Tetrahedron Asymmetry Vol. 3. No 12, pp. 1475-1504, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

TETRAHEDRON: ASYMMETRY REPORT NUMBER 13

ASYMMETRIC SYNTHESES WITH CHIRAL OXAZABOROLIDINES

Sabine Wallbaum and Jürgen Martens*

Fachbereich Chemie der *Carl von Ossietzky* Universität Oldenburg
Ammerländer Heerstraße 114-118, D-2900 Oldenburg i.O.

(*Received in UK 22 October* 1992)

Contents

1. Introduction

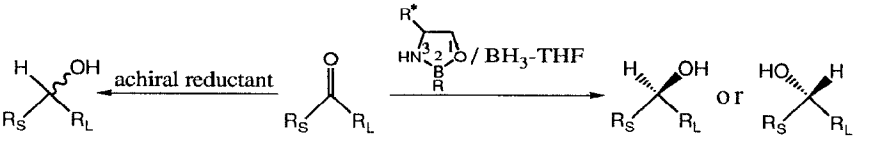
Fundamental phenomena and laws of nature result from chirality. In this regard, two enantiomeric biologically active agents often behave differently in a chiral surrounding. For this reason and for "chiral" economy[1] a lot of researchers are engaged in asymmetric synthesis[2]. Particularly stereoselective syntheses based on *intramolecular* asymmetric induction (diastereoselective reactions) play an important role in organic chemistry and are well understood today. By contrast, our knowledge concerning *intermolecular* transfer of asymmetry[3] (enantioselective reactions) is still at the beginning of understanding. The state of the art is the enantioselective homogeneous catalysis involving substoichiometric amounts of optically active auxiliaries.

Among the various asymmetric reactions enantioselective reductions of prochiral ketones to optically active alcohols have achieved great interest[4]. Homochiral alcohol products serve as useful starting materials for many syntheses and often they are the desired end product of a reaction sequence. *Itsuno et al.* developed 1,3,2-oxazaborolidines as a new generation of homochiral reduction catalysts[5]. In the last ten years oxazaborolidine chemistry has become a powerful tool for the enantioselective reduction of unsymmetrical ketones. Recently other asymmetric syntheses catalyzed by these heterocycles have been reported.

This review focusses on the historic and present results and applications of 1,3,2-oxazaborolidines in enantioselective synthesis.

2. General considerations

Usually the reduction of prochiral ketones with an achiral reductant leads to racemic secondary alcohols. Without chiral modification of the reductant neither face of the carbonyl moiety is preferred for hydride attack.



racemate prochiral ketone (*R*)-alcohol (*S*)-alcohol

Beside the use of microbial processes[6] or heterogeneous metal catalysts[7] the enantioselective homogeneous catalytic reduction using chirally modified hydride reagents[8] is the method of choice to introduce chirality.

The modification of borane with homochiral compounds containing an 1,3,2-oxazaborolidine moiety solves the problem of efficient enantioselective reductions[5]. Neither borane (stoichio-

metric reductant) nor the oxazaborolidine (catalyst) reduces ketones rapidly. But in combination these reagents form a complex which reduces ketones rapidly and gives the (*S*)- or (*R*)-alcohol in high chemical and optical yields[5,9]. The phenomenon of this so-called "ligand acceleration"[10] has been observed with other asymmetric reactions as well[11].

It was found that the rate difference between the catalyzed and non-catalyzed reduction leads to high enantiomeric excesses (*ee*) using only a substoichiometric quantity of the chiral auxiliary[9,12]. The reductions usually occur in a predictible manner depending on the absolute stereochemistry of the catalyst utilized.

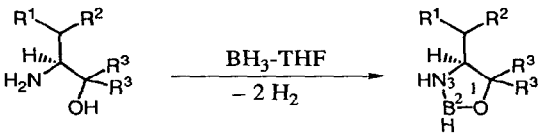
Because of the great interest in asymmetric reductions of prochiral ketones a large number of 1,3,2-oxazaborolidines prepared from β-amino alcohols (catalyst precursors) were tested as asymmetry inducing accelerators in borane reductions.

3. Oxazaborolidines in the enantioselective reduction of ketones

3.1. Stoichiometric application

The beginning of asymmetric reductions with optically active borane complexes was defined by *Fiaud* and *Kagan*[13] in 1969 who used homochiral amine borane complexes derived from desoxyephedrine in the asymmetric reduction of acetophenone. They obtained insignificant enantioselectivities in the range of 3.6 - 5 % *ee*. Increasing selectivities up to 20 % *ee* were achieved with amine and α-amino acid ester borane complexes as catalysts[14].

A mile stone was reached in 1981 by *Itsuno et al.*[5,15] who reported the first effective asymmetric borane reduction of aromatic ketones utilizing stoichiometric amounts of optically active 1,3,2-oxazaborolidines (*S*)-**1b** – (*S*)-**4b** prepared *in situ* from the β-amino alcohols (*S*)-**1a** – (*S*)-**4a** and borane-THF.



(*S*)-**1a** - (*S*)-**4a** (*S*)-**1b** - (*S*)-**4b**

As can be seen from Table 1 the best results were obtained with (*S*)-valine derivatives. Stereoselectivities up to 73 % *ee* (entry 6) in the presence of (*S*)-valinol (*S*)-**3a** were reached with aromatic ketones. In the reduction of aliphatic ketones the results were insignificant (entry 7). In each case the (*R*)-enantiomer of the secondary alcohol was formed preferentially. The catalyst precursors were easily obtained from $LiAlH_4$ reduction of homochiral (*S*)-α-amino acids.

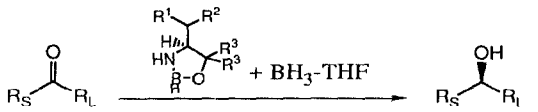


Table 1: Stoichiometric asymmetric reductions of various ketones to related secondary (*R*)-alcohols with borane-THF in the presence of oxazaborolidines prepared *in situ*.

entry	ketone	amino alcohol	R^1	R^2	R^3	*ee* [%][a]	ref.
1	EtCOPh	(*S*)-**1a**	Ph	H	H	37	5
2	EtCOPh	(*S*)-**2a**	C_2H_5	H	H	41	5
3	MeCOPh	(*S*)-**3a**	CH_3	CH_3	H	49	5
4	EtCOPh	(*S*)-**3a**	CH_3	CH_3	H	60	5
5	*n*-PropCOPh	(*S*)-**3a**	CH_3	CH_3	H	67-70	15
6	*n*-BuCOPh	(*S*)-**3a**	CH_3	CH_3	H	73	15
7	*n*-HexCOMe	(*S*)-**3a**	CH_3	CH_3	H	10	15
8	MeCOPh	(*S*)-**4a**	CH_3	CH_3	Ph	94	16a
9	EtCOPh	(*S*)-**4a**	CH_3	CH_3	Ph	94	16b
10	*n*-BuCOPh	(*S*)-**4a**	CH_3	CH_3	Ph	100	16b

a.) The ratio of β-amino alcohol : BH_3 : ketone was 1 : 2 : 0.8. Reaction was carried out at 30° C for 1-60 h.

In 1983 *Itsuno et al.*[16] presented a more bulky derivative of (*S*)-valinol (*S*)-(–)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (*S*)-**4a** which was obtained *via Grignard* reaction from (*S*)-valine methyl ester hydrochloride. The asymmetric borane reduction of prochiral aromatic ketones with the oxazaborolidine (*S*)-**4b** prepared from (*S*)-**4a** and borane *in situ* gave the corresponding aromatic secondary alcohols in 94 - 100 % *ee* and 100 % chemical yield (entries 8-10). In every case increased enantioselectivity was reached with increasing length of the aliphatic side chain of ketone. With other β-amino alcohols containing phenyl goups in α-position to the OH-function *ee* values in the range of 67-95 % were reached.

Itsuno and co-workers studied intensively the steric influence of various catalyst substituents and reaction conditions on optical yields[15]. Without knowing mechanistic details the ratio of β-amino alcohol to borane was found to be optimum at 1 : 2-3. The reduction was complete in 30 min at 30 °C. At lower temperatures the optical purities decreased. The effect of solvent was also studied. For efficient asymmetric reductions a donor solvent is essential.

The first structurally more rigid (*S*)-proline-based β-amino alcohol (*S*)-**5** was introduced by *Itsuno et al.* in 1981 as well[5]. The borane reduction of aromatic ketones catalyzed by the oxazaborolidine prepared *in situ* from (*S*)-**5** yielded the corresponding (*R*)-alcohols with insignificant enantiomeric excess only (Table 2, entries 1-2).

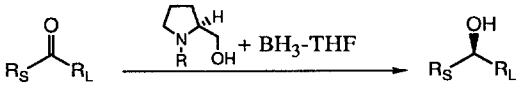


Table 2: Stoichiometric asymmetric reductions of aromatic ketones to related secondary (*R*)-alcohols with borane-THF in the presence of (*S*)-proline-based β-amino alcohols.

entry	ketone	amino alcohol	R	*ee* [%][a]	ref.
1	EtCOPh	(*S*)-**5**	H	44	5
2	MeCOPh	(*S*)-**5**	H	44	5
3	EtCOPh	(*S*)-**6**	*c*-C_6H_{11}	64	17
4	EtCOPh	(*S*)-**7**	CH_2Ph	67	17
5	EtCOPh	(*S*)-**8**	CH_2-Ph-Ⓟ	52-80	17

a.) The ratio of β-amino alcohol : BH_3 : ketone was 1 : 2 : 0.8. Reaction was carried out at 30° C for 48-72 h.

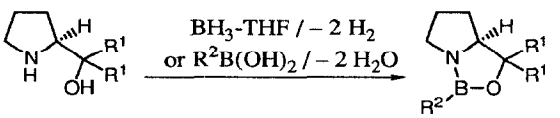
Catalysts (*S*)-**6** – (*S*)-**7** with a tertiary amino and a primary alcohol function do not serve as efficient catalysts in asymmetric reductions[17] (entries 3-5). For good optical yields generally a tertiary hydroxy and a secondary amino function are essential. The β-amino alcohols (*S*)-**6** – (*S*)-**7** can not form the oxazaborolidine moiety. Polymeric (*S*)-prolinol derivatives were shown to give alcohols of reasonably good optical purity (up to 80 %)[17].

3.2. Catalytic application

Itsuno et al. initiated the development of efficient *catalytic* asymmetric reductions with borane. In 1987 they reported the first enantioselective reduction[18] of ketoxime ethers using a catalytic amount of the (*S*)-valine derivative (*S*)-**4a** in the presence of borane as stoichiometric reductant. They isolated the resulting oxazaborolidine (*S*)-**4b** as a "white powder of unknown composition" and made the first attempts towards characterisation. On the basis of these observations *Corey et al.* fully identified the catalytic efficient species as the optically active oxazaborolidine (*S*)-**4b**[9]. Beside *Itsunos* catalyst *Corey et al.* tested the catalytic behaviour of the more sterically hindered oxazaborolidines based on (*S*)-(–)-2-diphenylhydroxymethyl-pyrrolidine[9,12] (*S*)-**9a** which was first introduced in borane reductions following *Itsunos* method by *Kraatz*[19] in 1986 and (*S*)-(–)-2-di-β-naphtylhydroxymethyl-pyrrolidine[20] (*S*)-**9b** two derivatives of (*S*)-proline.

The non-substituted oxazaborolidines (*S*)-**10a**[9] and (*S*)-**10d**[20] with R = H were prepared by reaction of the respective β-amino alcohol with excess borane and removal of solvent and borane *in vacuo*. In contrast to the non-substituted catalysts which are both air and moisture

sensitive, the *B*-alkylated products are more stable and can be stored at room temperature. Reaction of the respective amino alcohol (*S*)-**9a** or (*S*)-**9b** with methylboronic acid under dehydrating conditions (4Å molecular sieves or *Dean-Stark* trap) afforded (*S*)-**10b**[12a] and (*S*)-**10f**[20] as colourless solids. The corresponding *B*-*n*-butyl oxazaborolidines (*S*)-**10c**[21], (*S*)-**10g**[20] and the *B*-phenyl derivative (*S*)-**10d**[22a] were prepared similarly.



(*S*)-**9a** : R^1= Ph
(*S*)-**9b** : R^1= β-Nap

(*S*)-**10a** : R^1= Ph, R^2= H
(*S*)-**10b** : R^1= Ph, R^2= Me
(*S*)-**10c** : R^1= Ph, R^2= *n*-Bu
(*S*)-**10d** : R^1= Ph, R^2= Ph
(*S*)-**10e** : R^1= β-Nap, R^2= H
(*S*)-**10f** : R^1= β-Nap, R^2= Me
(*S*)-**10g** : R^1= β-Nap, R^2= *n*-Bu

The catalysts gave erratic results if water was not completely removed. For this reason *Blacklock et al.*[23] modified the synthesis of the oxazaborolidines by using trialkylboroxine instead of alkylboronic acid followed by three successive azeotropic distillations with toluene to remove residual water. This method afforded the catalyst in higher purity which is important because any trace of unreacted educts decreased the enantioselectivity. *Blacklock et al.* reported that in the synthesis of MK-0417, a carbonic anhydrase inhibitor, approximately 1 mg of water/ 1g of the substrate ketone decreases the *ee* from 95 % to 50 %[24]. Recently *Corey et al.* described a simple synthesis of two more reactive alkylboronic acid equivalents the bis(trifluoroethyl)alkylboronates $RB(OCH_2CF_3)_2$ (R = ethyl, *n*-butyl) and their use as reagents for the *in situ* formation of oxazaborolidines[25]. The effectiveness of this method has been pointed out by applying it to asymmetric reductions. The results were comparable to those obtained by conventional methods.

Acetophenone as the model substrate was reduced in the presence of the above mentioned (*S*)-configurated catalysts (*S*)-**10** under different reaction conditions. In each case (*R*)-1-phenyl ethanol was formed preferentially. As can be seen from Table 3 the results obtained with (*S*)-**4b** and the more sterically hindered (*S*)-**10a** are comparable with catalyst concentrations down to 2.5 mol %. Further reduction of catalyst amount led to dramatic decrease of enantioselection in the case of (*S*)-**4b** (59 % *ee*) whereas with (*S*)-**10a** a reasonably good result (80 % *ee*) was achieved[9] (entries 1-8). At low catalyst or high borane concentrations non-catalyzed reduction takes place. In regard of this, optimum conditions were found to depend extremely on catalyst concentration and amount of reductant. The more stable *B*-methylated oxazaborolidine (*S*)-**10b** gave equally good results. The results obtained with catalysts (*S*)-**10e** and (*S*)-**10f** bearing β-naphtyl substituents in α-position are comparable. The catalyst (*S*)-**10d** with a phenyl group attached to the boron prepared from (*S*)-**9a** and the more readily available and cheaper phenyl boronic acid are less effective with acetophenone[24]. In some other cases they are equal or

superior to the *B*-alkyl derivatives at a substantially lower cost[24, 22].

The oxazaborolidine (*S*)-**10c** works good at decreased temperature either with BH_3-dimethylsulfide (DMS) complex or with catecholborane as reductant.

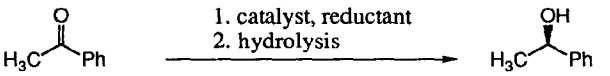


Table 3: Enantioselective reduction of acetophenone to (*R*)-1-phenyl ethanol in the presence of various oxazaborolidines.

entry	catalyst [mol %]	reductant [mol %]	reaction conditions	*ee* [%]	ref.
1	(*S*)-**4b** [100]	BH_3-THF [120]	23° C / 1 min.	94.7	9
2	(*S*)-**4b** [10]	BH_3-THF [120]	23° C / 1 min.	94.7	9
3	(*S*)-**4b** [2.5]	BH_3-THF [120]	23° C / 1 min.	99.9	9
4	(*S*)-**4b** [0.5]	BH_3-THF [120]	23° C / 1 min.	59	9
5	(*S*)-**10a** [100]	BH_3-THF [200]	25° C / 1 min.	97	9
6	(*S*)-**10a** [10]	BH_3-THF [100]	25° C / 1 min.	97	9
7	(*S*)-**10a** [2.5]	BH_3-THF [120]	25° C / 1 min.	95	9
8	(*S*)-**10a** [0.5]	BH_3-THF [120]	25° C / 1 min.	80	9
9	(*S*)-**10b** [10]	BH_3-THF [60]	2° C / 2 min.	96.5	12
14	(S)-**10c** [10]	BH_3-DMS [70]	–15° C	92	24
15	(*S*)-**10c** [10]	catecholborane [150]	–78° C / 15 h	94	21
10	(S)-**10d** [10]	BH_3-DMS [70]	–15° C	72	24
11	(*S*)-**10e** [10]	BH_3-THF [60]	23° C / 5 min.	97.8	20
12	(*S*)-**10f** [10]	BH_3-THF [60]	23° C / 5 min.	97.8	20
13	(*S*)-**10f** [5]	BH_3-THF [60]	23° C / 5 min.	96.1	20

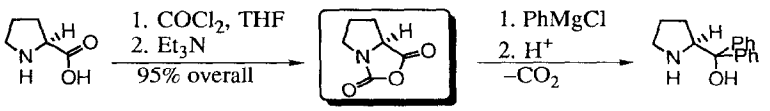
Itsunos original reduction procedure involving borane-THF complex as reductant was modified in some cases by *Corey et al.* because borane reacts with other functional groups which are sensitive to borane e. g. double bonds, amides *etc.*. Hydroborations or reductions lead to unwanted side reaction products. Further the original procedure loses stereoselectivity at lower temperatures. In contrast, the catecholborane procedure functions well at low temperatures which allows high enantioselective reductions of important types of substrates e.g. α,β-enones.

Because of the great interest in asymmetric reductions using (*S*)-2-diphenylhydroxymethylpyrrolidine (*S*)-**9a** as the catalyst precursor, several *EPC*- (enantiomerically pure compound) syntheses[26] for this β-amino alcohol are known.

Usually (*S*)-**9a** is prepared by an *ex chiral pool syntheses* starting from cheap (*S*)-proline (*S*)-**11** or its expensive enantiomer.

The *Grignard* reaction of (*S*)-proline ester hydrochlorides[27], the free esters[19,28], *N*-benzyloxycarbonyl-(*S*)-proline esters[9,12b,19] or the corresponding *N*-benzyl derivatives[29] with phenylmagnesium halides led to (*S*)-**9a**. The published chemical yields were in the range of 0-50 %, optical purities were between 80 and 100 %. Similarely other α-amino acid-based catalyst precursors were prepared. In our laboratories an alternative reaction led to optically pure (*S*)-**9a** with >95 % *ee*[30].

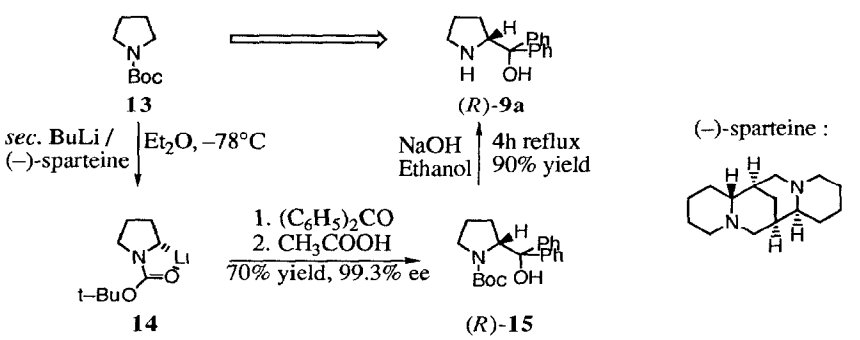
A more efficient new synthesis is based on (*S*)-proline-*N*-carboxanhydride (*S*)-**12** as the key intermediate which is allowed to react with phenylmagnesium chloride to give (*S*)-**9a** in 73 % yield with 99.4 % *ee*[23]. Reaction of (*S*)-proline-*N*-carboxanhydride with a range of other aryl *Grignard* reagents was also reported.



(*S*)-**11** (*S*)-**12** (*S*)-**9a**

Because of the high cost of (*R*)-proline (it is 50 times costlier than the (*S*)-enantiomer) *Corey et al.*[12a] prepared racemic (*RS*)-**9a** in 51 % yield by addition of PhMgCl to cheap (*RS*)-methyl pyroglutamate followed by reduction with borane. The optical resolution was carried out by recrystallisation of the *O*-acetylmandelate salt to give (*R*)-**9a** or (*S*)-**9a** (30% yield from (*RS*)-**9a**). An earlier report dealt with the preparation of racemic (*RS*)-**9a** in 60 % yield by addition of lithiated *N*-nitrosopyrrolidine to benzophenone[31].

The elegant asymmetric version of this procedure was recently reported by *Beak* and *Kerrick*[32].



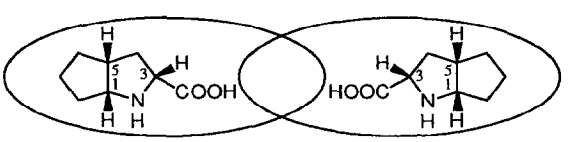
The enantioselective deprotonation of Boc-pyrrolidine **13** with *sec.* butyllithium in the presence

of (–)-sparteine as chiral inducer yielded the organolithium reagent **14**, which underwent reaction with benzophenone to give (*R*)-**15** in 75% yield and 90% *ee* (70% yield, 99.3% *ee* after one recrystallisation). Cleavage of the Boc group with sodium hydroxide gave (*R*)-**9a** in 90 % yield.

3.3. New catalysts in comparison

In the last five years a flood of papers have appeared dealing with the synthesis and application of new β-amino alcohols from non proteinogenic α-amino acids or camphor. Several chiral 1,3,2-oxazaborolidines (prepared *in situ* or isolated before application) have recently gained prominence as catalysts for a variety of moderate to highly efficient enantioselective reductions. Acetophenone as the model substrate was tested in almost every case. As can be seen from Table 4, the best enantioselectivities were obtained with (*S*)-2-diphenylhydroxymethyl azetidine[33,34] (*S*)-**17**, the tricyclic oxazaborolidine[35] (1*S*,5*R*,8*S*)-**20** and the (*S*)-indoline-2-carboxylic acid derivative[36] (*S*)-**22** as catalysts. The results are comparable to those achieved with oxazaborolidines obtained from (*S*)-**9a** and (*S*)-**9b**. The six-membered ring analogue[37] (*S*)-**18** is less efficient. The *ee* values of the derived alcohols are in all cases lower in the range of 5 - 10 % in comparison to the results obtained with (*S*)-**9a** and (*S*)-**17**. One can assume that this could be due to steric influence being less efficient with six-membered catalysts compared to five- and four-membered analogues.

We envisioned that a bicyclic proline analogue would encompass the structural requirements necessary for efficient catalytic asymmetric reductions of prochiral ketones[38]. The synthesis of the catalyst precursor of (1*R*,3*R*,5*R*)-**19** was accomplished starting from the bicyclic unnatural proline analogue (1*R*,3*R*,5*R*)-2-azabicyclo[3.3.0]octan-3-carboxylic acid[39] (1*R*,3*R*,5*R*)-**16**.



(1*R*,3*R*,5*R*)-**16** (1*S*,3*S*,5*S*)-**16**

The (*S*)-enantiomer is the precursor of the highly potent angiotensin converting enzyme (ACE) inhibitor Ramipril[40]. Surprisingly we obtained only moderate enantioselectivities with (1*R*,3*R*,5*R*)-**19** which could be due to steric influences of the second ring in the "cis"-conformation of this catalyst. Asymmetric reductions with the epimeric (1*R*,3*S*,5*R*)-**19** with the opposite configuration in 3-position are under investigation.

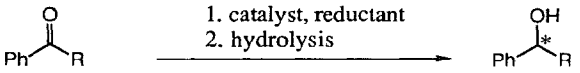
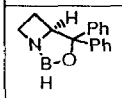
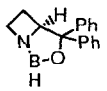
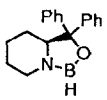
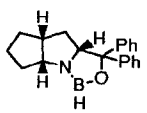
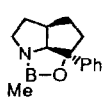
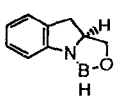
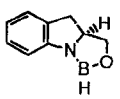
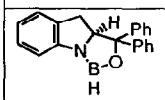
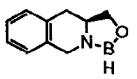
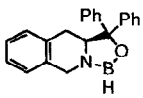
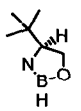
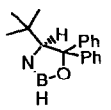
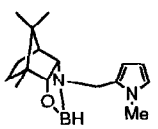
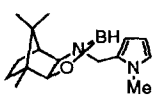


Table 4 : Enantioselective catalytic reduction of aromatic ketones to related secondary alcohols in the presence of various catalysts.

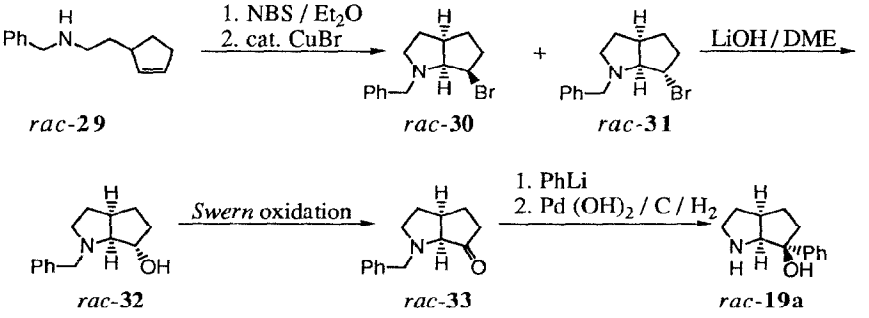
catalyst [mol %]		reductant [mol %]	ketone	*ee* [%]	ref.
 (*S*)-**17** (*in situ*)	[10 mol %]	BH_3-THF [90 mol %]	PhCOMe PhCOEt	98 (*R*) >99 (*R*)	33
 (*S*)-**17**	[10 mol %]	BH_3-THF [60 mol %]	PhCOMe	95 (*S*)[a]	34
 (*S*)-**18**	[10 mol %]	BH_3-THF [60 mol %]	PhCOMe	87 (*R*)	37
 (1*R*,3*R*,5*R*)-**19** (*in situ*)	[1 mol %]	BH_3-THF [100 mol %]	PhCOMe PhCOEt	61 (*S*) 59 (*S*)	38
 (1*S*,5*R*,8*S*)-**20**	[10 mol %]	BH_3-THF [60 mol %]	PhCOMe	97.5 (*R*)	35
 (*S*)-**21** (*in situ*)	[10 mol %]	BH_3-THF [100 mol %]	PhCOMe	8 (*R*)	36
 (*S*)-**21**	[100 mol %] [10 mol %]	BH_3-DMS [200 mol %] BH_3-DMS [200 mol %]	PhCOMe PhCOMe	97 (*R*) 59 (*R*)	41

catalyst [mol %]		reductant [mol %]	ketone	*ee* [%]	ref.
	[10 mol %]	BH_3-THF [100 mol %]	PhCOMe	91 (*R*)	36
	[2 mol %]	BH_3-THF [100 mol %]	PhCOMe	93 (*R*)	
	[10 mol %]	BH_3-THF [100 mol %]	PhCOEt	88 (*R*)	
(*S*)-**22** (*in situ*)					
	[10 mol %]	BH_3-THF [100 mol %]	PhCOMe	71 (*R*)	42
			PhCOEt	42 (*R*)	
(*S*)-**23** (*in situ*)					
	[10 mol %]	BH_3-THF [100 mol %]	PhCOMe	51 (*R*)	42
			PhCOEt	35 (*R*)	
(*S*)-**24** (*in situ*)					
	[10 mol %]	BH_3-THF [100 mol %]	PhCOMe	80 (*R*)	36
			PhCOEt	85 (*R*)	
(*S*)-**25** (*in situ*)					
	[10 mol %]	BH_3-THF [100 mol %]	PhCOMe	89 (*R*)	36
			PhCOEt	69 (*R*)	
(*S*)-**26** (*in situ*)					
	[5 mol %]	BH_3-THF [70 mol %]	PhCOMe	73 (*S*)	43
			PhCOEt	77 (*S*)	
(1*R*,2*S*,3*R*,4*S*)-**27** (*in situ*)					
	[5 mol %]	BH_3-THF [70 mol %]	PhCOMe	73 (*R*)	43
			PhCOEt	79 (*R*)	
(1*R*,2*R*,3*S*,4*S*)-**28** (*in situ*)					

a.) Because (*R*)-**17** was applied the stereochemistry is reversed.

The synthesis of the tricyclic catalyst (1*S*,5*R*,8*S*)-**20** was accomplished starting from commercially available (*RS*)-(2-cyclopentyl)-acetic acid[35]. The reduction of the benzylamide led to the secondary amine (*RS*)-**29** which upon treatment with *N*-bromosuccinimide (NBS) and

afterwards with a catalytic amount of CuBr cyclized stereoselectively and yielded the bicyclic diastereomeric amines **30** and **31** (1 : 30) and their enantiomers. Treatment with LiOH yielded the β-amino alcohol *rac*-**32** and unreacted *rac*-**30** which was separated from the product. *Swern* oxidation of alcohol *rac*-**32** afforded ketone *rac*-**33** which after reaction with phenyllithium and debenzylation provided racemic amino alcohol *rac*-**19a**.



The optical resolution yielded (+)-(1*S*,5*R*,8*S*)-8-phenyl-2-azabicyclo[3.3.0]octan-8-ol (1*S*,5*R*,8*S*)-**19a** and its enantiomer in 99 % optical purity. Reaction of this β-amino alcohol with methyl boronic acid afforded the corresponding oxazaborolidine (1*S*,5*R*,8*S*)-**19**. This catalyst was shown to be highly effective in the borane reduction of various prochiral ketones to optically active alcohols. With acetophenone 97.5 % *ee* was achieved.

The non-α-substituted (*S*)-indoline-2-carboxylic acid derivative[40,41] (*S*)-**21** gave high enantioselectivities when a stoichiometric amount of the oxazaborolidine was applied to the reduction of acetophenone with borane-DMS. Reduced catalyst concentration resulted in only moderate enantioselectivities. In our hands this catalyst led to just 8 % *ee* when borane-THF was used as reductant. With (*S*)-2-diphenylhydroxymethyl-indoline (*S*)-**22** much better results even with catalytic oxazaborolidine amounts were obtained[40].

The β-amino alcohol precursors[42] of (*S*)-**23** and (*S*)-**24** were prepared from (*S*)-porretine[44] another bicyclic α-amino acid which was easily obtained *via* a *Pictet-Spengler* reaction from (*S*)-phenylalanine and formaldehyde under acidic conditions[44b]. The *in situ* formed chiral oxazaborolidine catalyst from (*S*)-**23** gave better enantioselectivities than (*S*)-**24**. Both catalysts led to moderate stereoselectivities only compared with those obtained with the five-membered ring analogues (*S*)-**21** and (*S*)-**22**.

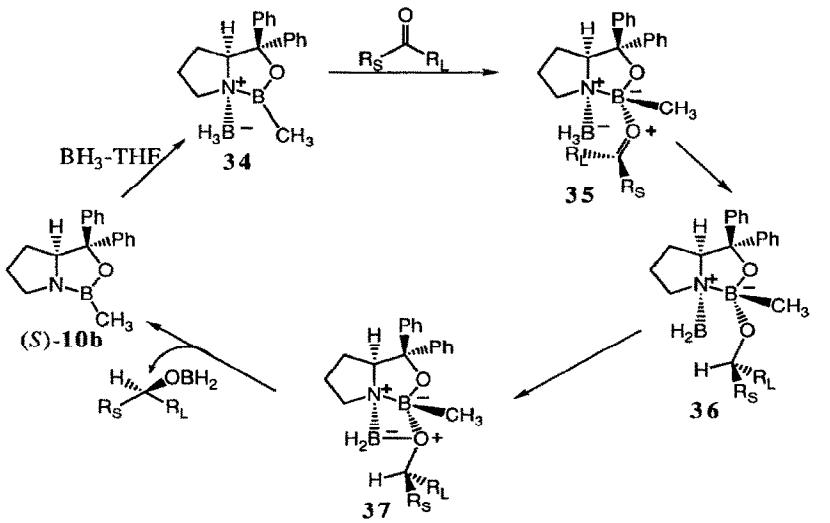
The two catalysts (*S*)-**25** and (*S*)-**26** from *tert*-(*S*)-leucine are not as efficient as the corresponding (*S*)-valine derivatives[36].

Sometimes it is difficult to synthesize both enantiomers of a catalyst, because both antipodes of a catalyst precursor are not always readily available or one is too expensive. In this case it is interesting to build up diastereomeric homochiral ligands based on only one optically active

educt. *Tanaka et al.*[43] prepared *exo*- and *endo*-2-hydroxy-3-(1-methyl-2-2pyrrolyl)methyl-aminobornanes (1*R*,2*S*,3*R*,4*S*)-**27** and (1*R*,2*R*,3*S*,4*S*)-**28** from *D*-camphor. With these diastereomeric secondary β-amino alcohols both enantiomers of the desired optically active alcohols can be obtained. The reduction of propiophenone in the presence of 5 mol % *exo*-compound (1*R*,2*S*,3*R*,4*S*)-**27** afforded (*S*)-1-phenyl propanol in 77% enantiomeric excess. In the presence of the diastereomeric *endo*-ligand (1*R*,2*R*,3*S*,4*S*)-**28** the stereoselectivity was reversed and the (*R*)-alcohol was obtained in 79 % *ee*.

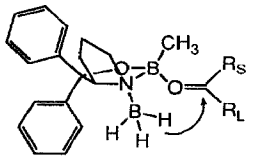
3.4. Mechanistic considerations

A reasonable reaction mechanism for the catalysis has been suggested. *Itsuno et al.* postulated that at first the oxazaborolidine reacts with a molecule BH_3-THF to form the reducing species **34** *in situ*[9,15]. With (*S*)-**10a** this was verified on the basis of NMR studies[9]. Recently the three dimensional structure of the borane adduct from (*S*)-**10b** has been determined by X-ray crystallography[45a]. The results of these studies provide additional evidence for transition state assembly **34**.



In the *Lewis* acid-base adduct **34** the boron of the oxazaborolidine moiety coordinates with the respective prochiral ketone *cis* to the BH_3 molecule. In **35** an intramolecular hydride transfer

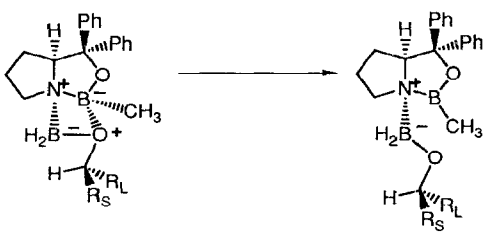
from the BH_3 moiety on the *re* face of the carbonyl substrate takes place *via* a six-membered transition state yielding the (*R*)-alcohol[45].



35

Summarized, the oxazaborolidine brings together the reductant and the carbonyl substrate. For this enzyme-like behaviour the oxazaborolidines have been named "molecular robots" or "chemzymes"[45b].

Some details of the catalysis mechanism including the role of a *Lewis* basic solvent have been evaluated recently also by using computional methods[46]. On the basis of *ab initio* molecular orbital methods *Nevalainen* calculated energies of formation and structural parameters of some simpler analogous model systems and reactive intermediates of the oxazaborolidine catalysts. His results have provided further support for the proposed mechanism. In his calculations complexes in which the borane and carbonyl moiety were *cis* about the *B-N* bond of the oxazaborolidine ring were found to be favoured[46a]. In *cis*-complexes the hydride of the BH_3 moiety is closer to the carbonyl group than in the corresponding *trans*-complexes. Effects of ketone substituents R_L and R_S also have been studied[46b]. *Nevalainen* suggested and calculated the proposed reactive intermediates that occur after the hydride transfer happens. His studies reveal that an 1,3-oxazadiboretane system **37** could be involved in the regeneration of the oxazaborolidine[46d].



37 **38**

The proposed oxazaboretane system **37** formed after the intramolecular hydride transfer could react further by eliminating the alkoxyborane moiety yielding (*S*)-**10b** or it could rearrange to the alkoxyborane adduct **38**. This could then function as a reducing species in the same way as **34** does. The alkoxyborane could after elimination coordinate back to the oxazaborolidine (*S*)-**10b** and serve as hydrogen donor as well. In most cases complete ketone reduction is achieved

when only 60 mol % of borane is applied[12]. The relative energetic advantages of the formation of borane adduct **34** and alkoxyborane adduct **38** of oxzaborolidines have been lately studied also by means of *ab initio* molecular orbital calculations[46e]. A comparison of the structural and electronic properties of these complexes reveal of that the alkoxyborane adduct **38** could in some cases be a reducing species with a comparable or even better effect than the corresponding borane adduct **34.**

All the time the oxazaborolidine system has been dealt with as a monomer although the catalyst has been suggested to exist in a dimeric form on the basis of NMR studies[9].

(*S*)-**10b** **39**

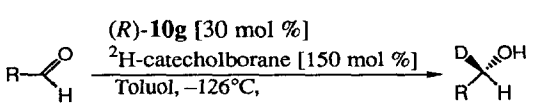
Nevalainen calculated that in the case of the (*S*)-2-diphenylhydroxymethyl-pyrrolidine derivative (*S*)-**10a** the *anti N,N*-adduct was favoured[46f]. In the presence of a *Lewis* basic solvent like THF monomers occur as indeed has been observed to be the case[9]. This context explains the influence of solvents on *ee* values.

3.5. Special Applications

Several syntheses have been carried out taking advantage of the recent advances in the enantioselective reduction of prochiral ketones to secondary alcohols by means of catalytic amounts of oxazaborolidines. The oxazaborolidines have been used as powerful tools in key steps to synthesize various interesting compounds e. g. natural products, drugs or plant-protective agents. In almost every case efficient enantioselective reduction with predictible absolute stereochemistry of the product was achieved.

Reduction and conversion of non-functionalized carbonyl compounds

Optically active primary alcohols deuterated on the secondary carbon have been used for studies concerning the mechanism of chemical reactions and biochemical transformations[47].

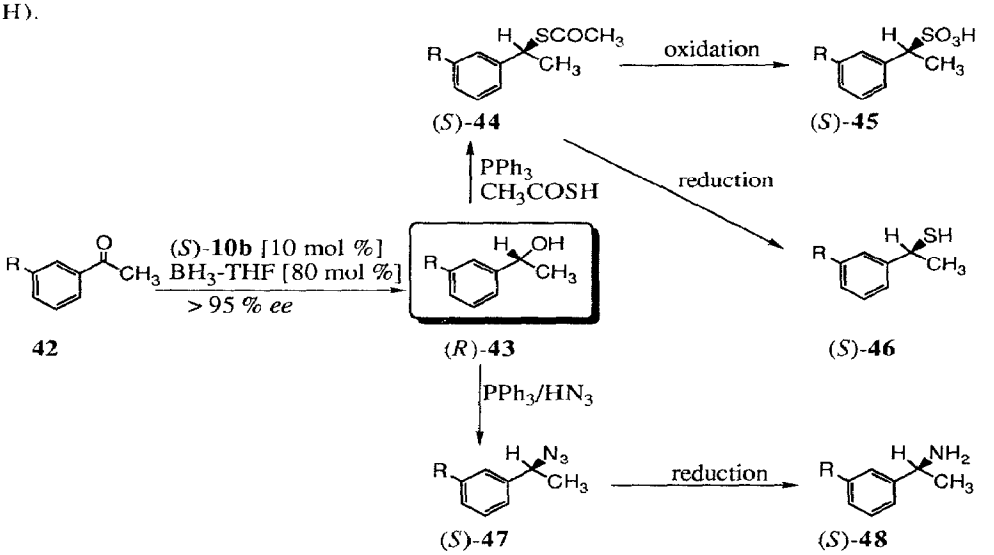


40 **41**

benzaldehyde 95 % *ee*
cyclohexane carbaldehyde 92 % *ee*
n-octanal 90 % *ee*

The reduction of aldehydes **40** with ^{2}H-catecholborane in a non-coordinating solvent at low temperatures in the presence of 30 mol % (*R*)-**10g** led to the corresponding deuterated products **41** in high chemical and optical yields[20].

The chiral sulfur compound (*S*)-**44** (R = H) was obtained *via* conversion of the optically active secondary alcohol (*R*)-**43** (R = H) with thio acetic acid under *Mitsunobu* reaction conditions with clean inversion of configuration[48]. Reductive work up of the (*S*)-thioacetate (*S*)-**44** led to the benzylic thiol (*S*)-**46** (R = H), oxidation to (*S*)-α-phenylethane sulfonic acid (*S*)-**45** (R = H).

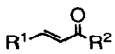
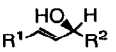
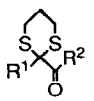
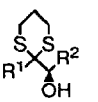


Prasad et al. transformed the reduction products of various α-arylketones **42** (R = Br, OMe, OH) into enantiopure α-arylethylamines (*S*)-**48** which play an important role in drug design[22b]. Displacement of the hydroxy function by an azide group under *Mitsunobu* reaction conditions led to the corresponding azides (*S*)-**47** with clean inversion of configuration. Conversion of the azides to the respective amines was achieved *via* reductive pathways. The α-arylethylamines (*S*)-**48** (R = Br, OMe, OH) were obtained in 70-93 % overall yield with > 95 % *ee*.

Reduction and conversion of α-functionalized carbonyl compounds

Extremely useful chiral allylic alcohols (*R*)-**50** and (*R*)-**52** for many asymmetric syntheses can be obtained by reduction of α,β-unsaturated ketones. The catecholborane modification of *Itsunos* original reduction procedure is the method of choice for the synthesis of such alcohols. Catecholborane does not lead to side reaction products as borane does. Optically active allylic alcohols (*R*)-**50** or (*R*)-**52** were produced in > 95 % yield with high *ee* values[20,21].

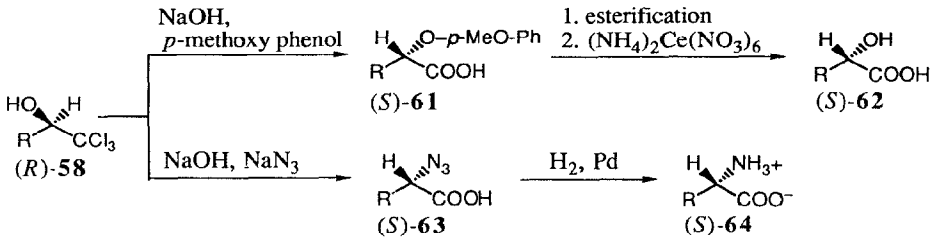
Table 5 : Enantioselective borane reduction of various α-functionalized carbonyl compounds.

educt	catalyst [mol %]	reductant [mol %]	product		*ee* [%]	ref.
 **49**	(*S*)-**10c** [10 mol%]	catecholborane [150-200 mol%]	 (*R*)-**50**	R= Me	93 (*R*)	21
 **51**	(*S*)-**10c** [10 mol%]	catecholborane [150-200 mol%]	 (*R*)-**52**	R^1= Ph, R^2= Me R^1= I, R^2= *n*-C_5H_{11}	92 (*R*) 86 (*R*)	21 21
 **53**	(*S*)-**10d** [15 mol%]	BH_3-THF [60 mol%]	 (*R*)-**54**	R^1= Bz, R^2= Me R^1= Ph, R^2= Me R^1= C_3H_7, R^2= Me	96 (*R*) 90 (*R*) 93 (*R*)	22a 22a 22a
 **55**	(*S*)-**10a** [1 mol%]	BH_3-THF [60 mol%]	 (*S*)-**56**		97 (*S*)	12b
 **57**	(*S*)-**10c** [10 mol%]	catecholborane [150 mol%]	 (*R*)-**58**	R= *n*-C_5H_{11} R= $C_6H_5(CH_2)_2$ R= *c*-C_6H_{11} R= *t*-C_4H_9 R= 2-naphtylmethyl	95 (*R*) 95 (*R*) 92 (*R*) 98 (*R*) 93 (*R*)	49 49 49 49 50
 **59**	(*S*)-**10c** [10 mol%]	catecholborane [150-200 mol%]	 (*R*)-**60**	R= 9-anthryl R= phenyl R= mesityl	94 (*R*) 90 (*R*) 100 (*R*)	21 21 51

One carbonyl group of 1,2-diketones can be reduced regioselectively in high chemical yields with moderate to excellent *ee*[22a] when the 2-acyl-1,3-dithianes **53** were applied to the reduction step. Ee values in the range of 90 - 96 % were reached. The alcohols (*R*)-**54** produced could be hydrolyzed to the α-hydroxyketones or the dithiane group can be removed reductively. *DeNinno et al.* found that the dithiane group enhanced the enantioselectivity since the reduction of the des-dithiane derivatives of **53** (R^1=Bz, R^2=Me) afforded the corresponding alcohol in 43 % *ee* only.

α-Halogenated ketones were applied sucessfully to asymmetric reductions. The reactive halogen of the resulting alcohols makes them useful as intermediates for further reactions. *Via* Cyclisation of the reduction product (*S*)-**56** from α-chloroacetophenone **55** (*S*)-(−)-phenyloxirane was obtained.

Some trichloromethyl ketones **57** were reduced enantioselectively with catecholborane (150 mol %) in the presence of 10 mol % (*S*)-**10c** at different optimum temperatures. Further reaction steps led to (*S*)-α-hydroxy acids[49] (*S*)-**62** or (*S*)-α-amino acids[50] (*S*)-**64** (for details see Table 5).



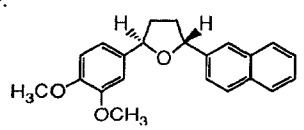
Optically active α-hydroxy acids (*S*)-**62** were produced on treatment of the trichloromethyl carbinols (*R*)-**58** with *p*-methoxy phenol in basic aqueous dimethoxyethane *via* the corresponding esters with clean inversion of configuration[49]. Recrystallisation of these esters increased the optical purities up to 100 % *ee*. Treatment of the (*R*)-(trichloromethyl)carbinols (*R*)-**58** with NaOH and sodium azide led to the (*S*)-α-azido acids (*S*)-**63** with inversion of configuration which upon reduction yielded the desired (*S*)-α-amino acids (*S*)-**64**. Some widely different α-amino acids were synthezised in high chemical and optical yields[50].

Further, some trifluoromethylketones **59** were reduced sucessfully to the corresponding alcohols (*R*)-**60** in excellent enantioselectivities[51].

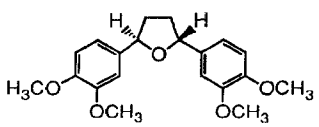
Synthesis of biologically active compounds

The oxazaborolidine-catalyzed reduction of ketones has been used as a key step in syntheses of a wide variety of chiral targets on the pathway to natural products.

*R*acemic *trans*-2,5-diarylfurans have been found to be potent antagonists of platelet activating factor (PAF)[52].



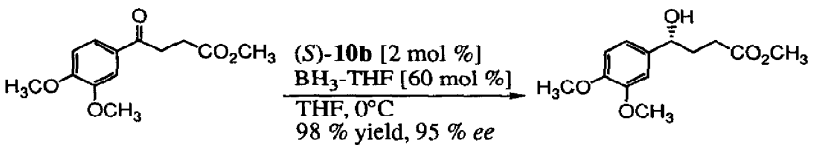
(2*R*,5*R*)-**65**



(2*R*,5*R*)-**66**

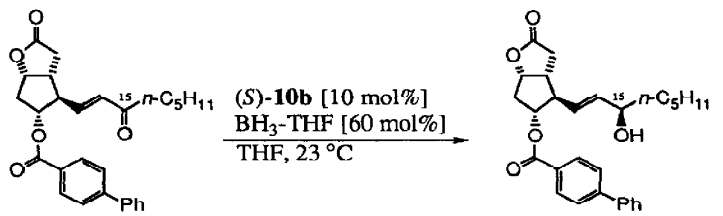
Corey et al.[12a] reported the first enantioselective route to the chiral *trans*-2,5-diarylfurans

(2*R*,5*R*)-**65** and (2*R*,5*R*)-**66**. The key step was the reduction of γ-ketoester **67** with 60 mol% borane in the presence of 2 mol % (*S*)-**10b** yielding (*R*)-**68** with 95 % *ee*.



67 (*R*)-**68**

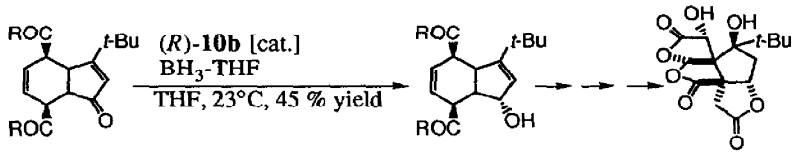
The chiral ketoester lactone **69**, a standard intermediate in prostaglandin synthesis underwent selective reduction[12a] of the keto group upon treatment with 60 mol % BH_3-THF in the presence of 10 mol % (*S*)-**10b** as catalyst to give the (15*R*)-alcohol (15*R*)-**70** and the (15*S*)-diastereomer in a ratio of 91:9.



69 (15*R*)-**70**

Aplysiatoxins and oscillatoxins are a class of natural products which are produced by some species of tropical marine bluegreen algae. These natural products are known to have a tumor promoting activity. In regard of this, the synthesis of these compounds is of great synthetic interest. The synthesis of the C9-C21 subunit involving a borane reduction step catalyzed by (*R*)-**10b** was demonstrated by *Walkup et al.*[53].

The total synthesis of (–)-bilobalide **73**, a C15 ginkgolide is also based on an enantioselective reduction step[54]. The desired epimer **72** was obtained with 10 : 1 selectivity from **71**.

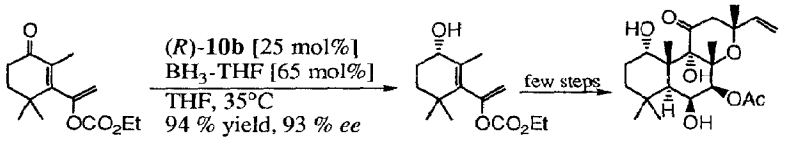


71 (R = (+)-menthoxy) **72** **73**

An optically active alcohol is the key intermediate on the enantioselective pathway to ginkgolide

B, a potent antagonist of platelet activating factor. It was also achieved *via* enantioselective borane reduction[55]. Ginkgolide B makes accessible ginkgolide A which posseses insect antifeedant activity[56].

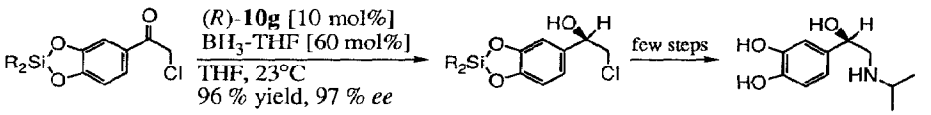
Two important key intermediates in the total synthesis of the diterpenoid forskolin **76**, an activator of ATP-AMP-cyclase, were synthesized involving an asymmetric reduction step[57]. Treatment of the dienone **74** with borane-THF in the presence of 25 mol % (*R*)-oxazaborolidine (*R*)-**10b** afforded enantioselectively the corresponding (*S*)-alcohol (*S*)-**75** in 94 % yield and 93 % *ee*.



74 (*S*)-**75** **76**

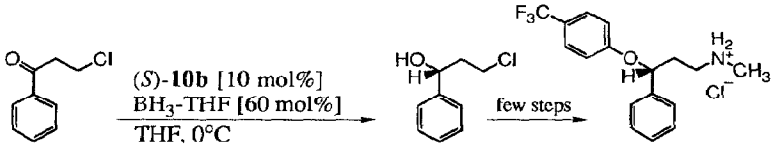
Recently an effective route for the total synthesis of antheridic acid involving an asymmetric borane reduction step with (*S*)-**10c** as catalyst to generate the initial stereogenic center was developed[58].

Isoproterenol (*R*)-**79**, a β-adrenoreceptor agonist was synthesized enantioselectively with 97 % *ee* from **77** *via* borane reduction utilizing (*R*)-**10g** as catalyst[59].



77 (R = *i*-Prop) (*R*)-**78** (*R*)-**79**

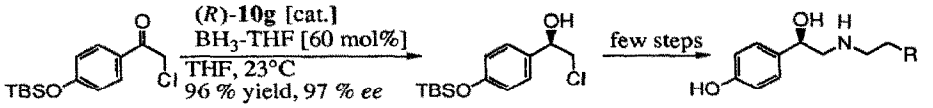
One of the most widespread antidepressants, the serotonin-uptake inhibitor fluoxetine (*R*)-**82** is sold in its racemic form. *Corey et al.* demonstrated an enantioselective pathway to this important drug[60].



80 (*R*)-**81** (*R*)-**82**

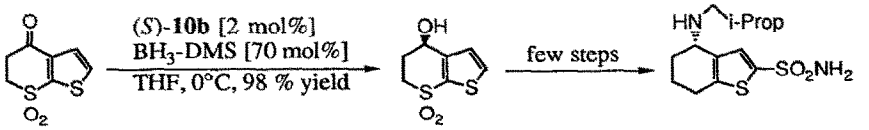
Arylethanolamines are key intermediates of β-adrenoreceptor drugs. The enantioselective reduction of the choromethyl ketone **83** to the corresponding alcohol (*R*)-**84** was achieved in

96 % yield with 97 % *ee*[61].Enantiomerically pure (*R*)-denopamine (*R*)-**85** (R = 3,4-methoxy phenyl) was obtained *via* few reaction steps.



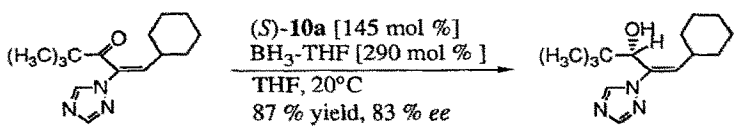
83 (TBS: *t*-Bu(Me)$_2$Si) (*R*)-**84** (*R*)-**85**

Enantiomerically pure MK-0417, a water soluble carbonic anhydrase inhibitor which has been used therapeutically for treating glaucoma patients has been prepared in nine steps from thiophene.



86 (*R*)-**87** (*R*)-**88**

The key step is the asymmetric reduction of sulfone **86** with borane and (*S*)-**10b** as catalyst[24].



89 (*S*)-**90**

The plant growth regulator triapenthenol (*S*)-**90** was obtained *via* reduction of the (*E*)-carbonyl substrate **89** with *in situ* prepared (*S*)-**10a** and borane-THF with 83 % *ee*[19].

4. Oxazaborolidines in various asymmetric reactions

4.1. Asymmetric reduction of ketoxime ethers

Much attention has been focussed on asymmetric syntheses of optically active amines. They play an important role as starting materials for many biologically active compounds[62].
Although the enantioselective *C=N* reduction which is complementary to the asymmetric *C=O* reduction should lead to optically active primary amines this concept has been relatively

neglected. In 1985 *Itsuno* and co-workers developed the first effective enantioselective reduction of ketoxime ethers so far reported[16a]. The *in situ* prepared oxazaborolidine (*S*)-**4b** from (*S*)-valine was sucessfully applied to borane reductions of various ketoxime ethers in stoichiometric and even catalytic amounts. As can be seen from Table 6 the asymmetric reduction of acetophenone oxime *O*-methyl ether was most efficient. Even with 25 mol % catalyst the reduction occured sucessfully with 90 % *ee*. With lower catalyst concentration the enantioselectivity decreased to 52 % *ee* only[18]. In any case the (*S*)-enantiomer of 1-phenyl ethylamine was formed preferentially. Other reducing agents were investigated but only poor to moderate *ee* values were reached.

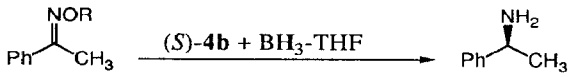


Table 6: Asymmetric reductions of acetophenone oxime *O*-alkyl ethers to (*S*)-phenyl ethylamine with borane-THF in the presence of *in situ* prepared (*S*)-**4b**.

entry	R	BH_3-THF [mol %]	catalyst [mol %]	*ee* [%]	ref.
1	Me	125	125	99	16a
2	$PhCH_2$	125	125	91	16a
3	Et	125	125	81	16a
4	CH_2Ph	400	100	95	18
5	CH_2Ph	100	25	90	18
6	CH_2Ph	100	10	52	18

Because of coordination of the boron with the ketoxime ether nitrogen complete reduction usually required 24 h under the same conditions as appplied to ketones. *Itsuno et al.* overcame this problem by addition of $AlCl_3$ as *Lewis* acid to the oxime ether before the reaction. Complete reduction then occured within three hours[16a].

4.2. Asymmetric reduction of imines

Cho and *Chun* reported the first asymmetric reduction of *N*-substituted ketimine derivatives in the presence of stoichiometric amounts of chiral oxazaborolidines (*S*)-**4b** and (*S*)-**10a** and borane-THF[63]. In the reduction of *N*-phenyl aromatic ketimines the best enantioselectivity with up to 88 % *ee* was achieved when (*S*)-**10a** was utilized as catalyst. In each case the (*R*)-configured amine was formed preferentially (Table 7).

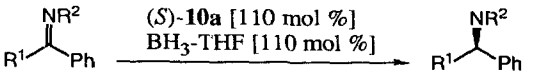
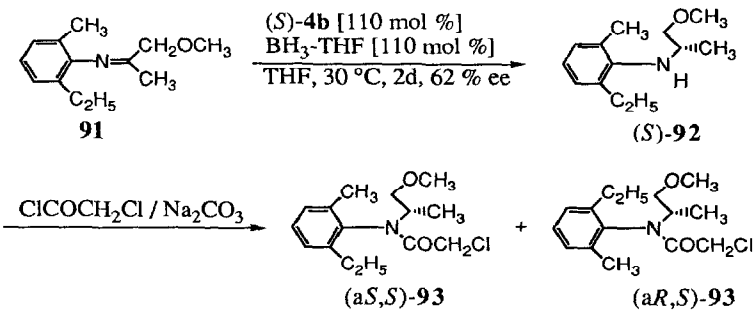


Table 7: Asymmetric reduction of ketimines to related (*R*)-configurated amines with borane-THF [110 mol %] in the presence of oxazaborolidine (*S*)-**10a** [110 mol %].

entry	R^1	R^2	*ee* [%]	ref.
1	Et	Ph	78	63
2	Et	Ph	87	63
3	*n*-C_3H_7	Ph	88	63
4	Me	*n*-C_7H_{13}	52	63

With increasing steric bulk of R^1 the optical yields increased. Aromatic *N*-alkyl ketimines provided moderate results only (entry 4) and *N*-substituted alkyl ketimines were even less effective (2-butanone *N*-phenylimine gave 9 % *ee* only).

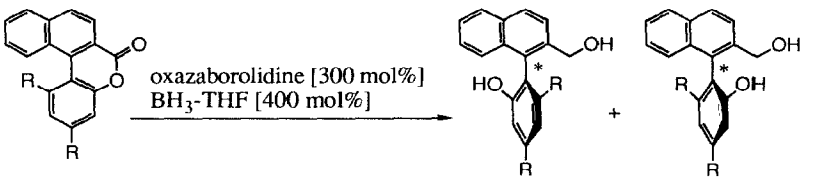
Metalochlor **93** one of the most widely used herbicides posesses a stereogenic center and the atropisomerism of the phenyl-*N* axis. Because of this, four stereoisomers are theoretically possible. The two diastereomers with the (*S*)-configurated carbon (a*S*,*S*)-**93** and (a*R*,*S*)-**93** exhibit higher herbicidal activity than the (*R*)-compounds.



Cho and *Chun* developed an asymmetric synthesis to metalochlor **93** which is based on the enantioselective reduction of imine **91** to the optically active amine (*S*)-**92**[64]. The atropisomers (a *RS*,*S*)-**93** were obtained in 62 % *ee* when (*S*)-**4b** was used as catalyst. With (*S*)-**10a** only 52 % *ee* was obtained.

4.3. Atrop enantioselective ring opening

Bringmann et al. reported the first atrop enantioselective ring opening of axial prochiral lacton bridged biaryl compounds giving bridged biaryls[65]. The prostereogenic lactones **94** and **95** were opened *via* reduction of the lactone with borane-THF in the presence of the three-fold amount of (*S*)-valine-derived oxazaborolidines (*S*)-**4b**, the *B*-methyl and *B*-*n*-butyl derivatives and the (*S*)-proline-based catalyst (*S*)-**10a**, (*S*)-**10b** and (*S*)-**10c** as asymmetry inducers in high chemical and optical yields. The *B*-substituted oxazaborolidines gave the highest asymmetric inductions.

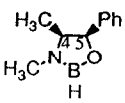


94 (R = OCH_3) **96a** **96b** (R = OCH_3)
95 (R = CH_3) **97a** **97b** (R = CH_3)

In each case the alcohols **96a** and **97a** were obtained preferentially in high enantioselectivities. The best result was achieved with lactone **95**. It was opened reductively with 98.5 : 1.5 selectivity in the presence of the bicyclic oxazaborolidine (*S*)-**10c** (one crystallisation step increased the ratio of **97a** : **97b** up to 99.9 : 0.1).

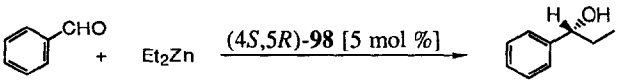
4.4. Catalytic asymmetric addition of diethylzinc to aldehydes

The first example of an oxazaborolidine-catalyzed enantioselective addition of diethylzinc to aldehydes was reported by *Brown et al.*[66]. Diethylzinc reacts with aldehydes very sluggisly at room temperature in non-coordinating solvents[67]. *Oguni* and *Omi* found that optical active amino alcohols accelerate the reaction and induce asymmetry[68]. From mechanistic considerations *Brown et al.* chose the oxazaborolidines from ephedrine and pseudoephedrine as catalysts. The highest enantiomeric excess was obtained with the *B*-non-substituted boron compound (4*S*,5*R*)-**98** from ephedrine.



(4*S*,5*R*)-**98**

With *B*-substituted oxazaborolidines decreased *ee* were obtained. The application of 5 mol % oxazaborolidine (4*S*,5*R*)-**98** in the reaction of diethylzinc with benzaldehyde **99** led to (*R*)-1-phenyl propanol (*R*)-**100** in 95% *ee*.

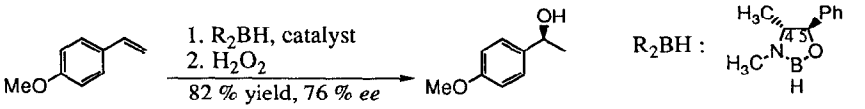


99 (*R*)-**100**

Other aromatic aldehydes gave comparable results, with an aliphatic aldehyde the enantiomeric excess was moderate (heptanal gave 52 % *ee*). With the diastereomeric oxazaborolidine (4*S*,5*S*)-**98** only insignificant enantioselectivities (2 % *ee*) were achieved.

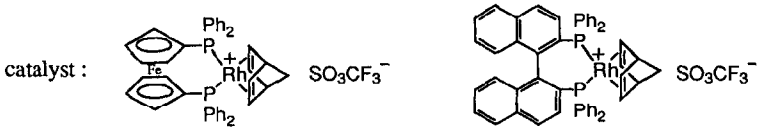
4.5. Rhodium-catalyzed asymmetric hydroboration

In 1990 *Brown* and *Lloyd-Jones* reported that the same homochiral oxazaborolidines **98** derived from ephedrine and pseudoephedrine undergo rhodium complex-catalyzed asymmetric hydroboration reactions with styrenes[69]. In these transformations the oxazaborolidines functioned as homochiral borane equivalents in overstoichimetric concentrations.



101 (*S*)-**102** (4*R*,5*R*)-**98**

In the hydroboration reaction of 4-methoxystyrene **101** both the regiochemistry and the enantioselectivity depended strongly on the structure of the rhodium catalyst and the respective oxazaborolidine.



103 **104**

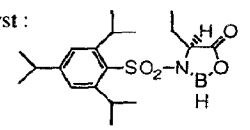
The most promising results were obtained with the ferrocenebiphosphine rhodium complex **103** in connection with the oxazaborolidine (4*R*,5*R*)-**98** derived from (4*R*,5*R*)-pseudo-

ephedrine. The analogous (*R*)- and (*S*)-BINAP catalysts **104** afforded the products in high enantioselectivities depending on the stereochemistry of oxazaborolidine as well but regioselectivities were low.

4.6. Catalytic asymmetric *Diels-Alder* reaction

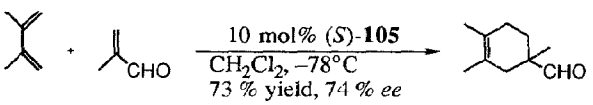
Optically active boron compounds are known as efficient catalysts for asymmetric *Diels-Alder* reactions[70]. In recent times oxazaborolidines have been utilized as chiral *Lewis* acids in asymmetric cycloadditions. The first examples have been reported by *Helmchen et al.*[71] and *Yamamoto et al.*[72] who prepared *B*-non-substituted oxazaborolidines from *N*-sulfonamides of α-amino acids and borane that catalyze various asymmetric *Diels-Alder* additions.

catalyst :



(*S*)-**105**

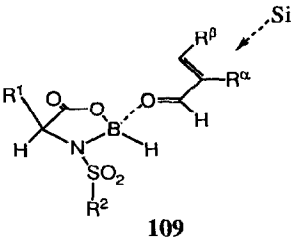
The best results were obtained with the (*S*)-ethylglycine-derived 2,4,6-triisopropylbenzenesulfonamide (*S*)-**105** as catalyst. The cycloaddition of methacrolein **107** and 2,3-dimethyl-1,3-butadiene **106** in the presence of 10 mol % (*S*)-**105** proceeded with 74 % *ee*.



106 **107** **108**

Helmchen et al. utilized the analogous mesitylsulfonamide of (*S*)-valine. They achieved the highest *ee* in the reaction of (*E*)-crotonaldehyde and cyclopentadiene in the presence of 20 mol% catalyst (72 % *ee*, *endo/exo*= 97 : 3).

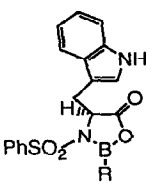
The same authors investigated the influence of various experimental parameters on the enantioselectivity[73]. Maximum enantioselectivity (methacrylaldehyde 86 % *ee endo/exo* = 1 : 99, crotonaldehyde 81 % *ee endo/exo* = 5 : 95) was achieved in donor solvents e. g. THF or acetonitrile. The transition state model **109**, which explains the stereochemical outcome of the reaction, was proposed.



109

The model in which a donor-acceptor interaction favours coordination of the dienophile at the face of the boron which is *cis* to the R^1 substituent was suggested. The amino acid moiety directs the sulfonyl group on the opposite face of the ring. This group controls the configuration of the boron stereogenic centre. The s-*cis* conformation is preferred. This leads to preferential attack of the diene at the C_α-Si enal face.

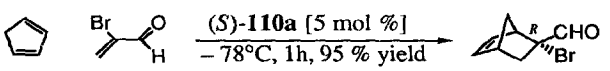
The highest *ee* so far achieved in asymmetric Diels-Alder reactions was reported by *Corey et al.* who utilized the (*S*)-trytophane-derived oxazaborolidines (*S*)-**110** as catalyst[74].



(*S*)-**110a**
R = *n*-Bu

(*S*)-**110b**
R = H

The catalysts were tested in the enantioselective cycloaddition of 2-bromoacrolein **112** and cyclopentadiene **111** yielding carbonyl compound (*R*)-**113**.



111 **112** (*R*)-**113**

In the presence of only 5 mol % of (*S*)-**110a** (*R*)-bromo aldehyde (*R*)-**113** was obtained in 95 % yield and 200 : 1 enantioselectivity (*exo*/*endo* = 96 : 4). With (*S*)-**110b** as catalyst comparable results were achieved.

5. Conclusion

In the field of asymmetric synthesis involving homochiral 1.3,2-oxazaborolidines as catalysts spectacular progress has been made over the last decade.

It has been shown that oxazaborolidines serve as excellent homogeneous catalysts for the enantioselective reduction of prochiral carbonyl compounds to optically active secondary alcohol products. Since the C=O group is a key function in organic chemistry this interesting new reduction procedure has attracted much attention over the last five years. Increasing demand for optically pure biological agents make oxazaborolidines important in asymmetric catalysis. The new reduction concept posesses a wide scope and predictable stereochemistry has been achieved in almost every case. Generally the catalyst precursors (β-amino alcohols) are easily prepared from readily available α-amino acids. The reductions usually occur within a few minutes with high chemical and optical yields. The catalyst precursors can be recovered quantitatively.

The rapidly growing number of other asymmetric reactions (C=N reductions, *Diels-Alder* cycloadditions, hydroborations, addition of diethyl zinc to aldehydes) catalyzed by oxazaborolidines shows the wide application scope of these heterocycles.

Our knowledge concerning the limitations and potentials of this fascinating young area of chemistry is still at the beginning. Further mechanistic and synthetic efforts have to be devoted to the investigations in the field of oxazaborolidine chemistry for the comprehensive understanding of enantioselection.

In conclusion, the use of oxazaborolidines as homogeneous chiral catalysts is at the forefront of asymmetric synthesis. One can expect to see in the future more examples of enantioselective reactions involving homochiral oxazaborolidines as catalysts.

References

1. A. Fischli, *Chimia* **1976**, *30*, 4-9.
2. J. D. Morrison, *Asymmetric Synthesis, Vols 1-5*, Academic Press, New York (1983).
3. (a) H. B. Kagan *Asymmetric Synthesis, Vol. 5*, Academic Press, New York (1983), p. 1-39. (b) K. Tomioka, *Synthesis* **1990**, 541-549.
4. (a) K. Singh, *Synthesis* **1992**, 605-617. (b) H. C. Brown, P. V. Ramachandran, *Acc. Chem. Res.* **1992**, *25*, 16-24.
5. A. Hirao, S. Itsuno, S. Nakahama, N. Yamazaki, *J. Chem. Soc. Chem. Commun.* **1981**, 315-317.
6. (a) R. Csuk, B. I. Glänzer, *Chem. Rev* **1991**, *91*, 49-97. (b) K. Nakamura, Y. Kawai, T. Kitayama, T. Miyai, M. Ogawa, Y. Mikata, M. Higaki, A. Ohno, *Bull. Inst. Chem. Res., Kyoto Univ.* **1989**, *67*, 156-168.
7. (a) S. L. Blystone, *Chem. Rev.* **1989**, *89*, 1663-1679. (b) M. Bartok, *Stereochemistry of heterogeneous metal catalysts*, Wiley & Sons, Chichester, New York, Brisbane, Toronto, Singapore (1985) p. 390 and references cited therein.
8. Lithiumaluminiumhydride reagents : (a) E. R. Grandbois, S. I. Howard, J. D. Morrison, *Asymmetric Synthesis, Vol. 2*, Academic Press, New York (1983) p. 71-90. (b) T. Mukaiyama, M. Asami, *Top. Curr. Chem. 127*, 133-167. Borohydride reagents : (c) M. M. Midland, *Chem. Rev.* **1989**, *89*, 1553-1561. (d) H. C. Brown, W. S. Park, B. T. Cho, P. V. Ramachandran, *J. Org Chem* **1987**, *52*, 5406-5412. (e) M. M. Midland, *Asymmetric Synthesis, Vol. 2*, Academic Press, New York (1983), p. 45-69. (f) H. C. Brown, P. K. Jadhav, A. K. Mandal, *Tetrahedron* **1981**, *37*, 3547-3587. Tinhydride reagents : (g) T. Oriyama, T Mukaiyama, *Chem Lett.* **1984**, 2069-2070 (h) M. Falorni, L. Lardicci, A. M.

Piroddi, G. Giacomelli, *Gazz. Chim. Ital.* **1989**, *119*, 511-512. (i) M. Falorni, L. Lardicci, *Tetrahedron Lett.* **1989**, *30*, 3551-3554; M. Falorni, G. Giacomelli, M. Marchetti, N. Culeddu, L. Lardicci, *Tetrahedron: Asymmetry* **1991**, *2*, 287-298.

9. (a) S. Itsuno, Y. Sakurai, K. Ito, A. Hirao, S. Nakahama, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395-396. (b) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**,*109*, 5551–5553.
10. E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schröder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970.
11. R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 34-55; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477-515.
12. (a) E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926. (b) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Org. Chem.* **1988**, *53*, 2861-2863.
13. J. C. Fiaud, H. B. Kagan, *Bull. Soc. Chem. Fr.* **1969**, 2742-2743.
14. (a) R. F. Borch, S. R. Levitan, *J. Org. Chem.* **1972**, *37*, 2347-2349. (b) M. F. Grundon, D. G. Cleery, J. W. Wilson, *Tetrahedron Lett.* **1976**, 295-296.
15. S. Itsuno, A. Hirao, S. Nakahama, Y. Yamazaki, *J. Chem. Soc. Perkin Trans. I* **1983**, 1673-1676.
16. (a) S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, *J. Chem. Soc., Perkin Trans. I* **1985**, 2039-2044. (b) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc., Chem. Commun.* **1983** 469-470.
17. S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc., Perkin Trans. I* **1984**, 2887-2893.
18. S. Itsuno, Y. Sakurai, K. Ito, A. Hirao, S. Nakahama, *Bull Chem. Soc. Jpn.* **1987**, *60*, 395-396.
19. U. Kraatz, German Patent DE 3609152 A1, **1987**.
20. E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1989**, *30*, 6275-6278.
21. E. J. Corey, R. K. Bakshi, *Tetrahedron Lett.* **1990**, *31*, 611-614.
22. (a) M. P. DeNinno, R. P. Perner, L. Lijewski, *Tetrahedron Lett.* **1990**, *31*, 7415-7418. (b) C.-P. Chen, K. Prasad, O. Repie, *Tetrahedron Lett.* **1991**, *32*, 7175-7178.
23. D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R. A. Reamer, J. J. Mohan, E. T. T. Jones, K. Hoogsteen, M. W. Baum, E. J. J. Grabowsky, *J.Org.Chem.* **1991**, *56*, 751-762.
24. T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. Jones, R. A. Reamer, F. E. Roberts, E. J. J. Grabowsky, *J. Org. Chem.* **1991**, *56*, 763-769.
25. E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1992**, *29*, 4141-4144.
26. D. Seebach, E. Hungerbühler in *Modern synthetic Methods*; ed. R. Scheffold, Salle & Sauerländer, Frankfurt /Aarau (1980), p. 91-171.
27. J. Kapfhammer, A. Matthes, *Hoppe–Seylers Zeit. Physiol. Chem* **1933**, *223*, 43-52.
28. (a) Roussel–Uclaf, French Patent FR 3638M, 1965.
29. D. Enders, H. Kipphard, P. Gerdes, L. J. Brena–Valle, V. Bhushan, *Bull. Soc. Chem. Belg.* **1988**, *97*, 691-704.
30. W. Behnen, J. Martens, unpublished results.
31. (a) D. Seebach, D. Enders, B. Renger, *Chem. Ber.* **1977**, *110*, 1852-1865. (b) D. Enders, R. Peiter, D. Seebach, in *Organic Synthesis*; ed. W. E. Noland; John Wiley & sons: New York (1988); *Collect. Vol. 6*, p. 542–549.
32. S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708-9709.
33. W. Behnen, Ch. Daueisberg, S. Wallbaum, J. Martens, *Synth. Commun.* **1992**, 22, 2143-2153.
34. A. V. R. Rao, M. K. Gurjar, V. Kaiwar, *Tetrahedron: Asymmetry* **1992**, *3*, 859-862.
35. E. J. Corey, C.-P. Chen, G. A. Reichard, *Tetrahedron Lett.* **1989**, *30*, 5547-5550.
36. J. Martens, Ch. Daueisberg, W. Behnen, S. Wallbaum, *Tetrahedron: Asymmetry* **1992**, *3*, 347–349.
37. A. V. R. Rao, M. K. Gurjar, P. A. Sharma, V. Kaiwar, *Tetrahedron Lett.* **1990**, *31*, 2341–2344.
38. S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1991**, *2*, 1093-1096.
39. V. Tcetz, R. Geiger, H. Gaul, *Tetrahedron Lett.* **1984**, *25*, 4479-4482.
40. (a) H. H. Donaubauer, D. Mayer, *Arzneim.–Forsch./Drug Res.* **1988**, *38* (I), 14-20. (b) R. Henning, U. Lerch, H. Urbach, *Synthesis* **1989**, 265-268. (c) H. Urbach, R. Henning, *Heterocycles* **1989**, *28*, 957-965.
41. I. K. Youn, S. W. Lee, C. S. Pak, *Tetrahedron Lett.* **1988**, *29*, 4453–4456.
42. K. Stingl, J. Martens, S. Wallbaum, *Tetrahedron: Asymmetry* **1992**, *3*, 223-226.
43. K. Tanaka, J. Matsui, H. Suzuki, *J. Chem. Soc., Chem. Commun.* **1991**, 1311-1312.

44. (a) P. L. Julian, W. J. Karpel, A. Magnani, E. W. Meyer, *J. Am. Chem. Soc.* **1948**, *70*, 180-183. (b) G. E. Hein, C. Nieman, *J. Am. Chem. Soc.* **1962**, *84*, 4487-4494.
45. (a) E. J. Corey, M. Azimiora, S. Sarshar, *Tetrahedron Lett.* **1992**, *33*, 3429-3430. (b) E. J. Corey, *Pure & Appl. Chem.* **1990**, *62*, 1209-1216.
46. (a) V. Nevalainen, *Tetrahedron: Asymmetry* **1991**, *2*, 63-74. (b) V. Nevalainen, *Tetrahedron: Asymmetry* **1991**, 2, 429-435. (c) V. Nevalainen, *Tetrahedron: Asymmetry* **1991**, 2, 827-842. (d) V. Nevalainen, *Tetrahedron: Asymmetry* **1991**, 2, 1133-1155. (e) V. Nevalainen, *Tetrahedron: Asymmetry* **1992**, *3*, 921-932. (f) V. Nevalainen, *Tetrahedron: Asymmetry* **1992**, *3*, 933-945.
47. D. Arigoni, E. L. Eliel, *Top. Stereochem.* **1969**, *4*, 127-243.
48. E. J. Corey, K. A. Cimprich, *Tetrahedron Lett.* **1992**, *33*, 4099-4102.
49. E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1992**, *33*, 3431-3434
50. E. J. Corey, J. O. Link, *J. Am. Chem. Soc.* **1992**, *114*, 1906-1908.
51. E. J. Corey, X.-M. Cheng, K. A. Cimprich, S. Sarshar, *Tetrahedron Lett.* **1991**, *32*, 6835-6838.
52. P. Braquet, J. J. Godfroid, *Trends Pharmacol. Sci.* **1986**, *7*, 397-403.
53. R. D. Walkup, R. R. Kane, P. D. Boatman, Jr. Cunningham, R. T. Cunningham, *Tetrahedron Lett.* **1990**, *31*, 7587-7590.
54. E. J. Corey, W. Su, *Tetrahedron Lett.* **1988**, *29*, 3423-3426.
55. E. J. Corey, A. V. Gavai, *Tetrahedron Lett.* **1988**, *29*, 3201-3204.
56. (a) E. J. Corey, *Chem. Soc. Rev.* **1988**, *17*, 111-133. (b) E. J. Corey, A. K. Ghosh, *Tetrahedron Lett.* **1988**, *29*, 3205-3206.
57. E. J. Corey, P. Da Silva Jardine *Tetrahedron Lett.* **1989**, *30*, 7297-7300.
58. E. J. Corey, H. Kigoshi, *Tetrahedron Lett.* **1991**, *32*, 5025-5028.
59. E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1990**, *31*, 601-604.
60. E. J. Corey, G. A. Reichard, *Tetrahedron Lett.* **1989**, *30*, 5207-5210
61. E. J. Corey, J. O. Link, *J. Org. Chem.* **1991**, *56*, 442-444.
62. G. Bringmann, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York (1986), *Vol. 29*, p.141-184.
63. B. T. Cho, Y. S. Chun, *J. Chem. Soc., Perkin Trans. 1* **1990**, 3200-3201.
64. B. T. Cho, Y. S. Chun, *Tetrahedron: Asymmetry* **1992**, *3*, 337-340.
65. G. Bringmann, T. Hartung, *Angew. Chem.* **1992**, *104*, 782-783.
66. N. N. Joshi, M. Srebnik, H. C. Brown, *Tetrahedron Lett.* **1989**, *30*, 5551-5554.
67. L. Miginiac, in *The Chemistry of the Metal-Carbon Bond*, ed. F. R. Hartley, Wiley, Chichester (1985), *Vol.1*.
68. N. Oguni, T. Omi, *Tetrahedron Lett.* **1984**, *25*, 2823-2824.
69. J. M. Brown, G. C. Lloyd-Jones, *Tetrahedron: Asymmetry* **1990**, *1*, 869-872.
70. H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007-1019.
71. D. Sartor, J. Saffrich, G. Helmchen, *Synlett* **1990**, 197-198.
72. M. Takasu, H. Yamamoto, *Synlett* **1990**, 194-196.
73. D. Sartor, J. Saffrich, G. Helmchen, C. J. Richards, H. Lambert, *Tetrahedron: Asymmetry* **1991**, *2*, 639-642.
74. E. J. Corey, T.-P. Loh, *J. Am. Chem. Soc.* **1991**, *113*, 8966-8967.