Asymmetric Boron-Catalyzed Reactions†

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Received July 28, 1992 (Revised Manuscript Received September 18, 1992)

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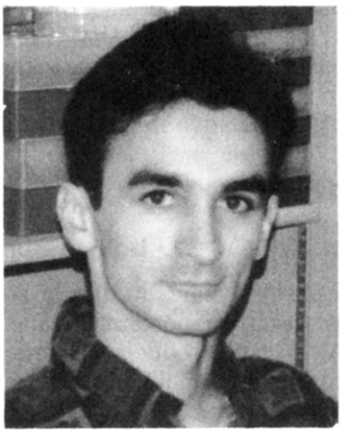
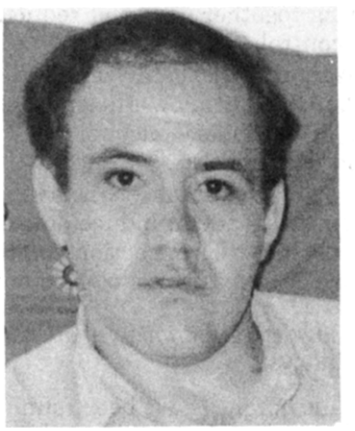


Laurent Deloux was born in 1968 in Paris, France. He received his B.S. and M.S. in 1992 from the Ecole Nationale Supérieure de Chimie de Lille, France. He joined Prof. M. Srebnik's group in January 1992 and is currently studying for his Ph.D. under his direction. His project involves the synthesis of boron-containing compounds as inhibitors of cholesterol biosynthesis. His research interests are in the area of synthetic organic and bioorganic chemistry.



Morris Srebnik received his Ph.D. in 1984 from the Hebrew University in Jerusalem, under Prof. Raphael Mechoulam. On a Lady Davis Fellowship, he joined Prof. H.C. Brown's group at Purdue where he studied the applications of organoboranes to synthesis until 1986. After a short stint at the Sigma-Aldrich Corporation he returned to Prof. Brown's group. In 1990 he accepted a position at the Department of Chemistry, University of Toledo. His areas of interest include developing organometallic methodologies in synthesis centered around boron, zinc, and zirconium, and investigating the potential uses of organoboranes in medicine.

I. Introduction

Asymmetric synthesis has received explosive interest during the last years.[1] Especially noteworthy is the development of homogeneous catalytic asymmetric reactions in which a small amount of chiral auxiliary can induce asymmetry for a given reaction. The possible applications rely on the selectivity of homogeneous catalysts which are therefore of great interest since they provide simple methods to synthesize complex molecules, involving steps which require enantiocontrol of the transformation.

† Dedicated to Professor H. C. Brown, Purdue University, on the occsion of his 85th birthday. Until 120.

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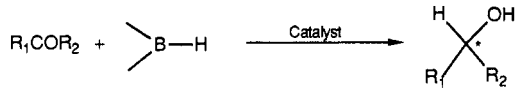
Scheme 1. Asymmetric Reduction of Ketones by Chiral Boron Catalyst



This review will be concerned with chirally modified boron complexes which have received increased interest due to their ability to induce chirality.[2] They have been successfully used for reactions such as reduction, Diels–Alder, aldol, and various miscellaneous reactions. We will describe and analyze the different types of catalyst and correlate them according to their efficiency, selectivity, and flexibility. Consequently, we will be concerned with their advantages and limitations.

II. Reduction

A. Reduction of the C=O Double Bond

During the past 40 years, studies of stereoselective reduction have led to important advances in organic synthesis.[3] As a result, reducing agents used for the reduction of carbonyl compounds are numerous. Methods for asymmetric reduction of carbonyl compounds with heterogeneous metal catalyst,[1,2d,4] stoichiometric quantities of chiral reagents,[1,2d,5] and biochemical methods[1,6] have been extensively reported in recent years.

But the real challenge is stereoselective reduction in good yields and good enantiomeric excess. In this matter, it appears that enantioselective homogeneous catalytic reduction is a promising method whose recent advances bring together chemical reduction and stereoselective control of the reaction.[1]

Chiral oxazaborolidines catalyze the chiral reduction of prochiral ketones and allow efficient enantioselective preparation of secondary alcohol with predictable configuration (Scheme 1).

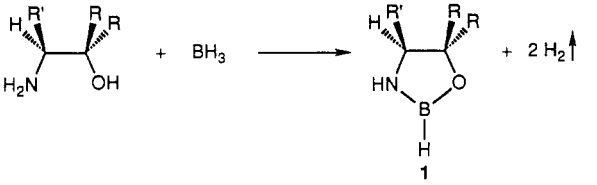
This review will discuss various reducing agents and correlate their efficiency to induce optical activity in the starting ketones. The reaction conditions, yield, and enantiomeric excess will also be summarized.

1. Historical Review: Description and Characteristics of the Main Catalysts

Several amine boranes have been found to be highly selective reducing agents for aldehydes and ketones under mild conditions,[7] and they are convenient reagents to use because of their stability, both thermal and hydrolytic, and solubility in a wide variety of solvents.[8] In the first attempt to use chiral amine borane complexes, Fiand and Kagan (1969) tested ephedrine boranes but only achieved 3.6–5% ee's in the reduction of acetophenone to 1-phenylethanol.[9] Related amine boranes in the presence of boron trifluoride etherate with various ketones yielded ee's <20%.[10–12]

The asymmetric reduction of ketones using chirally modified borohydrides as a catalyst has really been in use since 1981 when Itsuno et al.[13] reported an interesting enantioselective ketone reduction using an amino alcohol–borane complex as a catalyst. This complex consists of a boron hydride with various chiral ligands that are based on vicinal amino alcohols derived from the corresponding amino acids. The catalyst is a five-membered ring complex formed as shown in Scheme 2. The borane reacts readily with the alcohol initially to form a coordinated complex with the amine. However, the catalyst alone reduces the ketones only sluggishly. It is efficient when used in a mixture with a borane (BH_3·THF, BMS, catecholborane, etc.), which upon heating evolves 2 equiv of hydrogen and forms an oxazaborolidine.

Scheme 2. Formation of the Amino Alcohol–Borane Complex



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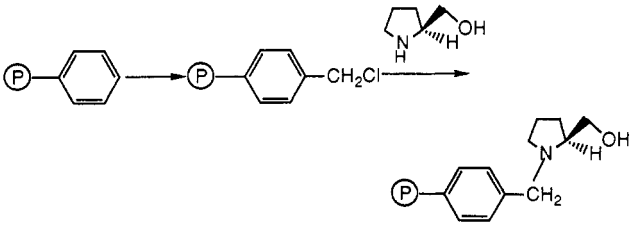
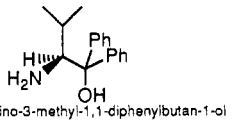
Scheme 3. Preparation of the Polymer-Bound Amino Alcohol Precursor



Further studies led him to improve the catalyst and to modify the reaction conditions.[14] THF seems to be the solvent of choice, a 1:2 molar ratio of amino alcohol and borane was found to be optimum for high stereoselectivity. A temperature of 30 °C and a reaction time of 2 h were selected as standard conditions. Itsuno also realized that a tertiary amino alcohol was more efficient for the reduction. He used a new chiral borane complex derived from (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol.[15] The asymmetric reduction of



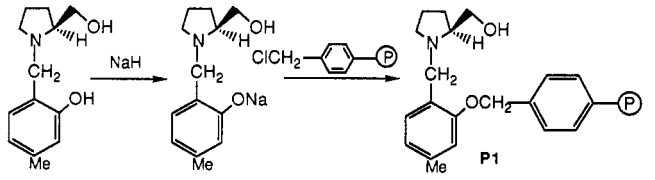
(S)-(-)-2-amino-3-methyl-1,1-diphenylbutan-1-ol

alkyl phenyl ketones with this catalyst proceeded in a highly stereoselective manner, giving alcohols with 94–100% optical yields. Nevertheless, asymmetric reduction of unsymmetrical dialkyl ketones with this reagent gave secondary alcohols of lower but still good enantioselectivity (55–78%).[15a,b] Furthermore, it proved that the catalyst could differentiate the small difference of steric size between R_1 and R_2 of the ketone.

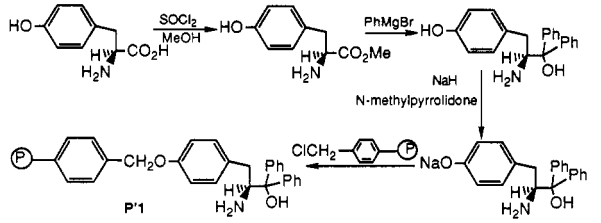
Despite experimental simplicity and efficient recoverability of the catalyst precursor (chiral amino alcohol), Itsuno was interested in chiral polymeric reagents.[16] Considering the ease of product isolation and the simple workup procedures due to polymer supported reactions, the group developed polymeric (*S*)-prolinol–borane reagents. A polymer-bound (*S*)-pyrrolidin-2-ylmethanol was synthesized by the reaction of chloromethylated polystyrene gel[17] with (*S*)-pyrrolidinylmethanol [(*S*)-prolinol] (see Scheme 3). Treatment with borane afforded the polymeric chiral borane catalyst.

As stated before, the stereoselectivity depends upon the molar ratio of borane and amino alcohol derivative.

Scheme 4. Preparation of the Polymer-Bound (*S*)-(−)-2-Pyrrolidinemethanol Precursor



Scheme 5. Preparation of the Polymer-Bound (*S*)-(−)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol Precursor



The highest stereoselectivity is obtained with a ratio of borane to amino alcohol of 2:1. The reaction mixture is evaporated to dryness after reaction to remove the excess of borane.

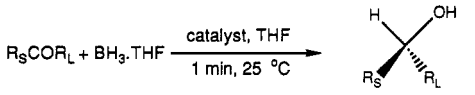
It was observed that the reduction of phenyl propyl ketone with the polymeric reagent sometimes gave better optical yields than the corresponding soluble reagent. Nevertheless, the stereoselectivity with the polymeric reagents depends upon the degree of ring functionalization and of cross-linking of the polymer support. With a small degree of functionalization (14%), the selectivity from the polymeric reagent was comparable with that in solution. However, with a degree of cross-linking of 1 or 2% and a higher degree of functionalization (50–69%), the polymeric reagent was more selective than the soluble one. Nevertheless, increasing the degree of functionalization still further resulted in a decreased selectivity, probably due to steric hindrance.

The reduction of alkyl phenyl ketones is comparable with the two methods. However, the reduction of dialkyl ketones with the polymeric reagent is less selective. But the same trend is observed with the reduction of butyl methyl ketones. The maximum selectivity is obtained with the *tert*-butyl which has the greatest steric hindrance.

The main difference between the two methods is in the rates of reduction, which are slower for the polymeric reagent. The rates are significantly affected by the degree of cross-linking and this is probably due to poor transport of ketone into the rigid polymer matrices. But according to Montanari and co-workers,[18] the rates of the reaction with polymer-bound phase-transfer catalyst are improved by inserting suitable spacers between the polymer backbone and the catalytic function. Consequently polymeric reagents were synthesized by making use of these spacers (Scheme 4 or 5, depending on the type of oxazaborolidines used).

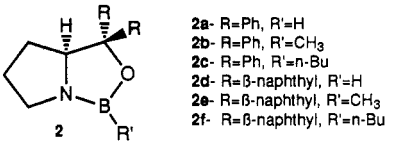
The results using this polymer-supported catalyst are better with respect to the reaction rates and comparable in optical yields. As stated previously, **P'1** is slightly more effective since it is a tertiary alcohol. Finally, an important improvement is that the spacers make this type of catalyst much more stronger mechanically compared to the previous one which was fragile and disintegrated to a fine powder after several experiments.

Scheme 6



Nevertheless, it seems that polymer-supported catalysis for the reduction of ketones has had a limited success to date. On the other hand, reduction using chirally modified borohydride in solution as catalyst has initiated more and more interest.

Since the initial report, numerous groups have investigated the asymmetric reduction of prochiral ketones to optically active alcohols with oxazaborolidines. This process pioneered by Itsuno was then developed by Corey et al. as the CBS process.[19] The CBS process is an enantioselective reduction with borane or catecholborane as stoichiometric reductant. The catalyst is an oxazaborolidine which behaves like an enzyme since it binds both the ketone and the hydride and releases them after the reaction. On the basis of Itsuno's studies, the Corey group introduced, isolated, and identified chiral oxazaborolidines such as



A good catalyst for the reduction of ketones is the oxazaborolidine made with R = Ph, R′ = H (**2a**) (see Scheme 6). It is prepared from (*S*)-(−)-2-(diphenylhydroxymethyl)pyrrolidine by heating at reflux with 3 equiv of BH_3·THF in THF. The results obtained for the reduction of different ketones are summarized in Table 1 which compare the different catalysts. The optimum conditions are usually 0.6 equiv of BH_3, 0.05 equiv of catalyst, THF as the solvent, 25 °C, and a reaction time of 1 min. Therefore, increasing the amount of BH_3·THF above 0.6 equiv or decreasing the temperature reduces the enantioselectivity of the reduction. Excellent yields and enantioselectivities are obtained with a wide variety of ketones, and the catalyst precursor is easily recovered upon workup.

Corey found that a better catalyst for the reduction of ketones corresponds to R = Ph, R′ = CH_3 (**2b**).[20] First, in contrast to the preceding catalyst, it is not air and moisture sensitive. Furthermore, the reduction with this catalyst proceeds generally with higher, or the same, enantioselectivity than with **2a** (R = Ph, R′ = H). By using the efficiency of this chiral catalyst, a number of synthetic routes to important compounds involving asymmetric reduction as their key enantioselective step were developed. These target molecules are compounds such as prostanoids,[18] *trans*-2,5-diarylfurans,[20] oxiranes,[21] ginkgolides A and B,[22] forskolin,[23] bilobalide,[24] and fluoxetine,[25] some of which are important therapeutic agents.

Bringmann et al. have also synthesized substituted chiral biaryls by the reduction of substituted 2-pyranones with BH_3·THF in the presence of **2b**.[26]

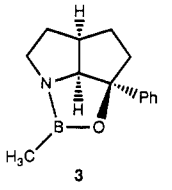
A group at Merck Sharp & Dohme Research Laboratories recently developed a more reproducible procedure for the large-scale synthesis of (*S*)-(−)-2-

(diphenylhydroxymethyl)pyrrolidine as chiral ligand and the corresponding *B*-methyloxazaborolidine.[27]

Catalysts such as **2c** are also being used.[28] A wide variety of ketones can be reduced by this process but using BH_3 as stoichiometric reductant may introduce some problems in the case of ketones containing functionality such as olefin or amide which could react with the borane. The Corey group solved this problem by using catecholborane with only one hydrogen as a hydride precursor, catalysts such as **2b** and **2c**, and toluene (or methylene chloride) as solvent.[28a,29] Under these conditions, α,β-enones were selectively reduced to allylic alcohols which after oxidation provided optically active α-hydroxy acids.[27a] Trichloromethyl ketones were also reduced to trichloromethyl carbinols using **2b**. Trichloromethyl carbinols provides a practical approach to α-amino acids[29a,b] and chiral benzylic thiols or sulfonic acid derivatives.[29c] (See Table 1 for optical yields induced during the reduction.) Changing R = Ph for R = β-naphthyl seems also to be an interesting evolution. It has been used in particular for the synthesis of therapeutic agents such as denopamine or (*R*)- and (*S*)-isoproterenol.[30]

Very recently, Corey et al. reported a new alkylboronic acid equivalent in order to speed the catalyst formation. They found that bis(trifluoroethyl) alkylboronates are outstanding reagents for oxazaborolidine formation. **2** can be formed in 30 min (110 °C, 0.07 Torr) compared to 3–10 h with an alkyl boronic acid and 48 h for the reaction with BH_3·THF.[31]

Catalysts such as **3** were also developed by Corey.[32] The performance of this catalyst for different ketones is summarized in Table 1.



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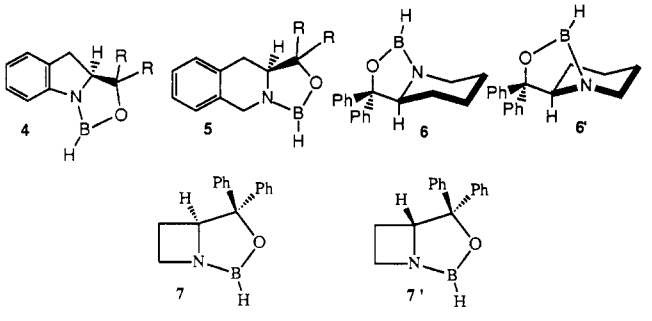
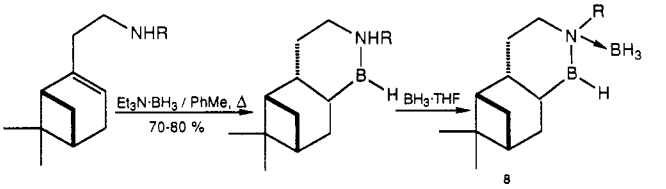
Following the first reports of enantioselective reduction of prochiral ketones by oxazaborolidines, several modifications and improvements were published. Now, simple and efficient catalysts are available. They are similar to the previous ones and are derived respectively from the following amino alcohol precursors: (*S*)-α,α-dialkyl(indolin-2-yl)methanol,[33] (*S*)-α,α-dialkyl(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol,[34] (*S*)- or (*R*)-α,α-diphenyl-2-piperidinemethanol[35] and (*S*)- or (*R*)-α,α-diphenyl-2-azetidinemethanol.[36,37]



4 **5** **6** **6'** **7** **7'**

These catalysts exhibit moderate to high enantioselectivity for the reduction of aliphatic (acyclic) and

Scheme 7. Preparation of Midland Reagent



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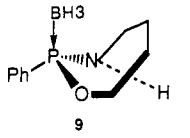
aromatic (aralkyl) ketones. It is to be noted that **6**, **6'** and **7**, **7'** correspond to two antipodes and give consequently the *R* or *S* alcohol after reduction, depending on the use of one or the other as catalyst. The two four-membered ring oxazaborolidines **7** and **7'** are structurally more rigid and thus improve the enantioselectivity. This is probably due to steric influence being less in the case of six-membered catalyst compared to five-membered oxazaborolidine.

Very recently, Midland et al. tried a different type of boron chiral reagent derived from terpenic 1,2-azaborocyclohexanes (Scheme 7).[38] Complexed with BH_3, they catalyzed the asymmetric reduction of different ketones. The complexes are formed in situ, and the best results are obtained when borane–methyl sulfide is used as a source of BH_3 in THF. Unfortunately, this type of reagent cannot be used in catalytic quantities for the reduction. However, promising results were obtained, and the best catalyst was found to be the *B*-methoxy reagent with R = *i*-Pr. The *B*-methyl reagent showed reduced selectivity, probably due to steric hindrance around the boron and the amine which prevents formation of the borane complex. Reduction by uncomplexed borane then becomes competitive. The preliminary results are provided in Table 1. The Midland reagents show equal efficiency for the reduction of aromatic and aliphatic ketones, which is somewhat different from the other catalysts.

In addition to oxazaborolidines, oxazaphospholidines have recently been reported as enantioselective reducing agents.[39] The chiral oxazaphospholidine borane complex is the catalyst whose structure has been shown to be the following:[40]



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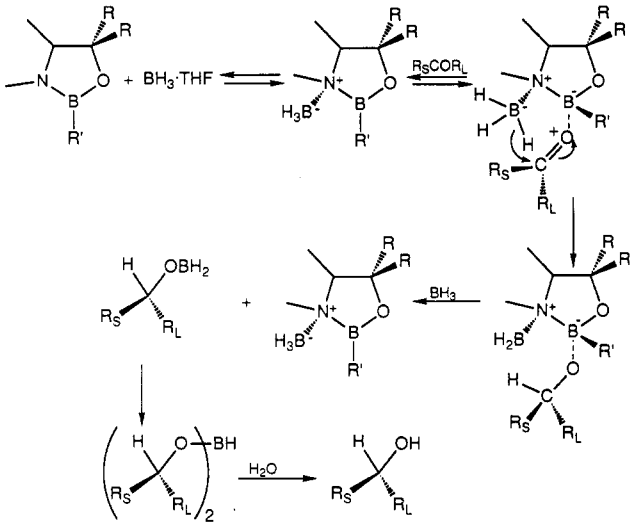
Under catalytic conditions, the enantioselectivity ranges between 33 and 92%. Under stoichiometric conditions, the reduction proceeded with 99% enantiomeric excess.[41]

It is probably the first example of enantioselective reduction catalyzed by this type of tricoordinated phosphorus–borane complex. The mechanistic features are currently under investigation.

2. Mechanism

The application of chiral amine–borane complexes to the catalytic asymmetric reduction of ketones is now well established. They have practical advantages as reducing agents, owing to their selectivity, their stability, and their solubility in protic or aprotic solvents. They belong to a new class of non-transition metal catalysts regarded as chemzymes. They can recognize

Scheme 8. Proposed Mechanism for the Reduction of Ketones by Oxazaborolidines



two different enantiomers, bind them in a specific and predictable manner and after activation, release the enantiomer of this selective reaction. The stoichiometric reagent is borane, and the catalyst is the chiral oxazaborolidine.

This is illustrated by the CBS process. A reasonable mechanism has been suggested by Corey[20] and is shown in Scheme 8.

The complex is made by ligand exchange on treating a solution of amino alcohol with BH_3·THF (or BMS). However, since the basicity of the nitrogen of the oxazaborolidine is considerably reduced, the boron is only loosely bound to the nitrogen. This complex is ideally structured to serve as an effective reagent for carbonyl reduction which occurs by coordination of the oxazaborolidine electrophilic boron and carbonyl oxygen. Then hydrogen transfer occurs from the NBH_3^- unit to the activated carbonyl via a six-membered ring transition state. Subsequent ligand exchange to form the alkoxy borane followed by displacement completes the catalytic cycle.

The reduction utilizes a borane (BH_3·THF, BMS, or catecholborane) as a source of hydrogen. When the reaction is performed with additional equivalents of BH_3·THF, the optical yield is lowered only marginally. This implies that the rate of reduction with the complexed catalyst is considerably faster than with BH_3·THF. However, this competing pathway is probably involved when low optical yields are obtained with some catalysts.

Ab initio molecular orbital calculations have been used to calculate the energy minima of the oxazaborolidine–borane–ketone adduct. For a complete study, see ref 42.

3. Efficiency of the Different Catalysts

Highly promising asymmetric reducing agents have been recently reported in the literature. However, a direct comparison between these catalysts is not easy due to the wide variety of ketones tested. This section will describe the effectiveness of these reducing agents with different classes of ketones.

The simplest and most efficient catalysts are summarized in Table 1.

Various catalysts have been mentioned for the reduction of ketones by chiral boron reagents. However, no one catalyst is effective for all types of ketones. Moreover, some catalysts require long reaction times, high temperatures, and/or stoichiometric amounts of reagent to be efficient. For each class of ketones, we have tried to analyze the most suitable catalyst with respect to efficiency–reaction conditions.

Acyclic Ketones (R_1COR_2). High optical yields are reliably achieved when R_1 is a tertiary alkyl group and R_2 is a small alkyl group (Me). In the other cases, the enantioselectivity tends to decrease. Although efficient, **1** and **8** require long reaction times and stoichiometric amounts. **2** and **3** seem to be the catalysts of choice. It is to be noted that **2** is efficient with R = Ph or R = β-naphthyl and R′ = H or R′ = Me. Nevertheless, R′ = H is less suitable since it is air and moisture sensitive. **9** has recently been developed and has been tried for the reduction of isopropyl methyl ketone. It gives the highest optical yields to date with this ketone but is used stoichiometrically and requires a relatively high temperature.

Aralkyl Ketones. Oxazaborolidine-type catalysts are the reagents of choice for aralkyl ketones. They are effective and give high % ee. But, considering the reaction conditions, some are better than others. **2** provides the best combination. (As previously, it is to be noted that R = H is air and moisture sensitive.) The other catalysts are effective but require more vigorous reaction conditions (longer reaction times specially) and have not been tested for a wide range of ketones.

Cyclic Conjugated. The comparison is not easy between the different ketones, but **2** and **3** are still very efficient.

Acyclic Conjugated. **2** gives good % ee (>80%) but the reaction are longer (15 h).

α-Halogenated Ketones. In a direct comparison between **1** and **2**, **2** is without a doubt better since it can be used catalytically and the reaction times are shorter. Otherwise the % ee and chemical yields are comparable.

Direct comparison is not possible for the other ketones mentioned. In all cases, the catalysts are effective. But it is clear that **2** (Corey's reagent) is the most promising catalyst. A balance between R and R′ has to be found. Indeed, bulky groups provide better stereocontrol of the reaction, but very bulky groups also decrease the enantioselectivity probably due to competition with the stoichiometric reduction by borane. The equilibrium of formation of the catalytic species is likely to be shifted to the left when very bulky substituents are employed.

B. Reduction of C=N Double Bond

Although highly effective asymmetric reduction of carbonyl compounds has been extensively investigated, efficient enantioselective reduction of imines derivatives to amines has been relatively neglected. Consequently, limited success has been achieved. However, active amines are important biological compounds and different methods have been developed for their preparation.[44] Similarly, interesting results have been obtained in the asymmetric reduction of ketoximes (ketoxime *O*-alkyl ethers or ketone oxime *O*-alkyl ethers) and ketimines using chirally modified borohydrides.

Table 1. Asymmetric Reduction of Ketones with Chiral Boron Catalysts

ketone	catalyst	stoichiometry	reaction time[c]	temp, °C	% ee	yield[a] %	configurn	ref
			Acyclic					
i-PrCOCH$_3$	8	1 equiv of borane or BMS, 1 equiv of cat	5 min	110	>99	75–80[a]	*R*	39
	1; R = Ph, R′ = *i*-Pr	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	30	60	100	*R*	15a, 14b
n-BuCOCH$_3$	1; R = Ph, R′ = *i*-Pr	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	30	55	100	*R*	15a, 12b
t-BuCOCH$_3$	1; R = Ph, R′ = *n*-Bu	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	0	96	100	*R*	14b
	2; R = Ph, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	2 min	−10	97.3	100	*R*	20
	2; R = Ph, R′ = H	0.6 equiv of borane, 0.05 equiv of cat	1 min	25	92	>99.7	*R*	19
	3	0.6 equiv of borane, 0.1 equiv of cat	15 min	0	98.3	>90[a]	*R*	32
	2; R = β-naphthyl, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	5 min	0	92.7	>90[a]	*R*	43
	7; R = Pr, R′ = OMe	1.3 equiv of BMS, 1.6 equiv of cat	1 h	RT	82	61		38
i-BuCOCH$_3$	1; R = Ph, R′ = *i*-Pr	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	30	61	100	*R*	14b
n-PentCOCH$_3$	1; R = Ph, R′ = *i*-Pr	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	30	56	100	*R*	15a
n-HexCOCH$_3$	7; R = Pr, R′ = OMe	1.3 equiv of BMS, 1.6 equiv of cat	1 h	RT	64	76		38
c-HexCOCH$_3$	2; R = Ph, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	2 min	−10	84	100	*R*	18
	3	0.6 equiv of borane, 0.1 equiv of cat	40 min	−22	91.8	>90[a]	*R*	32
	2; R = β-naphthyl, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	5 min	0	82.2	>90[a]	*R*	43
	2; R = β-naphthyl, R′ = H	0.6 equiv of borane, 0.1 equiv of cat	5 min	23	84.7	>90[a]	*R*	43
	2; R = β-naphthyl, R′ = H	0.6 equiv of borane, 0.1 equiv of cat	5 min	23	84.7	>90[a]	*R*	43
	2; R = Ph, R′ = *n*-Bu	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	76	100	*R*	27b
	1; R = 4-(CF$_3$)-C$_6$H$_4$, R′ = Me	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	76	100	*R*	27b
			Aralkyl					
MeCOPh	1; R = *i*-Pr, R′ = Ph	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	30	94	100	*R*	14b
	2; R = Ph, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	2 min	2	91	100	*R*	20
	2; R = Ph, R′ = Me	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	98	100	*R*	27b
	2; R = Ph, R′ = Me	1 (1.2) equiv of eq, 0.1 (0.05) equiv of cat	1 min	25	97 (95)	>99.7	*R*	19
	4; R = H, R′ = H	2 equiv of BMS, 1 equiv of cat	10 min	RT	97	96	*R*	33a
	4; R = Ph, R′ = H	borane, 0.02 equiv of cat	60 min	30	930	>90	*R*	33b
	6 (6′)	0.6 equiv of borane, 0.1 equiv of 6 (6′)	5 min	0	87 (87)	85< (<90)	*R* (*S*)	35
	7′	0.6 equiv of borane, 0.1 equiv of 7′	5 min	0	95	>90	*S*	36
	8	1 equiv of borane, 1 equiv of cat	5 min	110	>99	75–80[a]	*R*	39
	2; R = β-naphthyl, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat (0.05)	30–5 min	23	97.8 (96.1)	>90[a]	*R*	43
	7; R = Pr, R′ = OMe	1.3 equiv of BMS, 1.6 equiv of cat	1 h	RT	74	69		38
EtCOPh	1; R = *i*-Pr, R′ = Ph	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	30	94	100	*R*	14b
	2; R = Ph, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	2 min	−10	96.7	100	*R*	20
	2; R = Ph, R′ = Me	0.6 equiv of BH_3, 0.1 equiv cat	1 min	25	90	>99.7	*R*	19

Table 1. (Continued)

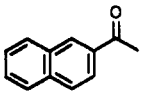
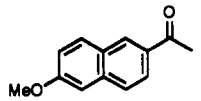
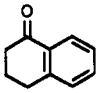
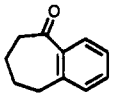
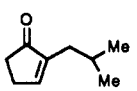
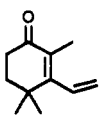
ketone	catalyst	stoichiometry	reaction time[c]	temp, °C	% ee	yield[a] %	configurn	ref
		Aralkyl						
	2; R = β-naphthyl, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	5 min	0	97.4	>90[a]	*R*	43
	4	2 equiv of BMS, 1 equiv of cat	10 min	RT	87	93	*R*	33a
	7	1.1 equiv of borane, 0.1 equiv of 7	2 h	30	>99		*R*	37
n-PrCOPh	1; R = *i*-Pr, R′ = Ph	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	30	96	100	*S*	14b
	4; R = Ph	borane, 0.1 equiv of cat	30–60 min	30	88	>90	*R*	33b
n-BuCOPh	1; R = *i*-Pr, R′ = Ph	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	30	100	100	*R*	14b
3-[(MeO)C_6H_4]COMe	6 (6′)	0.6 equiv of borane, 0.1 equiv of 6 (6′)	5 min	0	92 (96)	85< (<95)	*R* (*S*)	35
	7	0.6 equiv of borane, 0.1 equiv of 7	5 min	0	95	>90	*R*	36
4-[(MeO)C_6H_4]COMe	6 (6′)	0.6 equiv of borane, 0.1 equiv of 6 (6′)	5 min	0	90 (88)	85< (<95)	*R* (*S*)	35
4-[(Me_2CHCH_2)C_6H_4]COMe	6 (6′)	0.6 equiv of borane, 0.1 equiv of 6 (6′)	5 min	0	89 (89)	85< (<95)	*R* (*S*)	35
	7	0.6 equiv of borane, 0.1 equiv of 7	5 min	0	95	>90	*R*	36
	4	2 equiv of BMS, 1 equiv of cat	10 min	RT	88	97	*R*	33a
	2; R = Ph, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	2 min	23	96.5	100	*R*	20
		Cyclic Conjugated						
	2; R = β-naphthyl, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	5 min	31	94.5	>90[a]	*R*	43
	2; R = β-naphthyl, R′ = H	0.6 equiv of borane, 0.1 equiv of cat	5 min	23	95.3	>90[a]	*R*	43
	2; R = Ph, R′ = Me	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	94	100	*R*	27b
	2; R = Ph, R′ = Bu	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	96	100	*R*	27b
	2; R = Ph, R′ = Ph	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	94	100	*R*	27b
	3	0.6 equiv of borane, 0.1 (0.2) equiv of cat	40 min	−22	95.3 (97)	>90[a]	*R*	32
	2; R = Ph, R′ = Me	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	96	100	*R*	27b
	1; R = Ph, R′ = Me	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	98	100	*R*	27b
methyl 2-naphthyl ketone	4	borane, 0.02 equiv of amino alcohol	30–60 min	30	85	>90[a]	*R*	33b
	1; R = Ph, R′ = *n*-Bu	1.5 equiv of catecholborane, 0.1 equiv of cat	15 h	−78	93	>95	*R*	28a
	2; R = β-naphthyl, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	2 min	10	92	88[a]	*R*	22b
	2; R = β-naphthyl, R′ = Me	0.6 equiv of borane, 0.2 equiv of cat	*b*	35	90	91	*R*	23

Table 1. (Continued)

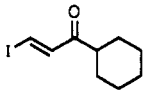
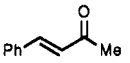
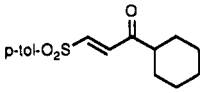
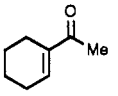
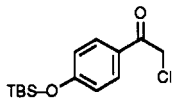
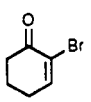
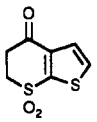
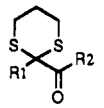
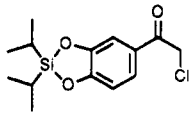
ketone	catalyst	stoichiometry	reaction time[c]	temp, °C	% ee	yield[a] %	configurn	ref
		Acyclic Conjugated						
	3	0.6 equiv of borane, 0.1 equiv of cat	40 min	−23	87.6	>90[a]	*R*	32
	2; R = Ph, R′ = *n*-Bu	1.5 equiv of catecholborane, 0.1 equiv of cat	15 h	−78	86	>95	*R*	28a
	2; R = Ph, R′ = *n*-Bu	1.5 equiv of catecholborane, 0.1 equiv of cat	15 h	−78	92	>95	*R*	28a
	2; R = Ph, R′ = *n*-Bu	1.5 equiv of catecholborane, 0.1 equiv of cat	15 h	−78	91	>95	*R*	28a
	2; R = Ph, R′ = *n*-Bu	1.5 equiv of catecholborane, 0.1 equiv of cat	15 h	−78	81	>95	*R*	28a
		α-Halo						
$ClCH_2COPh$	1; R = *s*-Bu, R′ = Ph	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	0	96	100	*S*	14b
	2; R = Ph, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	2 min	32	95.3	100	*S*	20
	2; R = Ph, R′ = H	0.6 equiv of borane, 0.05 equiv of cat	1 min	25	97	>99.7	*S*	19
	2; R = Ph, R′ = H	0.6 equiv of borane, 0.1 equiv of cat	10 min	20–30	96.5	97.1	*S*	21
	7 (7′)	0.6 equiv of borane, 0.1 equiv of 7 (7′)	5 min	0	97 (95)	>90	*S* (*R*)	36
$BrCH_2COPh$	1; R = *s*-Bu, R′ = Ph	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	0	83	100	*S*	14b
$(ClCH_2CH_2)COPh$	2; R = Ph, R′ = Me	0.6 equiv of BH_3, 0.1 equiv of cat	20–30 min	0	94	>99	*R*	25
$ClCH_2CO$*t*-Bu	1; R = *s*-Bu, R′ = Ph	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	1 h	30	90	100	*S*	14b
$BrCH_2CO$*t*-Bu	1; R = *s*-Bu, R′ = Ph	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	1 h	30	93	100	*S*	14b
	2; R = β-naphthyl, R′ = *n*-Bu	0.6 equiv of borane, 0.1 equiv of cat		23	97	96	*S*	30b
n-$C_5H_{11}COCCl_3$	2; R = Ph, R′ = *n*-Bu	1.5 equiv of catecholborane, 0.1 equiv cat	12 h	−60[d]	95		*R*	29a
$C_6H_5(CH_2)_2COCCl_3$			12 h	−78	95		*R*	29a
t-$C_4H_9COCCl_3$			12 h	23	95		*R*	29a
c-$C_6H_{11}COCCl_3$			48 h	−20[d]	92		*R*	29a
4-$C_6H_5C_6H_4CH_2COCCl_3$			10 h	−44	96		*R*	29a
2-naphthylmethyl trichloromethyl ketone			1.7 h	−23	93		*R*	29a
		α-Halo Cyclic Conjugated						
	2; R = Ph, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	2 min	23	91	100	*R*	20
	3	0.6 equiv of borane, 0.1 equiv of cat	40 min	−23	97.5	>90[a]	*R*	32
	2; R = β-naphthyl, R′ = Me	0.6 equiv of borane, 0.1 equiv of cat	5 min	36	90.3	>90[a]	*R*	43
	2; R = β-naphthyl, R′ = H	0.6 equiv of borane, 0.1 equiv of cat	5 min	36	90.7	>90[a]	*R*	43
	3	0.6 equiv of borane, 0.1 equiv of cat	40 min	23	95	>90[a]	*R*	32
PhCOCOOMe	1; R = Ph, R′ = *s*-Bu	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	1 h	30	25	100	*S*	14b
PhCOCOOEt	4; R = H, R′ = H	2 equiv of BMS, 1 equiv of cat	10 min	RT	64	46	*S*	33a

Table 1. (Continued)

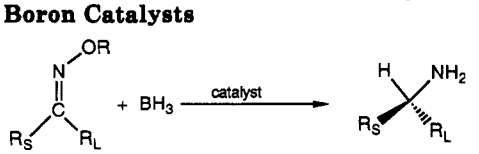
ketone	catalyst	stoichiometry	reaction time[c]	temp, °C	% ee	yield[a] %	configurn	ref
		β-Keto Ester						
$PhCOCH_2COOMe$	1; R = Ph, R′ = *s*-Bu	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	1 h	30	58	100	*S*	14b
$MeCOCH_2COOEt$	8	1 equiv of borane or BMS, 1 equiv of cat	5 min	110	>99	75–80[a]		39
		λ-Keto Ester						
$PhCO(CH_2)_2COOMe$	2; R = Ph, R′ = Me	0.6 equiv of BH_3, 0.1 equiv of cat	2 min	0	94	100	*R*	20
		δ-Keto Ester						
$PhCO(CH_2)_3COOMe$	2; R = Ph, R′ = Me	0.6 equiv of BH_3, 0.1 equiv of cat	2 min	0	96.7	100	*R*	20
		Heterocyclic						
	2; R = Ph, R′ = Me	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	96	100	*R*	27b
	2; R = Ph, R′ = Ph	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	96	100	*R*	27b
	2; R = Ph, R′ = 4-F-C_6H_4	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	98	100	*R*	27b
	2; R = Ph, R′ = 4-Me-C_6H_4	0.7 equiv of BMS, 0.1 equiv of cat	*b*	−15	98	100	*R*	27b
								
R_1 = Me R_2 = Me	2; R = Ph, R′ = Ph	0.6 equiv of borane, 0.15 equiv of cat	30 min	RT	94	>95	*R*	28b
R_1 = Pr R_2 = Me	1; R = Ph, R′ = Ph	0.6 equiv of borane, 0.15 equiv of cat	30 min	RT	93	>95	*R*	28b
R_1 = Benzyl R_2 = Me	1; R = Ph, R′ = Ph	0.6 equiv of borane, 0.15 equiv of cat	30 min	RT	96	>95	*R*	28b
R_1 = Ph R_2 = Me	1; R = Ph, R′ = Ph	0.6 equiv of borane, 0.15 equiv of cat	30 min	RT	90	>95	*R*	28b
R_1 = Ph R_2 = Et	1; R = Ph, R′ = Ph	0.6 equiv of borane, 0.15 equiv of cat	30 min	RT	609	>95	*R*	28b
R_1 = $TBSOCH_2$ R_2 = Me-$(CH_2)_4$-	1; R = Ph, R′ = Ph	0.6 equiv of borane, 0.15 equiv of cat	30 min	RT	95	>95	*R*	28b
	1; R = Ph, R′ = Ph	0.6 equiv of borane, 0.15 equiv of cat	30 min	RT	>96	>95	*R*	28b
R_1 = Ph R_2 = CH_2OSiMe_3	1; R = Ph, R′ = *s*-Bu	1 equiv of amino alcohol, 2 equiv of borane, 0.8 equiv of ketone	2 h	30	80	100	*S*	14b
	2; R = β-naphthyl, R′ = *n*-Bu	0.6 equiv of borane, 0.1 equiv of cat	2 min	23	97	96	*R*	30a

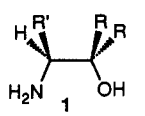
[a] Isolated yield. [b] Reaction went to completion. [c] After addition of the last reagent. [d] These reactions were initiated at −78 °C and brought to the indicated temperature after 1 h.

1. Reduction of Ketoxime O-Alkyl Ethers

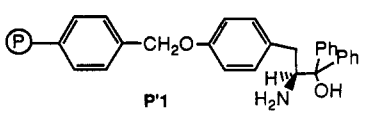
In contrast to the large number of papers dealing with carbonyl compounds, only a few references appeared in the literature on the catalytic asymmetric reduction of compounds with C=N double bond. Nevertheless, after reporting the asymmetric reduction of ketones with chiral reducing agents based on amino alcohol derivatives and boranes, Itsuno et al. directed their attention to the asymmetric reduction of the isoelectronic imino group, ketoxime *O*-alkyl ethers, using this type of catalyst (Scheme 9).[14b,16b] In the course of their study, they used various chiral reducing agents such as Itsuno's reagent[14b] or Corey's reagent[19] and decided to investigate the catalytic behavior of the monomeric (soluble) and polymeric reagents (**1** and **P′1**).

Scheme 9. Reduction of Ketoxime *O*-Alkyl Ethers by Chiral Boron Catalysts





1



P′1

The monomeric reducing agents are relatively effective

Table 2. Asymmetric Reduction of Ketoxime *O*-Alkyl Ethers with 1 and P'1

ketoxime: $R_1R_2C{=}NOR_3$	catalyst	% ee	yield (%)	configurn	ref
R_1 = Ph, R_2 = Me, R_3 = Me	1	99	100	*S*	14b
	P'1	18	100	*S*	16b
R_1 = Ph, R_2 = Me, R_3 = Et	1	81	100	*S*	14b
R_1 = Ph, R_2 = Me, R_3 = CH_2Ph	1	91	100	*S*	14b
	P'1	26[a]	100	*S*	16b
R_1 = Ph, R_2 = Me, R_3 = $SiMe_3$	1	62	100	*S*	14b
R_1 = Ph, R_2 = Me, R_3 = COMe	1	8.7	100	*R*	14b
R_1 = naphthyl, R_2 = 1-Me, R_3 = Me	1	70	100	*S*	14b
R_1R_2 = α-tetralone, R_3 = Me	1	69	100	*S*	14b

[a] The ratio of borane to catalyst is 3:1.

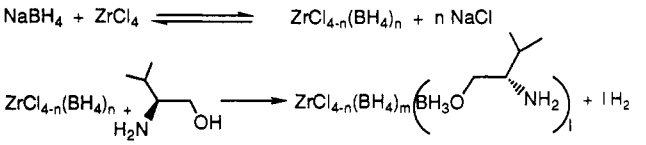
for this type of reduction (at least for R_1 = Ph, R_2 = alkyl, R_3 = alkyl). On the other hand, the optical yields obtained with polymeric reagents are low (see Table 2). The reaction conditions are the following: stoichiometry, 2 equiv of borane, 1 equiv of catalyst, 0.8 equiv of ketoxime; reaction time, 24 h after mixing all the reagents; reaction temperature, 30 °C.

Unlike ketones' reduction, the reduction of ketoximes is slow. Nevertheless, it was found, in the case of the polymeric reagent, that the addition of a Lewis acid to the ketoxime before the reaction not only activates but also induces asymmetry during the reduction. The optical yields are increased but are still low.

Another difference as compared with ketone reduction is that catalysts 1 and P'1 reduce asymmetrically ketoximes to give the primary amine having the *S* configuration, which is the reverse of that obtained with ketones. A reasonable explanation is given by Itsuno: "Because of the anti-configuration of ketoxime, steric hindrance by the *O*-alkyl group trans to the large phenyl group may become a dominant factor in the stereoselectivity."[16b]

Still, the enantiomeric excess is low and new methods need to be developed. On the basis of the fact that a combination of sodium borohydride and transition-metal catalyst[45] has been frequently used for the asymmetric reduction of various functional groups, Itsuno et al.[46] applied the combination of sodium borohydride and zirconium tetrachloride to the reduction of C=N bond. This type of combination has been previously reported as a mixture of lithium aluminum hydride and zirconium tetrachloride and used for hydrogenation of olefins.[47] However, it was the first time that zirconium tetrachloride was combined with sodium borohydride. Using this new reducing agent, the Itsuno group then decided to prepare a chirally modified mixture of $NaBH_4$–$ZrCl_4$.[48]

Scheme 10. Preparation of the Zirconium Aminoalkoxy Borohydride Reagent



This reagent is considered to be a mixed borohydride. The reducing species is probably a mixture of zirconium aminoalkoxy borohydride (Scheme 10).

In the course of their study, Itsuno et al. observed that THF is the solvent of choice and that the optimum ratio [NaBH4]:[ZrCl4]:[amino alcohol]:[ketoxime] should be 60:15:15:12. The highest % ee and good chemical yield were obtained when the reaction was carried out at room temperature with a reaction time of 2 days (after addition of the last reagent).

The results obtained with different types of ketoximes are summarized in Table 3.

It is clear that the reaction is promising and should be further developed. The reduction gives reasonable to good % ee. It is interesting to note that, under the same conditions, there is little change in the selectivity of the reduction of the *O*-methyloxime of an alkyl phenyl ketone (R_1 = Ph; R_2 = Me, Et, *i*-Pr; R_3 = Me). Moreover, the introduction of a bulky benzyl group in the ether increases somewhat the selectivity. The chiral amino alcohol 1, R = Ph, R' = *i*-Pr, having two phenyl groups gives the highest % ee. It would probably be interesting to develop this catalyst for a wide range of ketoximes. On the basis of his experience with polymer-supported catalysts which can be easily separated from the reaction mixture by simple filtration, Itsuno et al. also tried to develop equivalent polymeric reagents. However, the optimum optical yield for the reduction of acetophenone *O*-methyloxime was only 35% ee.

To conclude this section on the asymmetric reduction of ketoximes, it seems that the first method described (reducing agent based on chiral amino alcohols and boranes) provides at the present time the best com-

Table 3. Asymmetric Reduction of Ketoxime *O*-Alkyl Ethers with the Reagent Prepared from $NaBH_4$, Lewis Acid, and a Chiral Amino Alcohol

ketoxime: $R_1R_2C{=}NOR_3$	amino alcohol[a]	ratio	% ee	yield (%)	configuration	ref
R_1 = Ph, R_2 = Me, R_3 = Me	1; R = Ph, R' = *i*-Pr	40:40:15:12	90	95	*S*	46
	1; R = Ph, R' = *i*-Pr	60:15:15:12	95	92	*S*	48a
	1; R = Ph, R' = H	60:15:15:12	81	96	*S*	48a
	1; R = Ph, R' = H	40:40:15:12	64	95	*S*	48a
R_1 = Ph, R_2 = Et, R_3 = Me	1; R = Ph, R' = H	40:40:15:12	66	93	*S*	48
R_1 = Ph, R_2 = *i*-Pr, R_3 = Me	1; R = Ph, R' = H	40:40:15:12	61	90	*S*	48
R_1 = Ph, R_2 = Me, R_3 = Bz	1; R = PH, R' = H	40:40:15:12	69	91	*S*	48
R_1 = Ph, R_2 = Et, R_3 = Bz	1; R = Ph, R' = H	40:40:15:12	72	88	*S*	48
R_1 = 1-naph, R_2 = Me, R_3 = Me	1; R = Ph, R' = H	40:40:15:12	55	85	*S*	48
R_1 = 2-naph, R_2 = Me, R_3 = Me	1; R = Ph, R' = H	40:40:15:12	61	90	*S*	48
3,4-dihydrohaphthalen-1(2*H*)-one oxime	1; R = Ph, R' = H	40:40:15:12	67	86	*S*	48
R_1 = *t*-Bu, R_2 = Me, R_3 = Me	1; R = Ph, R' = H	40:40:15:12	42	78	*S*	48

[a] The numbering refers to the amino acid precursor of 1. (See p 3.) [b] Isolated yield.

Scheme 11. Reduction of Ketimines by Chiral Boron Reagents

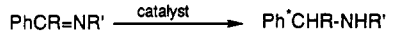


Table 4. Asymmetric Reduction of N-Substituted Ketimines with 10[c]

R	R'	time (h)	% ee[a]	yield %	configuration
Me	Ph	20	73	98 (87)	(*R*)-(−)
Et	Ph	22	87	97 (89)	(*R*)-(−)[b]
i-Pr	Ph	24	71	96 (90)	(+)
n-Pr	Ph	24	88	97	(*R*)-(−)[b]
Me	Bz	20	46	98	(*R*)-(−)
Me	*n*-C_7H_{13}	20	52	96	(*R*)-(−)[b]

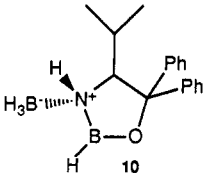
[a] The figures in parentheses indicate isolated yield after column chromatography. [b] The absolute configuration is unknown, but is probably *R* based on the order of elution of MPTA derivatives and the sign of rotation. [c] For structures see Scheme 11.

bination. The yields and % ee are higher. The reaction times are faster. However, zirconium tetrachloride is inexpensive and easy to use and further study on asymmetric reduction by use of this reagent is in progress and should lead to promising results.

2. Reduction of Imines

As in the case for ketoximes, the reduction of imines would provide optically active amines which are of synthetic interest for the preparation of biologically active compounds. The method used is similar to the previous one and is based on chiral reducing agents such as Itsuno's[14b] or Corey's[19] reagent. The choice of these catalysts arises from their ability to reduce ketones quantitatively and in good enantiomeric excess (Scheme 11).[49]

In the course of the study, **10** was selected to investigate the asymmetric reduction of N-substituted ketimines.[50] The reductions were carried under the



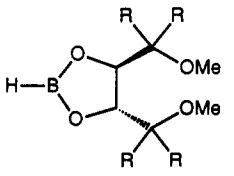
10

same conditions as those applied for the reduction of ketones. The results are summarized in Table 4, and the reaction conditions are the following: the reductions were carried out in THF at 30 °C for 22 h; the ratio [amino alcohol]:[BH_3]:[ketimine] is 1:2:1; the N-substituted ketimine derivative studied is alkylphenone *N*-alkylimine (PhCR=NR').

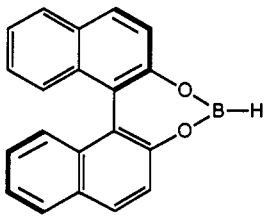
All the ketimines examined are reduced to the corresponding amines in high yield. For *N*-phenyl ketimines (R' = Ph), high optical yields are obtained (71–88%). This is, according to the authors, the only method that provides such high asymmetric induction. Moreover, increasing the steric bulk of the R group leads also to high optical yields. However, reduction of *N*-alkyl ketimine results in poor optical induction.

On the other hand, reduction of *N*-phenylimines derived from dialkyl ketones gives only poor results. Consequently, a requirement to obtain a good optical induction is to reduce N-phenylimines derived from alkyl aryl ketones. Good results ought to be obtained but the application to a large number of N-substituted ketimines will be reduced.

Recently, Hino et al. described the asymmetric reduction of prochiral *N*-phenylimines, *N*-benzylimines, and 1-methyl-3,4-dihydro-β-carboline with chiral dialkoxyborane reagents.[51] The reagent that gave the best results is **11**. However, 5 equiv have to be used, and the reaction must be carried out in the presence of $MgBr_2{\cdot}OEt_2$ (1.2 equiv), otherwise the reduction does not take place. Other additives have been tried, but they were less effective.



11 a: R=Me
b: R=Et
c: R=H



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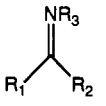
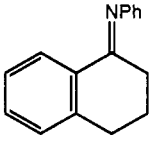
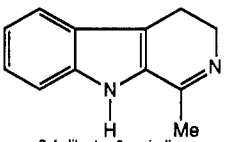


a: R_1=Ph, R_2=Et, R_3=Ph
b: R_1=Ph, R_2=Me, R_3=Ph
c: R_1=Ph, R_2=n-Pr, R_3=Ph
d: R_1=Ph, R_2=i-Pr, R_3=Ph
e: R_1=Ph, R_2=n-Bu, R_3=Ph
f: R_1=i-Pr, R_2=Me, R_3=Ph
g: R_1=Ph, R_2=Me, R_3=CH_2Ph
h: R_1=Ph, R_2=n-Pr, R_3=CH_2Ph



I: R_1, R_2=α-tetralone, R_3= Ph

Imines derived from phenyl primary alkyl ketones and aniline (b, c, and e) gave modest enantioselectivities with good chemical yields. Better enantioselectivity was obtained with alkyl ketimines, 3-methyl-2-butanone (f) and *N*-benzylimine (g). Imines d, h, and i gave poor optical yields. In contrast with Itsuno reagent, it is to be noted that **11a** could reduce 3,4-dihydro-β-carboline (see Table 5).



3,4-dihydro-β-carboline

III. Diels–Alder Reaction

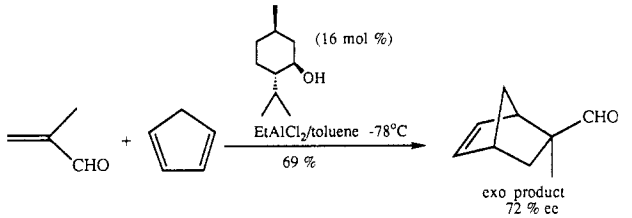
The Diels–Alder reaction is one of the most useful structural transformations in organic synthesis, providing consequently a reliable tool for the synthesis of natural compounds.[52] Development of methods for the asymmetric induction of Diels–Alder reaction is thus of considerable interest.[53] The influence of Lewis acid catalysts on the rate of reaction and on both regioselectivity and stereoselectivity is well documented.[54] Thus, achieving enantioselectivity with chiral Lewis acid is a very challenging goal. The type of dienophile that are subject to catalysis are typically those with a carbonyl activating group. Lewis acids are good cat-

Table 5. Reduction of Imines by Alkoxyborane Reagents

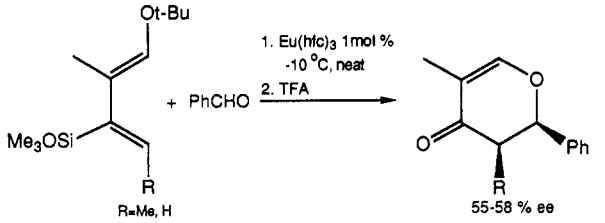
imine	chiral borane	reaction time (h)	temp (°C)	% ee	yield %[a]	abs config
a	**11a**	23	RT	73	91	(*S*)-(+)
a	**11b**	1 (23)	0 (RT)	41	73	(*S*)-(+)
a	**11c**	0.5	0	15	96	(*S*)-(+)
a	**12**	1 (23)	0 (RT)	20	94	(*R*)-(−)
b	**11a**	0.5 (15)	0 (RT)	56	89	(*R*)-(−)
c	**11a**	2 (14)	0 (RT)	65	94	(*S*)-(+)
d	**11a**	1 (24)	0 (RT)	18	85	(−)
e	**11a**	1 (25)	0 (RT)	65	95	(−)
f	**11a**	1 (2)	0 (RT)	71	75	(−)
g	**11a**	1 (23)	0 (RT)	72	70	(*R*)-(+)
h	**11a**	1 (23)	0 (RT)	36	81	(+)
i	**11a**	1 (25)	0 (RT)	12	79	(+)

[a] Isolated yields. [b] The numbers in parentheses gave the same results, but the reaction was performed at different temperature and reaction time.

Scheme 12



Scheme 13



alysts because of their ability to form complexes with carbonyl oxygens. This increases the electron-withdrawing capacity of the carbonyl group and thus accentuates both the energy and orbital distortion of this substituent. As a result, the reactivity and selectivity of the dienophile are enhanced.

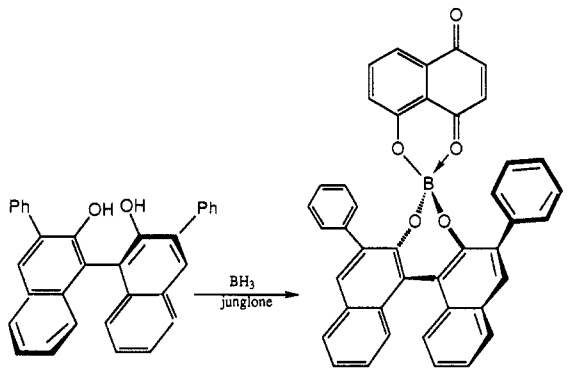
Lewis acid catalyzed Diels–Alder reactions are well established. Chiral Lewis acid catalyzed reactions were initiated by Koga et al. (Scheme 12).[55]

The catalyst, (menthyloxy)aluminum dichloride, is prepared in situ from menthol and ethylaluminum dichloride. It catalyzes the reaction of 2-methyl-2-propenal and cyclopentadiene and provides the exo adduct in 72% ee.

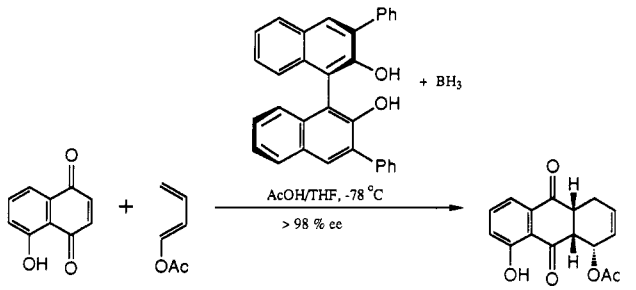
Europium was also found to catalyze the hetero-Diels–Alder reaction between Danishefsky-type dienes and aldehydes with asymmetric induction (Scheme 13).[56] Various Lewis acids have been used including boron, aluminum, titanium, ruthenium, and europium.[52,54c]

In this review, we wish to report the most recent advances using chiral boron reagents as catalyst. However, these chiral reagents were preceded by achiral models that are simple boron derivatives used to catalyze the reaction. They do not induce stereoselectivity, but they have the ability to enhance the rate and the regioselectivity in the Diels–Alder reaction between unsymmetrical dienes and dienophiles.[57]

Scheme 14



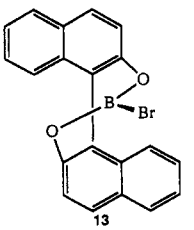
Scheme 15



A. Chiral Boron Reagents Prepared from Disubstituted Binaphthol

The first example reported on the use of such a chiral boron complex has been reported by Kelly et al. in 1986.[58] It promotes the reaction of naphthoquinone (juglone) and various dienes. It was prepared from juglone (a *peri*-hydroxyquinone which is the dienophile for the Diels–Alder reaction) and a 3,3′-diphenyl-1,1′-bi-2-naphthol. The hydroxy group of the *peri*-hydroxyquinone can serve as a ligand for the Lewis acid and reduce the conformational mobility of the complex. The binaphthol derivative serves as the other ligand for the boron. It is also useful since this bidentate ligand possess C_2 symmetry leading consequently to the formation of only one complex, whereas two enantiomers could be formed with other ligands which do not possess C_2 symmetry (Scheme 14). The reaction provides anthraquinones derivatives in good ee (Scheme 15). Since this reaction proceeds via coordination of the boron to the dienophile, the use of one equivalent of chiral boron is required.

Recently, while investigating this type of catalysts, Kaufmann et al. tried to prepare analogs incorporating this 1,1′-binaphthyl fragment.[59] To their surprise, the reaction of monobromoborane dimethyl sulfide and 1,1′-binaphthol did not lead to the same type of intermediate. They expected a compound such as **13** and realized that monobromoborane dimethyl sulfide reacts



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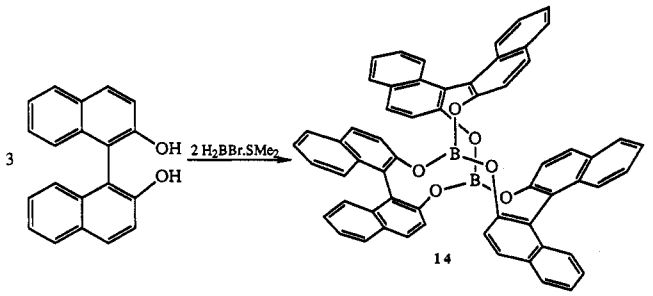
Scheme 16



with 1,1′-binaphthol in a 2:3 ratio to give **14**, according to X-ray structural analysis (Scheme 16).

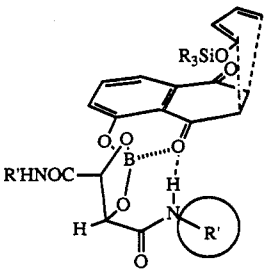
This catalyst gives excellent results for the reaction of cyclopentadiene and methacrolein. In contrast to the uncatalyzed Diels–Alder reaction which provides only a 15% yield after 42 h at 20 °C (exo/endo 86/14). The reaction at −78 °C with 3 mol % of catalyst furnished the (−)-exo aldehyde in 85% yield, 97.4% exo selectivity, and 90% enantiomeric excess.

A reasonable mechanism involves probably complexation of the carbonyl group of methacrolein with the boron. Noteworthy is the easy preparation of the catalyst which is obtained in a single step from the commercially available 1,1′-binaphthol.

B. Chiral Boron Reagents Prepared from Tartrate Amide–Diol Derivatives

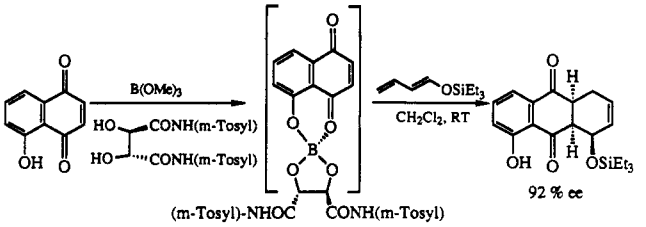
These chiral boron reagents were developed in 1986 by Yamamoto et al.[60] They are based on tartaric acid derivatives and a boron reagent developed by two different groups.[61] Similar to the catalysts developed by Kelly et al.,[58] these reagents catalyze the reaction of juglone and various dienes to synthesize anthracyclinones. The borane reagent used is trimethyl borate. Different tartrate derivatives have been tried and (*R*,*R*)-(+)-tartaric acid diamide proved to be the most efficient. The best results were obtained in the reaction of juglone and (triethylsilyloxy)buta-1,3-diene catalyzed by a combination of methyl borate and (*R*,*R*)-(+)-tartaric acid diarylamide (CONH(*m*-tosyl)). The use of an equimolar amount of chiral boron is necessary (Scheme 17).

The reaction was run for 12 h at room temperature and gave the chiral adduct in 92% ee and 73% chemical yield. Consequently, the regio- and stereoselectivity are good. However, the dialkyl and diamide tartrate derivatives are not so effective. This could be explained by the structure of the following intermediate:

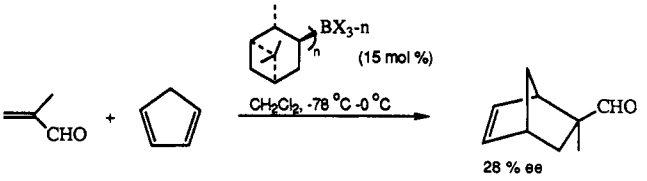


The hydrogen bond between the amide hydrogen and the naphthoquinone carbonyl makes the diene preferentially approach from the top of the dienophile and

Scheme 17



Scheme 18



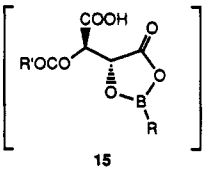
explains, consequently, the enantioselectivity observed. Moreover, the use of an arylamide (R′ = *m*-Tosyl) which is electron withdrawing makes the hydrogen bond stronger and explains the rate enhancement observed.

C. Chiral Boron Reagents Prepared from Isopinocampheylhaloboranes

Mono- and diisopinocampheylboranes have been used as catalysts in reduction for more than 20 years.[62] Kaufmann et al. investigated various analogs as a potent catalyst for the Diels–Alder reaction.[63] They synthesized different mono- and diisopinocampheylhaloboranes and analyzed their efficiency for the reaction of 2-methyl-2-propenal and cyclopentadiene (Scheme 18). In contrast to other catalysts, only catalytic amounts are required, but poor enantioselectivity is obtained. Nevertheless, the exo adduct is obtained in excess in a 90:10 exo–endo ratio.

D. Chiral Boron Reagents Prepared from Monoacyl Tartaric Acid and Diborane (Acyloxyborane)

Recently, Yamamoto et al. developed a new catalyst prepared in situ from monoacyl tartaric acid and diborane.[61] An acyloxy borane is recognized to be the initial intermediate in the reaction.[62] It is formed by rapid reaction between carboxylic acids and borane.



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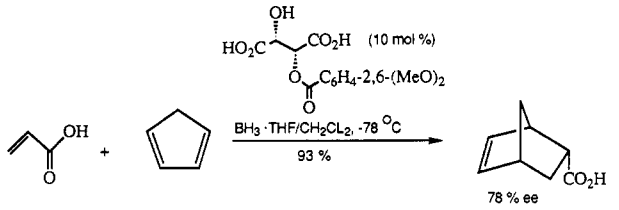
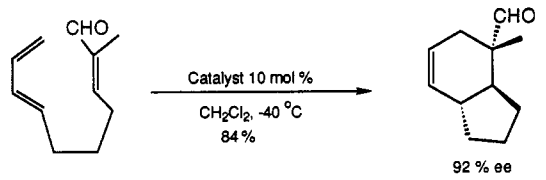
They obtained excellent results for the reaction of acrylic acid and cyclopentadiene (Scheme 19). The reaction is applicable to other dienes and α,β-unsaturated acids or aldehydes. It was further investigated by Yamamoto et al.,[66] and the results are very promising. Diels–Alder reaction of acrylic acid and cyclopentadiene gave 96% ee. However, the following trend is observed. The α-substituent on the dienophile increases the enantioselectivity (acrolein/methacrolein), while β-substitution decreases the selectivity. Noteworthy is the

Scheme 19



Scheme 20



Scheme 21

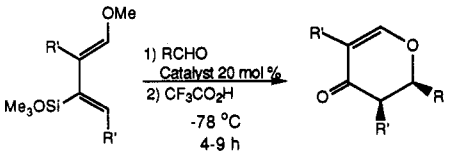


Table 6. Asymmetric Diels–Alder Reaction Catalyzed by CAB

aldehyde	diene (Scheme 21)	*B*-alkyl group on catalyst	% ee	yield %[a]
PhCHO	R′ = H	2,4,6-(*i*-Pr)$_3$Ph	95	55
		o-MeOPh	79	80
	R′ = Me	Bu	93	56
		Ph	87	65
(*E*)-PhCH=CHCHO	R′ = H	*o*-MeOPh	86	63[b]
	R′ = Me	*o*-MeOPh	97	86
CH_3CH=CHCHO	R′ = Me	*o*-MeOPh	92	79[b]

[a] Isolated yield. [b] Reaction carried out at −78 °C for 20 h.

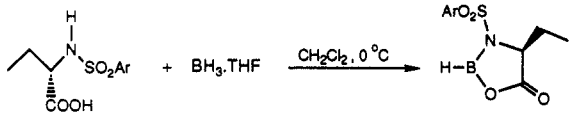
result of both α- and β-substitution where the α-substitution overcomes the effect of the β-substitution.

After the success of the catalyst for the intermolecular Diels–Alder reaction, Yamamoto et al. decided to test it for the intramolecular Diels–Alder reaction (Scheme 20).[67] The trend observed is similar to that of the intermolecular Diels–Alder reaction. The triene used contains an α,β-unsaturated aldehyde. Removing the α-methyl substituent of the α,β-unsaturated aldehyde moiety lowers the enantioselectivity (46% ee).

Another interesting application of this type of catalyst is the hetero-Diels–Alder reaction. Very recently, Yamamoto et al.[68] decided to investigate the efficiency of the catalyst for this type of reaction. The catalyst was prepared by mixing tartaric acid derivative and an arylboric acid. Consequently, it was B-alkylated, and they obtained **15** with R = Ph or alkyl and not H. The advantage is that it is stable and not air and moisture sensitive as the previous catalyst.[69] The reaction is the following (see Scheme 21 and Table 6).

The enantioselectivity is lower than for the corresponding hydride-type catalyst, but it is an excellent catalyst for this type of reaction and it is easier to handle. Table 6 gives the very interesting and highly stereoselective results. Consequently, this reaction is really one of the best systems found to date. However, bulky phenylboronic acid is required for asymmetric induction. But very bulky groups lead to a drop in the

Scheme 22

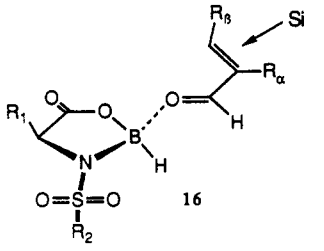


reactivity probably due to a shift in the equilibrium of formation of the catalyst to the left.

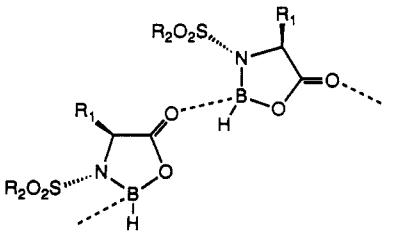
E. Chiral Boron Reagents Prepared from an Amino Acid Derivative (1,3,2-Oxazaborolidine)

The approach is similar to the previous one. A simple chiral boron catalyst is prepared from sulfonamides of amino acids and borane (Scheme 22). The reaction was first reported by Yamamoto et al.[70] After investigation, they concluded that the 2,4,6-triisopropylbenzenesulfonamide of α-amino butyric acid was the most efficient catalyst. Thus, they decided to use this catalyst for the Diels–Alder reaction of a variety of ketones and dienophiles. The reaction was carried out at −78 °C with 10 mol % of catalyst. The asymmetric induction is not very high (51–74%), but was increased by the bulky aromatic group of benzene sulfonyl group.

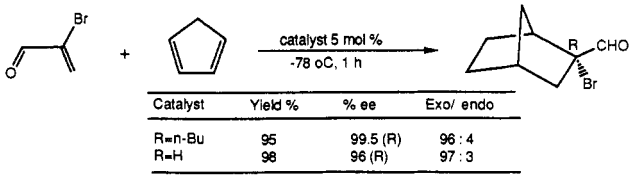
At the same time, Helmchen et al. reported enantioselective Diels–Alder reaction with a similar type of catalyst.[71] By using various alkyl sulfonyl groups, they obtained similar results with cyclopentadiene and various dienophiles (64–72%). The reaction was carried out at −78 °C with a 1:1 ratio of Lewis acid to aldehyde. Helmchen et al. proposed the following transition state to explain the selectivity:



This model, based on steric effect and conformational preference, leads to attack of the diene at the Cα–Si enal face.[72] Helmchen et al. also insisted on the importance of variables in the system. These variables are the concentration, mode of preparation, age, and enantiomeric purity of the catalyst; also nature of the solvent and structure of the starting material are important. He concluded that a donor solvent (THF or even acetonitrile) are necessary for asymmetric induction. Otherwise, there is association of the catalyst via the carbonyl group and thus decrease of selectivity due to shielding of the C$_\alpha$–Si enal face (see **16**). This



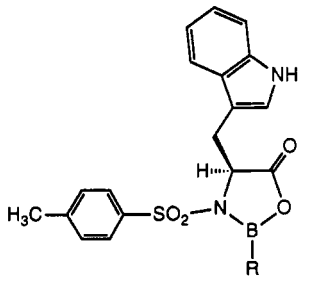
Scheme 23



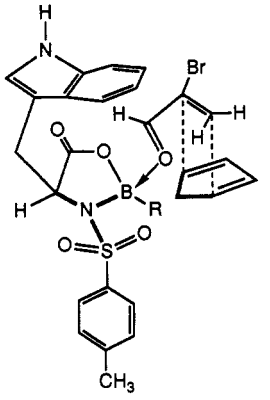
Catalyst	Yield %	% ee	Exo/ endo
R=n-Bu	95	99.5 (R)	96 : 4
R=H	98	96 (R)	97 : 3

was reinforced by the dependence of enantioselectivity on the catalyst concentration in solvent other than THF.

On the basis of his experience with oxazaborolidines,[19] Corey et al. also decided to investigate the ability of this type of reagent to catalyze the Diels–Alder reaction.[73] The catalyst used is the (*S*)-tryptophan derived oxazoborolidine. For the reaction of 2-bromoacrolein



and cyclopentadiene, the transition state is in total agreement with the experimental data. The enantio-



selectivity, regioselectivity, and yield obtained are high (Scheme 23). The reaction is consequently of considerable synthetic value.

It should be noted that the use of (*S*)-tryptophan gives the *S* enantiomer in contrast to (*S*)-valine and (*S*)-hexahydrophenylalanine that were described previously. This tends to support the transition state described.

F. Chiral Boron Reagents Prepared from Boron Tribromide and a Chiral Prolinol Derivative

Kobayashi et al. recently described the Diels–Alder reaction of α,β-unsaturated aldehydes with dienes using this novel chiral boron reagent prepared from boron tribromide and a chiral prolinol derivative.[74]

The catalyst is formed in situ, and it is believed that it is as the HBr salt (Scheme 24). However, high stereoselectivity was obtained only for the reaction between acrolein and cyclopentadiene (97%).

G. Chiral Alkyldichloroborane Reagents

Catalysis of Diels–Alder reaction by chiral alkyldihaloboranes ($RBCl_2$) has been reported recently by

Scheme 24

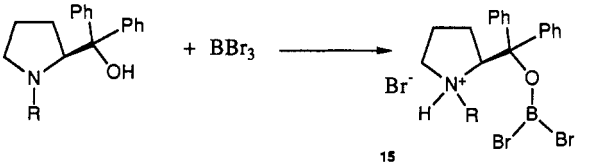


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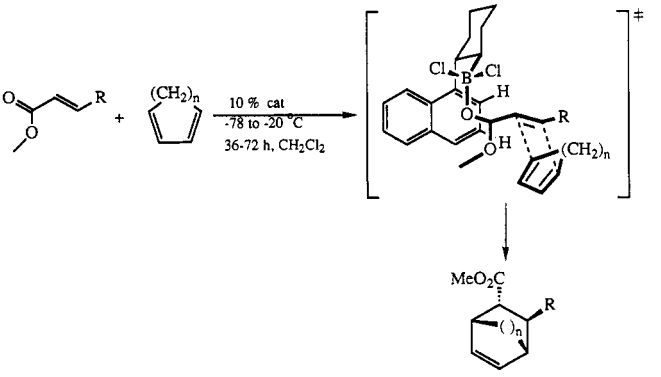
Table 7. Asymmetric Diels–Alder Reaction Catalyzed by Chiral Alkyldichloroborane Reagent[a]

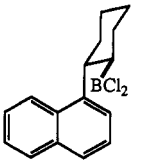
R	*n*	% ee	yield %
H	1	97	97
Me	1	93	91
CO_2Me	1	90	92
H	2	86	83

[a] For structures, see Scheme 25.

Scheme 25



Hawkins et al.[75] The structure of the catalyst is the following:



The system gives excellent enantiomeric purity (see Table 7). The mechanism and steric interactions have been thoroughly analyzed and are consistent with approach of the diene to the open face of the dienophile (see Scheme 25).

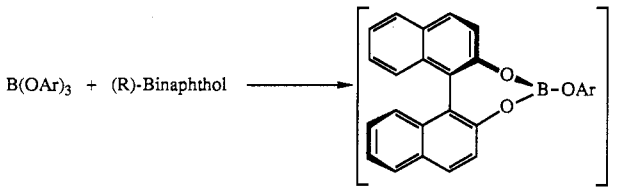
H. Asymmetric Aza-Diels–Alder Reaction Mediated by a Chiral Boron Reagent Prepared from Binaphthol

Catalytic asymmetric reaction involving imines, in contrast with carbon–carbon bond forming reactions, has never received an explosive interest. However, recently, Yamamoto et al. reported an asymmetric aza-Diels–Alder reaction of an imine catalyzed by a chiral boron reagent.[76] The complex is prepared as described in Scheme 26.

Using this catalyst, the authors obtained good enantiomeric purity for the aza-Diels–Alder reaction between aldimines and Danishefsky dienes (see Scheme 27 and Table 8).

It is to be noted that the choice of the solvent is important since THF or propionitrile generated low

Scheme 26



Scheme 27

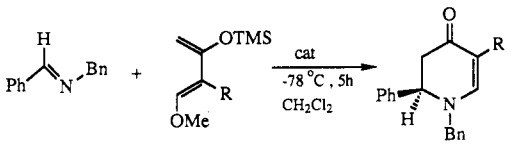
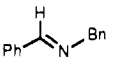
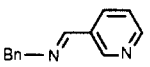
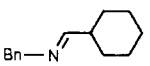
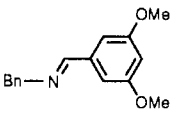
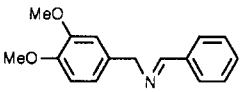
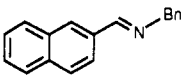


Table 8. Asymmetric Aza-Diels–Alder Reaction Catalyzed by a Chiral Boron Reagent Prepared from a Binaphthol Derivative

imine	diene (R, Scheme 27)	cat (Ar)[a]	% ee	yield %[b]
	H	phenyl	82	75
	H	phenyl[c]	85	70
	H	2-tolyl	84	76
	H	3,5-xylyl[c]	86	82
	Me	phenyl	81	72
	Me	3,5-xylyl	87	66
	H	phenyl	90	71
	H	phenyl	76	45
	H	3,5-xylyl	72	49
	Me	phenyl	78	35
	Me	2-tolyl	81	31
	H	phenyl	74	89
	H	phenyl	85	73
	H	phenyl	84	83

[a] The reactions were carried out with 1 equiv of catalyst and 1.2 equiv of diene. [b] Yields after isolation by column chromatography. [c] The reaction was carried at −100 °C for 5 h.

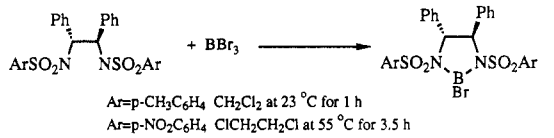
optical yields. This method is very interesting for the synthesis of alkaloids.

IV. Aldol and Other Carbonyl–Carbanionoid Reactions

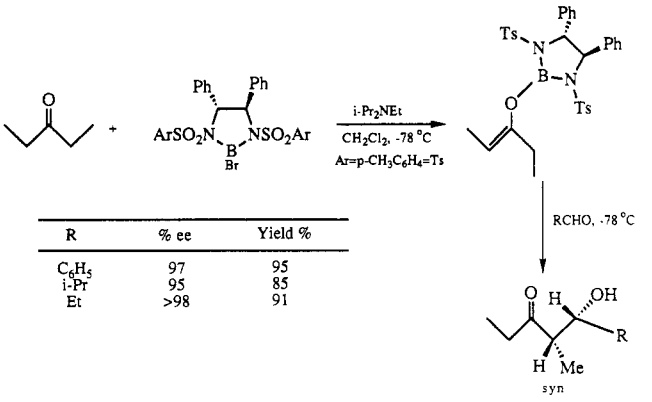
A. Aldol Reaction

In the aldol condensation, the α-carbon of one aldehyde or ketone adds to the carbonyl carbon of another. There is carbon–carbon bond formation and creation of a new stereocenter. Consequently, stereo- and enantioselective control of the reaction appears to be an attractive challenge for the construction of complex molecules. In this prospect, the use of a chiral boron catalyst provides a remarkable route to asymmetric induction.

Scheme 28

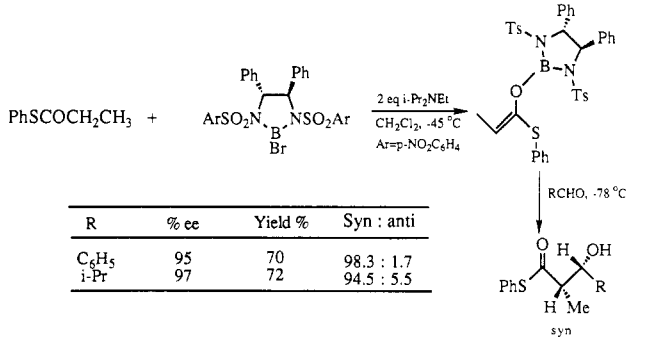


Scheme 29



R	% ee	Yield %
C_6H_5	97	95
i-Pr	95	85
Et	>98	91

Scheme 30



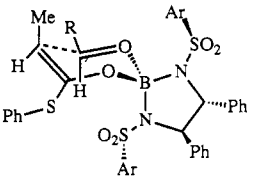
R	% ee	Yield %	Syn : anti
C_6H_5	95	70	98.3 : 1.7
i-Pr	97	72	94.5 : 5.5

1. Chiral Boron Reagents Prepared from Stilbenediamine Derivatives (Stien Reagent)

In 1989, Corey et al. reported that a new chiral reagent, the stien controller, had been successfully applied to enantioselective aldol reactions.[77] It is a diazaborolidine formed from sulfonamide derivatives[78] and boron tribromide (Scheme 28).

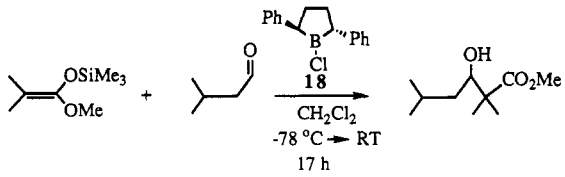
The reaction of diethyl ketone and aldehydes with stien reagent proceeds with high stereoselectivity to form the *syn*-aldol adducts. However, the reagent has to be used stoichiometrically (Scheme 29).

The system is also efficient for the aldol condensation between acetate esters and aldehydes. Scheme 30 illustrates the reaction of various aldehydes with phenyl thioacetate. The transition-state is in agreement with the results obtained (see 17). The phenyl groups of the catalyst are bulky enough to force the sulfonyl group to be oriented in the opposite direction. Consequently, they create stereoelectronic and steric control on the favored transition state observed and lead to one enantiomer in excess.



17

Scheme 31



Scheme 32

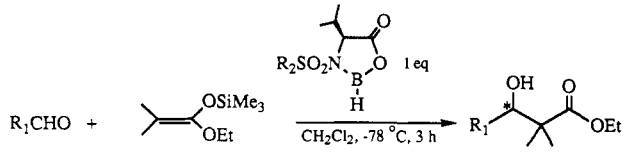


Table 9. Enantioselectivity of the Lewis Acid Mediated Aldol Reaction of 1-(Trimethylsiloxy)-1-ethoxy-2-methyl-2-propene with Aldehydes[b]

R_1	R2	R3	% ee	yield %[a]
Ph	p-$CH_3C_6H_4$	i-Pr	86	83
Ph	p-$CH_3C_6H_4$	t-Bu	77	92
Ph	α-naphthyl	i-Pr	79	90
Ph	β-naphthyl	i-Pr	85	93
(E)-PhCH=CH	p-$CH_3C_6H_4$	i-Pr	80	85
$PhCH_2CH_2$	p-$CH_3C_6H_4$	i-Pr	87	93

[a] Isolated yields. [b] For structures, see Scheme 32.

2. Oxazaborolidines

Chiral boranes prepared from the sulfonamides of amino acids were reported simultaneously by Yamamoto[64] and by Helmchen[71] for their ability to induce asymmetry in the Diels–Alder reaction. According to the ability of the boron to complex the carbonyl moiety in this type of catalyst, it was clear that they might be efficient to promote the reaction of silyl ketene acetal with various aldehydes.

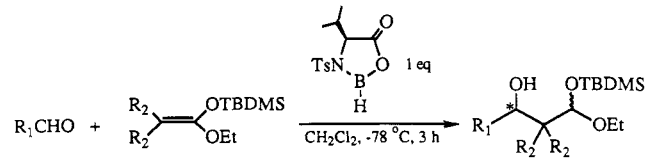
This reaction of silyl ketene acetal with aldehydes was previously reported by Reetz et al.[79] who used 18 as chiral reagent stoichiometrically. However, the aldol addition of 1-(trimethylsiloxy)-1-methoxy-2-methyl-1-propene and 3-methylbutanal provided the aldol in only 57% yield, but in 90% ee (Scheme 31).

Nevertheless, the use of oxazaborolidines as chiral reagent seems to be more effective for this reaction which proceeds faster and with higher yields and enantiomeric excess. Recently, Kiyooka et al. described the use of various chiral oxazaborolidines, derived from sulfonamides of α-amino acids and borane, in the course of the selective aldol reaction between silyl ketene acetals and aldehydes (Scheme 32).[80] They obtained relatively high stereoselectivity and yields (see Table 9).

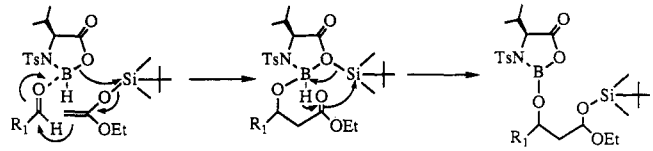
In spite of these results, the authors found that the nature of the trialkylsilyl group was indeterminant, giving different reaction pathways and thus different products. Changing the trimethylsilyl (TMS) group not only increased the selectivity but also the product of the reaction. β-Hydroxy acetals are now obtained instead of (S)-hydroxy esters. They investigated the reaction course with various *tert*-butyldimethylsilyl ketene acetals and aldehydes with the catalyst corresponding to R_2 = p-$CH_3C_6H_4$ and R_3 = i-Pr (Scheme 33).

The acetal is probably formed by hydride transfer to an intermediate ester (second step). The *tert*-butyl group apparently stabilizes the second intermediate and consequently changes the reaction course. It is to be noted that the first cyclic intermediate is stabilized by coordination of the borane with the oxygen of the carbonyl (Scheme 34). The results obtained are outstanding when R_2 = CH_3 (92–98%). However, the selectivity and yield decrease when R_2 = H (45–62%).

Scheme 33



Scheme 34



Scheme 35

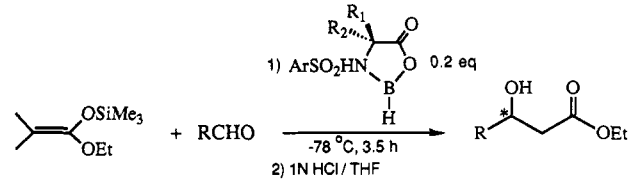


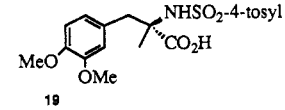
Table 10. Catalytic Aldol Reaction of Silyl Ketene Acetal with Aldehydes by 19 or 20[b]

R (aldehyde)	ligand	% ee[a]	yield %
Ph	**19**	84 (R)	80
Ph	**20**	91 (R)	83
c-C_6H_{11}	**19**	91 (R)	68
c-C_6H_{11}	**20**	96 (R)	59
$CH_3(CH_2)_2$	**19**	>98	81
$CH_3(CH_2)_2$	**20**	>98	82
$(CH_3)_2CHCH_2$	**19**	97	87
$(CH_3)_2CHCH_2$	**20**	>98	89
$Ph(CH_2)_2$	**19**	>98	83
$Ph(CH_2)_2$	**20**	>98	83
$BnO(CH_2)_2$	**19**	99	86

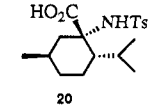
[a] Absolute configuration indicated when determined. [b] For structures, see Scheme 35.

Masamune et al. tried to improve this process by using chiral boranes prepared from α,α-disubstituted glycine arenesulfonamides.[81] They were interested in the aldol reaction of silyl ketene acetals with aldehydes (Scheme 35).[80]

The initial result of their study is that disubstitution at the α-carbon of the ligand enhances the catalytic activity ($R_1 \neq H$, $R_2 \neq H$).[82] Thus, two ligands were selected; the results obtained are listed in Table 10.



19



20

In a more recent article, Masamune et al. carry on their study after selecting **19** as their ligand of choice (Scheme 36).[83] Results were obtained with unsubstituted ketene acetals (see Table 11). As can be seen, changing R_3 does not markedly affect the course of the

Scheme 36

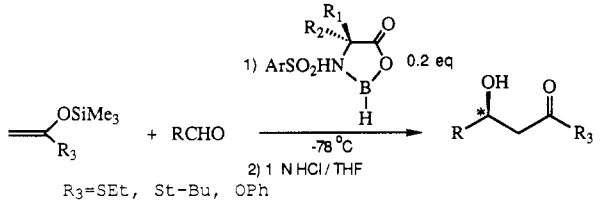
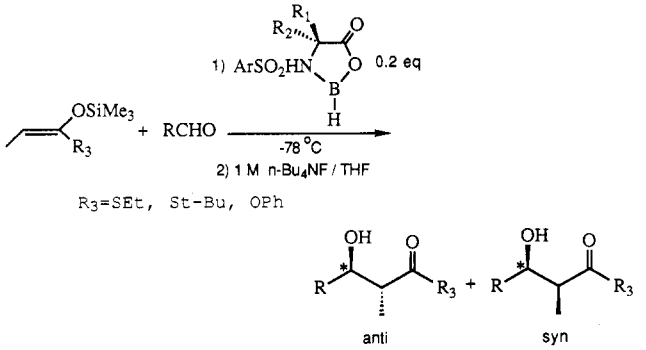


Table 11. Catalytic Aldol Reaction of Silyl Ketene Acetals with Aldehydes Mediated by Borane Complex[b]

R (aldehyde)	R_3	% ee[a]	yield %
Ph	S(*t*-Bu)	87 (*S*)	86
Ph	SEt	99 (*S*)	89
Ph	OPh	93 (*S*)	77
$Ph(CH_2)_2$	S(*t*-Bu)	91 (*R*)	77
$Ph(CH_2)_2$	SEt	89 (*R*)	82
$Ph(CH_2)_2$	OPh	85 (*R*)	78
$CH_3(CH_2)_2$	S(*t*-Bu)	92 (*R*)	91
c-C_6H_{11}	SEt	81 (*S*)	75
c-C_6H_{11}	OPh	84 (*S*)	87
n-PrCH=CH	S(*t*-Bu)	82	91
	S(*t*-Bu)	85	98

[a] Absolute configuration indicated when determined. [b] For structures, see Scheme 36.

Scheme 37



reaction. Next, the effect of a β-carbon (methyl) substituent was investigated (see Scheme 37 and Table 12). The reaction yields a mixture of anti and syn products. The anti product is favored, but both are produced only in decent optical yield.

Consequently, the catalyst proved to be useful for the enantioselective aldol condensation of unsubstituted, methyl-substituted, and dimethyl-substituted ketenes acetals with aldehydes. β-Hydroxy esters are formed. With methyl-substituted, the product favored is the *anti*-(*S*)-hydroxymethyl ester.

3. Chiral (Acyloxy)borane Complex

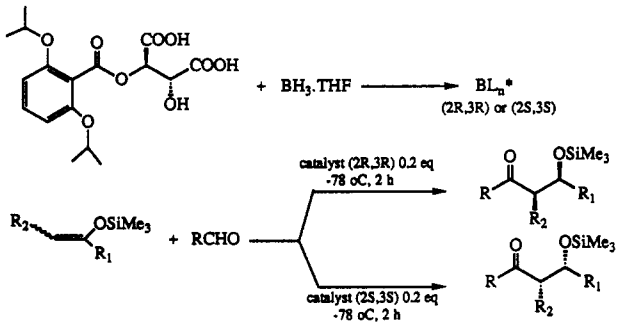
As stated previously, catalysts for the Diels–Alder reaction are often efficient for the aldol condensation. Consequently, Yamamoto et al. investigated the asymmetric aldol reaction catalyzed by chiral (acyloxy)-borane reagents (CAB).[84] They investigated the CAB complex for the Mukaiyama condensation between enol silyl ethers of ketones and aldehydes. The borane complex is formed by addition of BH_3·THF to a solution of tartaric acid derivative (Scheme 38). Note that the stereochemical outcome is opposite to that observed

Table 12. Catalytic Aldol Reaction of Silyl Ketene Acetals with Aldehydes Mediated by Borane Complex

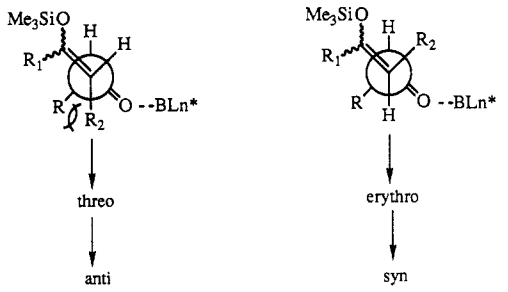
R (aldehyde)	R_3	ligand	% ee[a]	anti/ syn	yield %
Ph	SEt	20	80(*R*,*S*)/ 94(*S*,*S*)	87/13	89
Ph	S(*t*-Bu)	20	82(*R*,*S*)/66	94/6	78
Ph	OPh	20	87(*R*,*S*)/ >98	77/23	77
Ph	SEt[Z(O)]	20	64(*R*,*S*)/ >98(*S*,*S*)	45/55	84
	SEt	20	89/90	66/33	94
	S(*t*-Bu)	20	79(*R*)/55	88/12	54
p-MeO-Ph	SEt	20	75(*R*)/>98	89/11	78
(*Z*)-n-PrCH=CH	SEt	20	60(*S*)/73	80/20	80
$Ph(CH_2)_2$	SEt	19	82(*S*)/81	91/9	85
$Ph(CH_2)_2$	OPh	19	75/>98	90/10	72
$CH_3(CH_2)_2$	SEt	19	70(*R*,*R*)/81	88/12	81

[a] Absolute configuration indicated when determined. [b] For structures, see Scheme 37.

Scheme 38



when the reaction is catalyzed by oxazaborolidines.[83] The syn product is favored. This can be explained considering the acyclic transition state.



Because of steric interactions, the erythro transition state is favored. This is further confirmed by experimental data. For the results (of Table 13), the tartaric acid derivative ligand used was the 2*R*,3*R*.

B. Allylation of Aldehydes

In 1991, Yamamoto et al. reported the first catalytic asymmetric allylation of aldehydes with allylsilanes using the chiral (acyloxy)borane complex.[85] The CAB complex is formed by addition of a solution of BH_3·THF to a tartaric acid derivative and promotes the formation of homoallylic alcohols (see Scheme 39).

The results give moderate to good yields. Simple allyltrimethylsilanes are not reactive enough under the

Table 13. Asymmetric Aldol Condensation Catalyzed by BL_n*

silyl ether (Scheme 38)	aldehyde	% ee	erythro/ threo	yield %[a]
R^1 = *n*-Bu, R_2 = H	benzaldehyde	85 (*I*)		81
	pentanal	80 (*I*)		70
R_1 = Ph, R_2 = H	benzaldehyde	85 (*R*)		98
	cinnamaldehyde	83 (*I*)		88
R_1 = Ph, R_2 = Me	benzaldehyde	95 (*I*)	95/5	86
	butanal	80 (*I*)	88/12	62
R_1 = Et,[b] R_2 = Me	benzaldehyde	96 (*R*)	94/6	96
	benzaldehyde[d]	96 (*S*)	94/6	99
	benzaldehyde	90 (*R*)	88/12	95
	benzaldehyde	77 (*R*)	82/18	55
	crotonaldehyde	93 (*R*)	>94/6	79
	butanal	88 (*S*)	80/20	61
R_1 = Et,[c] R_2 = Me	benzaldehyde	>95 (*I*)	>95/5	57

[a] Isolated yields. [b] *E*/*Z* = 2/98. [c] *E*/*Z* = 4/1. [d] (2*S*,3*S*) was used.

Scheme 39

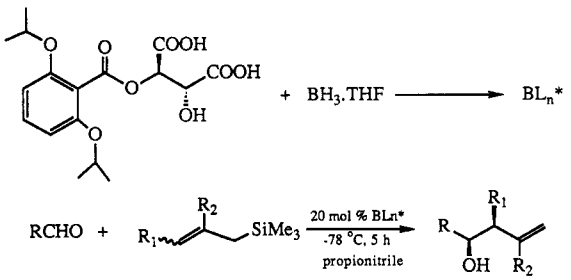
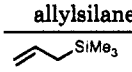
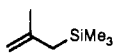
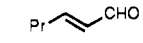
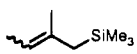
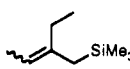
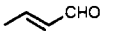


Table 14. CAB-Catalyzed Asymmetric Allylation Reaction

allylsilane	aldehyde	% ee (config)[a]	yield %	erythro/ threo
	PhCHO[d]	55 (*R*)	46	
	PhCHO	82 (*R*)	66	
		80	50	
[b] 	PhCHO	90	63	96/4
	C_4H_9CHO	85	30	94/6
[c] 	PhCHO	96 (*R*)	74	97/3
		89	21	95/5
	C_3H_7CHO	86 (*S*)	36	95/5

[a] Configuration corresponds to the alcoholic carbon of the major isomer. [b] *E*/*Z* = 61.39. [c] *E*/*Z* = 65/35. [d] Reaction at −20 °C.

reaction conditions, but γ-alkylated allylsilanes exhibit good diastereo- and enantioselectivity. Efficiency is higher with benzaldehyde and aliphatic aldehydes produce lower enantioselectivity (slightly) and chemical yield (see Table 14).

To increase the chemical yields obtained with aliphatic aldehydes, Marshall et al. decided to replace the allylsilane nucleophiles with the more reactive allylstannanes.[86] In order to increase the catalyst turnover, the authors found that trifluoroacetic anhydride [$(CF_3CO)_2O$] was very efficient as a promoter (Scheme 40). This method gave good yields (somewhat lower with butyraldehyde and isobutyraldehyde) and good enantioselectivity (see Table 15).

Scheme 40

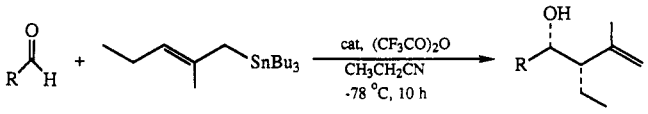
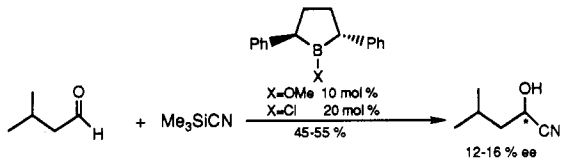


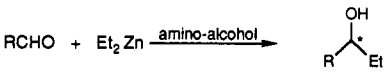
Table 15. Addition of Allylstannane to Aldehydes in the Presence of CAB and $(CF_3CO)_2O$

R(RCHO)	% ee	yield %	syn:anti
Ph	85	99	90:10
BuC≡C	70	92	71:29
(*E*)-MeCH=CH	95	85	92:8
(*E*)-MeCH=CMe	86	70	94:6
n-C_3H_7	81	61	97:3
i-C_3H_7	85	44	94:6

Scheme 41



Scheme 42



C. Hydrocyanation of Aldehydes

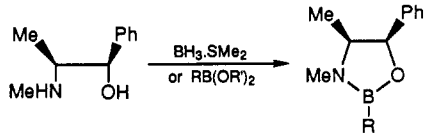
Hydrocyanation of aldehydes provides access to synthetically important α-hydroxy carboxylic acids. Hydrocyanation of aldehydes can be catalyzed by acids and bases, but acid catalysis is more suitable since the presence of a base leads to racemization of cyanohydrins.[87] Reetz et al. found that chiral 1-boracyclopentyl chloride or methoxide could be used as a catalyst in the reaction of 3-methylbutanal and trimethylsilyl cyanide (Scheme 41).[79] The asymmetric induction and yield are not good, but this is the first example of chiral induction by an organoborane for the hydrocyanation of aldehydes. Undoubtedly, improvements will follow.

D. Alkylation of Aldehydes with Dialkylzinc

The reaction of diethylzinc with aldehydes provides useful secondary alcohols. The reaction is reluctant under normal conditions. However, in 1984 Oguni and Omi reported that small amounts of amino alcohols could accelerate the reaction. Moreover, the use of optically active amino alcohols also introduced asymmetry during the reaction course (Scheme 42).[88] In the course of the reaction study, catalysts were improved and employed successfully. Still, the chiral auxiliaries are complex and some limitations remain.

However, in 1989 Brown et al. reported the use of chiral oxazaborolidines as catalyst for this reaction.[89] This is the first example of the use of a chiral boron reagent as catalyst for this type of reaction. The oxazaborolidine is formed from the amino alcohol and BH_3·SMe_2 or $RB(OR')_2$ (Scheme 43). The reaction was carried out with various catalysts and R = H seems to be the best combination (Scheme 44). The reaction rate and the ee are optimum when the boron is unhindered and the methyl and phenyl group on the catalyst are cis.

Scheme 43



Scheme 44

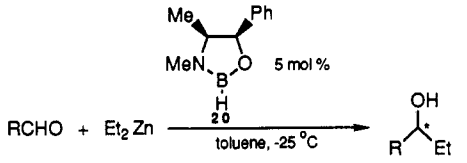


Table 16. Alkylation of Aldehydes with Diethylzinc Catalyzed by 20

aldehyde	time (h)	% ee	absol config
benzaldehyde	30	95	*R*
1-methoxybenzaldehyde	48	91	*R*
4-methoxybenzaldehyde	48	93	*R*
4-chlorobenzaldehyde	48	96	*R*
2-furaldehyde	64	66	*R*
heptanal	88	52	*R*

The results gave good enantioselectivity with aromatic aldehydes and moderate enantioselectivity for aliphatic aldehydes. The yields obtained are all higher than 85% (see Table 16).

Despite the promising results, some limitations occur. First this system has to be improved for aliphatic aldehydes. Second, only one of the two alkyl groups from the zinc is transferred to the aldehyde. Third, competitive reduction of the aldehyde takes place when the dialkylzinc contain a β-hydrogen (diethylzinc being an exception).

V. Conclusion

Chiral boron catalysts appear to be the state of art in asymmetric synthesis. The reasons for this success can be explained by the wide scope of reactions that can be catalyzed, the availability of the different chiral catalysts in either enantiomeric form, the predictable configuration of the products, the easy recoverability of the catalyst chiral precursor, the high chemical and optical yields generally attainable, and the experimental simplicity and economy.

Consequently, further development of these type of catalysts will provide enantiomerically pure compounds. This is important in the case of drugs where one enantiomer is usually responsible for biological activity. Homochiral compounds are increasingly important in the development of chiral polymers, liquid crystals, and other devices. Chiral homogeneous catalysts are thus of great interest, and they are now being studied intensively as can be seen from the growing number of papers published in this area.

Note Added in Proof

After the manuscript was ready, various papers appeared related to boron-catalyzed reactions. Ab initio molecular orbital calculations are being pursued and are used to study the effects controlling the coordination of borane to chiral oxazaborolidines in the catalytic asymmetric reduction of ketones.[90] A recent paper by Corey and co-workers provides a mechanistic and structural analysis, explaining the high enantioselectivity observed in the oxazaborolidine-catalyzed reduction of trihalomethyl ketones by catecholborane.[91] Corey also described a new type of oxazaborolidine derived from tryptophan used to effect enantioselective Mukaiyama aldol and aldol–dihydropyrone annulation reactions.[92] Investigations on asymmetric reduction of ketones is still an active area of research. The articles of ref 93 have appeared recently.[93] It has also been reported recently that amine–borane complexes could catalyze enantioselective α-hydrogen atom abstraction from esters.[94] An article summarizing work with oxazaborolidines has appeared.[95]

VI. Acknowledgments

L.D. and M.S. thank the University of Toledo for financial support which made the writing of this manuscript possible. They are also indebted to the reviewers for helpful suggestions.

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