Dual Enantioselective Control in Asymmetric Synthesis

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ABSTRACT

It is desirable and practical to produce both enantiomers of a target from the same chiral starting material by stereodifferentiation of prochiral compounds, for instance utilizing a chiral ligand derived from a natural (L) amino acid. During the past 7 years, excellent results have been achieved in several cases by multiple stereodifferentiation of chiral ligands derived from (*S*)-indoline-2-carboxylic acid: highly diastereo- and enantioselective pinacol coupling reactions of chiral α-ketoamides gave both (*S,S*)- and (*R,R*)-quaternary tartaric acid for the first time; asymmetric Diels−Alder cyclization of chiral acrylamides in the presence of Lewis acid afforded extremely high diastereoselectivities of both opposite configurations of the cyclized diastereomers depending upon the structures of chiral ligands and Lewis acids; and asymmetric alkylation of aldehydes to both enantiomers of secondary alcohols and asymmetric hydrogenation of ketones to both enantiomers of chiral secondary alcohols have been achieved using catalysts derived from (*S*)-indoline-2-carboxylic acid.

Introduction

Numerous chiral catalysts or auxiliaries have been designed and synthesized utilizing natural sources such as chiral amino acids, amines, carboxylic acids, and carbohydrates. In chemical transformations, the synthesis of individual enantiomers is generally achieved by using chiral natural sources. However, sometimes natural sources of one of the enantiomers of the *S*- and *R*-forms are quite limited. For instance, most amino acids have the *S* configuration. Numerous asymmetric syntheses using chiral catalysts or auxiliaries derived from amino acids have been reported. In general, a well-designed chiral catalyst or auxiliary gives one enantiomer as the major product. A chiral catalyst or auxiliary bearing *S* (or *R*) configuration gives for example one *R* (or *S*) configuration of the major product. Since the energy barrier between transition states for formation of both *R* and *S* configurations is so small ($\Delta\Delta G^{\ddagger} = 1.5$ kcal/mol)[1] in asymmetric alkylation of ketones, it is difficult to control stereodifferentiation between diastereomeric transition states. In most asymmetric syntheses, chiron or enzyme approaches are restricted to the production of only one enantiomer by a given route, despite the ability of some researchers to produce both enantiomers of a target from the same chiral starting source. Only a few examples have been reported where the same reaction system gives both enantiomers depending on reaction conditions or by changing the reaction time[2a,b] and temperature,[2c] for instance in asymmetric reduction of ketones. Recently, both enantiomers in asymmetric reduction of imines have been obtained depending on the solvents[2d] used, and both diastereomers and enantiomers in asymmetric aldol reactions have been obtained depending on the catalyst structures[2e] derived from the same chiral sources. An effect of fluorine substitution of dihydroxy binaphthyl (F_8BINOL) afforded the opposite sense of chiral induction in the sulfoxidation process.[2f] Therefore, to produce both enantiomers from the same starting material with a high degree of stereoselectivity, efforts must be focused toward well-designed chiral ligands whose complexes with metals can differentiate between diastereomeric transition states with accuracy.

In the past 7 years, we have concentrated on design and synthesis of suitable chiral ligands. (*S*)-Indoline-2-carboxylic acid has been found to be one of the best starting materials for the synthesis of the new chiral ligands. There are several examples of production of both diastereomers or enantiomers with high stereoselectivity using chiral catalysts or ligands derived from the same starting material of (*S*)-indoline-2-carboxylic acid. Extremely high diastereoselectivities of both stereoisomers in pinacol coupling reactions and Diels−Alder cyclizations have been obtained. Asymmetric alkylations of arylaldehydes or reductions of aryl alkyl ketones afforded the corresponding secondary alcohols of both enantiomers with high enantioselectivities.

Intermolecular Pinacol Coupling Reactions

Multidentate and chiral C_2-symmetric ligands are well known to possess an ability to impart asymmetry to transition and main group elements.[3] C_2-symmetric diols or diphenols are frequently used, especially in the area of asymmetric catalysis.[4] Most diol ligands have been derived from C_2-symmetric molecules which occur naturally in optically pure forms (such as tartaric acid).[4] However, the number of chiral precursors available from natural products is seriously limited.

Pinacol coupling was first described a long time ago,[5] but this reaction is still a versatile tool for chemists. The intermolecular coupling of various aldehydes or ketones

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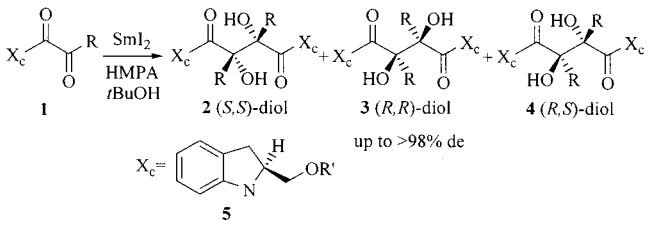
Scheme 1



1a: R= R'= Me **1e**: R= Et, R'= TBPS **5a**: R'= Me
1b: R= Et, R'=Me **1f**: R= *n*Pr, R'= TBPS **5b**: R'= TBPS
1c: R= Ph, R'= Me **1g**: R= *n*Hex, R'= TBPS
1d: R= Me, R'= TBPS **1h**: R= Ph, R'= TBPS

Table 1. Pinacol Coupling of 1a−h

substrate	SmI_2 (equiv)	time (h)	yield (%)	**2**:**3**:**4**
1a	2.0	1	61	95:0:5
1b	2.0	0.1	39	98:0:2
1c	2.0	5		
1d	2.5	5	69	96:0:4
1e	2.5	5	79	>99:0:1
1f	2.5	5	67	>99:0:1
1g	2.5	5	83	97:0:3
1h	2.5	5		

to the corresponding pinacols has been extensively studied. However, enantiopure pinacols have not really been obtained using this type of coupling.[6] Although the asymmetric dihydroxylation of olefins mediated by osmium tetroxide has become one of the most useful methods for the preparation of C_2-symmetric diols,[7] asymmetric dihydroxylation of tetrasubstituted olefins is extremely rare[8a] and gives low enantioselectivity.[8]

SmI_2 has been utilized successfully as a one-electron-donating agent for diverse organic reactions[9] including intermolecular[10] or intramolecular[11,12] pinacol coupling reactions of aldehydes. However, the intermolecular coupling of ketones has afforded low diastereoselectivities.[13]

Chiral 2,3-dialkyltartaric acids could be utilized for designing chiral catalysts or auxiliaries for use in various asymmetric reactions and as chiral intermediates in the synthesis of natural products. However, to our knowledge, the synthesis of enantiopure 2,3-disubstituted tartaric acid (a quaternary pinacol) has never been reported, although a chiral 2,3-dimethyltartaric acid was obtained by chiral resolution.[17] A chiral tertiary pinacol can be obtained by photolysis of ketones in a chiral solvent[13a] or by using a chiral auxiliary;[13b] however, the diastereoselectivities are low.

It has been found that the coupling of the chiral α-ketoamides **1** in the presence of SmI_2, HMPA, and *t*BuOH in THF gave pinacol **2** with extremely high diastereoselectivity (>98% de in some cases; Scheme 1).[14] This is the first example of such high stereoselectivity for disubstituted tartaric acid derivatives in intermolecular pinacol coupling reactions of α-ketoamides.

The results obtained are summarized in Table 1. The coupling of pyruvamide **1a** using SmI_2 in the absence of HMPA and *t*BuOH gave low stereoselectivity. However, the coupling of **1a** in the presence of SmI_2, HMPA, and *t*BuOH occurred with high diastereoselectivity (**2**:**3**:**4** = 95:0:5). Moreover, the coupling of **1e** and **1f** resulted in extremely

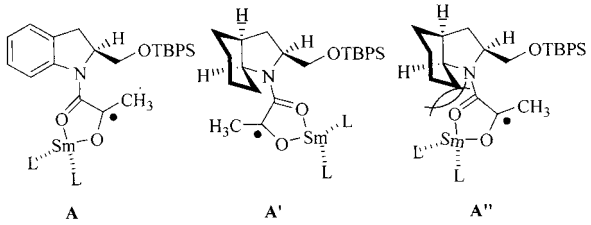


FIGURE 1. Possible intermediates of the asymmetric pinacol coupling reactions.

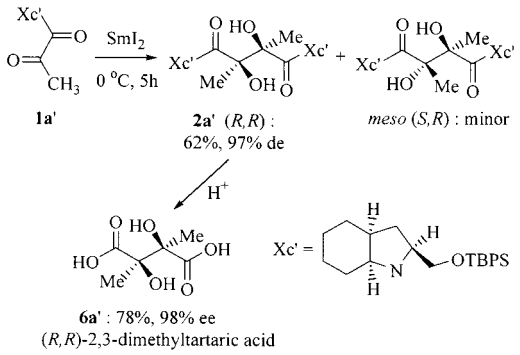
high diastereofacial selectivity (**2**:**3**:**4** = >99:0:1). HMPA is known to increase the reaction rate and stereoselectivity of SmI_2-mediated reactions, and *t*BuOH is often used as a proton source for these reactions.[15] The pinacol coupling reaction can form three stereoisomers of (*S*,*S*), (*R*,*R*), and (*S*,*R* or *R*,*S*; *meso* form). The *meso* form was easily confirmed by ^{13}C NMR spectroscopy;[16] however, formation of (*R*,*R*)-pinacol could not be detected by a chiral column.

When the *tert*-butyldiphenylsilyl (TBPS) substituent was introduced to give the chiral auxiliary **5b**, the pinacol coupling reactions of **1d**−**g** had a longer reaction time (5 h) and gave extremely high diastereoselectivities (**2**:**3**:**4** up to >99:0:1), probably due to the steric effect of the bulky TBPS moiety. The coupled product **2a** was readily hydrolyzed with 3 M HCl in dioxane at 25 °C for 4 h to give (*S*,*S*)-2,3-dimethyltartaric acid (**6a**) (85% yield), together with recovered chiral auxiliary, (*S*)-2-methoxymethylindolione (90%), with no loss of chirality. (*S*,*S*)-2,3-Diethyltartaric acid was obtained by hydrolysis of **2b** and shows an sign of specific rotation ($[\alpha]^{16}_D = -6.37$ ($c = 0.926$, H_2O)) opposite to that of (*S*,*S*)-2,3-dimethyltartaric acid ($[\alpha]^{16}_D = +13.1$, $c = 0.598$, H_2O; lit. $[\alpha]^{20}_D = +13.4$, $c = 4.0$, H_2O). As the specific rotation and the absolute configuration of (*S*,*S*)-2,3-diethyltartaric acid have not been reported previously, its absolute configuration was determined by comparing the CD spectrum of *O*,*O*-dianisoyl-2,3-diethyltartaric anhydride with that of the previously known *O*,*O*-dianisoyl-2,3-dimethyltartaric anhydride.[17] The absolute configuration of **2d** was also determined by X-ray analysis.

Although the detailed mechanism is not clear, the reaction appears to be initiated by formation of a ketyl radical **A** with a one-electron transfer to SmI_2 followed by coupling of the two ketyl radicals (Figure 1). The coupling takes place at the sterically less hindered *si* face and gives high diastereoselectivities.

As previously mentioned, it is desirable and important to obtain both enantiomers by stereodifferentiation reactions of prochiral compounds that utilize the same chiral source.[18] We have found that (2*S*,3a*S*,7a*S*)-*N*-pyruvoyl-2-(*tert*-butyldiphenylsilyloxy)octahydroindoline (**1a′**) (99.8% ee)[19] affords the opposite configuration of **2a′** (*R*,*R* diol: 97% de) (Scheme 2).[14] The ratio of *R*,*R*:*S*,*S*:*meso* is 98.5:0:1.5. The ratio was determined by chiral HPLC analysis with a Daicel OD column. The absolute configuration of **2a′** was determined by comparison of the measured optical rotation of (*S*,*S*)-2,3-dimethyltartaric acid (**6a′**) ($[\alpha]^{20}_D = -13.2$ ($c = 4.0$, H_2O)), obtained by hydrolysis of **2a′**.

Scheme 2



The different configurations of the adducts produced can be rationalized by the different intermediates formed from **1a** and **1a′** with SmI_2. Instead of **A**, the intermediate **A′** is favorable in the case of **1a′**, more so than **A″** due to the steric repulsion between the chair formation of the cyclohexane ring and the amide carbonyl moiety (Figure 1).

We have demonstrated diastereo- and enantioselective pinacol coupling reactions of chiral α-ketoamides mediated by SmI_2 with extremely high diastereoselectivities (>99% de in some cases). Enantiopure (*S*,*S*)- or (*R*,*R*)-2,3-dialkyltartaric acid derivatives can now be synthesized for the first time depending on the structure of α-ketoamides. When a similar chiral auxiliary, (*S*)-*N*-pyruvoyl-2-(*tert*-butyldiphenylsilyloxy)proline was used, low diastereoselectivities were obtained.

Diels−Alder Cycloadditions

Various types of chiral dienophiles such as chiral esters,[20] *N*-acyloxazole derivatives,[21] *N*-acylsultams,[22] acrylates,[23] and acylamides[24] have been developed. Metal coordination is important for diastereofacial selectivity in the asymmetric synthesis. Lewis acids have been used for chelate formation in Diels−Alder cyclizations to obtain high diastereofacial selectivities. In general, the *S*-form of the chiral dienophiles (auxiliary) exclusively affords the *endo*-*R* adduct over the *endo*-*S* one, and the *R*-form exclusively gives the *endo*-*S* adduct over the *endo*-*R* one. Issues associated with this absolute stereochemical control depending on Lewis acids and the structures of dienophiles provide an important challenge in the area of practical Diels−Alder reaction designs.[22a,b]

In the hope of obtaining the opposite configuration of the *endo* adduct and understanding the mechanism, three different dienophiles, **7**, **8**, and **9**, were prepared and reacted with dienes in the presence of various Lewis acids. Intriguing results were obtained during development of Lewis acid-dependent stereocontrol toward both *endo*-*R* and *endo*-*S* configuration with high diastereofacial selectivity. To generalize the results, the requisite dienophile**s** **7**−**9** were synthesized from (*S*)-indoline-2-carboxylic acid.[18,19] They were purified, and their optical purities (>99.8% ee) were determined by HPLC (Daicel chiral OD column, *i*PrOH−*n*-hexane, 5:95). The preliminary studies involved reaction of **7**−**9** with **10**, as shown in Scheme 3.

Scheme 3

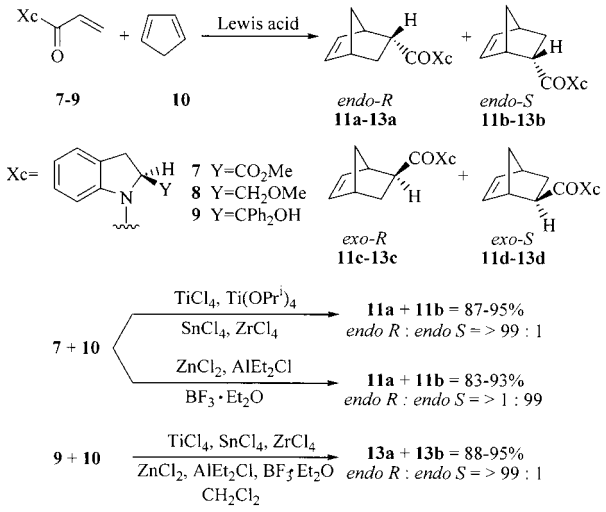


Table 2. Asymmetric Diels−Alder Cycloaddition with 7 and 9

dienophile	Lewis acid	yield (%)	*endo*:*exo*	*endo* dsn	config
7	Et_2AlCl	95	90:10	>99:1	*S*
7	$BF_3{\cdot}Et_2O$	90	94:6	>99:1	*S*
7	$ZnCl_2$	90	83:17	99:1	*S*
7	$TiCl_4$	92	95:5	99:1	*R*
7	$Ti(OPr^i)_4$	87	72:28	94:6	*R*
7	$SnCl_4$	92	95:5	99:1	*R*
9	Et_2AlCl	95	>99:1	>99:1	*R*
9	$AlCl_3$	88	>99:1	>99:1	*R*
9	$BF_3{\cdot}Et_2O$	91	>99:1	>99:1	*R*
9	$ZnCl_2$	90	>99:1	>99:1	*R*
9	$TiCl_4$	90	>99:1	>99:1	*R*
9	$Ti(OPr^i)_4$	89	>99:1	>99:1	*R*
9	$SnCl_4$	91	98:2	98:2	*R*
9	$ZnCl_4$	93	>99:1	>99:1	*R*
8	$EtAlCl_2$	83	88:12	86:14	*S*
8	$TiCl_4$	75	85:15	97:3	*R*

Extremely high levels of asymmetric induction can be achieved in Diels−Alder cycloadditions of **7** or **9** with **10**; in contrast to other general dienophiles, **7** containing a carboxylate moiety reacts with **10** to give differently configured adducts depending on the Lewis acids employed. In the presence of $TiCl_4$, $Ti(OPr^i)_4$, or $SnCl_4$, **11a** was obtained as the major diastereomer (**11a**:**11b** = *endo*-*R*:*endo*-*S* = >99:1, Table 2), but with $AlEt_2Cl$, $ZnCl_2$, or $BF_3{\cdot}Et_2O$ the opposite configuration of **11b** was obtained (**11a**:**11b** = 1:>99).[25] In the case of **8**, the same trend of **12b** was observed, but in a less diastereoselective manner than for **7**. In particular, **9** containing a diphenyl-substituted tertiary alcohol moiety affords exceptionally high diastereofacial selectivities (**13a**:**13b** = >99:1, yield > 90%), regardless of the nature of the Lewis acid. The *endo* configurations were readily ascertained by iodolactonization of **1**−**13a** with I_2 in DMF. The *exo* compound cannot be lactonized under the same reaction conditions. The absolute configuration of **11a**, **12b**, or **13a** was determined by reductive cleavage of **11a** to the known norbornene-2-methanol and subsequent comparison of $[\alpha]_D$ values.[26] The differently configured adducts produced can be rationalized by the different intermediates formed between **7**−**9** and the metals of the Lewis acids. Compounds **7**−**9** react with **10** to favor formation of *endo*-*R* species

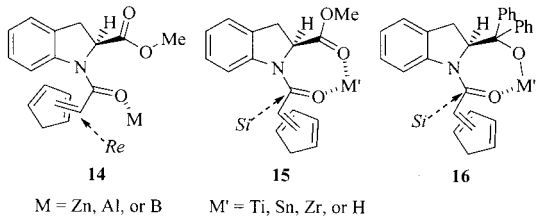


FIGURE 2. Possible intermediates in Diels–Alder reactions.

11a or **13a** with $TiCl_4$, $Ti(OPr^i)_4$, $SnCl_4$, or $ZrCl_4$, probably via formation of seven-membered ring chelates with the acryloyl moiety of **15** or **16** having a *cisoid* conformation.[23,24] Helmchen and co-workers reported the first evidence of formation of a seven-membered ring chelate complex.[23] It is noteworthy that even in the absence of any Lewis acid, **9** reacts with **10** to give an excellent chemical yield (92%) and high stereofacial selectivity (*endo*:*exo* = >99:1, *endo*-*R*:*endo*-*S* = >99:1) at 25 °C after a long reaction time (24 h). The results can be attributed to the hydrogen-bonded *cisoid* conformation intermediate **16**, where the hydrogen acts as a Lewis acid. On the other hand, **7** or **8** prefers *endo*-*S* formation of **11b** or **12b** with $ZnCl_2$, $AlEtCl_2$, or $BF_3{\cdot}Et_2O$, with high diastereofacial selectivity probably resulting from intermediate **14** (Figure 2). In contrast to Ti or Sn Lewis acids, relatively weaker Lewis acids such as Zn, Al, or B may not form a seven-membered ring complex, instead forming a weak coordination with the amide carbonyl group (**14**).[23] In the case of the Evans's model dienophile, an α,β-unsaturated *S*-oxazolidinone, the *endo*-*R* form was obtained[21a] and explained by formation of a six-membered ring intermediate with Et_2AlCl, which was confirmed by a ^{13}C NMR study.[21b] However, in contrast to a significant chemical shift change in the **7**–$SnCl_4$ chelation complex **16**, ^{13}C NMR measurement of the **7**–Et_2AlCl mixture did not show significant changes in the chemical shifts for either of the amide or ester carbonyl peaks, which can be explained by a weak coordination (**14**) between **7** and Et_2AlCl.

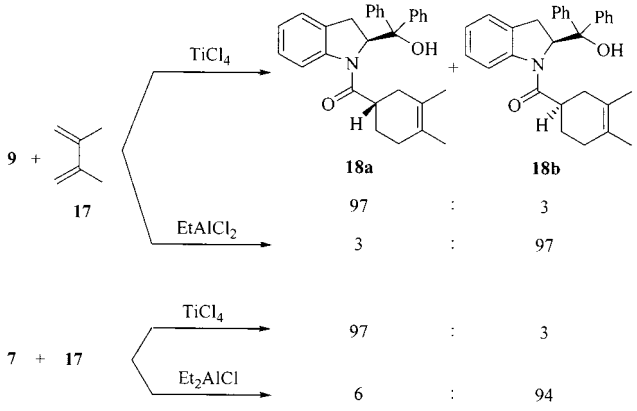
Dienophiles **7** and **9** also reacted with less reactive 2,3-dimethylbutadiene **17** at 25 °C to result in the same trend: for **7** with $TiCl_4$, the ratio of *endo*-*R*:*endo*-*S* was 97:3, while with $EtAlCl_2$ the ratio was reversed to 6:94, which is comparable to the results obtained from **9** with both $TiCl_4$ and Et_2AlCl (Scheme 4).

In summary, asymmetric Diels–Alder cycloadditions of **7** or **9** with **10** proceed with absolutely stereocontrolled diastereofacial selectivities in both *endo*-*S* and *endo*-*R* (up to >99% de), depending on the Lewis acids used and the structures of chiral dienophiles deriving from (*S*)-indoline-2-carboxylic acid.

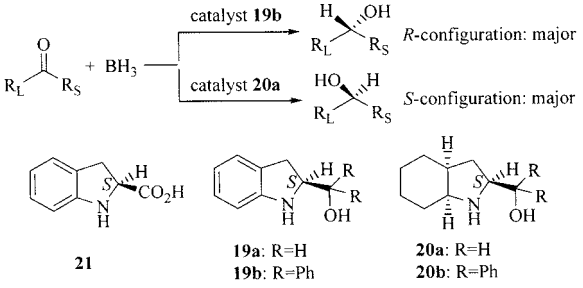
Asymmetric Reductions of Ketones

There have been numerous reports concerning asymmetric reductions of prochiral ketones with a variety of chiral catalysts.[3b,27] Chiral β-amino alcohols have been synthesized and tested as chiral ligands for the enantioselective reduction of ketones.[28–30] Although several efficient catalysts have been developed, most of the oxazaborolidines derived from L-amino acids[31–35] give access

Scheme 4



Scheme 5

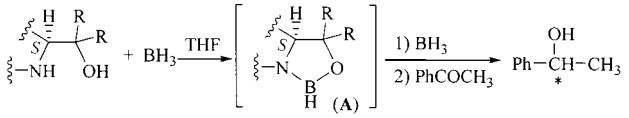


to only one enantiomer of the secondary alcohols; namely, (*S*)-amino alcohol–borane systems have been reported to give arylalkyl alcohols with the *R* configuration. However, chiral auxiliaries that effect the highly stereocontrolled enantioselective reductions of ketones to alcohols of both the *R* and *S* configurations are desirable and important. Indeed, a few (*S*)- and (*R*)-chiral amino alcohols derived from L- and D-amino acids and from D-camphor have been reported to afford the corresponding *R*- and *S*-alcohols, respectively, in asymmetric reductions of ketones.[36,37] However, in contrast to L-amino acids which are readily available from natural sources, enantiopure D-amino acids are often difficult to obtain.

A remarkable reversal of enantiofacial selectivity in the asymmetric reduction of ketones with borane is demonstrated when the new β-amino alcohol chiral auxiliaries **19** and **20** are used (Scheme 5). Amino alcohols **19** and **20** were readily prepared from (*S*)-indoline-2-carboxylic acid (**21**),[38] and their ability to effect enantioselective reductions of ketones was examined.

When acetophenone was reduced with borane in the presence of a catalytic amount (0.1 equiv) of **19b**, (*R*)-1-phenylethanol was obtained in high optical yield (96% ee, Table 3). In contrast, the same reduction in the presence of **20a** gave the oppositely configured (*S*)-1-phenylethanol (90% ee, Table 3). The optical purities of the alcohols were determined by GC analysis of the corresponding (menthyloxy)carbonyl esters or by their optical rotation values. The chiral β-amino alcohols **19b** and **20a** were recovered in over 90% yield after workup with dilute aqueous acid. The results of several stereocontrolled asymmetric reductions of acetophenone and the remarkable reversed enantiofacial selectivity are shown in Table 3.

Table 3. Comparison of Asymmetric Reduction of Acetophenone with Borolidiners of 19a, 19b, 20a, and 20b



amino alcohol	borolidine (**A**, equiv)	yield (%)	ee (%)	config
19a	0.1	96	82	*R*
19b	1.0	95	96	*R*
19b	0.1	94	96	*R*
19b	0.05	92	95	*R*
19b	0.025	90	82	*R*
20a	0.1	95	90	*S*
20b	0.1	96	49	*S*

Table 4. Asymmetric Reduction of Ketones

ketone	amino alcolhol	yield (%)	% ee (config)
$PhCOCH_3$	**19b**	93	96 (*R*)
	20a	92	90 (*S*)
$PhCOC_2H_5$	**19b**	92	90 (*R*)
	20a	94	85 (*S*)
$PhCH_2COCH_3$	**19b**	93	92 (*R*)
	20a	91	86 (*S*)
α-tetralone	**19b**	91	79 (*R*)
	20a	92	79 (*S*)
$C_3H_7COCH_3$	**19b**	92	59 (*R*)
	20a	90	58 (*S*)

It is interesting to note that the β-amino alcohol **19b** substituted with diphenyl groups at the α-position afforded the (*R*)-alcohol (96% ee), and the unsubstituted β-amino alcohol **20a** gave the (*S*)-alcohol (90% ee). The unsubstituted β-amino alcohol **19a** and disubstituted β-amino alcohol **20b** gave lower optical yields. To generalize the effects of the structures of the (*S*)-β-amino alcohols, various ketones were reduced to the corresponding secondary chiral alcohols with both **19b** and **20a** (Table 4). In the presence of **19b**, all the ketones were reduced to the corresponding (*R*)-alcohols; in contrast, in the presence of **20a**, all the ketones were reduced to the (*S*)-alcohols. The optical and chemical yields were high for all the ketones except methyl propyl ketone. Generally, asymmetric reductions of simple dialkyl ketones are well known to give reduced alcohols with low optical yields.[29] To our knowledge, **20a** is the first β-amino alcohol chiral auxiliary to give (*S*)-secondary alcohols with such high enantiomeric excesses.

Judging from the results in Table 4, the structure of catalysts **19b** and **20a** must play an important role in controlling the asymmetric induction. Possible models and intermediates are illustrated in Figure 3. The steric effect of the diphenyl group in **19b** appears to be an important factor leading to the formation of the favorable intermediate **B**, but in the case of **20a**, the steric effect of the cyclohexyl group appears to enforce the approach of the chiral auxiliary to the opposite face of the carbonyl group for the formation of intermediate **C**. Intermediates **B** and **C** lead to the (*R*)- and (*S*)-phenylethyl alcohols, respectively. It has been well established by chemistry[31] and calculation[39] that coordination of Lewis acid boron anti to the large group (R_L) of the ketone is favored. The transition state **C** may be more favorable than **C′** because of steric repulsion between the cyclohexane ring and the methyl group of the substrate.

The structure of the β-amino alcohol chiral auxiliary plays an essential role in controlling the asymmetric reduction in carbonyl compounds, and either enantiomer of the secondary alcohol can be obtained by choosing the appropriate catalyst.

Asymmetric Alkylation of Aldehydes

The enantioselective additions of organometallic reagents to aldehydes using chiral ligands have been intensively studied.[40] An asymmetric addition of the alkyl group of the dialkylzinc to aldehydes catalyzed by the chiral β-amino alcohols has been developed for the preparation of optically active alkylated secondary alcohols. Various types of chiral β-amino alcohols have been synthesized and examined as possible chiral ligands to provide an enantioselective addition of dialkylzinc to aldehydes.[41−45] Although several efficient catalysts that can convert alde-

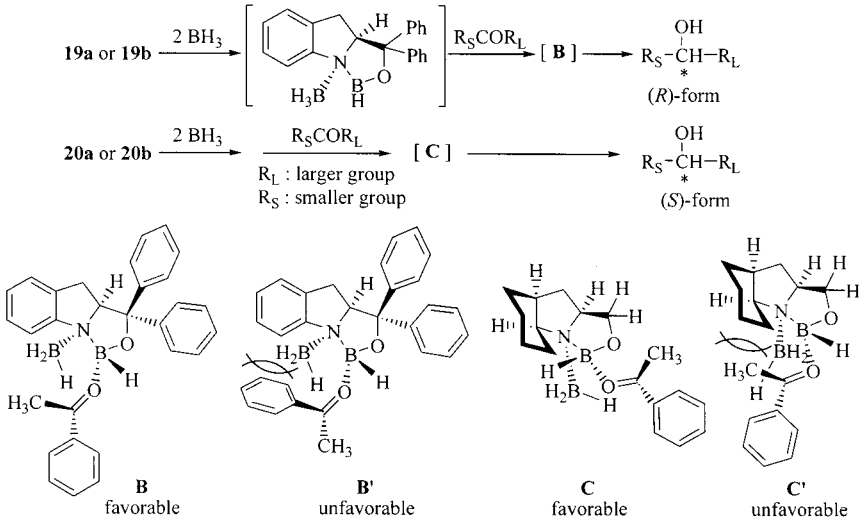


FIGURE 3. Possible models for oxazaborolidine reduction.

Scheme 6

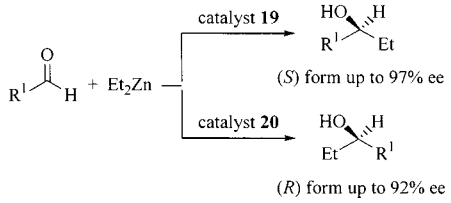


Table 5. Asymmetric Addiition of Et_2Zn to Benzaldehyde

catalyst	yield (%)	ee (%)	config
19a	96	72	*S*
19b	94	96	*S*
20a	94	90	*R*
20b	93	56	*R*

hydes to corresponding alcohols in high optical yields have been discovered, they provide one excess enantiomer of the chiral alcohols: most β-amino alcohols of *S* configuration afford *S* configuration alcohols in enantiomeric excess. However it has been noticed that the opposite (*R*)-alcohols can be formed in enantiomeric excess, depending on the substituent effects of the (*S*)-β-amino alcohols.[43] Thus, a series of new chiral β-amino alcohols (**19a**, **19b**, **20a**, and **20b**) were prepared from (*S*)-indoline-2-carboxylic acid and examined to determine whether they could bring about a stereocontrolled enantioselective ethylation of aldehydes.

The asymmetric addition of diethylzinc to aldehydes by use of the chiral catalysts, **19** and **20**, gave a remarkable reversal of enantiofacial selectivity (Scheme 6).

To compare stereodifferentiation effects of the two catalysts, enantioselective addition of diethylzinc to benzaldehyde was carried out at 0 °C in the presence of a catalytic amount (5 mol %) of **19** and **20**. Table 5 shows different relations of absolute configurations between the enantiomeric excess of 1-phenylpropanol. The chemical yields of 1-phenylpropanol were more than 90%. The effects of the structures of the (*S*)-β-amino alcohol derivatives were compared in the asymmetric additions.

The presence of **19a** and **19b** afforded (*S*)-1-phenylpropanol with up to 96% ee. On the other hand, the presence of **20a** and **20b** afforded the opposite configuration of (*R*)-1-phenylpropanol in high enantiomeric excess (90% ee). As shown in Table 5, **19a** and **19b** respectively resulted in high optical yields of 1-phenylpropanol of the opposite configuration.

Catalysts **19b** and **20a** were chosen to examine the asymmetric ethylation of other aldehydes. The results are summarized in Table 6. The presence of **19b** led to high optical yields of (*S*)-secondary alcohols (96−97% ee), but the presence of **20a** led to high optical yields of (*R*)-secondary alcohols (90−92% ee).[38]

The chemical yields of the alcohols are almost all higher than 90%. This is the first time that such a high enantiomeric excess of the opposite (*R*)-ethylated alcohols from (*S*)-β-amino alcohols has been obtained. Even aliphatic 3-methylbutyraldehyde was ethylated in 76% ee. In general, asymmetric alkylation of alkylaldehydes gives a lower optical yield.[43]

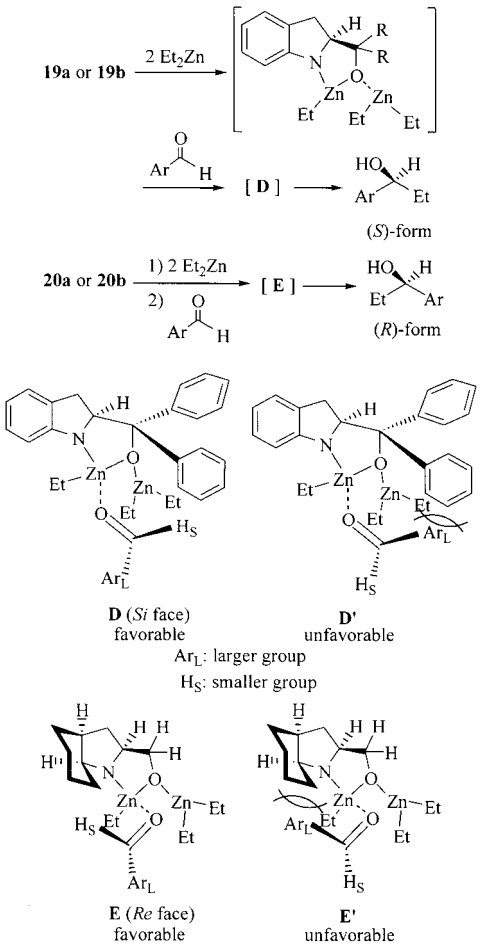


FIGURE 4. Possible models for alkylation.

Table 6. Asymmetric Addition of Et_2Zn to Aldehydes

aldehydes	catalyst	yield (%)	% ee (config)
benzaldehyde	**19b**	94	96 (*S*)
	20a	93	90 (*R*)
4-chlorobenzaldehyde	**19b**	93	97 (*S*)
	20a	92	92 (*R*)
4-methoxybenzaldehyde	**19b**	95	96 (*S*)
	20a	94	90 (*R*)
(*E*)-cinnamaldehyde	**19b**	91	96 (*S*)
	20a	92	91 (*R*)
3-methylbutyraldehyde	**19b**	90	76 (*S*)
	20a	89	64 (*R*)

The asymmetric addition of diethylzinc to the aldehydes and a possible mechanism are illustrated in Figure 4. It is considered that the structures of **19b** and **20a**, which result in high enantioselective ethylations (*S*, 96% ee by **19b**; *R*, 90% ee by **20a**), play an important role in controlling stereodifferentiation for the asymmetric induction.

The steric effect of diphenyl groups in **19b** seems to be important in the formation of intermediate **D** by a *si* face approach of the aldehyde. The fact that the enantioselectivity from **19b** (*S*, 96% ee) when compared with that of **19a** (*S*, 72% ee) is higher may be attributed to the larger steric effects of two bulky phenyl groups of **19b** (R = Ph). Thus, intermediate **D** seems to be more favorable than **D′**. The steric effect of the cyclohexyl group in **20a** appears to enforce the opposite side approach of the aldehyde (*re* side) to the zinc complex favoring the formation of **E**.

In the cases of **20a** and **20b** (Table 5), the presence of **20a** resulted in higher enantioselective induction (**20a**, *R*, 90% ee and **20b**, *R*, 56% ee). The low steric repulsion between the larger moiety (Ph) of the aldehyde substrate may also play an important role. Thus, in the case of **20a**, intermediate **E** seems to be more favorable than **E′**.

In the asymmetric reduction of aryl alkyl ketones to alcohols using **19b** and **20a** in the presence of borane, the same results were obtained: from **19b**, a high optical yield of (*R*)-alcohols, but from **20a**, a high enantiomeric excess of (*S*)-alcohols.

In summary, the structure of the added β-amino alcohols plays an essential role in stereocontrolling the asymmetric induction of the alkylation of aldehydes to give both enantiomers of the alcohols produced. Comparing **19a** with **20a**, the structure of **20a** is different from **19a** in that it has a cyclohexane ring moiety instead of a benzene ring as in **19a**. It is noteworthy that **20a**, which has the *S* configuration at the β-carbon, like **19a**, induced high enantioselectivity of the opposite *R* configuration of alcohols.

Conclusion

Pinacol coupling reactions of α-ketoamides bearing the 2-(*S*)-indoline moiety (**1**) or the 2-(*S*)-octahydroindoline moiety (**1′**) with SmI_2 afforded (*S*,*S*)-diol (**2**) or (*R*,*R*)-diol (**2′**) respectively with extremely high diastereoselectivity. Hydrolysis of **2** and **2′** resulted in both (*S*,*S*)- and (*R*,*R*)-quaternary tartaric acid, respectively, for the first time. Asymmetric Diels–Alder cyclization of chiral amides with Lewis acids afforded extremely high diastereoselectivity of both opposite configurations of the diastereomers, depending on the structure of the chiral ligands and Lewis acid used. Asymmetric reductions of ketones to both enantiomers of secondary alcohols have been achieved with high enantiomeric excess. Asymmetric alkylations of aldehydes to both enantiomers of secondary alcohols have also been attained with high enantiomeric excess. One can expect in the future to see the development of additional chiral auxiliaries or catalysts deriving from natural products and displaying a dual enantioselective control in catalytic or stoichiometric asymmetric synthesis.

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References

(1) (a) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice Hall Inc.: Englewood Cliffs, NJ, 1971; pp 6–14. (b) Althouse, V. E.; Feigl, D. M.; Sanderson, W. A.; Mosher, H. S. Asymmetric Reductions XIII, Optically Active Benzyl-α-d Alcohol and *n*-Butyl-1-d Alcohol via Reduction by Actively Fermenting Yeast. *J. Am. Chem. Soc.* **1966**, *88*, 3595–3599.

(2) (a) Yamaguchi, S.; Mosher, H. S. A Reversal in Stereoselectivity Depending upon the Age of a Chiral Lithium Alkoxyaluminohydride Reducing Reagent. *J. Am. Chem. Soc.* **1972**, *94*, 9254–9255. (b) Yamaguchi, S.; Mosher, H. S. Asymmetric Reduction with Chiral Reagents from Lithium Aluminum Hydride and (+)-(2*S*,3*R*)-4-Dimethylamino-3-methyl-1,2-diphenyl-2-butanol. *J. Org. Chem.* **1973**, *38*, 1870–1877. (c) Nishihashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. Chiral Oxazolinylferrocene-Phosphine Hybrid Ligand for the Asymmetric Hydrosilylation of Ketones. *Organometallics* **1995**, *14*, 5486–5487. (d) Tani, K.; Onouchi, J.-I.; Yamagata, T.; Kataoka, Y. Iridium(I)-Catalyzed Asymmetric Hydrogenation of Prochiral Imines; Protic Amines as Catalyst Improvers. *Chem. Lett.* **1995**, 955–956. (e) Kobayashi, S.; Hirobe, M. Highly Enantioselective Synthesis of Enantiomeric 2,3-Dihydroxy Thioester by Using Similar Type of Chiral Sources Derived from L-Proline. *J. Am. Chem. Soc.* **1994**, *116*, 9805–9806. (f) James, L.; Martyn, P.; Pandiaraju, S.; Yudin, A. Catalytic Application of F_8BINOL: Asymmetric Oxidation of Sulfide to Sulfoxide. *J. Organomet. Chem.* **2000**, *603*, 98–104.

(3) For C_2-symmetric molecules, see: (a) Whitesell, J. K. C_2 Symmetry and Asymmetric Induction. *Chem. Rev.* **1989**, *89*, 1581–1590. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(4) For C_2-symmetric dihydroxy ligands in metal-mediated asymmetric synthesis, see: (a) Shibasaki, M.; Sasai, H.; Arai, T. Asymmetric Catalysis with Heterobimetallic Compounds. *Angew. Chem.* **1997**, *109*, 1290–1310; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236–1256. (b) Duthaler, R. O.; Hafner, A. Chiral Titanium Complexes for Enantioselective Addition of Nucleophiles to Carbonyl Groups. *Chem. Rev.* **1992**, *92*, 807–832. (c) Mikami, K.; Terada, M.; Nakai, T. Asymmetric Glyoxylate-Ene Reaction Catalyzed by Chiral Titanium Complexes: A Practical Access to α-Hydroxy Esters on High Enantiomeric Purities. *J. Am. Chem. Soc.* **1989**, *111*, 1940–1941.

(5) (a) Balu, N.; Nayak, S. K.; Banerji, A. Influence of External Ligands and Auxiliaries on the Reactivity of Low-Valent Titanium in McMurry Reaction: Selectivity and Mechanistic Profile. *J. Am. Chem. Soc.* **1996**, *118*, 5932–5937. (b) Lebrun, A.; Namy, J.-L.; Kagan, H. B. Samarium Dibromide, an Efficient Reagent for the Pinacol Coupling Reactions. *Tetrahedron Lett.* **1993**, *34*, 2311–2314. (c) Lipski, T. A.; Hilfiker, M. A.; Nelson, S. G. Ligand Modified Catalysts for the McMurry Pinacol Reaction. *J. Org. Chem.* **1997**, *62*, 4566–4567. (d) Barden, M. C.; Schwartz, J. Stereoselective Pinacol Coupling in Aqueous Media. *J. Am. Chem. Soc.* **1996**, *118*, 5484–5485. (e) Gansauer, A. Pinacol Coupling of Aromatic Aldehydes Catalysed by a Titanocene. *Chem. Commun.* **1997**, 457–458.

(6) (a) Wirth, T. New Reagents for the Old Pinacol Coupling Reaction. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 61–63. (b) Barden, M. C.; Schwartz, J. Stereoselective Pinacol Coupling of 2,3-*O*-Isopropylidene-D-glyceraldehyde. *J. Org. Chem.* **1997**, *62*, 7520–7521. (c) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. Pinacol Cross Coupling of 2-[*N*-(Alkoxycarbonyl)amino] Aldehydes and Aliphatic Aldehydes by $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$. Synthesis of *syn*,*syn*-3-[*N*-(Alkoxycarbonyl)amino] 1,2-Diols. *J. Am. Chem. Soc.* **1994**, *116*, 1316–1323. (d) Kammermeier, B.; Beck, G.; Jacobi, D.; Jendralla, H. Vanadium(II)- and Niobium(III)-Induced Diastereoselective Pinacol Coupling of Peptide Aldehydes to C_2-Symmetrical HIV–Protease Inhibitors. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 685–687.

(7) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483–2547.

(8) (a) Morikawa, K.; Park, J.; Anderson, P. G.; Hashiyama, T.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation of Tetrasubstituted Olefins. *J. Am. Chem. Soc.* **1993**, *115*, 8463–8464. (b) Sharpless, K. B.; Akashi, K. Osmium Catalyzed Vicinal Dihydroxylation of Olefins by *tert*-Butyl Hydroperoxide under Alkaline Conditions. *J. Am. Chem. Soc.* **1976**, *98*, 1986–1987.

(9) (a) Molander, G. A.; Harris, C. R. Sequencing Reactions with Samarium(II) Iodide. *Chem. Rev.* **1996**, *96*, 307–338. (b) Molander, G. A. Diverse Methods for Medium Ring Synthesis. *Acc. Chem. Res.* **1998**, *31*, 603–609. (c) Skrydstrup, T. New Sequential Reactions with Single-Electron-Donating Agents. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 345–347. (d) Krief, A.; Laval, A.-M. Coupling of Organic Halides with Carbonyl Compounds Promoted by SmI_2, the Kagan Reagent. *Chem. Rev.* **1999**, *99*, 745–777.

(10) (a) Namy, J.-L.; Souppe, J.; Kagan, H. B. Efficient Formation of Pinacols from Aldehydes or Ketones Mediated by Samarium Diiodide. *Tetrahedron Lett.* **1983**, *24*, 765–766. (b) Nomura, R.; Matsune, T.; Endo, T. Samarium Iodide Catalyzed Pinacol Coupling of Carbonyl Compounds. *J. Am. Chem. Soc.* **1996**, *118*, 11666–11667. (c) Yanada, R.; Negoro, N. Reductive Coupling of Carbonyl Compounds to Pinacols by Using Sm–I_2–MeOH or Sm–I_2–Ti(O-*i*Pr)$_4$–MeOH Systems. *Tetrahedron Lett.* **1997**, *38*, 3271–3274.

(11) Taniguchi, N.; Hata, T.; Uemura, M. Enantiomerically Pure Cyclic trans-1,2-Diols, Diamines, and Amino Alcohols by Intramolecular Pinacol Coupling of Planar Chiral Mono $Cr(CO)_3$ Complexes of Biaryls. *Angew. Chem., Int. Ed.* **1999**, *38*, 1232–1235.

(12) (a) Ohmori, K.; Kitamura, M.; Suzuki, K. From Axial Chirality to Central Chiralities: Pinacol Cyclization of 2,2′-Biaryldicarbaldehyde to trans-9,10-Dihydrophenanthrene-9,10-diol. *Angew. Chem., Int. Ed.* **1999**, *38*, 1226−1229. (b) Guidot, J. P.; Gall, T. L.; Mioskowski, C. Samarium Diiodide Mediated Synthesis of D-3,4,5,6-tetra-*O*-benzylmyoinositol. *Tetrahedron Lett.* **1994**, *35*, 6671−6672.
(13) (a) Seebach, D.; Oei, H. A. Mechanism of Electrochemical Pinacolization. The First Asymmetric Synthesis in a Chiral Medium. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 634−636. (b) Muroi, M.; Inouye, Y.; Ohno, M. Partial Asymmetric Synthesis *via* a Cyclic Alkoxyphosphorane. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2948−2951.
(14) Kim, S. M.; Byun, I. S.; Kim, Y. H. Diastereoselective Pinacol Coupling Reactions of α-Ketoamides Mediated by SmI_2: Synthesis of Enantiomerically Pure *R* and *S* Quarternary Tartaric Acids. *Angew. Chem., Int. Ed.* **2000**, *39*, 728−731.
(15) (a) Shiue, J. S.; Lin, C. C.; Fang, J. M. Samarium Diiodide/Hexamethylphosphoramide Promoted Dimerization of Benzaldehydes. *Tetrahedron Lett.* **1993**, *34*, 335−338. (b) Fukuzawa, S.; Iida, M.; Nakanishi, A.; Fujinami, T.; Sakai, S. Intramolecular Reductive Cyclization of Unsaturated Keto- or Aldo-esters by Samarium(II) Diiodide: A Ready Synthesis of Bicyclic γ-Lactones. *J. Chem. Soc., Chem. Commun.* **1987**, 920−921.
(16) Molander, G. A.; McKie, J. A. Synthesis of Substituted Cyclooctanols by a Samarium(II) Iodide Promoted 8-Endo Radical Cyclization Process. *J. Org. Chem.* **1994**, *59*, 3186−3192.
(17) Tatsumi, S.; Izumi, Y.; Imaida, M.; Fukuda, Y.; Akabori, S. Studies of C−Substituted Tartaric Acid. I. The Preparation of Optically Active 2-Methyltartaric and 2,3-Dimethyltartaric Acid. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 602−604.
(18) Kim, Y. H.; Park, D. H.; Byun, I. S.; Yoon, I. K.; Park, C. S. Stereocontrolled Catalytic Asymmetric Reduction of α-ketoamides with Oxazaborolidine Derivatives from New Chiral Amino Alcohols. *J. Org. Chem.* **1993**, *56*, 4511−4512.
(19) (a) Kim, Y. H.; Kim, S. H.; Park, D. H. Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides to New Chiral Acrylamides Derived from (*S*)-Indoline-2-Carboxylic Acid. *Tetrahedron Lett.* **1993**, *34*, 6063−6066. (b) Kim, Y. H.; Choi, J. Y. Diastereoselective Addition of Organolithium to New Chiral Hydrazones. *Tetrahedron Lett.* **1996**, *37*, 5543−5546.
(20) (a) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3. (b) Oppolzer, W. Asymmetric Diels−Alder and Ene Reactions in Organic Synthesis. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876−889.
(21) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. Asymmetric Diels−Alder Cycloaddition Reactions with Chiral α,β-Unsaturated *N*-Acyloxazolidinones. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. (b) Castellino, S.; Dwight, W. J. Et_2AlCl Complexes of an *N*-Acyloxazolidinone: NMR Investigation. *J. Am. Chem. Soc.* **1993**, *115*, 2986−2987.
(22) (a) Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. Chiral Toluene-2, α-sultam Auxiliaries: Asymmetric Diels−Alder Reactions of *N*-Enoyl Derivatives. *Tetrahedron Lett.* **1990**, *31*, 5015−5018. (b) Curran, D. P.; Kim, B. H.; Daugherty, J. D.; Heffner, T. A. The Preparation of Optically Active Δ_2-Isooxazolines. A Model for Asymmetric Induction in the Non-Lewis Acid-Catalyzed Reactions at Oppolzer's Chiral Sultam. *Tetrahedron Lett.* **1988**, *29*, 3555−3558.
(23) Poll, T.; Metter, J. O.; Helmchen, G. Concerning the Mechanism of the Asymmetric Diels−Alder Reaction: First Crystal Structure Analysis of a Lewis Acid Complex of a Chiral Dienophile. *Angew. Chem., Int. Ed.* **1985**, *24*, 112−114.
(24) Boeckman, R. K., Jr.; Nelson, S. G.; Gaul, M. D. Toward the Development of a General Chiral Auxiliary. 1. Preparation of a New Class of Camphor Lactam Imides and their Application to the Construction of Quaternary Centers via Diels−Alder Cycloaddition. *J. Am. Chem. Soc.* **1992**, *114*, 2258−2260.
(25) Park, D. H.; Kim, S. H.; Kim, J. D.; Kim, Y. H. A Lewis Acid Dependent Asymmetric Diels−Alder Process in the Cyclization of New Chiral Acrylamides with Dienes. *J. Chem. Soc., Chem. Commun.* **1999**, 963−964.
(26) (a) Berson, J. A.; Remanick, A.; Suzuki, S.; Warnhoff, D. R.; Willner, D. The Absolute Configuration of Some Simple Norbornane Derivatives. A Test of the Conformational Asymmetry Model. *J. Am. Chem. Soc.* **1961**, *83*, 3986−3997. (b) Krimse, W.; Siegfried, R. 2-Norbornanediazonium Ions Revisited. *J. Am. Chem. Soc.* **1983**, *105*, 950−956.
(27) Reduction of C=O. In *Asymmetric Synthesis*; Hayashi, T., Tomioka, K., Yonemitsu, O., Eds.; Codansha Ltd. Gordon and Breach Science Publisher: 1998; pp 17−42.
(28) Mukaiyama, T.; Asami, M. In *Topics in Current Chemistry*; No. 127, Organic Chemistry; Springer-Verlag: Berlin, 1985; pp 133−167.
(29) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito. K.; Hirao, A.; Nakahama, S. Asymmetric Synthesis Using Chirally Modified Borohydrides. Part 3. Enantioselective Reduction of Ketones and Oxime Ethers with Reagents Prepared from Borane and Chiral Amino Alcohols. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039−2044.
(30) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. Asymmetric Synthesis Using Chirally Modified Borohydrides. Part 4. Enanatioselective Reduction of Ketones and Oxime Ethers with the Reagents Prepared from Borane and Polymer-supported (*S*)-(−)-2-Amino-3-(*p*-hydroxyphenyl)-1,1-diphenylpropan-1-ol. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2615−2619.
(31) Corey, E. J.; Bakshi, R. K.; Shibata, S. Highly Enantioselective Borane Reduction of Ketones Catalyzed by Chiral Oxazaborolidines. Mechanism and Synthetic Implications. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.
(32) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. A Stable and easily Prepared Catalyst for the Enantioselective Reduction of Ketones. Applications to Multistep Syntheses. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926.
(33) Corey, E. J.; Shibata, S.; Bakshi, R. K. An Efficient and Catalytically Enantioselective Route to (*S*)-(−)-Phenyloxirane. *J. Org. Chem.* **1988**, *53*, 2861−2863.
(34) Yoon, I. K.; Lee, S. W.; Park, C. S. Asymmetric Borane Reduction of Ketones Catalyzed by Oxazaborolidine. *Tetrahedron Lett.* **1988**, *29*, 4453−4456.
(35) Martens, J.; Dauelsberg, Ch.; Behnen, W.; Wallbaum, S. Enantioselective Catalytic Borane Reductions of Achiral Ketones: Syntheses and Application of Two Chiral β-Amino Alcohols from (*S*)-2-Indoline carboxylic Acid. *Tetrahedron: Asymmetry* **1992**, *3*, 347−350.
(36) Rama Rao, A. V.; Gurjar, M. K.; Sharama, P. A.; Kaiwar, V. Enantioselective Reductions of Ketones with Oxazaborolidines Derived from (*R*) and (*S*)-α,α-Diphenyl-2-Piperidine Methanol. *Tetrahedron Lett.* **1990**, *31*, 2341−2344.
(37) Tanaka, K.; Mutsui, J.; Suzuki, H. Enantiocontrolled Reduction of Prochiral Aromatic Ketones with Borane Using Diastereoisomeric Secondary Aminoalcohols as Chiral Catalysts. *J. Chem. Soc., Chem. Commun.* **1991**, 1311−1312.
(38) Kim, Y. H.; Park, D. H.; Byun, I. S. Stereocontrolled Enantioselective Addition of Diethylzinc to Aldehydes Using New Chiral Aminoalcohols. *Heteroatom Chem.* **1992**, *3*, 51−54.
(39) Nevalinen, V. Quantum Chemical Modeling of Chiral Catalysis on the Mechanism of Catalytic Enantioselective Reduction of Carbonyl Compounds by Chiral Oxazaborolidines. *Tetrahedron: Asymmetry* **1991**, *2*, 63−66.
(40) Solladie, G. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 6.
(41) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. Catalytic Asymmetric Induction. Highly Enantioselective Addition of Dialkylzincs to Aldehydes. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072.
(42) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. Enantioselective Addition of Dialkylzincs to Aldehydes Promoted by Chiral Amino Alcohol. Mechnism and Nonlinear Effect. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036.
(43) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. Catalytic Asymmetric Induction. Highly Enantioselective Addition of Dialkylzincs to Aldehydes. Using Chiral Pyrrolidinylmethanols and Their Metal Salts. *J. Am. Chem. Soc.* **1987**, *109*, 7111−7115.
(44) Soai, K.; Niwa, S.; Watanabe, M. Polymer-Bound Ephedrine as an Efficient Chiral Catalyst for the Enantioselective Addition of Dialkylzincs Addition of Dialkylzincs to Aldehydes. *J. Org. Chem.* **1988**, *53*, 927−928.
(45) Corey, E. J.; Yuen P.-W.; Hannon, F. J.; Wierda, D. A. Polyfunctional, Structurally Defined Catalysts for the Enantioselective Addition of Dialkylzinc Reagents to Aldehydes. *J. Org. Chem.* **1990**, *55*, 784−786.

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