyl	HMPA (6)	**14i** (85)	66	*R*
13	2-naphthyl		**14j** (96)	50	*R*
14	2-phenanthyl		**14k** (94)	87	
15	2-fluorenyl		**14l** (95)	81	
16	2-furyl		**15** (88)	52	*R*
17	2-thienyl		**16a** (90)	83	*R*
18	2-(3-methylthienyl)		**16b** (92)	54	
19	2-(5-chlorothienyl)		**16c** (92)	61	
20	2-(5-bromothienyl)		**16d** (94)	63	
21	PhCH=CH		**17** (93)	50	*R*
22	PhCH=CH	LiI(1)	**17** (91)	52	*R*
23	1-cyclohexenyl		**18** (89)	74[d]	*R*

[a] Refer to the footnote of Table 1 for reaction conditions, isolated yields, ee values, optical yields, and absolute configuration of major enantiomers. [b] Based on the amount of respective ketone. [c] The alcohol product was treated with phenyl isocyanide to give the corresponding carbamate, of which the ee value was determined by HPLC analysis. [d] The alcohol product was treated with 3,5-dinitrobenzoyl chloride to give the corresponding ester, of which the ee value was determined by HPLC analysis.

Several mono- and disubstituted acetophenones were reduced by LAH/**10b** (Table 2) to afford the corresponding phenylethanols **14a**−**h** (Figure 2) in favor of the *R* configuration alcohols (62−91% ee). The chiral reducing agent was prepared in situ by mixing a standardized Et_2O stock solution of LAH with modifier **10b** at room temperature for 1 h. THF solutions of prochiral ketones were then added at −78 °C and stirred for another 1 h to furnish the corresponding secondary alcohols in 83−96% chemical yields. The nitro group did not interfere with the reduction of methyl 2-nitrophenyl ketone (Table 2, entry 7), giving 85% of the desired alcohol. The chiral modifier **10b** was recovered nearly quantitatively (>96%) from the reaction mixture by silica gel chromatography. Among the examined examples, the reduction of 2′-methoxyacetophenone and 2′,5′-dimethoxyacetophenone

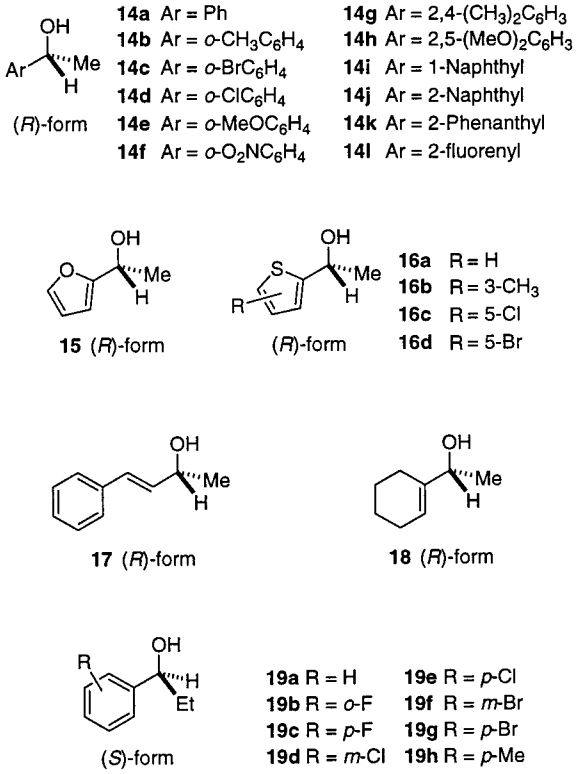

Figure 2. In this study, the asymmetric LAH reduction gave predominantly (*R*)-alcohols **14**−**18**, whereas the asymmetric Et_2Zn addition gave predominantly (*S*)-alcohols **19**.

(Table 2, entries 6 and 9) gave the highest optical yield (97%) by calculation based on the maximum optical purity (93.8%) of the modifier **10b**.

A wide range of aromatic and alkenyl methyl ketones can be reduced by LAH in the presence of modifier **10b** to give chiral secondary alcohols in synthetically useful yields and enantioselectivities. 1-Acetylnaphthalene, 2-acetylnaphthalene, 2-acetylphenanthrene, and 2-acetylfluorene were reduced to give 80, 50, 87, and 81% ee, respectively. Heterocyclic compounds, such as 2-acetylfuran and 2-acetylthiophenes (Table 2, entries 16−20), were similarly reduced to achieve 52−83% ee. The reductions of 4-phenyl-3-buten-2-one and cyclohexenyl methyl ketone also produced the corresponding allylic alcohols with predominance of *R* enantiomers. No 1,4-reduction products were observed in such instances.

A 1:10 mixture of Et_2O/THF appeared to be the solvent of choice for the asymmetric LAH reduction. When the reduction of 1-acetylnaphthalene was conducted in Et_2O or Et_2O/THF (1:1) solution, the enantioselectivity dropped dramatically, giving **14i** with 31−35% ee. As the addition of HMPA or lithium iodide is known to affect the enantioselectivities in certain reactions (such as alkylation reactions of enolates or allylmetals),[7] we also examined their effects in the LAH reductions. Our results indicated that the enantioselectivity of the alcohol products was increased in some instances by addition of LiI (Table 2, entries 2, 11, and 22). On the other hand, the enantioselectivity decreased in the reduction of 1-acetylnaphthalene in the presence of the cosolvent HMPA (Table 2, entry 12).

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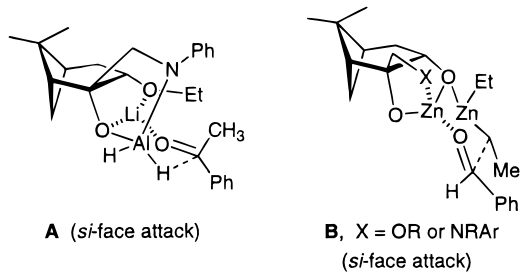

A (*si*-face attack) **B**, X = OR or NRAr (*si*-face attack)

Figure 3. Favorable transition states proposed for the asymmetric LAH reduction (**A**) and Et_2Zn addition (**B**).

The facial selectivities realized in the LAH reduction of aromatic methyl ketones using modifier **10b** are superior to those utilizing simple terpenic diol modifiers (<30% ee).[8] Our results demonstrated the importance of the anilino substituent at C-10 in the modifier **10b**, compared with the *N*-methylanilino substituent of **11** or the benzyloxy substituent of **12**, for the control of chirality in the enantioselective LAH reduction of ketones. The asymmetric induction was further improved by the ethoxy group at C-3 of modifier **10b**, compared with the hydroxyl group of modifiers **5**−**9**. A possible transition state for the stereochemical outcome, as exemplified by the reaction of acetophenone, is illustrated in Figure 3 (**A**).[6] The chiral LAH/**10b** reagent is presumably formed by O−Al−N bondings and O−Li−O chelation. The ethoxy group at C-3 thus plays a role to differentiate two reaction faces of this chiral reducing agent. The incoming carbonyl group would coordinate with the Li^+ ion to form a chairlike transition state, in which the aryl group is equatorially oriented. Attack of hydride thus occurs at the *si*-face of acetophenone to furnish the observed *R* alcohol. The alternative transition state by placing the bulkier aryl group on the axial position is disfavored as it would exert repulsions against the anilino and ethoxy groups. Diols **5**−**9** are poor modifiers because their hydroxyl groups at C-2 and C-3 would compete in bonding with aluminum hydride and thus reduce the face selection.

Et_2Zn Addition. Unlike LAH reduction, modifiers **5**−**10** operated differently in the addition of diethylzinc onto benzaldehyde. The diol ligands **5**−**9** turned out to be better promoters than the alcohol ligand **10** for the asymmetric Et_2Zn addition reactions. The addition reaction with benzaldehyde was generally carried out at room temperature by using 2.2 equiv of Et_2Zn and 2 mol % of a pinane-type promoter (Table 3). The reaction using alcohol ligands **10a**−**d** gave the product 1-phenylpropanol (**19a**) in favor of the *R* enantiomer (9−50% ee), whereas that using diol ligands **5**−**9** gave predominantly the *S* enantiomer (up to 88% ee).

The chemical yields of *S* enriched alcohol **19a** were in the range of 75−92%, and the chiral ligands were recovered in good yields (ca. 94%) from the reaction mixture by silica gel chromatography. The ee value of **19a** was determined by HPLC on a Chiralcel OD column. In most cases, the reactions performed in hexane solution tended to show higher asymmetric induction than those performed in toluene. The Et_2Zn addition reactions using either the ligand **8e** or the diastereomer **8f**, prepared from (1*R*)-myrtenol with (*S*)- or (*R*)-1-phenylbutanol,

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Table 3. Chiral Ligand Promoted Reaction of Benzaldehyde with Diethylzinc, Giving Alcohol 19a[a]

entry	ligand	yield[b]/%	ee[b]/%	config[b]
1	**10a**	(60)[c]	(9)[c]	*R*
2	**10b**	(73)[c]	(47)[c]	*R*
3	**10c**	(68)[c]	(50)[c]	*R*
4	**10d**	(66)[c]	(46)[c]	*R*
5	**5a**	85 (81)[c]	82 (62)[c]	*S*
6	**5b**	84 (83)[c]	82 (79)[c]	*S*
7	**5c**	83 (81)[c]	88 (79)[c]	*S*
8	**5d**	84 (82)[c]	82 (79)[c]	*S*
9	**6a**	87 (77)[c]	37 (16)[c]	*S*
10	**6b**	81 (80)[c]	77 (69)[c]	*S*
11	**6c**	77 (77)[c]	69 (62)[c]	*S*
12	**6d**	83 (79)[c]	86 (78)[c]	*S*
13	**6e**	84 (84)[c]	84 (85)[c]	*S*
14	**6f**	79 (75)[c]	23 (11)[c]	*S*
15	**7b**	86 (88)[c]	77 (57)[c]	*S*
16	**7c**	87 (83)[c]	81 (72)[c]	*S*
17	**7d**	86 (84)[c]	86 (80)[c]	*S*
18	**7e**	84 (87)[c]	81 (73)[c]	*S*
19	**8a**	88 (88)[c,d]	76 (74)[c,d]	*S*
20	**8b**	84 (85)[c]	77 (71)[c]	*S*
21	**8c**	81 (88)[c]	70 (79)[c]	*S*
22	**8d**	84 (85)[c]	79 (78)[c]	*S*
23	**8e**	91 (92)[c,d]	86 (82)[c,d]	*S*
24	**8f**	(68)[e]	(70)[e]	*S*
25	**9a**	80 (85)[c]	70 (80)[c]	*S*
26	**9b**	85 (90)[c]	84 (84)[c]	*S*
27	**9c**	82 (85)[c]	61 (75)[c]	*S*
28	**9d**	85 (89)[c]	83 (79)[c]	*S*

[a] The reaction was conducted in hexane solution at room temperature for 16 h with a molar ratio of PhCHO/Et_2Zn/ligand = 1.0:2.2:0.02. [b] Refer to the footnote of Table 1 for isolated yields, ee values, and absolute configuration of major enantiomers. [c] The number in parentheses indicates the result of a similar reaction conducted in toluene solution. [d] The yield and ee value of the alcohol product **19a** decreased when the reaction was performed with 1.2 equiv of Et_2Zn in toluene solution. Using **8a**: 68% yield, 66% ee. Using **8e**: 72% yield, 75% ee. [e] The reaction was performed with 1.2 equiv of Et_2Zn in toluene solution.

Table 4. Nonlinear Effect of Optically Enriched Ligand 8e in the Reaction of Benzaldehyde with Diethylzinc, Giving Alcohol 19a[a]

entry	ee/% of **8e**	yield/%	ee/% of **19a**	config
1	14.1	88	33	*S*
2	23.5	87	41	*S*
3	37.6	89	54	*S*
4	47.0	88	67	*S*
5	70.5	88	77	*S*
6	93.8	91	82	*S*

[a] Molar ratio PhCHO/Et_2Zn/**8e** = 1.0:2.2:0.02. The reaction was conducted in hexane solution, refer to Table 3 for detailed conditions.

occurred with the same enantiotopic face selection (compared entries 23 and 24 of Table 3). The enantioselectivity slightly decreased when the reaction was conducted with 1.2 equiv of Et_2Zn (entries 19 and 23, Table 3). A nonlinear asymmetric effect was observed by using the chiral ligand **8e** of different optical purities to promote the addition of Et_2Zn with PhCHO. The product (*S*)-**19a** was obtained in a higher optical yield by comparison with the optical purity of the starting ligand **8e**, when **8e** had 70.5% or less enantiomeric excesses (entries 1−5, Table 4).

Using diol ligands **5c** or **8e** as the chiral promoters, the addition reactions of Et_2Zn to various substituted benzaldehydes also afforded the products **19b**−**h** in dominance of *S* enantiomers (Table 5). The ee values of **19b**−**h** were determined by HPLC analyses of their

Table 5. Chiral Ligand Promoted Reaction of Substituted Benzaldehydes with Diethylzinc[a]

entry	aldehyde	ligand	product[b]	yield/%	ee/%	config[c]
1	*o*-FC_6H_4CHO	**5c**	**19b**	80	75	*S*
2	*o*-FC_6H_4CHO	**8e**	**19b**	80	78	*S*
3	*p*-FC_6H_4CHO	**5c**	**19c**	81	80	*S*
5	*m*-ClC_6H_4CHO	**5c**	**19d**	89	79	*S*
6	*m*-ClC_6H_4CHO	**8e**	**19d**	84	71	*S*
7	*p*-ClC_6H_4CHO	**5c**	**19e**	84	84	*S*
8	*p*-ClC_6H_4CHO	**8e**	**19e**	81	82	*S*
9	*m*-BrC_6H_4CHO	**5c**	**19f**	80	79	
10	*m*-BrC_6H_4CHO	**5c**	**19f**	86	72	
11	*p*-BrC_6H_4CHO	**5c**	**19g**	80	65	*S*
12	*p*-BrC_6H_4CHO	**8e**	**19g**	78	55	*S*
13	*p*-MeC_6H_4CHO	**5c**	**19h**	87	67	*S*
14	*p*-MeC_6H_4CHO	**8e**	**19h**	86	54	*S*

[a] The reaction was conducted in hexane solution with a molar ratio of aldehyde/Et_2Zn/ligand = 1.0:2.2:0.02. Refer to Table 3 for detailed conditions. [b] The alcohol products or their 3,5-dinitrobenzoate derivatives were analyzed by HPLC on a Chiralcel OD column to determine the ee values. [c] Configuration of the major enantiomer was assigned according to the measurement of optical rotation.

corresponding 3,5-dinitrobenzoate derivatives on a Chiralcel OD column.

As the addition reaction showed a nonlinear asymmetric effect, it may involve a quite complicated mechanism.[3,9] To explain why the diol ligands **5**−**9** are better promoters than the alcohol ligands **10** for the formation of **19a** with higher chemical yields and ee values, one can assume that a diol ligand favors to react with Et_2Zn to form a cyclic dialkoxyzinc intermediate.[9] The zinc ion in this intermediate is also chelated with the anilino or alkoxy group at C-10 (Figure 3, **B**). By analogy to previously proposed intermediates[3,9] for diol ligand-promoted Et_2Zn addition reactions, a transition state illustrated in **B** is a reasonable working hypothesis. It involves a chairlike form with the participation of two Et_2Zn molecules. The bulkier phenyl group would take the energetically favorable equatorial position and transfer of an ethyl group occurs at the *si*-face of PhCHO to furnish the observed (*S*)-alcohol. Several other possible intermediates were excluded for steric reasons according to examination of their molecular models.

Conclusion

We have demonstrated that asymmetric LAH reduction of ketones and Et_2Zn addition to aldehydes are effectively promoted by pinane-type tridentate ligands. These two methods are complementary in the preparation of optically active secondary alcohols. Formation of (*R*)-alcohols is favored in the LAH reduction, whereas formation of (*S*)-alcohols is favored in the Et_2Zn addition. The diol ligands **5**−**9** are efficient promoters for asymmetric Et_2Zn additions, whereas the alcohol **10b** is the best modifier for LAH reductions according to our current results. We have also found that asymmetric Et_2Zn addition promoted by alcohols **10** showed an enantiotopic preference opposite to those reactions using diol promoters **5**−**9**. The designed compounds **5**−**10** may not be ideal modifiers by comparison with those reagents showing extremely high enantioselectivity in the similar reactions.[2,3] However, the present methods are still practical as the pinane-type reagents are easily prepared, and these chiral modifiers are recovered from the reaction mixture in nearly quantitative yields.

Experimental Section

All reactions were carried out under nitrogen atmosphere except as otherwise noted. Melting points are uncorrected. ^1H NMR spectra were recorded at 200, 300, or 400 MHz; ^{13}C NMR spectra were recorded at 50, 75, or 100 MHz. Chloroform (δ = 7.24 ppm) was used as internal standard in ^1H NMR spectra. Mass spectra were recorded at an ionizing voltage of 70 or 20 eV. Merck silica gel 60F sheets were used for analytical thin-layer chromatography. Column chromatography was performed on SiO_2 (70−230 mesh); gradients of EtOAc and *n*-hexane were used as eluents. Enantiomeric excess was determined by HPLC using a Chiralcel OD column (0.46 cm i.d. × 25 cm). The optical rotations were measured in $CHCl_3$ solution on a digital polarimeter with a cuvette of 1 cm length.

General Procedure for the Preparation of C-10 Substituted α-Pinanediols 5−9. To a stirred suspension of KH (24 mmol) in dry THF (20 mL) was added dropwise the nucleophile (12 mmol, aniline or alcohol) via a syringe, and the reaction was stirred at room temperature for 30 min after the completion of the addition. A solution of myrtenyl bromide (12 mmol) dissolved in THF (10 mL) was then added slowly. The reaction was stirred at room temperature for 3−6 h. The reaction was quenched by addition of H_2O (2 mL). THF was removed under reduced pressure, and the residue was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash column chromatography (EtOAc/hexane = 1:20) to give the C-10 substituted α-pinenes **3** and **4** (65−85% chemical yields).

To a stirred solution of the α-pinene derivative (**3** or **4**, 10 mmol) in THF (28 mL)/water (3 mL)/acetone (10 mL) was added trimethylamine *N*-oxide (12 mmol) at room temperature. A 1% w/w OsO_4−THF solution (8 mL, 3 mol %) was added, and the mixture was refluxed. The reaction was monitored by TLC until no starting material could be detected (ca. 4 days). The reaction mixture was quenched by addition of saturated $NaHSO_3$ solution (20 mL). The solvent was removed by rotary evaporation. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane = 1:10) to furnish the desired C-10-substituted α-pinanediols **5**−**9** (50−81% chemical yields).

General Procedure for the Preparation of C-3 Alkoxy-Substituted α-Pinanols 10−12. To a stirred suspension of NaH (3 mmol) in dry THF (20 mL) was added a THF solution (5 mL) of the diol **5**−**9** (1 mmol). After 30 min, a solution of alkyl bromide (1.1 mmol) in THF (3 mL) was added via a syringe, and the mixture was stirred at room temperature for 24 h. The reaction was quenched by addition of H_2O (1 mL). THF was removed under reduced pressure, and the residue was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash column chromatography (silica

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gel) with elution of hexane/EtOAc to give the corresponding C-3 alkoxy-substituted α-pinanol products **10**−**12** (76−92% chemical yields).

General Procedure for the LAH Reduction of Methyl Ketones (Tables 1 and 2). A stock solution of lithium aluminum hydride (0.6 mL of 1 M solution in Et_2O) was placed in a 10 mL round-bottomed flask. An appropriate chiral modifier (**10a**−**e**, 0.66 mmol, 1.1 equiv) in THF solution (3 mL) was added dropwise at room temperature, and evolution of hydrogen was apparent. The mixture was stirred at room temperature for 1 h and cooled to −78 °C, and a solution of methyl ketone (0.3 mmol, 0.5 equiv) in THF (3 mL) was added dropwise. The reaction was complete in 1 h as shown by TLC analysis. A solution of dilute aqueous HCl (5%) solution (3 mL) was added slowly, and the mixture was warmed to room temperature and stirred for 4 h. After removal of THF by rotary evaporation, the mixture was extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a silica gel column by elution with gradients of EtOAc/hexane to give the desired alcohol products **14a**−**18** (83−96% chemical yields) and the modifier **10a**−**e** (90−96% recovery). The ee values of the alcohol products were determined by HPLC on a Chiralcel OD column (2-propanol/hexane elution). The absolute configuration of major enantiomers was assigned by comparison of the optical rotations with the reported values.

General Procedure for the Addition of Diethylzinic to Aldehydes (Tables 3−**5).** The chiral catalyst (**5**−**10**, 0.038 mmol, 0.02 equiv) was dissolved in hexane (10 mL) and Et_2Zn (4.2 mmol, 2.2 equiv, 1 M standard solution in hexane) was injected. An appropriate aldehyde (1.9 mmol, 1 equiv) was added dropwise via a syringe, and the mixture was stirred for 16 h. The mixture was quenched by addition of 5% HCl (3 mL). The hexane layer was separated and subsequently washed with brine. After drying over $MgSO_4$ and filtration, the hexane was removed under reduced pressure, and the crude alcohol products **19**−**22** (60−92% chemical yields) were purified by flash column chromatography (hexane/EtOAc). The chiral catalyst was recovered in 92−96% yields. The ee values of the alcohol products were determined by HPLC on a Chiralcel OD column (2-propanol/hexane elution). The absolute configuration of the major enantiomer was assigned by comparison of the optical rotation with the reported value.

(1*R*,2*S*,3*S*,5*R*)-(+)-6,6-Dimethyl-2-(*N*-butylanilino)-methylbicyclo[3.1.1]heptane-2,3-diol (5c): solid; mp 80−81 °C; $[\alpha]^{25}_D = +11.1$ ($c = 0.94$, $CHCl_3$); IR ($CHCl_3$) 3520 (OH), 1605, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (dd, J = 8.0, 7.8 Hz, 2 H), 6.92 (d, J = 8.0 Hz, 2 H), 6.79 (t, J = 7.8 Hz, 1 H), 4.09 (dd, J = 9.3, 5.7 Hz, 1 H), 3.48 (d, J = 15.0 Hz, 1 H), 3.33 (t, J = 7.8 Hz, 2 H), 3.30 (d, J = 15.0 Hz, 1 H), 2.53−2.43 (m, 1 H), 2.24−2.16 (m, 1 H), 2.15 (t, J = 6.0 Hz, 1 H), 1.97−1.91 (m, 1 H), 1.70 (ddd, J = 13.8, 5.4, 2.4 Hz, 1 H), 1.58−1.26 (m, 4 H) 1.47 (d, J = 9.6 Hz, 1 H), 1.28 (s, 3 H), 1.04 (s, 3 H), 0.93 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.89, 129.18 (2 C), 118.41, 115.46 (2 C), 76.00, 67.64, 61.33, 53.43, 51.43, 40.55, 38.82, 38.00, 28.03, 27.74, 27.67, 24.28, 20.21, 13.86; MS *m*/*z* (rel intensity) 317 (13, M^+), 162 (100), 149 (9); HRMS calcd for $C_{20}H_{31}NO_2$ 317.2355, found 317.2353.

(1*R*,1′*R*,2*S*,3*S*,5*R*)-(+)-6,6-Dimethyl-2-(1-phenylbutoxy)-methylbicyclo[3.1.1]heptane-2,3-diol (8e): solid; mp 62−63 °C; $[\alpha]^{25}_D = +61.6$ ($c = 0.7$, $CHCl_3$); IR ($CHCl_3$) 3570, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.23 (m, 5 H), 4.24 (dd, J = 7.8, 5.7 Hz, 1 H), 4.04 (dt, J = 9.3, 5.7 Hz, 1 H), 3.39 (s, 1 H, OH), 3.29 (d, J = 9.3 Hz, 1 H), 3.25 (d, J = 9.3 Hz, 1 H), 3.02 (d, J = 3.8 Hz, 1 H, OH), 2.44−2.36 (m, 1 H), 2.21−2.16 (m, 1 H), 2.10 (t, J = 6.0 Hz, 1 H), 1.91−1.76 (m, 2 H), 1.71−1.56 (m, 2 H), 1.48 (d, J = 9.9 Hz, 1 H), 1.43−1.27 (m, 2 H), 1.19 (s, 3 H), 0.89 (t, J = 7.2 Hz, 3 H), 0.71 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.24, 128.43 (2 C), 127.65, 126.66 (2 C), 82.79, 78.25, 75.14, 66.09, 48.95, 40.56, 40.28, 38.65, 37.10, 27.77, 27.74, 23.83, 17.10, 13.90; MS *m*/*z* (rel intensity) 318 (1, M^+), 155 (72); HRMS calcd for $C_{20}H_{30}O_3$ 318.2195, found 318.2198.

(1*R*,2*S*,3*S*,5*R*)-(−)-2-Anilinomethyl-6,6-dimethyl-3-ethoxybicyclo[3.1.1]heptan-2-ol (10b): oil; $[\alpha]^{25}_D = +11.5$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$) 3520, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, J = 8.0 Hz, 2 H), 6.67 (t, J = 8.0 Hz, 1 H), 6.59 (d, J = 8.0 Hz, 2 H), 4.24 (br s, 1 H, NH), 4.15 (s, 1 H, OH), 3.74−3.66 (m, 2 H), 3.52−3.46 (m, 1 H), 3.17 (d, J = 11.7 Hz, 1 H), 3.08 (d, J = 11.7 Hz, 1 H), 2.43−2.38 (m, 1 H), 2.26−2.17 (m, 2 H), 1.97−1.78 (m, 1 H), 1.75 (ddd, J = 13.8, 5.1, 2.7 Hz, 1 H), 1.47 (d, J = 9.9 Hz, 1 H), 1.26 (s, 3 H), 1.22 (t, J = 3.6 Hz, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.11, 129.26 (2 C), 117.06, 112.93 (2 C), 75.23, 73.92, 65.31, 53.49, 49.43, 40.42, 38.29, 35.40, 27.64, 27.56, 24.16, 15.54; MS *m*/*z* (rel intensity) 289 (15, M^+), 106 (100); HRMS calcd for $C_{18}H_{27}NO_2$ 289.2042, found 289.2036.

***N*-[6,6-Dimethyl-3-ethoxy-2-hydroxybicyclo[3.1.1]hept-10-yl]-*N*-phenyl-3,5-dinitrobenzamide (13):** HPLC (Chiralcel OD, 2-propanol/hexane (2:1), 1 mL/min) t_R 31.5 min [(1*R*,2*S*,3*S*,5*R*)-isomer], 42.3 min [(1*S*,2*R*,3*R*,5*S*)-isomer].

1-(1-Cyclohexenyl)ethanol (18):[19] $[\alpha]^{25}_D = +7.4$ ($c = 2.6$, $CHCl_3$) (74% ee favoring the *R* enantiomer) (lit.[19] $[\alpha]^{25}_D$ +3.29 ($c = 2.49$, $CHCl_3$)); HPLC for the 3,5-nitrobenzoate derivative (Chiralcel OD, 2-propanol/hexane (1:40), 0.41 mL/min) t_R 42.2 min (*S*-enantiomer), 46.6 min (*R*-enantiomer).

1-(2-Fluorophenyl)propanol (19b):[21] $[\alpha]^{25}_D = -22.4$ (c = 2.0, $CHCl_3$) (75% ee favoring the *S*-enantiomer) (lit.[21] $[\alpha]^{25}_D$ −20.06 ($c = 1.77$, $CHCl_3$, 62% ee favoring the *S* enantiomer); HPLC for the 3,5-nitrobenzoate derivative (Chiralcel OD, 2-propanol/hexane (1:5), 0.48 mL/min) t_R 36.4 min (*R* enantiomer), 43.4 min (*S* enantiomer).

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Supporting Information Available: Additional physical and spectral data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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