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Chiral 1,3,2-oxazaborolidines in asymmetric synthesis: recent advances

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Abstract. The use of chiral 1,3,2-oxazaborolidines in asymmetric organic synthesis, particularly, in enantioselective reduction of ketones, imines and oxime ethers, asymmetric Diels – Alder reactions, aldol condensation and atroposelective reduction of lactones is reviewed. Reactions of immobilised 1,3,2-oxazaborolidines are also considered. The bibliography includes 266 references.

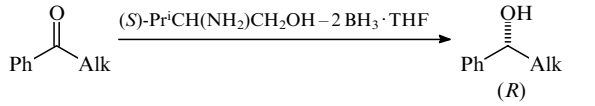
I. Introduction

Enantioselective reduction of ketones, imines and oximes by boranes in the presence of chiral catalysts, *viz*., 1,3,2-oxazaborolidines, is one of the most convenient methods for the preparation of enantiomerically enriched secondary alcohols and amines. This rapidly developing research area has been the subject of numerous reviews;[1–7] however, early papers [1–4] encompass the literature published before 1993, and the review of 1998 [5] and some selected chapters in monographs [6,7] are devoted exclusively to enantioselective reduction of ketones using Corey – Bakshi – Shibata catalysts (CBS catalysts).

A great number of papers concerned with this problem have been published recently. Some papers report on the possible use of chiral 1,3,2-oxazaborolidines as Lewis acids, which significantly expands the area of application of these derivatives in synthetic organic chemistry. We undertook an attempt to systematise the results of investigations carried out in this field in the past decade (references to earlier publications having fundamental significance are also given).

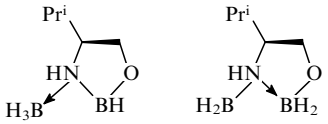
II. 1,3,2-Oxazaborolidines as catalysts of enantioselective reduction of ketones

This trend in asymmetric synthesis dates back to 1981 when Itsuno [6–10] reported the reduction of prochiral ketones by an (*S*)-valinol – $BH_3 \cdot THF$ mixture (1 : 2) to optically active secondary alcohols in up to 100% yields and with enantiomeric excess (*ee*) up to 73%.[8]



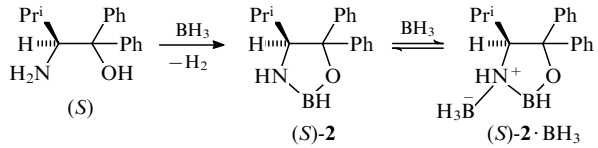
Alk = Me, Et, Pr, Bu. (*ee* 49% – 73%)

According to Itsuno, this reaction is catalysed by 1,3,2-oxazaborolidine (**1**) (form **A** or **B**).



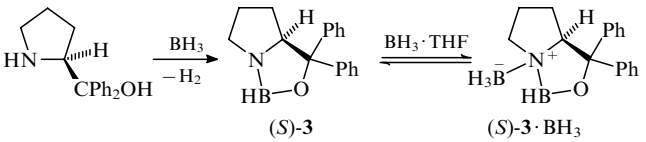
1A **1B**

Later, Corey showed [11] that hydrogen (2 equiv.) is released in the reaction of (*S*)-diphenylvalinol with 2 equiv. of borane in THF at 35 °C. On removal of residual amounts of borane and the solvent in vacuum and twofold distillation of the residue (105 – 130 °C, 0.05 Torr), a colourless crystalline compound with a molecular mass of 265.16365 (265.16379, according to the mass spectrometric data) was obtained. This compound was formulated as **2** · BH_3.



According to X-ray diffraction analysis data of this compound, this exists in the form **A**.

The same group of investigators have succeeded in obtaining 1,3,2-oxazaborolidine **3** · BH_3 and its *B*-methyl derivative.[12]



It was shown that (*S*)-perhydro-3,3-diphenylpyrrolo-[1,2-*c*][1,3,2]oxazaborolidine-borane [(*S*)-**3** · BH_3] and its

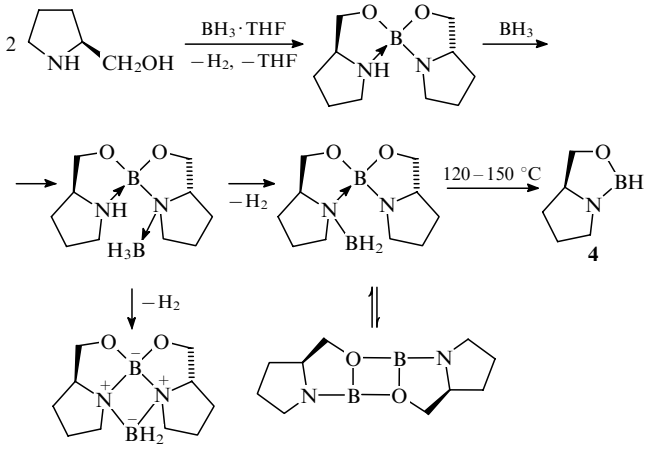
V A Glushkov, A G Tolstikov Institute of Technical Chemistry, Urals Branch of the Russian Academy of Sciences, ul. Lenina 13, 614990 Perm, Russian Federation. Fax (7-3422) 12 62 37. Tel. (7-3422) 39 63 10. E-mail: chemist@mpm.ru (V A Glushkov). Tel. (7-095) 420 21 43. E-mail: tagtolst@presidium.ras.ru (A G Tolstikov)

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B-methyl derivative catalyse enantioselective reduction of ketones even more efficiently than (*S*)-4-isopropyl-5,5-diphenyl-1,3,2-oxazaborolidine-borane [(*S*)-**2**·BH_3] and reduce acetophenone to (*R*)-1-phenylethanol in more than 99% yield and *ee* 97%.[12,13] The structure of the *B*-methyl derivative was studied by X-ray diffraction analysis.[14]

In the general case, synthesis of 1,3,2-oxazaborolidines containing a B–H bond is accompanied by the formation of various dimers (Scheme 1); this was confirmed by ^{11}B NMR spectroscopy (see Refs 15–17) and X-ray diffraction analysis.[16]

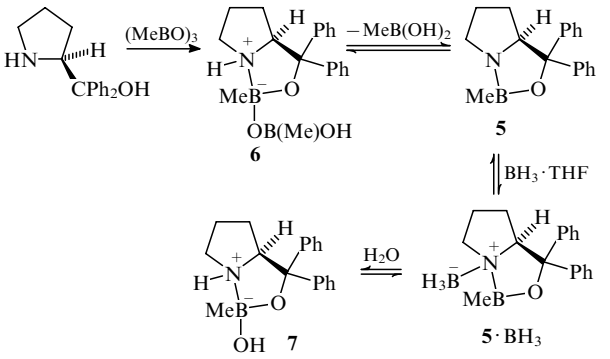
Scheme 1



Whereas the ^{11}B NMR spectrum of compound **2** (THF, 23 °C)[11] contains a broad signal at δ 28.1 (relative to $Et_2O \cdot BF_3$, external standard), the ^{11}B NMR spectrum of compound **3** (0.17 M solution in THF, 23 °C) contains signals at δ 28.3 and 7.6, which were assigned to the monomer and the dimer, respectively. The dimers are converted into monomers (*e.g.*, **4**) upon heating; therefore, the procedure used for the synthesis of substituted 1,3,2-oxazaborolidine plays a crucial role in the catalytic reduction of carbonyl compounds (for temperature regime and the solvent see below).

Methyl-substituted 1,3,2-oxazaborolidine **5** was prepared using two approaches, *viz*., starting from methylboronic acid[13] and from trimethylboroxine.[18] The presence of additional signals in the ^{11}B NMR spectra in 1,3,2-oxazaborolidine (*S*)-**5** prepared from (*S*)-diphenylprolinol and trimethylboroxin is explained by the formation of side products of the type **6** and **7** (Scheme 2).[18]

Scheme 2

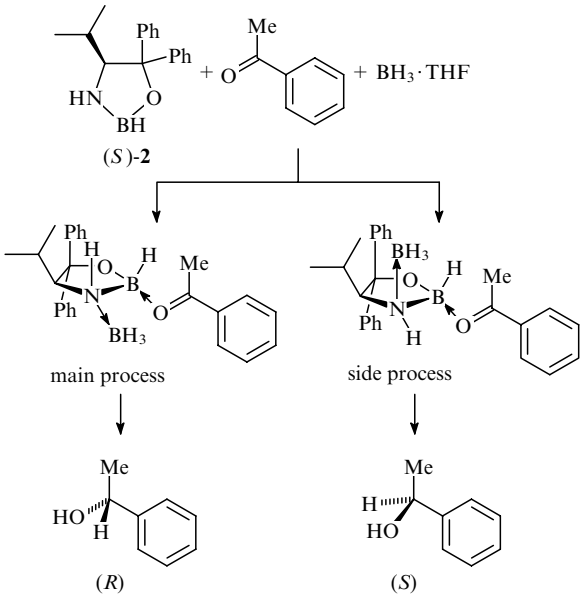


In contrast to compounds **2** and **3**, compound **5** is more resistant to the action of atmospheric oxygen,[13] but undergoes hydrolysis in the presence of moisture. It is of note that all 1,3,2-oxazaborolidines undergo hydrolysis, therefore, all manipulations with these compounds demand thorough dehydration of the solvents.

1. The reduction mechanism

The mechanism of reduction of acetophenone by the complex (*S*)-**2**·BH_3 is shown in Scheme 3.

Scheme 3



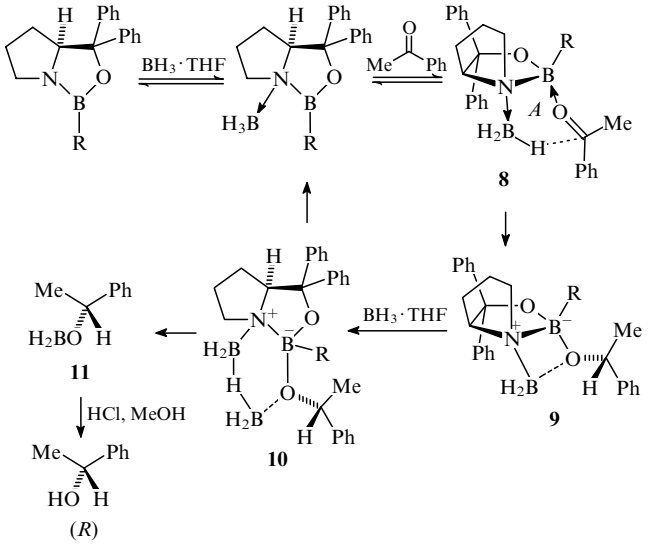
Of fundamental importance is the fact that 1,3,2-oxazaborolidine **2** itself does not reduce ketones and becomes active only after addition of the second equivalent of borane.[11] During the formation of a catalytic complex, borane coordinates the nitrogen atom of 1,3,2-oxazaborolidine in such a way that it itself comes to occupy the *trans*-position relative to the isopropyl group; the *cis*-position of borane results in a steric strain in the complex. Subsequent coordination of acetophenone and the hydride ion transfer also proceed in a stereospecific manner to afford (*R*)-1-phenylethanol with high *ee* (up to 99%). The stereospecificity of the CBS catalyst is comparable to that of enzymes; therefore, Corey termed it 'chemzyme' (a chemical catalytic system similar to an enzyme).[19] If a catalyst based on an (*R*)-amino acid is used, the reduction of a ketone results in an (*S*)-alcohol. The possibility of control over stereoselectivity is an attractive feature of reductions based on the use of the CBS catalysts.

A mechanistic model of the reaction of an active catalytic complex with a substrate has been developed in order to explain high stereospecificity of ketone reduction.[5–7] Let us consider the mechanism of ketone reduction in which (*S*)-diphenylprolinol is used as a catalyst in more detail (Scheme 4).

This model implies a multistep reduction mechanism of acetophenone. In the first step, a catalytically active complex of 1,3,2-oxazaborolidine with BH_3 is formed. The coordination of the nitrogen atom by borane strongly increases the Lewis acidity of the boron atom of the heterocycle[5] as a result of which it acquires the ability to coordinate the carbonyl group of acetophenone. This is followed by the hydride ion transfer from the boron atom of borane to the carbon atom of the carbonyl group (direct reduction).

It was suggested that coordination of a ketone affords a transition state (complex **8**) with a six-membered quasi-heterocycle *A* where the bulkier ketone substituent (the phenyl radical) occupies an equatorial position. In other words, the boron atom of the 1,3,2-oxazaborolidine ring coordinates the electron pair of the oxygen atom of the ketone occupying the *anti*-position relative to the phenyl group, which ensures high enantioselectivity of the reduction similar to that in enzyme systems.[5] This hypothesis was also confirmed by the results of quantum-chemical calculations.[20–25]

Scheme 4



R = H, Me.

The last step includes the decomposition of the complex **9** (presumably, *via* the intermediate complex **10**) resulting in the original catalytically active complex and the ester **11**. The latter is converted into the final product, *viz*., (*R*)-1-phenylethanol.

The conformation of the transition state was also considered. According to semi-empirical MNDO calculations, the transition state **8** where the heterocycle *A* acquires a chair conformation possesses much lower energy than in the case of a boat conformation.[20] A detailed analysis of *ab initio* quantum-chemical calculations of various conformations of all the transient species **8**–**11** in the basis sets 3-12G, 4-13G, 6-31G, 4-31G* and 6-31G* has been carried out.[23–27] The transition state **8** has two stable conformations, *viz*., *twist-boat* and *twist-chair*.[24]

According to quantum-chemical calculations,[21] the potential energy of the formation of the transition state **8** (coordination of the ketone) was similar to that of the transition state **9** (the hydride ion transfer), and the kinetic isotope effect k_H/k_D = 1.8 (23 °C) calculated for the reduction of acetone by the complex (*S*)-**5**·BH_3 virtually coincided with the experimental value k_H/k_D = 1.7 for the reduction of acetophenone.[28] It was therefore supposed that the hydride ion transfer is the rate-determining step.[28] The kinetics of reduction of *para*-substituted acetophenones was studied in order to establish the limiting step of the overall catalytic process. The rate ratios for the reduction of *p*-nitro- and *p*-methoxy acetophenones to that of non-substituted acetophenone were 3.4 and 1.8, respectively.[28] This suggests that the hydride ion transfer step, like the ketone complex formation with the catalyst, controls the rate of the overall process.[5]

The formation of the transient species of the types **8, 9** and **10** was also confirmed by ^{11}B NMR spectroscopy.[29]

2. Structural types of 1,3,2-oxazaborolidines

Further perfection of structures of catalysts of enantioselective reduction of ketones (CBS catalysts) followed several routes. These involved modification of the rigid skeleton of a chiral amino alcohol and selection of substituents in the alcoholic group of the starting amino alcohol † and at the boron atom of the borane. Thus Bu-substituted 1,3,2-oxazaborolidine (**12**) was synthesised along with the Me-substituted catalyst **5**.[30]

The dependence of enantioselectivity of the reduction using CBS catalysts on the nature of the substituent at the HO-bearing carbon atom of the amino alcohol has been reviewed.[5–7] Bulky substituents provide stereochemical control over the reaction, but hinder the complexation of the ketone with 1,3,2-oxazaborolidine. Besides, they decrease the optical yields due to competitive non-catalytic reduction. In some cases, bulky substituents 'reverse' the selectivity so that *S*-enantiomers are formed instead of *R*-enantiomers.

The dependence of enantioselectivity on the nature of the substituent R at the boron atom has been studied. It should be noted that in terms of the mechanistic model of the transition state **8** (see Scheme 4) the steric strain between the substituent R at the boron atom and the substituents at the carbonyl group of the ketone is critical for the discrimination between different types of ketone coordination. Thus the presence of bulky aromatic substituents at the boron atom favours their steric interactions with more remote fragments of a coordinated ketone molecule,[5] as a result of which the enantioselectivity of reduction increases considerably. Thus, in each concrete case the choice of an optimum substituent R at the borane B atom should depend on the nature of the substrate (ketone). However, it is 1,3,2-oxazaborolidines carrying H-, Me- and Bu-substituents at the boron atom that are commonly used as catalysts because of the ease of their preparation.

A representative set of CBS catalysts based on various chiral amino alcohols is listed in Table 1. Natural amino acids or their analogues served as starting compounds in the synthesis of many of these catalysts.[27,35–38] The results presented in Table 1 were obtained for catalytic variants of the reaction, *viz*., the reduction of a ketone by 0.6–1.0 equiv. of $BH_3 \cdot THF$ or $BH_3 \cdot Me_2S$ in the presence of 0.05–0.10 equiv. of a catalyst (1,3,2-oxazaborolidine), although in some cases the catalyst, the reducing agent and the substrate were used in equal amounts in order to ensure higher enantioselectivity. The amount of the reducing agent (borane) is usually 0.6–0.7 equiv. per carbonyl group of the ketone, since 2 equiv. of the hydride ion are transferred.[5–7] The chemical yields of secondary alcohols are usually > 90%.

The majority of papers devoted to enantioselective reduction of ketones describe the reduction of acetophenone. As can be seen from Table 1, 1,3,2-oxazaborolidines **26** and **30** based on prolinol derivatives are the best catalysts for the acetophenone reduction.

The use of catalysts based on phenylalanine in the enantioselective hydrogenation of acetophenone also gives good results, the catalyst based on *o*-chlorophenylalanine **15** manifesting somewhat higher enantioselectivity in comparison with its unsubstituted analogue **14**. Presumably,[36] this is due to the formation of an additional coordination bond between the boron and chlorine atoms.

1,3,2-Oxazaborolidines **13** and **51** based on two diastereomers of 2-amino-1,2-diphenylethanol effectively catalyse the reduction of many carbonyl compounds (see, *e.g*., Refs 34 and 71), whereas the catalyst **48** based on 2-amino-1,1,2-triphenylethanol (R = Me) was found to be suitable for the reduction of alkyl methyl ketones[66] (*ee* of the product is 70%).

The catalysts based on diastereomeric 1-aminoindan-2-ols (compounds **27** and **39**)[47–49,59,61,71] and 1-amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene **41**,[60] as well as on spiro derivatives (**28**–**31**, **55**) also appeared to be highly efficient.[50,51,68,69]

As can be seen from Table 1, the use of the catalyst **49** based on norephedrine for the reduction of tetralone gives good results,[27,67] while its analogue **50** prepared from pseudo-ephedrine is ineffective.[27] The catalyst **46** containing a 1-naphthyl group is less active in the reduction of butyrophenone than the catalyst **47** containing a 2-naphthyl group.[65] It was noted that the stereoselectivity of the reaction increases upon introduction of the 2-naphthyl group into the carbon atom of the C–O fragment of 1,3,2-oxazaborolidine.[19] The catalysts **18** and **38** with aziridine[39] and azetidine[58] rings, respectively, manifested higher activities than the catalyst **19** with the pyridine ring.[40] The enantioselectivity of the reduction in the case of the catalyst **23** is lower than that

† The starting (*S*)- and (*R*)-diphenylprolinols commonly used in the synthesis of 1,3,2-oxazaborolidines can be prepared by different methods (see, *e.g*., Refs 13, 31–33).

Table 1. Catalytic enantioselective reduction of carbonyl compounds (in THF).

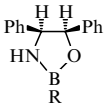
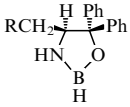
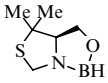
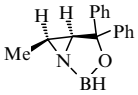
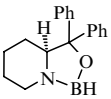
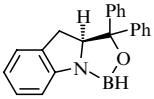
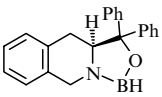
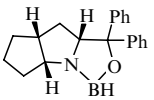
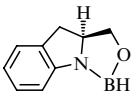
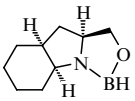
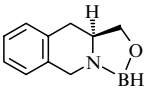
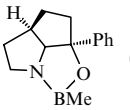
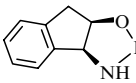
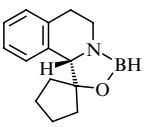
Ketone	Catalyst	Amount of the catalyst [a]	Amount of the reducing agent [a]		T /°C	Configuration of the alcohol	*ee* (%)	Ref.
			$BH_3 \cdot THF$	$BH_3 \cdot Me_2S$				
PhC(O)Me	 (**13**, R = Me)	0.1		0.7	25	*R*	92	34
	 (**14**, R = Ph)	0.05		0.7	25	*R*	82	35
	(**15**, R = C_6H_4Cl-*o*)	0.1	excess		30	*R*	94.6	36
	(**16**, R = SPh)	0.1	1		50 – 65	*R*	74.5	37
	 (**17**)	1	1		25	*S*	84	38
	 (**18**)	0.05		1 [b]	25	*R*	94	39
	 (**19**)	0.1	0.6		0	*R*	87	40
	 (**20**)	0.1	excess		30	*R*	91	41
	 (**21**)	0.1	1.1		50	*R*	51	42
	 (**22**)	0.1	1		25	*S*	61	43
	 (**23**)	0.1		1.1	25	*R*	59	44
		0.1		1.1	25	*R*	8	41
		0.1		1.1	25	*R*	82	45
	 (**24**)	0.1	1		25	*S*	90	45
	 (**25**)	0.1	1.1		50	*R*	71	42
	 (**26**)	0.1	0.6		0	*R*	98	46
	 (**27**, R = H)	0.1		0.6	25	*S*	88	47
	(**27**, R = Me)	0.1	2		0	*S*	84	48, 49
	 (**28**)	0.05	1		30	*R*	88	50

Table 1 (continued).

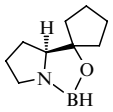
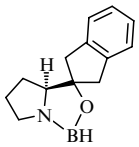
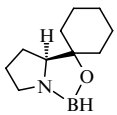
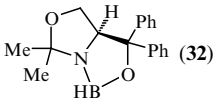
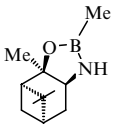
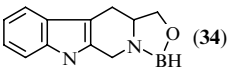
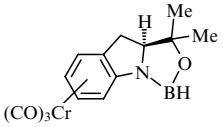
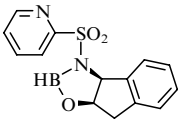
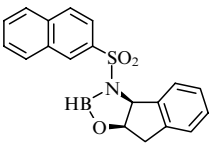
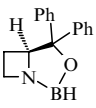
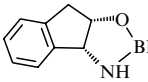
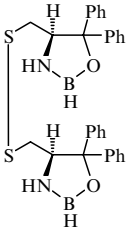
Ketone	Catalyst	Amount of the catalyst [a]	Amount of the reducing agent [a]		T /°C	Configuration of the alcohol	*ee* (%)	Ref.
			$BH_3 \cdot THF$	$BH_3 \cdot Me_2S$				
PhC(O)Me	 (**29**)	0.16	excess		0	*S*	67	51
	 (**30**)	0.16	"		0	*S*	96	51
	 (**31**)	0.16	"		0	*S*	71	51
	 (**32**)	0.2	1.1 [c]		20	*R*	49	52
	 (**33**)	0.1		0.6	0–5	*R*	93	53, 54
	 (**34**)	0.1	0.6		50	*R*	88	55
	 (**35**)	0.1	excess		25	*R*	20	56
	 (**36**)	0.1		1	40	*R*	80	57
	 (**37**)	0.1		1	40	*R*	24	57
$PhC(O)CH_2Cl$	**5**	0.5	0.5		30	*S*	97	11
	 (**38**)	0.1	0.6		23	*S*	97	58
	 (**39**, R = H)	0.1		1	0–25	*S*	92	59
	(**39**, R = Me)	0.1	0.8		0	*S*	94	49
$PhC(O)CH_2Br$	 (**40**)	0.05	1		50–65	*S*	87	37

Table 1 (continued).

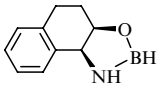
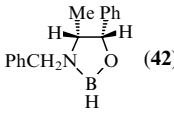
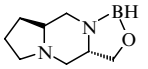
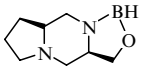
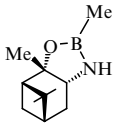
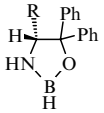
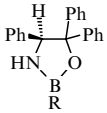
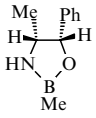
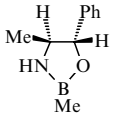
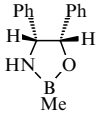
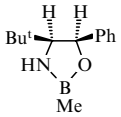
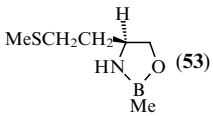
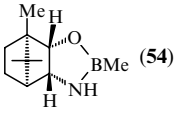
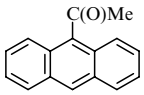
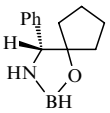
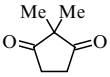
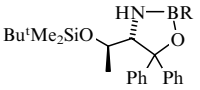
Ketone	Catalyst	Amount of the catalyst [a]	Amount of the reducing agent [a]		T /°C	Configuration of the alcohol	*ee* (%)	Ref.
			$BH_3 \cdot THF$	$BH_3 \cdot Me_2S$				
$PhC(O)CH_2Br$	 (**41**)	0.05		0.65	25	*S*	90	60
	27 (R = Me)	0.1	2		0	*R*	96	61
m-$ClC_6H_4C(O)CH_2Br$	 (**42**)	0.05	1		0	*R*	91	62–64
PhC(O)Et	**1**	1.25	1.25		30	*R*	61	9
	2	1.25	1.25		30	*R*	94	10
	 (**43**)	0.2	1.1 [c]		20	*S*	78	52
	 (**44**)	0.2	1.1 [c]		20	*S*	58	52
	 (**45**)	0.1		0.6	0–5	*S*	92	53, 54
$PhC(O)Pr^n$	 (**46**, R = 1-naphthyl)	0.05	1		39	*S*	58.6	65
	(**47**, R = 2-naphthyl)	0.05	1		39	*S*	100	65
$PhC(O)Pr^i$	**44**	0.2	1.1 [c]		20	*R*	29	52
$MeC(O)Bu^n$	 (**48**, R = Me)	0.1		1.2	0	*S*	70	66
	 (**49**)	0.05		0.7	25	*S*	94	27, 67
	 (**50**)	0.05		0.7	25	*S*	2	27
	 (**51**)	0.1		0.7	25	*R*	94	34
	 (**52**)	0.05		0.7	25	*R*	82	27
	 (**53**)	0.05		0.7	25	*R*	36	27
	 (**54**)	0.05		0.7	25	*R*	78	27

Table 1 (continued).

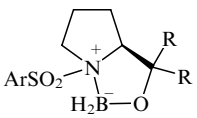
Ketone	Catalyst	Amount of the catalyst [a]	Amount of the reducing agent [a]		T /°C	Configuration of the alcohol	*ee* (%)	Ref.
			$BH_3 \cdot THF$	$BH_3 \cdot Me_2S$				
	 (**55**)	0.1	0.9		30	*S*	90	68
 (1*R*,4*R*)	**55**	0.1	1		30	see [d]		69
	 (**56**, R = Me) [e]	1	5		0–25	see [f]	>99	70
$PhC(O)CH_2OSiMe_2Bu^t$	**13** (R = H)	0.1	0.6		25	*S*	74	71
	48 (R = H)	0.1	0.6		25	*S*	52	71
	27 (R = H)	0.1	0.6		25	*S*	84	71

[a] The amount of the catalyst and the reducing agent is expressed in equiv. (equiv. of ketone)$^{-1}$; [b] The reaction is carried out in toluene; [c] The reaction is carried out in the presence of 0.2 equiv. of diethylaniline; [d] A mixture of (1*R*,2*R*,4*R*) and (1*R*,2*S*,4*R*) isomers (6 : 94) was obtained; [e] For other reactions with this catalyst, see Refs 72 and 73; [f] A mixture of *dl*- and *meso*-isomers with predominance of the *dl*-isomer (*dl* : *meso* > 99 : 1) was obtained.

with its diphenyl-substituted (**20**) and fully hydrogenated (**24**) analogues.

A search for cheap and renewable sources of raw materials for the commercial production of CBS catalysts has stimulated the synthesis of 1,3,2-oxazaborolidines **33**, **45** and **54** from chiral amino alcohols of the terpene series which gave encouraging results (*ee* 80%–93%).[27, 53, 54] An attempt to increase *ee* by replacing 1,3,2-oxazaborolidines by their chromotricarbonyl complexes [56] was unsuccessful (*cf*. *ee* obtained in the presence of the catalysts **35, 20** and **23**).

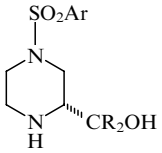
Considerable recent interest in sulfonylated 1,3,2-oxazaborolidines is explained by their higher stabilities and ease of purification and regeneration in comparison with the classical CBS catalysts. It is believed that these catalysts form more stable complexes owing to additional coordination of the hetero atom to the boron atom within the catalytic complex.[57] For example, *N*-arylsulfonylated (*S*)-diphenylprolinol is a good catalyst for the reduction of bromoacetophenone. When the reaction is carried out in boiling toluene, the yield of (*R*)-2-bromo-1-phenylethanol is 96% (*ee* is 91%).[74] This suggests that the amino alcohol reacts as the complex (**57**).



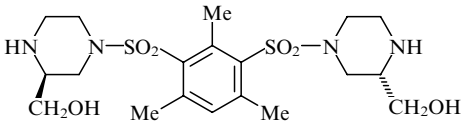
57

R = H: Ar = *p*-MeC_6H_4, 1-naphthyl, 2-naphthyl, 2,4,6-$Pr^i_3C_6H_2$;
R = Ph: Ar = *p*-MeC_6H_4.

It is believed that in the case of enantiomerically pure 2-hydroxymethylpiperazines (**58** and **59**) as catalysts, the formation of dimeric 1,3,2-oxazaborolidines takes place.[75]



58



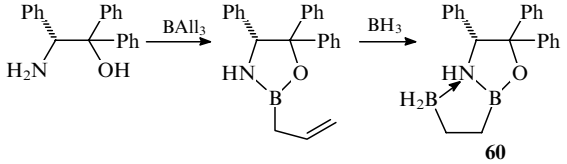
59

R = H, Ph; Ar = *p*-MeC_6H_4, 1-naphthyl, 2-naphthyl, 2,4,6-$Pr^i_3C_6H_2$.

1,3,2-Oxazaborolidine prepared from compound **59** catalyses the reduction of acetophenone to (*S*)-2-phenylethanol with *ee* 71%.

Dimeric 1,3,2-oxazaborolidines are presumably also formed in the reduction by (1*R*,4*R*,2*S*,3*S*)-1,4-diamino-1,4-dibenzylbutane-2,3-diol and BH_3.[76]

The formation of the original chelate 1,3,2-oxazaborolidine **60** has been reported:[66]



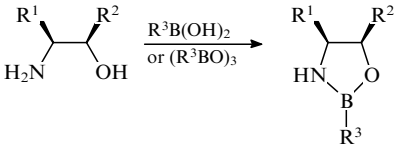
60

The reduction of acetophenone by borane in the presence of binary mixtures of homochiral amino alcohols (1*S*,2*R*)-1-amino-2-indanol, (*S*)-prolinol and (*S*)-phenylglycinol has been studied.[77]

On the whole, the analysis of literature data suggests that the relatively accessible catalysts for ketone reduction, 1,3,2-oxazaborolidines **3** and **5** based on (*S*)-diphenylprolinol recommended by Corey are the most efficient.[5, 11–13] The use of other boron-substituted (*S*)-diphenylprolinol-based 1,3,2-oxazaborolidine derivatives in the reduction of ketones has recently been reported. All these catalysts manifest high enantioselectivity in the reduction of various carbonyl compounds and are successfully used in asymmetric Diels–Alder reactions, aldol condensation, enantioselective cleavage of acetals, *etc*. (see below).

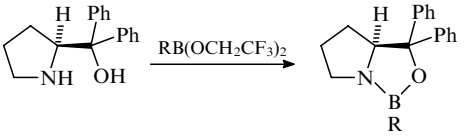
3. Effects of the catalyst preparation procedure, temperature, solvent and reducing agent on the enantioselectivity of the ketone reduction

The purity of a catalyst was shown [5,7,18,33,76] to be of crucial importance for obtaining high *ee* in the enantioselective catalytic reduction of carbonyl compounds. The presence of admixtures of starting amino alcohols and boronic acids decreases *ee*. Some CBS catalysts are available from Aldrich and Lancaster, but the catalysts do not always meet necessary requirements.[18,78] Their application in laboratory practice gives irreproducible results due to high content of admixtures and poor storage stability.[78] Therefore, the preparation of a catalyst is a key step in the reduction. 1,3,2-Oxazaborolidines can be prepared using various approaches, *e.g.,* (a) by reactions of amino alcohols with 3 equiv. of $BH_3 \cdot THF$ or $BH_3 \cdot Me_2S$ in an argon atmosphere in boiling THF or toluene with a subsequent removal of the solvent *in vacuo* (the product formed is used without additional purification [7–10] or is purified by sublimation [11–13]); (b) boiling of an amino alcohol with the corresponding alkylboronic acid $RB(OH)_2$ in toluene with azeotropic distillation of water formed;[30] (c) boiling of an amino alcohol with boroxine $(RBO)_3$ [18,27,30] in toluene in the presence of molecular sieves 3–5 Å with azeotropic distillation of water formed.



R^1, R^2 = Alk, Ar; R^3 = Me, Bu, Ar.

In many cases, the catalyst is prepared *in situ* by mixing an amino alcohol with $Me_2S \cdot BH_3$ or $BH_3 \cdot THF$ at room temperature, which is especially convenient for the synthesis of 1,3,2-oxazaborolidines non-substituted at the boron atom based on non-cyclic amino acid derivatives. An express method for the synthesis of 1,3,2-oxazaborolidines with a substituted boron atom (1 h) has been developed.[79] In this approach, the amino alcohol is mixed with bis(2,2,2-trifluoroethyl) alkylboronate in toluene. Subsequent vacuum evaporation of toluene, trifluoroethanol and the excess of $RB(OCH_2CF_3)_2$ and heating (110 °C, 0.07 Torr) give pure 1,3,2-oxazaborolidine.



R = Alk, Ar. (*S*)

As mentioned above, special care should be taken over the removal of traces of moisture from the catalyst, reagents and solvents, since water decomposes the 1,3,2-oxazaborolidine ring.[33] It was found [61] that the addition of 2.5 mg of H_2O per g of bromoacetophenone decreases *ee* of the (*R*)-1-phenyl-2-bromoethanol formed from 96% to 85%, while the addition of 10 mg of H_2O per g of the substrate decreases it to 50%. The content of H_2O in the reaction mixture should not exceed 40 μg ml^{-1} at the ketone concentration of 70 mg ml^{-1} (see Ref. 78), while the maximum *ee* is reached at the H_2O content not exceeding 20 μg ml^{-1} (see Ref. 18). Contrariwise, the addition of propan-2-ol or any other aliphatic alcohol increases *ee*,[80,81] which suggests its involvement in the decomposition of the intermediates **9** and **10** (see Scheme 4).

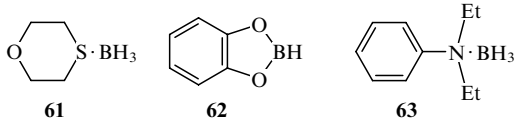
The effect of temperature on the enantioselectivity of the reduction has been considered in several publications.[76,82,83] The dependence of *ee* on temperature is usually described by a curve with a maximum at 30–50 °C, which is typical of catalysts prepared *in situ*. At temperatures below −30 °C, 1,3,2-oxazaborolidine is formed at a very slow rate, the reaction mixture contains many catalytically inactive components and non-selective reduction of the carbonyl compound by borane predominates.[5] The low values of *ee* observed at temperatures exceeding the optimum temperature corresponding to the maximum value of *ee* can be explained by thermal decomposition of the catalytic complex. Thus compound **5** is decomposed at 124–126 °C with liberation of B_2H_6.[18]

However, there is still no unambiguous answer to the question of the effect of temperature on the value of *ee*. In some cases, high values of *ee* were obtained when the reaction was carried out in toluene at temperatures below −10 °C with additional amounts of a freshly prepared catalyst $\mathbf{5} \cdot BH_3$ added to the reaction mixture in the course of the reduction.[18,78] In others, the highest values were reached when the reaction was performed in boiling toluene.[15,74] This suggests that the optimum temperature should be selected in each concrete case and for each concrete catalyst.

The value of *ee* also depends on the rate of addition of the ketone and the nature of the solvent. The lower the rate of ketone addition the higher the *ee*. In some solvents favouring coordination of borane (*e.g.*, THF) only 10% of the catalyst is involved in the complexation with BH_3. This factor should also be taken into consideration in the optimisation of reduction processes.[18]

As a rule, high enantioselectivity is attained in the presence of as little as 0.05–0.1 equiv. of the $BH_3 \cdot Cat$ complex (Cat is 1,3,2-oxazaborolidine) with respect to the substrate (ketone). However, in some cases the optical yield of the target product depends on the amount of the catalyst used. Thus the value of *ee* for (*R*)-1-phenylethanol in the reduction of acetophenone by the complex $BH_3 \cdot THF$ in the presence of the catalyst **4** increases from 63% and 89% to > 95% as the concentration of the catalyst is increased, correspondingly, from 2 mol.% and 4 mol.% to 10 mol.%.[15]

Other reducing agents, *e.g.*, the borane complex with 1,4-thioxane (**61**),[83] catecholborane (**62**) and the *N,N*-diethylaniline complex with borane (**63**), are used along with $BH_3 \cdot THF$ and $BH_3 \cdot SMe_2$ in the reduction of ketones. Compounds **61**–**63** are less reactive than $BH_3 \cdot THF$ and $BH_3 \cdot SMe_2$, however in some cases they give better results.



61 **62** **63**

Thus the use of catecholborane **62**, which does not require any additional ligands for its stabilisation, allows highly enantioselective reduction of ketones in non-coordinating solvents (*e.g.*, toluene, CH_2Cl_2).[5,30] This reagent was used in the reduction of trihaloketones,[73,84] α,β-enones [85] and oxophosphonates [86] as well as in the preparation of (3*S*)-2,3-epoxysqualene [87] and non-natural amino acids.[88] If the reaction is carried out at −78 °C and lower temperatures, the reduction of carbonyl compounds occurs without the involvement of other functional groups (C=C, C≡C) sensitive to hydroboration under ordinary conditions.[5]

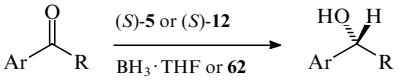
In some cases, enantioselectivity can be increased if tertiary amines are added to the reaction mixture.[38,52,70] The catalytic reduction of aromatic ketones by oxazaborolidines prepared *in situ* from amino alcohols and borane complexes with tertiary amines has been studied.[89] Thus the reduction of acetophenone by the complex **63** in the presence of the catalyst **3** has made it possible to increase *ee* of (*R*)-1-phenylethanol to 99% (see Refs 90 and 91).

The *ee* of the product also depends on the presence of admixtures in commercial reducing agents. According to most recent reports,[92] the admixtures of $NaBH_4$ added to the commercial reagent $BH_3 \cdot THF$ for its stabilisation favour non-catalytic reduction and thus decrease *ee* of the reduction product. It is recommended to use the reverse order of addition of reagents to increase *ee*, *e.g.*, to add ketone to the catalyst and the reducing agent.[92] This should also be taken into consideration in those

cases where borane is synthesised *in situ* using the $I_2 - NaBH_4$ (see Ref. 89) or the $Me_3SiCl - NaBH_4$ system.

4. Examples of reduction of carbonyl compounds

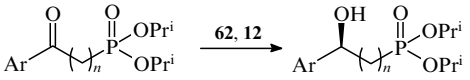
Let us consider some characteristic features of enantioselective reduction of carbonyl compounds (particularly those not listed in Table 1) in more detail. The reduction of aromatic ketones by $BH_3 \cdot THF$ or catecholborane (**62**) in the presence of catalysts [(*S*)-**5** or (*S*)-**12** based on (*S*)-diphenylprolinol] has been studied in especially great detail.



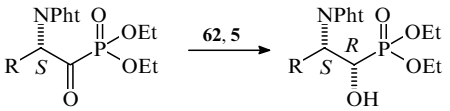
R = CH_2Cl,[82,90] CH_2Br,[90,93,94] CH_2OTHP (THP is tetrahydropyranyl),[95] CH_2N_3 (*ee* 91% – 100%),[96] $(CH_2)_nC(O)R$ (R = Me, Bu^t, Ph; *n* = 0 – 4, both carbonyl groups are reduced simultaneously),[97] CH_2SO_2Ar,[98] $(CH_2)_nP(O)(OPr^i)_2$ (*n* = 1, 2),[86,99] CF_3,[57,84] CCl_3;[28,84,88] Ar = Ph, *m*(*p*)-$R'C_6H_4$ (R′ = Alk, Hal),[100–103] α(β)-$C_{10}H_7$ *etc*.

A large body of experimental evidence has made it possible to formulate a general rule, *viz*., the greater the difference in the size (steric discrimination) between the Ar and R groups the higher the *ee* in enantioselective reduction of ketones.[5–7] The enantioselectivity of reduction of acetophenone, propiophenone and other alkyl aryl ketones by boranes is rather high (*ee* is 94% – 98%, see Table 1).

In the presence of the catalyst **12**, catecholborane reduces α-, β- and γ-oxophosphonates to α-, β- and γ-hydroxy phosphonates (*ee* 51% – 99%) depending on the nature of the substituents in the aromatic nucleus (it is of note that the phosphonate group is considered to be bulkier than the aromatic radical).[86] 1-Oxo-(2*S*)-phthalimidophosphonates are reduced by catecholborane exclusively to (1*R*)-hydroxy-(2*S*)-phthalimidophosphonates (yields 63% – 77%).[99]

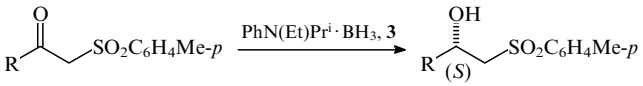


Ar = Ph, XC_6H_4 (X = Hal, Me, OMe); *n* = 0 – 2.



R = $PhCH_2$, Pr^iCH_2, Me, *p*-$BnOC_6H_4CH_2$; Pht is phthalimido.

In contrast to oxophosphonates, the arylsulfonyl group of β-oxosulfones is considered to be less bulky than the aromatic residue; such compounds are usually reduced by borane in the presence of the catalyst **3** to give (*S*)-enantiomers of β-hydroxy sulfones.[98]



(*ee* 97% – 99%)

R = Ar, Alk.

$BH_3 \cdot THF$ (in the presence of the catalyst **5**)[100] and catecholborane **62** [in the presence of the catalyst **3** generated *in situ* from (*S*)-diphenylprolinol and $NaBH_4 - Me_3SiCl$] were used for the reduction of 2-acetylnaphthalene.[101] The *ee* of naphthylethanol formed was 96% – 98%. Efficient reduction of cyclic ketones, such as 1-tetralone (see Table 1), 1-indanone[18] and 1-suberone, also occurs under similar conditions.[18]

If the substrate to be reduced contains a nitro group[104] or other functional groups able to coordinate the boron atom,[105] the reducing agent should be used in larger amounts, an additional equivalent should be added. Chiral alcohols containing a heterocyclic substituent were prepared from 2-acylfurans,[16,106] 3-acetylpyridine[5] and 2-acylthiophenes.[96,106]

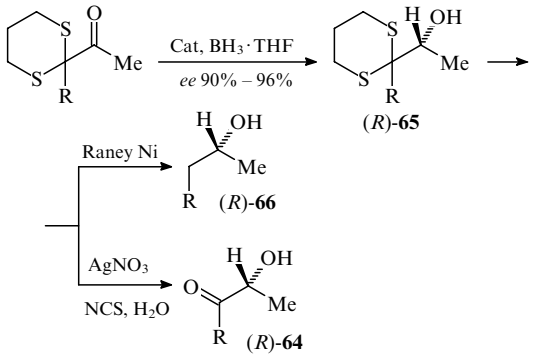
The reduction of substituted benzophenones[104] and 2-benzoylpyridinium triflates[107] yields optically active benzhydrols. It was found that the introduction of substituents into the *ortho*-position of the aromatic nucleus of alkyl aryl ketones (MeCOAr and EtCOAr) decreases the *ee* of the alcohols formed upon their reduction by the system $BH_3 \cdot Me_2S$ in the following order: Ph > *o*-Tol > Mes.[108]

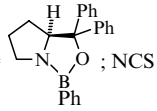
Modest enantioselectivity was achieved in the reduction of aliphatic ketones: high values of *ee* were obtained only for sterically hindered ketones where the spatial difference between two alkyl substituents was high enough. Thus the reduction of isopropyl methyl ketone and *tert*-butyl methyl ketone gave the corresponding alcohols with *ee* 91% and 93% – 97.3%, respectively.[13,66,90] High values of *ee* (99%) were also obtained in the reduction of cyclohexyl methyl ketone by the complex **63**.[90]

It is of note that the reduction product of cyclopropyl isopropyl ketone has a configuration in which the cyclopropyl group plays the role of a bulky substituent (R_L) and the isosteric isopropyl group acts as a minor substituent (R_S).[5] This can be attributed to the fact that the cyclopropyl group is a more potent electron donor than the isopropyl group; therefore, the former increases the electron density of the free electron pair of the carbonyl group which is in the relative *anti*-position (the intermediate **8** in Scheme 4).[104]

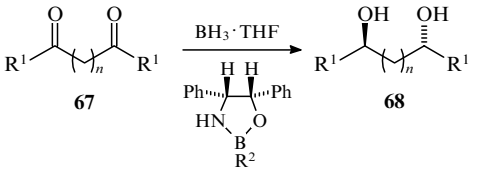
The use of 1,3,2-oxazaborolidines for the enantioselective reduction of alkanones does not give good results;[109,110] only alkyl methyl ketones containing alkyl substituents C_nH_{2n+1} ($n \geqslant 4$) are reduced with satisfactory enantioselectivity [*ee* of the alcohol (*R*)-MeCH(OH)Bu^n is 47% (see Ref. 34) or 66%,[105] *ee* of (*R*)-MeCH(OH)C_6H_{13}-n is 70%[66]]. The reduction of phenylacetone proceeds with moderate stereoselectivity, *viz*., in the presence of $Me_2S \cdot BH_3$ and the catalyst **48**, (2*R*)-phenylpropan-2-ol is formed with *ee* 61%,[66] whereas in the presence of $BH_3 \cdot THF$ and the catalyst **4** *ee* is 81%.[15]

The reduction of ketones containing alkyl and 1,3-dithianyl substituents is a convenient method for the synthesis of optically active ketols **64**.[72,111] The bulky 1,3-dithianyl substituent possesses a high discriminative ability which increases *ee* of ketols **64**. This reaction proceeds *via* the alcohols **65**. The desulfurisation of the alcohols **65** by Raney nickel yields the secondary alcohols **66**.



R = Alk, Ar; Cat =  ; NCS is *N*-chlorosuccinimide.

It is known that the non-catalytic reduction of dicarbonyl compounds by borane yields diols in the *meso*-form.[97] In the catalytic reduction of diphenyl diketones **67** (R^1 = Ph) (10 mol.% of the catalyst **51**), the *meso* : *R*,*R* (or *S*,*S*) ratio varies from 48 : 52 (*n* = 1) to 21 : 79 (*n* = 2), 9 : 91 (*n* = 3) or 2 : 98 (*n* = 4).[112–114]



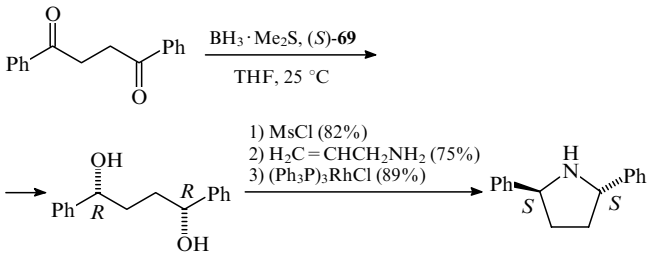
67 **68**

n = 1 – 4; R^1 = Me, Bu^t, Ph; R^2 = H, Me.

After crystallisation of the diol **68**, *ee* of the *S*,*S*-enantiomer was 99% (the content of the *meso*-form was < 1%). (For n = 1, the configuration of the diol formed was *R*,*R*).

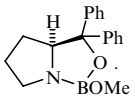
α-Diketones RC(O)C(O)Ph (R is a heterocyclic substituent) are reduced to (*S*,*S*)-RCH(OH)CH(OH)Ph by $BH_3 \cdot SMe_2$ in the presence of the catalyst (*S*)-**3** with *ee* 99%.[113]

The reduction of 1,4-diphenylbutane-1,4-dione by the $BH_3 \cdot SMe_2$ complex in the presence of 1,3,2-oxazaborolidine (*S*)-**69** proceeds with high selectivity. The diol **68** formed (*ee* 99%) is easily converted into chiral 2,5-diphenylpyrrolidine with high *ee*.[114] The catalyst (*S*)-**69** was obtained *in situ* from (*S*)-diphenylprolinol and trimethyl borate.



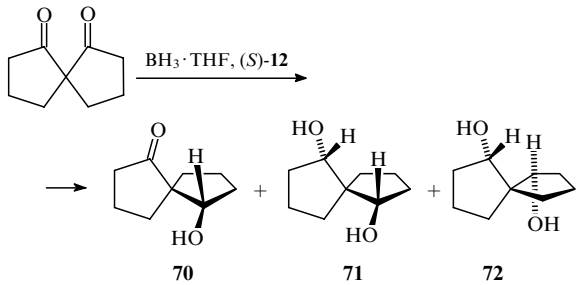
68 (96%, *ee* 99%) (55%, *ee* 99%)

(*S*)-**69** =



The reduction of hexane-2,5-dione under identical conditions yields the corresponding diol with *ee* 33%.[114]

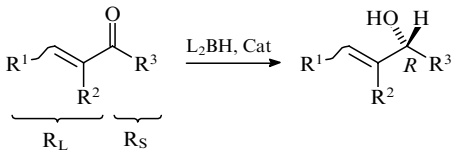
The reduction of spiro[4.4]nonane-1,6-dione (1.5 equiv. of borane, 0.1 equiv. of the catalyst (*S*)-**12**) at 78 °C gives ketol **70** (60%) and *trans*,*trans*-spirodiol **71** (40%). With an increase in temperature to 22 °C and of borane concentration to 2 equiv., a mixture of *cis*,*trans*-spirodiol **72** (83%) and the *trans*,*trans*-isomer **71** (17%) is formed.[115]



70 **71** **72**

A simple method for the synthesis of (1*S*,2*R*)-indenoxide with *ee* > 99% and (1*S*,2*S*)-*trans*-2-bromoindan-1-ol with *ee* 87% has recently been developed. The enantioselective reduction of 2-*p*-tolylsulfonyloxy-1-indanone was carried out using a borane complex with *N*-ethyl-*N*-isopropylaniline in the presence of the catalysts **5** and **39** (R = Me).[116]

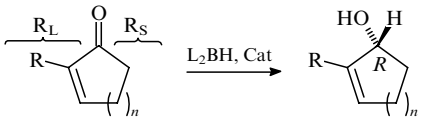
A detailed description of enone reduction is given in the reviews.[5–7] To prevent the non-catalytic reduction of the double bond, enones are usually reduced by catecholborane **62** at low temperatures in the presence of the catalysts **5** and **12**. It is of note that the alkene residue of acyclic enones plays the role of the larger substituent (R_L).[5–7, 112, 117] In conformity with this rule, the catalytic reduction of enones in the presence of 1,3,2-oxazaborolidines (*S*)-**5** and (*S*)-**12** yields (*R*)-enantiomers of substituted allylic alcohols.[5, 30, 103, 118–123]



(*S*)-Enantiomers are formed exclusively in the presence of α-substituents in R^2 and R^3 groups (see Ref. 117).

The enantioselective catalytic reduction of alk-2-ene-1,4-diones is documented in the studies.[112, 124]

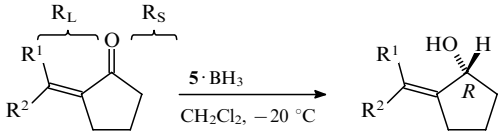
The catalytic reduction of cyclic enones containing an endocyclic double bond yields allylic alcohols with *ee* > 90%. In this case, the key role in the selectivity control is played by the nature of the substituent R at the α-carbon atom.[5]



n = 1, 2.

The reduction of enones with R = Me,[30] Br,[13, 125–127] Bu^{t}Me$_2$SiOCH$_2$ [128] and (MeO)$_2$CHCH$_2$ [129] in the presence of the catalysts (*S*)-**5** and (*S*)-**12** gave exclusively (*R*)-enantiomers of allylic alcohols.

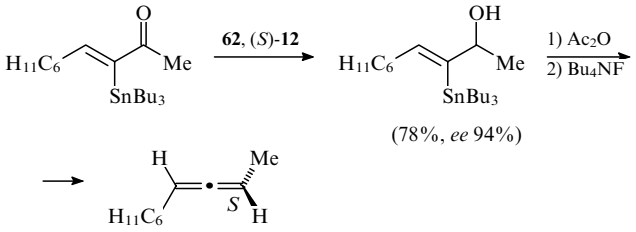
The alkene residue of cyclic enones containing an exocyclic double bond also plays the role of a bulky group R_L.[130]



73 **74**

The yield of the alcohol **74** in the reduction of the ketone **73** (R^1 = H, R^2 = Ph) was 84% and its enantiomeric excess was 96%. To ensure high selectivity, the reduction was performed in dichloromethane at low temperature by slowly adding the enone solution to the reducing agent ($BH_3 \cdot SMe_2$) (the enone : reducing agent : catalyst ratio was 1 : 1 : 0.2).[130]

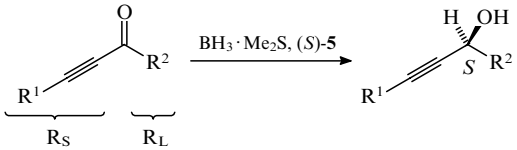
A method for the synthesis of chiral allenes from α-tributylstannylated allylic alcohols has been developed:[118]



(78%, *ee* 94%)

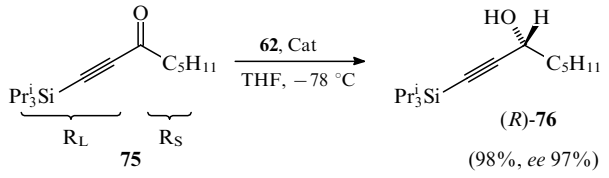
(*ee* 94%)

The reduction of acetylenic ketones gave unexpected results. It was found that the acetylene residue plays the role of a minor substituent R_S irrespective of the size of the substituent R^1 as a result of which the reduction of acetylenic ketones yields (*S*)-enantiomers of acetylenic alcohols.[124, 131]



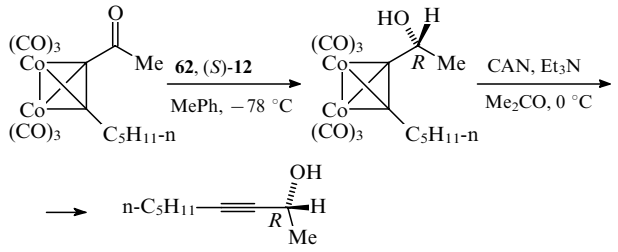
R^1 = H, Ph; R^2 = Me, Et, n-C_6H_{13}, Pr^i, cyclo-C_6H_{11}.

The introduction of a bulky $SiPr^i_3$ group into the acetylene residue converts it from R_S into R_L. Thus the reduction of the ketone **75** by catecholborane **62** in the presence of 1,3,2-oxazaborolidine based on (*S*)-diphenylprolinol having a trimethylsilyl substituent at the B atom results in the formation of the (*R*)-acetylenic alcohol **76**.[85]



75

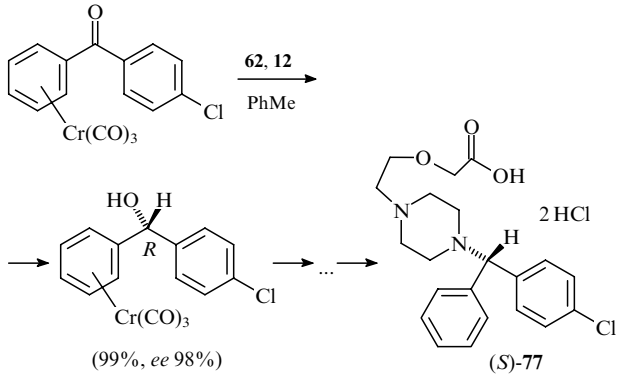
In order to make the acetylenic substituent play the role of a bulky R_L group, this can be converted into a π-complex with dicobalthexacarbonyl. Following the reduction, the complex is converted into an acetylenic alcohol by oxidative decomplexation.[104]



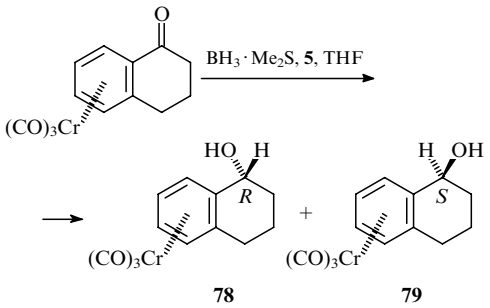
CAN = $(NH_4)_2Ce(NO_3)_6$.

The enantioselective reduction of acetylenic diketones and their π-complexes with dicobalthexacarbonyl has been described.[124]

The reduction of 4-(η^6-chromotricarbonylbenzoyl)chlorobenzene[104] was used in the synthesis of the second-generation histamine antagonist Cetirisine (**77**).[132]

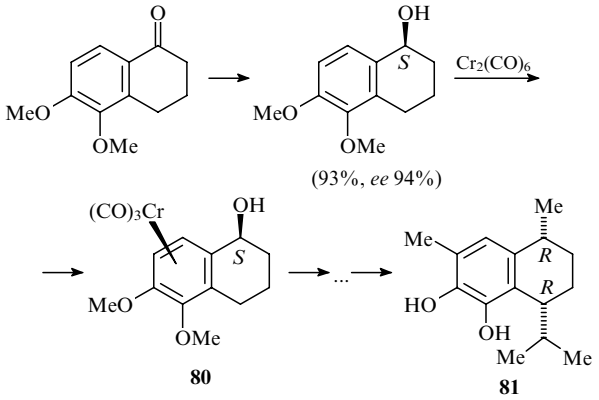


An attempt to perform the kinetic resolution of η^6-chromotricarbonyl complexes of 1-tetralone using CBS reduction failed.[133] It was expected that this reaction would result in the predominant formation of the *endo*-isomer **78** (which could correspond to the hydride ion transfer from the side opposite to the ligand $Cr(CO)_3$). However, under kinetic resolution conditions (*i.e.,* in the presence of 0.3 equiv. of the reducing agent) the reaction mixture contained the starting ketone (44% – 54%), the *endo*-isomer **78** (36% – 42%) and the *exo*-isomer **79** (10% – 14%); a mixture of the alcohols **78** and **79** (52 : 48) was formed in the presence of an excess of the reducing agent and after complete conversion of the original complex.



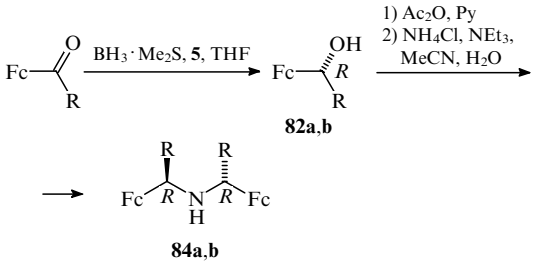
78 **79**

These results are rationalised as being due to the hydride ion transfer from the side of the $Cr(CO)_3$ group. An approach which includes primary catalytic reduction of the tetralone‡ and subsequent formation of the chromiumtricarbonyl complex **80** (the latter was used in the synthesis of (1*R*,4*R*)-7,8-dihydroxycalamenene **81**) appeared to be far more efficient.[134] The reduction of dimethoxytetralone by $Me_2S \cdot BH_3$ was carried out in THF in the presence of 0.2 equiv. of a catalyst based on (*R*)-proline which provided the (*S*)-configuration of the substituted tetralol. The stereospecific formation of the chromiumtricarbonyl *endo*-complex **80** is attributed to the regulatory effect of the hydroxy group which forms a complex with the chromium atom. Subsequent stereoselective alkylation of the complex **80** is well known in the chemistry of η^6-$Cr(CO)_3$ – arene complexes.



80 **81**

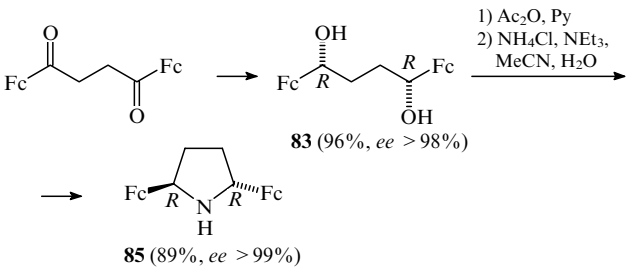
The catalytic reduction of the ferrocene derivatives[135–137] in the presence of 1,3,2-oxazaborolidines yields the chiral alcohols **82a**,**b** and **83** which were used in the synthesis of the chiral amines **84a,b** and **85**.§ The latter are used in enantioselective deprotonation and alkylation reactions.[136]



Compound	R	Yield (%)	*ee* (%)
82a	Me	97	98
82b	Ph	94	97
84a	Me	52	> 99
84b	Ph	90	> 99

‡ In this reaction, the enantiomeric excess of (*S*)-tetralol was 94%, while that after recrystallisation from EtOAc was 99%.

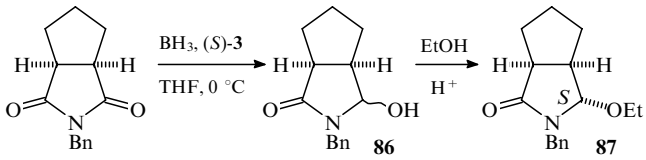
§ This reaction is similar to that involving the diols **68**.[114]



83 (96%, *ee* > 98%)

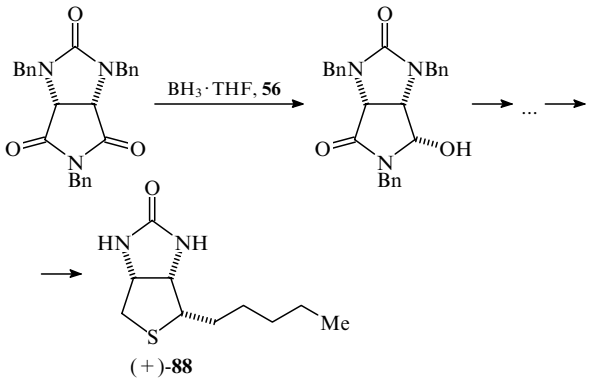
85 (89%, *ee* > 99%)

The reduction of cyclic *meso*-imides in the presence of the catalyst (*S*)-**3** yields a mixture of *cis*- and *trans*-5-hydroxypyrrolidones **86**; however, their rapid treatment with an EtOH – H_2SO_4 mixture yields predominantly *trans*-ethoxy lactam **87** in 73% yield (*ee* 75%).[138,139]



86 **87**

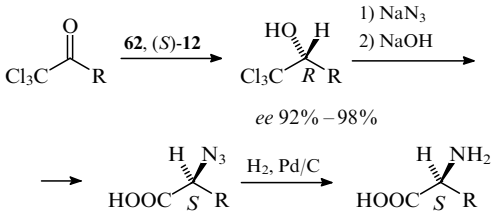
The reduction of imides in the presence of 1,3,2-oxazaborolidine **56** (R = H) was used in the synthesis of (+)-deoxybiotin **88**.[140]



(+)-**88**

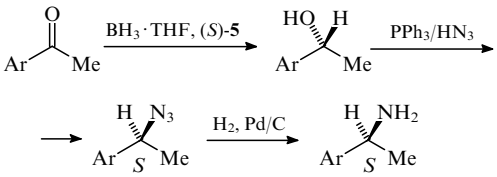
5. Synthesis of biologically active substances and natural compounds

The catalytic reduction of trichloromethyl ketones by catecholborane **62** in the presence of 0.1 equiv. of (*S*)-**12** can be used in the synthesis of both natural and non-natural (*S*)- or (*R*)-amino acids.[88]



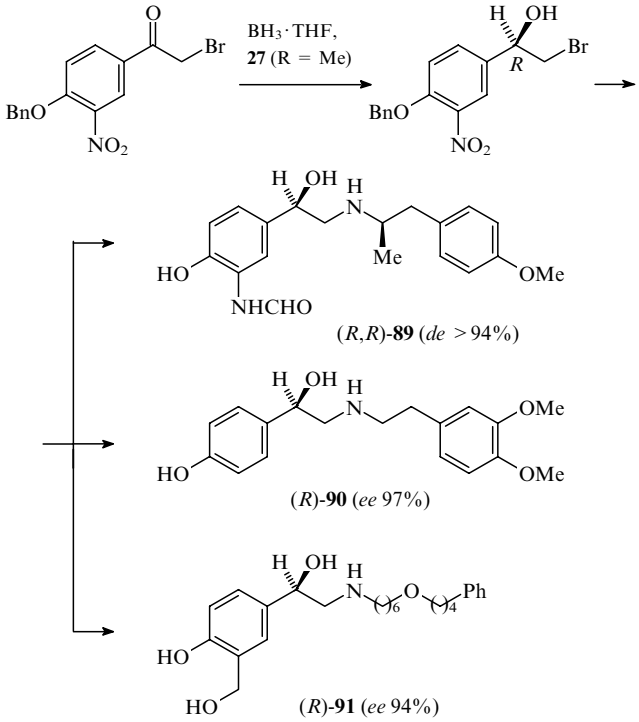
R = Alk, Ph.

A combination of enantioselective reduction with the Mitsunobu reaction opens up new routes to the synthesis of enantiomerically pure azides [141] and substituted 1-arylethylamines.[100]



Ar = C_6H_4Br-*m*, C_6H_4OH-*m*, C_6H_4OMe-*m*.

The reduction of α-haloacetophenones catalysed by 1,3,2-oxazaborolidines is the most promising approach to secondary amino alcohols: (*R*,*R*)-formoterol (**89**),[61,94] (*R*)-denopamine (**90**)[142] and (*R*)-salmeterol (**91**),[93] which represent β-adrenoreceptor agonists [the biological activity is manifested predominantly by (*R*)-enantiomers].

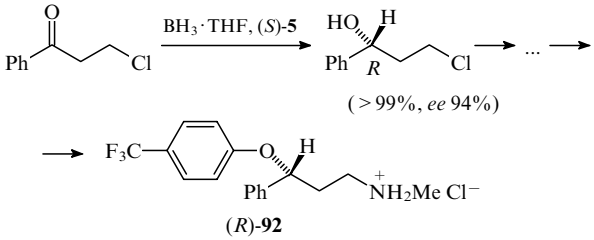


(*R*,*R*)-**89** (*de* > 94%)

(*R*)-**90** (*ee* 97%)

(*R*)-**91** (*ee* 94%)

The antidepressant fluoxetine (**92**) (Prozac©) is a potent selective serotonin uptake inhibitor and is widely used in medicine [143] (for the synthesis of fluoxetine and its metabolites see Ref. 144 and references cited therein). It was found that the (*R*)-enantiomer **92** possesses biological activity; the first step in its synthesis includes CBS reduction of β-chloropropiophenone.[143]



(> 99%, *ee* 94%)

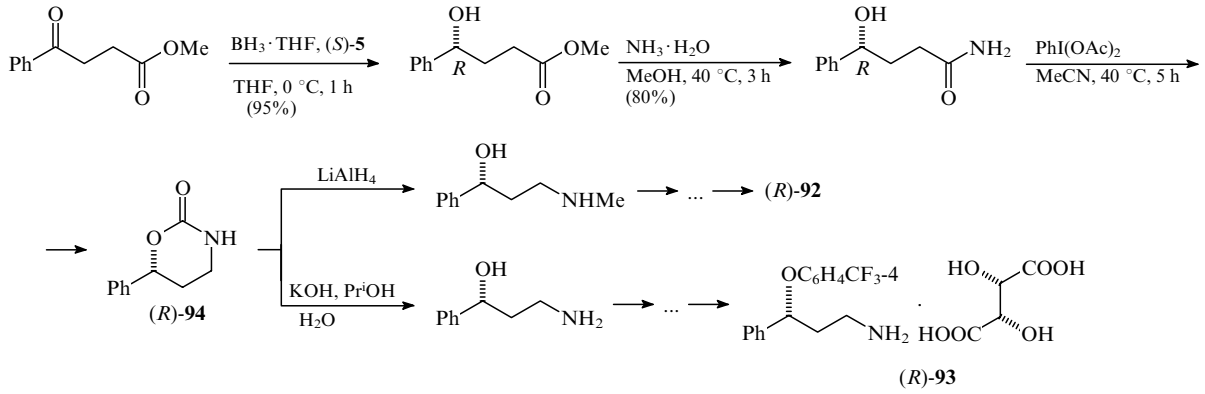
(*R*)-**92**

An improved method for the synthesis of (*R*)-fluoxetine **92** and its main metabolite (*R*)-norfluoxetine **93** (isolated as D-tartrate) includes CBS reduction, Hoffmann rearrangement induced by diacetoxyiodobenzene and cleavage of the intermediate cyclic carbamate **94** (Scheme 5).[144]

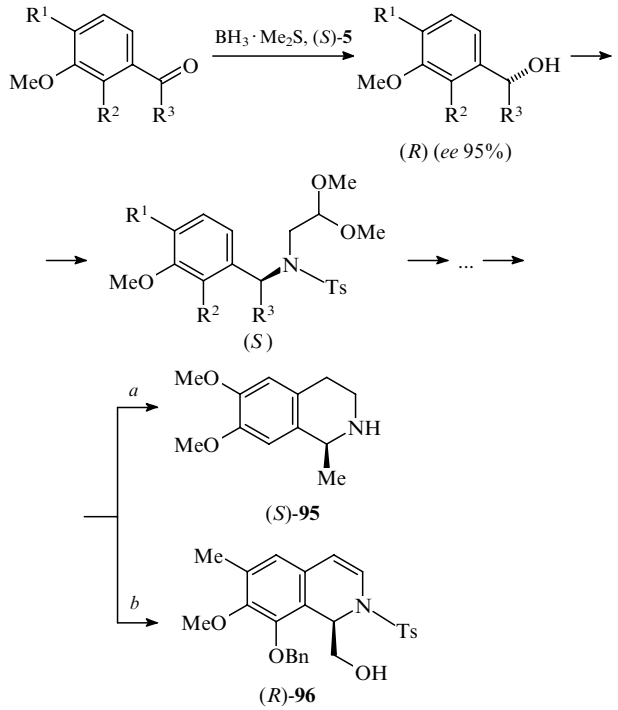
Catalytic CBS reduction was used by Kaufman for the synthesis of chiral 1,2,3,4-tetrahydro- and 1,2-dihydroisoquinolines, *viz*., (*S*)-(−)-salsolidine (**95**) [145] and the intermediate (*R*)-**96** used in the synthesis of the β-adrenoreceptor antagonist MY336-a (Scheme 6).[102]

The stereoselective (*ee* 94%) synthesis of (3*R*,4*E*)-19-methyleicos-4-en-1-yn-3-ol (**97**) (a metabolite from the sea sponge *Cribrochalina vasculum*), which possesses immunosuppressive and antitumour properties, has been described.[146] This example is interesting in that the molecule of the starting compound **98** contains simultaneously the C=C and C≡C bonds. In this case, the role of the minor substituent R_S is played by the acetylenic fragment. The borane – dimethyl sulfide complex (THF, 0 °C) was

Scheme 5

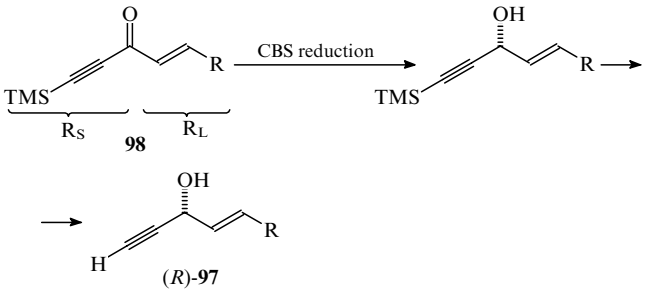


Scheme 6



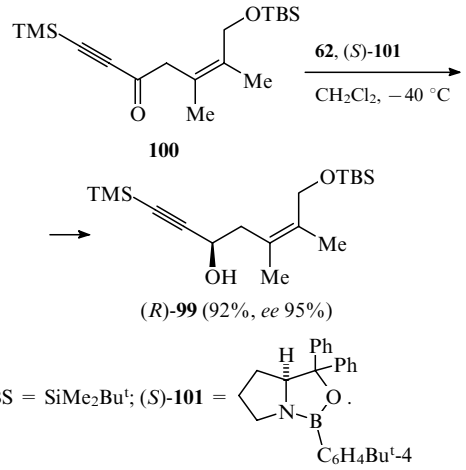
(*a*) R^1 = OMe, R^2 = H, R^3 = Me;
(*b*) R^1 = Me, R^2 = OBn, R^3 = CH_2OBn.

used as a reducing agent while (*R*)-**5** or (*R*)-**48** (R = Me) was used as a catalyst.

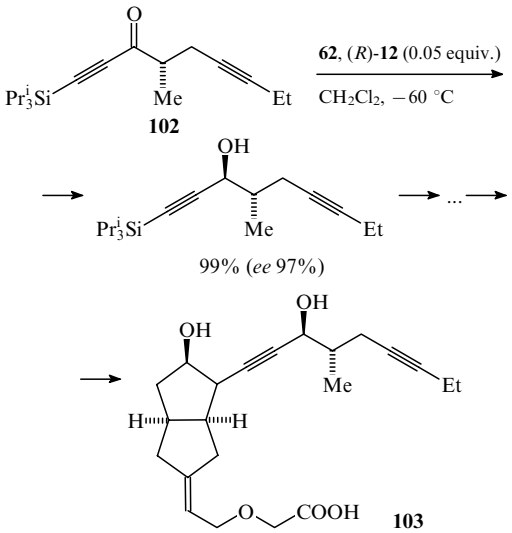


R = $(CH_2)_{13}Pr^i$, TMS = $SiMe_3$.

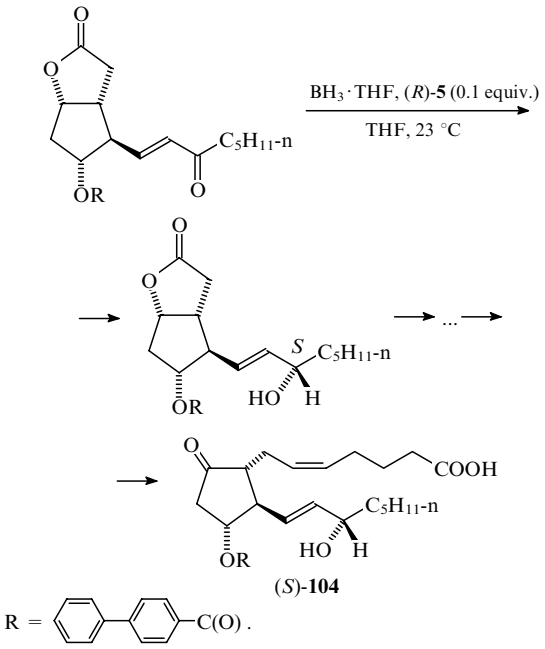
The key synthon (*R*)-**99** used in the synthesis of nicandrenones was prepared by CBS reduction of ketones **100** using (*S*)-**101** as a catalyst.[147]



The mild conditions of CBS reduction have made possible its wide application in the chemistry of prostaglandins. Thus the enantioselective catalytic reduction of diynone **102** by catecholborane (**62**) was used in the synthesis of the ω-chain of the orally active cicaprost **103**, a metabolically stable analogue of prostaglandin I_2.[5]



The stereoselective introduction of a hydroxy group into the C(15) atom in the synthesis of the protected prostaglandin PGE_2 **104** [(*S*) : (*R*) ≈ 10 : 1] is carried out in a similar way.[13]

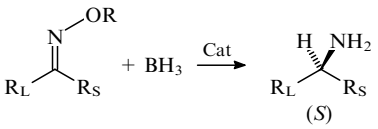


Other examples of the synthesis of biologically active and natural compounds by enantioselective reduction of carbonyl compounds can be found in the reviews.[5,6]

The above data suggest that CBS reduction of prochiral ketones has a number of advantages over other reduction procedures. These include versatility, *i.e.*, the possibility of reduction of different types of carbonyl compounds, predictable stereochemistry of the alcohol formed, relative availability of catalysts in any of their enantiomeric forms, easy regenerability of the catalyst precursor (an amino alcohol), low cost, high yields and relative simplicity of the experimental procedure.

III. Reduction of oximes and imines

The unflagging interest of investigators in optically active amines is due to the wide diversity of their practical applications, *e.g.*, in separation of enantiomers,[148] preparation of drugs[149] and as auxiliary reagents in asymmetric synthesis and catalysis.[150] It is therefore not surprising that the enantioselective reduction of ketones in the presence of chiral oxazaborolidines was extended to the synthesis of optically active amines. In this case, oxime ethers were used as the starting compounds.[10,151]



R = Me, Et, Bn, $SiMe_3$; R_L = Ph, 1(2)-naphthyl; R_S = Me, Alk.

On the whole, the product yields and the stereoselectivity of reduction of oxime ethers are lower than those of ketones.¶

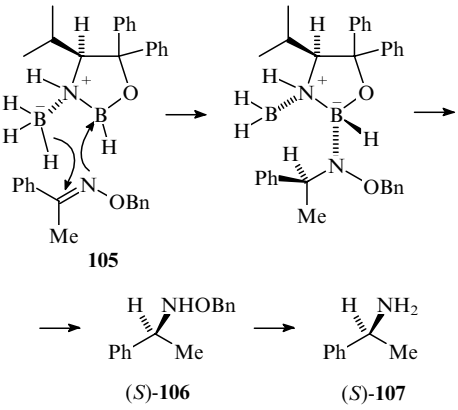
Let us point out the differences in the conditions of preparation of optically active alcohols and amines.

First, the synthesis of amines requires that the reaction is carried out with only individual geometrical oxime isomers, since the stereochemistry of the final product (an amine) depends on the configuration of the precursor [*e.g.*, the (*S*)-enantiomer of the amine is usually formed from the *E*-isomer of the oxime containing small R_L and R_S fragments].[2,152] Second, high efficiency of the catalytic reaction (high values of *ee*) requires usually an increase in the reaction time up to 20–70 h and the use of equivalent amounts of 1,3,2-oxazaborolidine[153] (only a few examples of effective catalytic reactions are known[154,155]). Third, in the case of oxime ethers the *ee* value of the reaction product depends on the nature of the substituent R [the reduction of oximes non-substituted at the oxygen atom is non-selective (*ee* 0.6%), the best results are achieved for R = Me or CH_2Ph] and the catalyst type.[10,75]

As a rule, 2 equiv. of borane and 1 equiv. of the catalyst (**2**,[151–153] **3**[151,153] or 1,3,2-oxazaborolidine based on norephedrine[152]) are used per 0.8–1 equiv. of the oxime ether;† the reaction is carried out in THF at 30 °C for 24 h.

Let us consider the mechanism of reduction of oxime ethers in more detail (Scheme 7).[152]

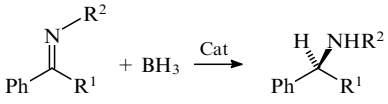
Scheme 7



As was shown above in the example of the Corey model for ketones[5] (see Section II), the addition of borane to chiral 1,3,2-oxazaborolidine **2** occurs from the side opposite to the isopropyl group. The nitrogen atom of the *E*-isomer of the oxime ether coordinates the endocyclic boron atom by the free electron pair to form a six-membered transition state **105** where the bulkier phenyl radical of the oxime occupies an equatorial position. Subsequent stereoselective hydride ion transfer yields protected (*S*)-hydroxylamine **106** which is reduced to the (*S*)-enantiomer of the amine **107**. In some cases, hydroxylamines (*S*)-**106** were isolated together with the amines (*S*)-**107**.[152]

A somewhat different, but essentially similar interpretation for the formation of the (*S*)-enantiomer was given by Itsuno[156] who suggested that the steric interaction of the *O*-benzyl group with the *trans*-phenyl group is critical for the stereoselectivity (the solid-phase enantioselective reduction of ketoxime ethers[157–158] will be considered in Section V).

The reduction of imines occurs in a similar way.



R^1 = Me, Et, Pr^i; R^2 = Ph, Bn, Alk.

The imines with R^2 = Ph are reduced best of all, the yields of the corresponding amines are 96%–98%, *ee* is 71%–88%.[153,159] The reduction of *N*-alkylketimines is less selective (*ee* 46%–52%), while the selectivity of reduction of dialkyl ketone imines is very low (*ee* 7.4%–24%).[153] The *ee* increases with an increase in the size of the radical R^1.

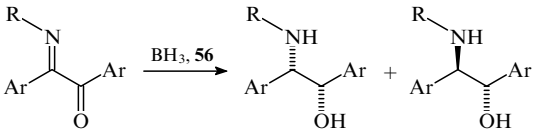
The structure of the catalyst is known to influence the course of the reduction of oxime ethers and imine.[75] It was found that the

¶ The early procedures[10,151] were further improved which enabled one to obtain semi-preparative amounts of substituted (*S*)-1-phenylethylamines with *ee* 90%–99%.[152] Hence, enantioselective reduction of oxime ethers and imines by boranes in the presence of chiral 1,3,2-oxazaborolidines is one of the most efficient methods for the synthesis of optically active amines.

† An experimental procedure for the regeneration of the catalyst **2** as a hydrochloride is reported.[152]

reduction of acetophenone *O*-methyloxime to 1-phenylethylamine by 1 equiv. of $BH_3 \cdot THF$ in the presence of *N*-arylsulfonylated 1,3,2-oxazaborolidine derived from **58** results in the formation of either an (*S*)- or an (*R*)-enantiomer depending on the nature of the substituents in compound **58**. Thus the (*S*)-enantiomer is formed with Ar = Tol-*p*, R = H (yield 61%, *ee* 84%), while (*R*)-2-phenylethylamine is formed with Ar = 1-naphthyl, R = H (yield 31%, *ee* 84%).[75] This is an illustrative example of a reversal of stereoselectivity due to replacement of a substituent in the arylsulfonyl group from tolyl to naphthyl. A similar dependence is observed in the reduction of prochiral ketones.[75]

The possibility of preparing chiral amino alcohols, which are valuable intermediates in asymmetric synthesis, by diastereoselective reduction of imino ketones and *O*-ethers of α-hydroxyimino ketones has also been studied.[154, 160–163] In the first experiments, the enantioselectivity and diastereoselectivity were rather low.[160] Thus the reduction of the imino ketone **108** (R = *p*-$MeOC_6H_4$, Ar = Ph) by the complex $BH_3 \cdot THF$ in the presence of 0.2 equiv. of the catalyst **56** (R = H) (see Table 1) gave a mixture of *syn*-(1*S*,2*S*)- and *anti*-(1*S*,2*R*)-isomers **109** (58 : 42) with the enantiomeric purity of the products < 14% (yield 88%).[162]

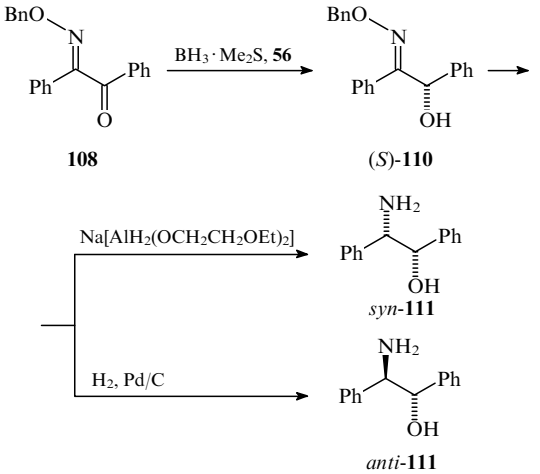


108 *syn*-(1*S*,2*S*)-**109** *anti*-(1*S*,2*R*)-**109**

R = *p*-$MeOC_6H_4$, BnO, *p*-$MeC_6H_4SO_2$;
Ar = Ph, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-BrC_6H_4, 2-furyl.

The stereoselectivity increased on going from α-imino ketones (R = *p*-$MeOC_6H_4$) to ethers of α-hydroxyimino ketones (R = OBn): the enantiomeric purity of the target product reached 88%. In the presence of 1 equiv. of the catalyst **56** and $Al(OPr^i)_3$, the enantioselectivity increased to 90%, however, the diastereoselectivity was not changed (the *syn* : *anti* ratio was 47 : 53). It was thus concluded that under these conditions the catalytic reduction of the keto group was followed by non-selective reduction of the oxime group by borane.[162] This process was complicated by the formation of a side 1,3,2-oxazaborolidine from BH_3 and the amino alcohol formed, which catalysed the reduction in a non-selective manner.[160]

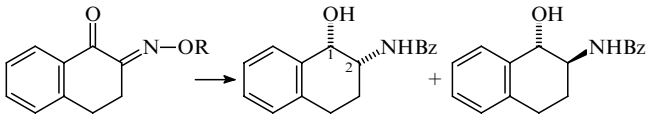
It was found experimentally that the keto group is reduced more easily than the oxime group.[154, 160] The stereoselectivity could be increased, if stepwise reduction was used under optimum conditions for each step.[162, 163] The reduction of the ether of hydroxyimino ketone **108** (R = OBn, Ar = Ph) in the presence of 1 equiv. of the catalyst **56** (R = H) at room temperature gave (*S*)-hydroxy oxime **110** (yield 78%, *ee* 98%).[162]



108 (*S*)-**110** *syn*-**111** *anti*-**111**

Subsequent reduction of the oxime function was carried out in the absence of 1,3,2-oxazaborolidine. The *syn*-isomer **111** was prepared by treatment of compound **110** with the complex hydride $Na[AlH_2(OCH_2CH_2OEt)_2]$, while the *anti*-isomer **111** was obtained by catalytic reduction of compound **110** with hydrogen in the presence of 10% Pd/C.[162, 163]

The reduction of ethers of α-hydroxyimino ketones **112** yields predominantly the *cis*-amino alcohols *cis*-(1*S*,2*R*)-**113**, *cis* : *trans* = 10 : 1 (for R = Bu^tPh_2Si, *ee* is 96%, after recrystallisation *ee* > 99%),[154] or 9 : 1 (for R = CPh_3, *ee* 90%).[160]

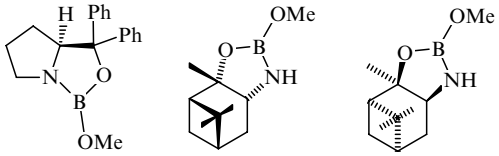


112 *cis*-(1*S*,2*R*)-**113** *trans*-(1*S*,2*S*)-**113**

R = Bu^tPh_2Si, Ph_3C.

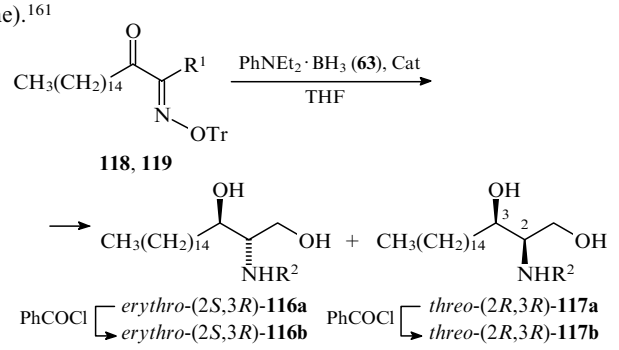
The reduction of compounds **112** containing less bulky groups in the ether moiety proceeds with lower selectivity.

The reduction of ketoxime ethers by a borane–dimethyl sulfide complex in the presence of chiral 1,3,2-oxazaborolidines **69**, **114** and **115** prepared from trimethyl borate and the corresponding alcohols has been described.[160]



69 **114** **115**

The introduction of a bulky *O*-trityl (Tr) group into oximes is yet another approach to increase the selectivity of reduction of α-hydroxyimino ketones.[160, 161] This approach was used in the diastereoselective synthesis of sphinganine (dihydrosphingosine).[161]



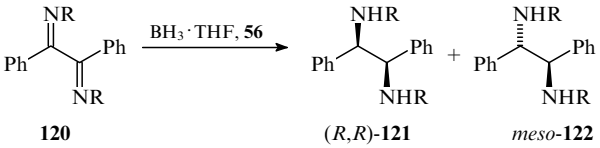
118, **119**

R^1 = CO_2Me (**118**), $CH_2OSiMe_2Bu^t$ (**119**); R^2 = H (**116a**, **117a**), PhCO (**116b**, **117b**); Cat = **69**, **114**, **115**.

Depending on the substrate, the catalyst and reduction conditions, one can obtain either the *erythro*-(2*S*,3*R*)-isomer **116** or the *threo*-(2*R*,3*R*)-isomer **117** [natural sphingosine has the *erythro*-(2*S*,3*R*)-configuration]. These conversions provide a typical example of so-called 'substrate control'.

Substrate	Catalyst	Reducing agent	*erythro* : *threo*	*ee* (%)
118	**69**	**63**	13 : 87	89 (*threo*)
119	**115**	**63** + $BH_3 \cdot SMe_2$	98 : 2	97 (*erythro*)

The catalytic reduction of diimines of the type **120** in the presence of 0.05 equiv. of the catalyst **56**, which yields substituted (*R*,*R*)-1,2-diphenylethylenediamines with *ee* 99% [the (*R*,*R*)-**121** : *meso*-**122** ratio is 95 : 5], has been described.[155]

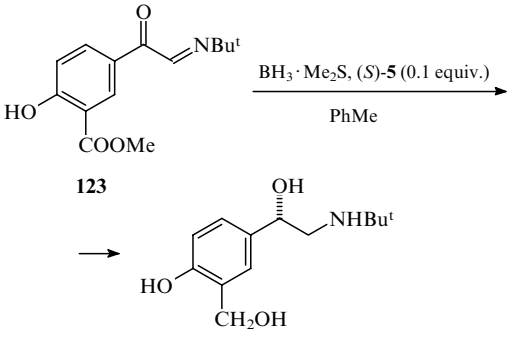


120 (*R*,*R*)-**121** *meso*-**122**

R = *p*-$MeOC_6H_4$.

An attempt to use this method for the reduction of 1,2-dioximes failed.[155]

The reduction of α-imino ketone **123** is the key step in the synthesis of the β-blocker (*S*)-albuterol (**124**).[164]



123

124 (90%, *ee* 93%–95%)

Despite the obvious success in the reduction of imines and oxime ethers, this reaction has a number of limitations. Thus no 1,3,2-oxazaborolidines able to catalyse effectively the reduction of 3,4-dihydroisoquinolines and carbolines have been found so far.[2] There are virtually no publications devoted to large-scale semi-industrial synthesis of chiral amines required for the synthesis of some medicinal drugs, *e.g.*, α- and β-adrenoblockers, antidepressants, *etc.*[149]

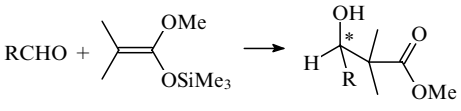
IV. Use of 1,3,2-oxazaborolidines in miscellaneous reactions

In addition to reduction of ketones, imines and oximes, chiral 1,3,2-oxazaborolidines find wide application in other branches of synthetic organic chemistry. Some applications of these catalysts in the Diels–Alder reaction, aldol condensation and some other reactions are considered in the review;[165] however, the articles cited therein were published before 1991. Therefore, we thought it expedient to systematise the literature data published in the past decade.

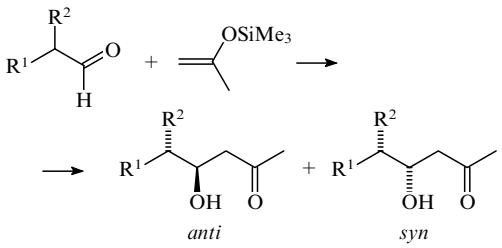
1. Aldol condensation

At the end of the 20th century, the efforts of many chemists were focused on the development of methods for enantioselective and diastereoselective aldol condensation [166–168] owing to the high versatility and wide applicability of this reaction in the synthesis of natural compounds, of macrolide antibiotics, in particular.

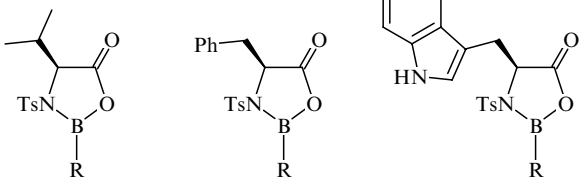
The aldol condensation of aldehydes with enol silyl ethers or ketone silyl acetals catalysed by Lewis acids (the Mukaiyama reaction) [169–171] can be implemented in an asymmetric version.[172]



If an aldehyde introduced into the reaction contains a chiral α-carbon atom, the condensation product will contain two chiral centres.[172, 173]



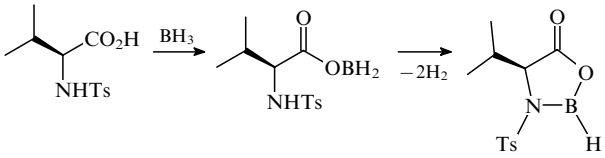
In the general case, this reaction yields a mixture of diastereomers. In a recent study,[174] the possibility of effective control over *syn*- and *anti*-selectivities by changing the spatial structure of the catalyst (the latter is used in amounts not exceeding 20 mol.%) has been demonstrated. It was found that high enantioselectivity (*syn* : *anti* > 98 : 2) can be achieved with a proper catalyst chosen with due regard to the nature of the substituents R^1 and R^2 in the starting aldehyde.[175, 176] This type of reaction can be referred to as a catalytically controlled process.[172] (Far from all reactions considered in this section can be carried out under conditions of catalytic control, often equimolar amounts of the catalyst are required.) The minor diastereomer formed is easily separated by chromatography.[172] Chiral *N*-acyl- and *N*-tosyl-1,3,2-oxazaborolidin-5-ones were found to be suitable catalysts for such conversions. The use of these compounds as catalysts was proposed simultaneously by Corey,[177, 178] Yamamoto,[179] Helmchen [180, 181] and Masamune.[182] Catalysts based on natural (*S*)-enantiomers of the amino acids **125a–e**,[172, 183] **126a–e** [184] and **127a–e** [185] are the most common.



(*S*)-**125a–e** (*S*)-**126a–e** (*S*)-**127a–e**

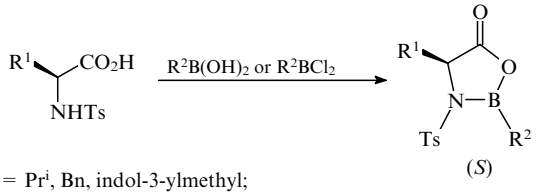
R = H (**a**), Me (**b**), Bu (**c**), Ph (**d**), 3,5-$(CF_3)_2C_6H_3$ (**e**).

Compounds **125a, 126a** and **127a** were prepared by treatment of the corresponding *N*-tosylated amino acid with borane.[186] For example:



(*S*)-**125a**.

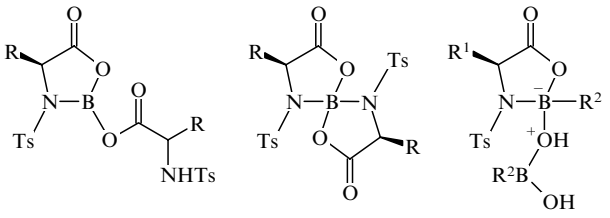
Esters of alkyl- or aryl-boronic acids were used instead of BH_3 in the synthesis of compounds **125b–e**, **126b–e** and **127b–e** containing B—Alk or B—Ar bonds.[184, 185]



(*S*)

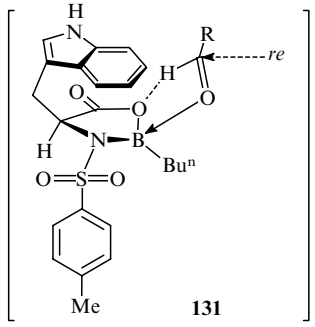
R^1 = Pr^i, Bn, indol-3-ylmethyl;
R^2 = Me, Bu, Ph, 3,5-$(CF_3)_2C_6H_3$, CH_2Bn.

Using negative ion mass spectrometry,[186, 187] it was shown that this reaction is accompanied by the formation of side products **128** and **129** (for R = H) or **130** (for R^1, R^2 = Alk, Ar).



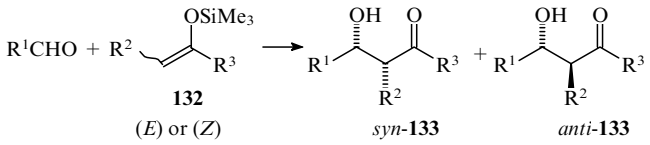
128 **129** **130**

Quantum-chemical methods were used to study the adducts formed upon coordination of formaldehyde with *N*-tosyl-1,3,2-oxazaborolidin-5-ones[183,188] and to determine the energies of their formation.[189] These calculations confirmed the previous assumption[190] on the possible formation of B–O···H–C and B···O=C bonds. The structures of the aldehyde adducts with *N*-tosyl-1,3,2-oxazaborolidin-5-ones were finally established only after the appearance of the publication by Corey *et al.*[191] devoted to X-ray diffraction analysis of some stable adducts where the existence of a hydrogen bond B–O···H–C between the oxygen atom of the 1,3,2-oxazaborolidine ring and the hydrogen atom of the aldehyde group was confirmed. According to Corey *et al.*,[191] the formation of such a non-trivial hydrogen bond is possible due to the high acidity of the hydrogen atom of the H–C(O) group upon coordination of its oxygen atom to the boron atom. This hydrogen bond is the structure-forming element in the rigid structure **131** resulting from the *re*-frontal attack of the nucleophile and governing the enantioselectivity of the aldol condensation and the Diels–Alder reaction (see below) catalysed by 1,3,2-oxazaborolidines (in this case, by compound **127c**).[191]



131

Other examples of the Mukaiyama-type aldol condensation of a series of aldehydes R^1CHO (R^1 = Ph, Pr^n, Pr^i, PhC≡C) with (*Z*)- and (*E*)-enol silyl ethers **132** are considered in the review.[185]

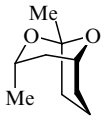


132 (*E*) or (*Z*) *syn*-**133** *anti*-**133**

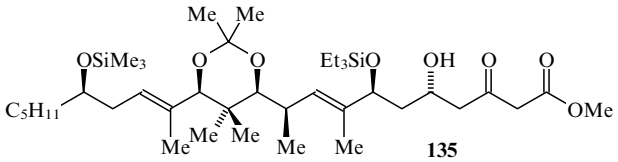
R^1 = Ph, Pr^n, Pr^i, PhC≡C; R^2 = Me, R^3 = Ph, $R^2–R^3$ = $(CH_2)_4$.

The predominant formation of the *syn*-isomers **133** in this reaction is in accord with the model of the transition state **131**. The ratio of the *syn*-**133**:*anti*-**133** products in the condensation of benzaldehyde with trimethylsilyloxycyclohexene [$R^2–R^3$ = $(CH_2)_4$, *E*-isomer] in the presence of the catalyst **127e** was 78:22 with the total yield 99% (*ee* of compound *syn*-**133** was 89%),[185] while that in the condensation of propanal with the (*Z*)-isomer of trimethylsilyl ether **132** (R^2 = Me, R^3 = Ph) was > 99:1 with the total yield 99% (*ee* of compound *syn*-**133** was > 99%). These reactions were carried out in propionitrile at −78 °C for 12 h in the presence of 5 mol.%–10 mol.% of the catalysts **127a–e** (the catalyst **127e** manifested the highest efficiency).

Kiyooka *et al.*[172,192–204] have carried out a comprehensive analysis of the 1,3,2-oxazaborolidin-5-one catalysed Mukaiyama reaction and applied this methodology to the synthesis of bicyclic acetals, *e.g.*, compound **134**[195] and some natural compounds, *e.g.*, compound **135** which is a precursor of the macrolide acutiphycin, the key intermediate of the polyene macrolide filipin and the non-proteinogenic *N*-benzyloxycarbonylgalantinic acid.[201,205–207]



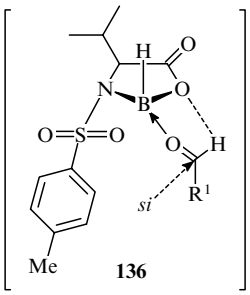
134



135

These reactions were carried out in the presence of stoichiometric amounts of 1,3,2-oxazaborolidine (*S*)-**125a** and its (*R*)-enantiomer (Schemes 8 and 9).

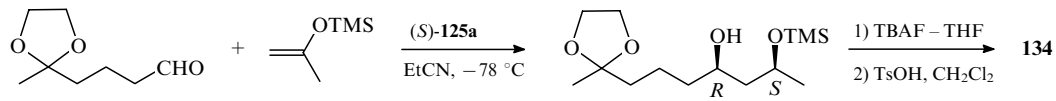
Three aldol condensations in the multistep synthesis of compound **135** (Scheme 9) were performed in the presence of the catalyst (*S*)-**125a** and the last one, in the presence of (*R*)-**125a**, which ensured the desired orientation of the asymmetric centres in the molecule **135**. It was found that the relative configuration of the stereocentres is governed by the stereochemistry of the oxazaborolidine and does not virtually depend on the nature of the substrate. According to Corey,[191] the structure of the transition complex formed in the Mukaiyama reaction catalysed by compound (*S*)-**125a** differs from that of the complex **131**. In this case, *si*-frontal attack of the nucleophile occurs resulting in predominant formation of *anti*-isomers.



136

The *anti*:*syn* ratio varies from 2:1 to 10:1 [the use of (*R*)-**125a** results in the predominant formation of *syn*-isomers].[172,204] The isopropyl group in the complex **136** is *trans* relative to the tosyl group and *cis* relative to the B–H bond; the hydrogen bond C–H···O–B formed ensures fixation of the addition of the aldehyde to the catalyst **125a** thus providing high diastereoselectivity of its condensation with enol silyl ethers.

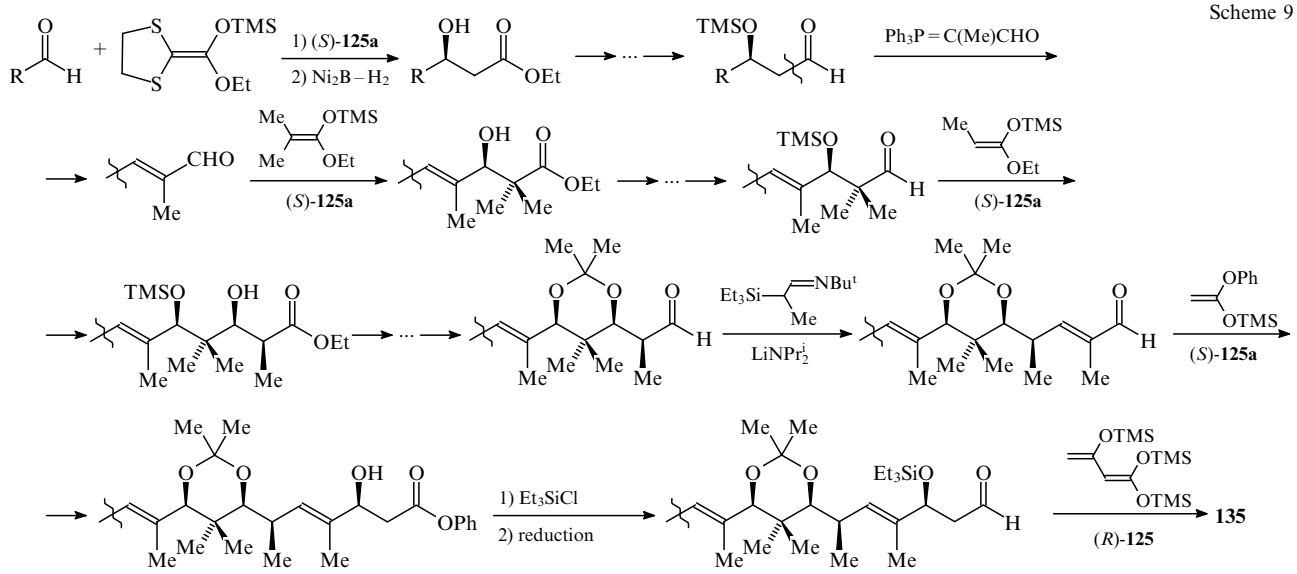
Scheme 8



TBAF — Bu^n_4NF.

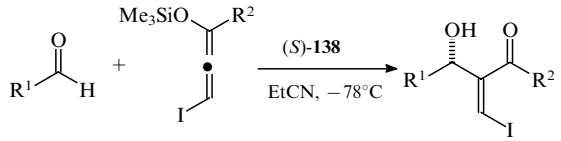
syn

Scheme 9



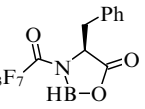
R = $CH_3(CH_2)_4$.

1,3,2-Oxazaborolidine **138** (0.2 equiv.) was used as a catalyst in the enantioselective aldol condensation of the silyl ether **137**.[208]

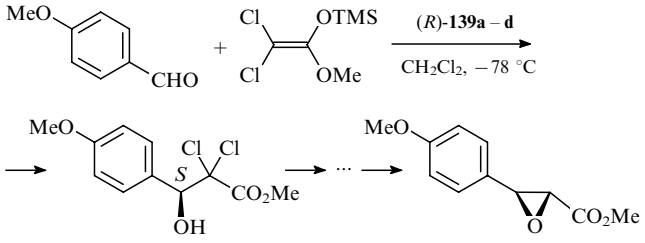


137

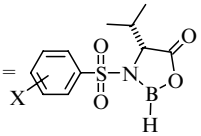
(60% – 70%, *ee* 61% – 98%)

R^1 = Me, Ph; R^2 = Me, Et; (*S*)-**138** = 

The Mukaiyama reaction in the presence of chiral 1,3,2-oxazaborolidin-5-ones **139a**–**d** was used in the synthesis of (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate **140**, a key intermediate in the synthesis of the calcium antagonist diltiazem.[209]



(*ee* 96%) (–)-**140** (*ee* > 96%)

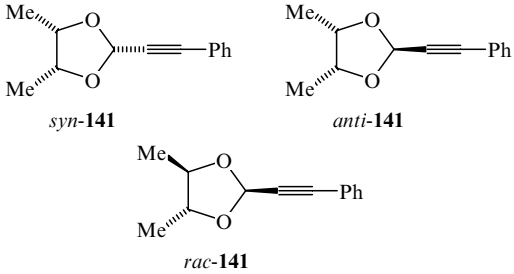
(*R*)-**139a**–**d** = 

X = *p*-Me (**a**), *o*-NO_2 (**b**), *p*-NO_2 (**c**), *p*-OMe (**d**).

2. Enantioselective opening of the dioxolane ring

Desymmetrisation of *meso*-1,2-diols by asymmetric ring opening of 1,3-dioxolanes and other cyclic acetals under the action of chiral 1,3,2-oxazaborolidin-5-ones has been described by Harada *et al.*[210–215] In these reactions, 1,3,2-oxazaborolidin-5-one [*e.g.*, (*S*)-**126**] plays the role of a stereodifferentiating agent with respect to the enantiotopic oxygen atoms in the cyclic acetal and is predominantly coordinated to one of them. Treatment of this complex with a nucleophile results in the dioxolane ring opening.

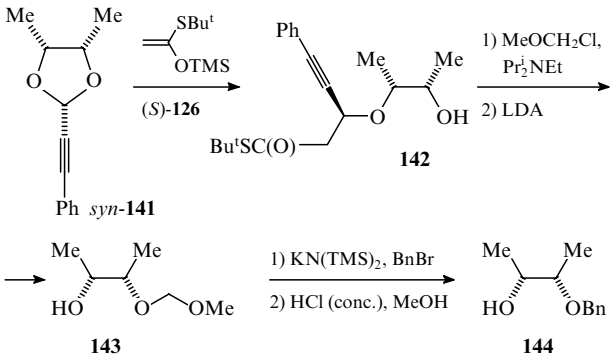
Treatment of commercial 2,3-butanediol, which represents a mixture of *meso*- and *dl*-isomers (~ 2 : 1), with 3-phenylpropynal yields 68% of a mixture of acetals, 2-phenylethynyl-1,3-dioxolane isomers, *viz.*, *syn*-**141**, *anti*-**141** and *rac*-**141** (63 : 3 : 34).[210]



syn-**141** *anti*-**141**

rac-**141**

Treatment of this mixture with $Me_2C{=}C(SBu^t)OSiMe_3$ in the presence of 10 mol.% of the catalyst (*S*)-**126** at –78 °C results in the opening of the acetal ring of *syn*-**141** and the formation of the product **142** (yield 64%, *ee* 96%) (the diastereomeric acetal *anti*-**141** is not cleaved under these conditions).‡ The *anti*-**141** – *rac*-**141** mixture (7 : 93) is isolated after termination of the reaction.



142

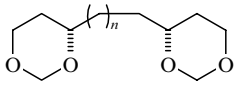
143 **144**

Thus a mixture of *meso*- and *dl*-forms of butanediol yields derivatives of optically active diols **143** and **144**.[210] Such desymmetrisation of *meso*-acetals is undoubtedly useful, since various 1,2-diols are available as mixtures of *meso*- and *dl*-forms (*e.g.*, they

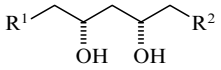
‡ The phenylethynyl substituent appeared to be a suitable functional group, which allows one to perform all transformations in the highest optical yield.

can be prepared by SmI_2-induced reductive dimerisation of aldehydes).[210]

The desymmetrisation of bisacetals **145**[212] and diols **146** has also been described.[213]



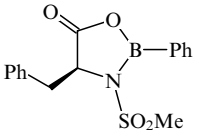
145 (n = 0, 1)



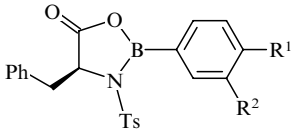
146

R^1 = OBn; R^2 = H, Me, Bu, OBn

(*S*)-**147** and (*S*)-**148a**,**b** can be used as catalysts along with (*S*)-**126.**[212,214]



(*S*)-**147**



(*S*)-**148a**,**b**

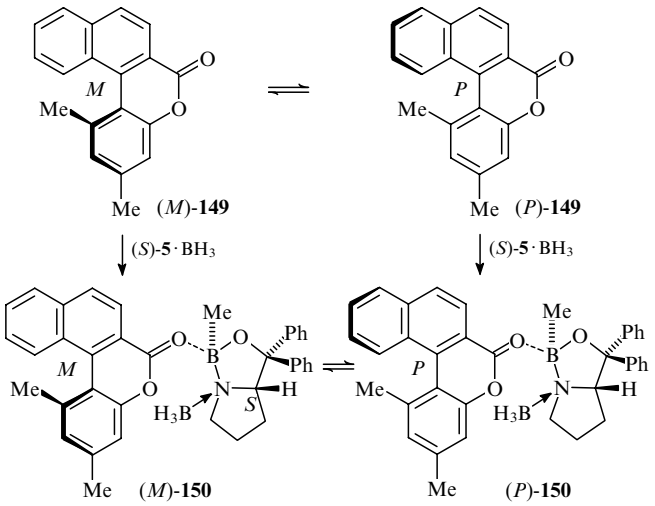
148a: R^1 = H, R^2 = Cl;
148b: R^1 = Cl, R^2 = H.

All these catalysts play the role of contact ion pairs in enantiodifferentiating coordination of acetals with chiral substituted 1,3,2-oxazaborolidin-5-ones.[215]

3. Atroposelective opening of the lactone ring

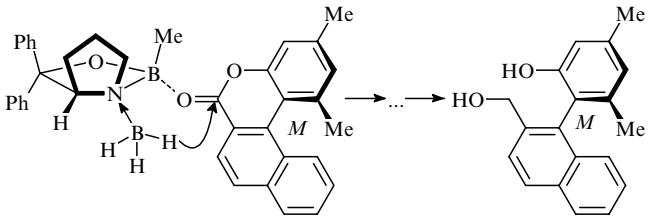
In developing methods for the synthesis of natural naphthyltetrahydroisoquinoline alkaloids, Bringmann *et al.*[216–221] proposed the use of atroposelective opening of the lactone ring of 1,3-dimethylbenzo[*b*]naphtho[1,2-*d*]pyran-6-one (**149**). This method is a convenient procedure for the synthesis of atropoisomers.

The atroposelective reduction of lactone **149** by the complex (*S*)-**5**·BH_3 was studied first.[216–218] This lactone exists in two forms, *viz.*, (*P*)-**149** and (*M*)-**149**§ which are configurationally unstable and are easily interconverted. They form (*P*)-**150** and (*M*)-**150** complexes with the catalyst (*S*)-**5**·BH_3, respectively.



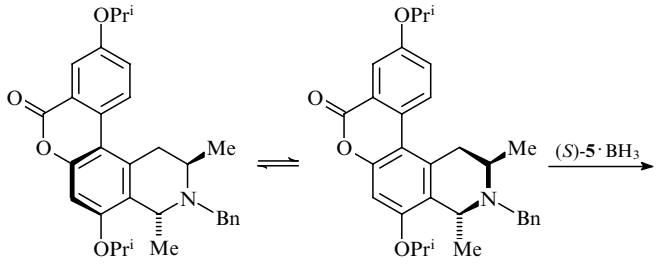
It was found that it is in the complex (*M*)-**150** that the enantioselective hydride transfer with subsequent formation of compound (*M*)-**151** takes place at −78 °C, which is due to the peculiarities of the spatial structure of the complex (*M*)-**150**. The isomeric complex (*P*)-**150** is not reduced under these conditions, it is first converted into (*M*)-**150** and then into (*M*)-**151**. Thus, the kinetic separation of two atropoisomers and their conversion into the same product, *viz.*, (*M*)-**151** (*ee* 97%), take place.[216–218]

§ For the (*P*) and (*M*) nomenclature of atropo-hindered biaryls, see Ref. 222.

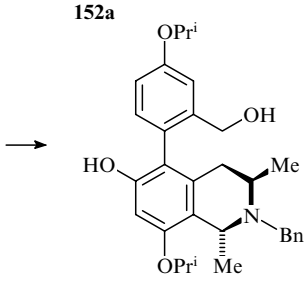


(*M*)-**150** (*M*)-**151**

This method was used by Bringmann for the total synthesis of naphthylisoquinoline alkaloids korupensamines. A mixture of lactones **152a** and **152b** (**152a** : **152b** = 4 : 96) was used as starting compounds, their reduction accompanied by kinetic resolution gives the key intermediate **153**.[219]

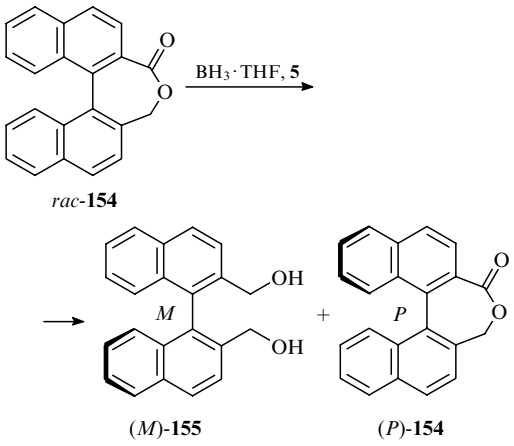


152a **152b**



153

The reduction of the racemic lactone **154** proceeds with high enantioselectivity in a similar way (k_{rel} = 50).[220] As in the case of compound **149**, only the (*M*)-isomer is reduced under these conditions; the configurationally stable isomer (*P*)-**154** remains in the reaction mixture and can be separated. A procedure was developed which allowed isolation of the product (*M*)-**155** and the starting compound (*P*)-**154** in 33% and 30% yields (*ee* 93% and 95%, respectively) at ~ 33% conversion.[220] After separation, the enantiomer (*P*)-**154** can be reduced to (*P*)-**155** using $LiAlH_4$. This conversion allows the preparation of both enantiomers of 2,2′-dihydroxymethyl-1,1′-binaphthyl **155**.



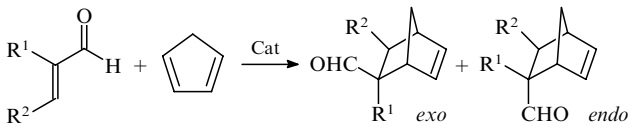
rac-**154**

(*M*)-**155** (*P*)-**154**

The reactions described in this section were also studied using quantum-chemical methods.[218,221]

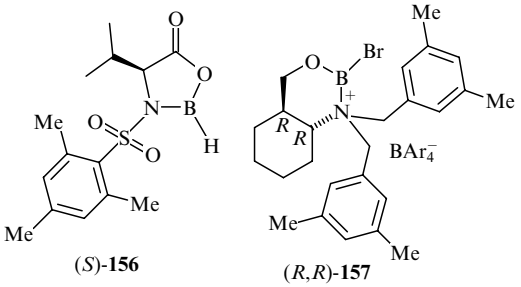
4. Cycloaddition reactions

The Diels–Alder reaction is one of the most popular reactions in organic synthesis. It is known that Lewis acids form complexes with the oxygen atom of the carbonyl group of dienophiles and thus increase its electrophilicity and facilitate the reaction. In this context, the idea of gaining control over the enantioselectivity of the Diels–Alder reaction using chiral 1,3,2-oxazaborolidines seems to be justified. One of the pioneering works [184] devoted to the use of 1,3,2-oxazaborolidines in the Diels–Alder reaction describes model reactions of acrolein, methacrolein and crotonaldehyde with cyclopentadiene.



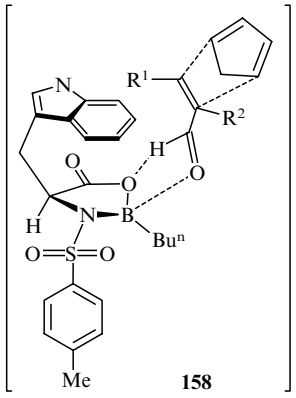
$R^1 = R^2 = H$; $R^1 = Me$, $R^2 = H$; $R^1 = H$, $R^2 = Me$.

The *exo* : *endo* ratio for methacrolein ($R^1 = Me$, $R^2 = H$) is 99 : 1 (*ee* of the *exo*-isomer is 86%), that for crotonaldehyde ($R^1 = H$, $R^2 = Me$) is 7 : 93 (*ee* of the *endo*-isomer is 59%). These reactions are catalysed by (*S*)-**125a** and (*S*)-**156**. The best results were obtained with the spatially hindered catalyst (*S*)-**156**. The use of (*S*)-**127a**–**c** and (*R*,*R*)-**157** as catalysts in the Diels–Alder reactions was first proposed by Corey.[223]



(*S*)-**156** (*R*,*R*)-**157**

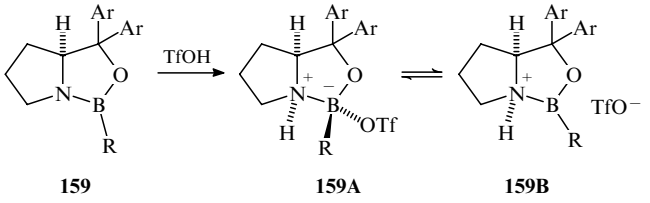
It has already been noted that high enantio- and diastereoselectivity of the Mukaiyama aldol condensations are determined by the complexation of 1,3,2-oxazaborolidin-5-ones with aldehydes and the formation of a stable intramolecular hydrogen bond C–H···O–B.[191] The same was observed for the reaction of the aldehydes $R^2CH=CR^1CHO$ with cyclopentadiene in the presence of the catalyst (*S*)-**127c** (the structure of the intermediate **158** formed is similar to that of the intermediate **131**).



158

The structure of the complex **158** determines the regio- and stereoselectivity of the Diels–Alder reaction.

An increase in the Lewis acidity of the catalyst increases the stability of the 1,3,2-oxazaborolidine–aldehyde complex and, correspondingly, the enantioselectivity of the reaction. Recent studies by Corey have shown [224] that this effect can be attained if 1 equiv. of CF_3SO_3H (TfOH) is added to the reaction mixture.

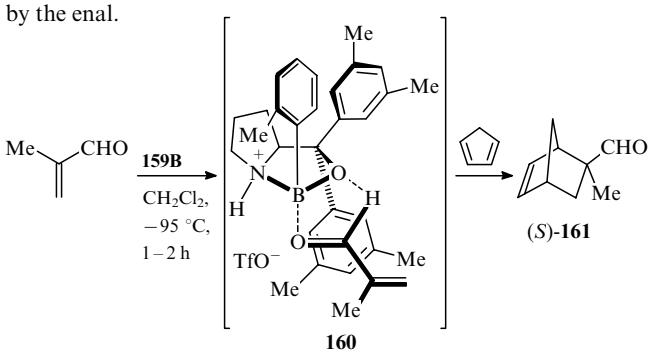


159 **159A** **159B**

R = Me, Bu, Ph, 2-MeC_6H_4, 1-naphthyl;
Ar = Ph, 2-naphthyl, 3,5-$Me_2C_6H_3$.

^{1}H NMR spectroscopy has shown that two forms of the catalyst **159**, *viz*., **A** and **B**, exist in solution at equilibrium at −78 °C in the presence of TfOH.[224]

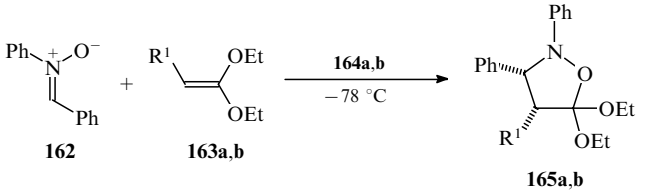
The coordination of the electron-deficient methacrolein in the complex **160** occurs in such a way that its donor–acceptor π–π interaction with the π-electrons of the aromatic ring of the Ar-substituent in the *cis*-position of the C(5) atom of 1,3,2-oxazaborolidine **159** is possible.[224] As a result, the enantioselectivity of the reaction increases. Thus the bulky 3,5-dimethylphenyl group (as an Ar substituent) effectively shields the rear-side attack by the enal.



160

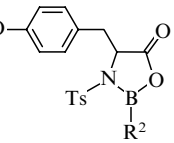
The addition of 6 mol.% of TfOH is sufficient to obtain good results. The yield of the product **16** is 73%–98%, the *exo* : *endo* ratio varies from 83 : 17 to 93 : 7 and *ee* varies from 75% to 91%. The best results were obtained when the catalyst **159** where R = 2-MeC_6H_4 and Ar = 3,5-$Me_2C_6H_3$ was used. In this case, the yield of the product **161** was 99%, *ee* was 96%, the *exo* : *endo* ratio was 89 : 11. This reaction does not occur in the presence of the spatially hindered catalysts **159** (R = 2-$Pr^iC_6H_4$, 2,6-$Me_2C_6H_3$). The addition of $MeSO_3H$ instead of CF_3SO_3H does not favour the reaction (in this case, the yields of the products do not exceed 30%).

Along with [4 + 2]-cycloaddition 1,3-dipolar cycloaddition was also studied.[180, 183, 225–230] However, the use of 1,3,2-oxazaborolidin-5-ones in the 1,3-dipolar cycloaddition did not give any positive results. When the reaction of diphenylnitrone **162** with the ketene acetals **163a**,**b** was carried out in the presence of the catalysts (*S*)-**164a**,**b** (20 mol.%), the yields of the products **165a**,**b** did not exceed 10%, although the enantioselectivity of the reaction was rather high: *ee* was 74% (for **165a**) and 62% (for the *cis*-isomer of **165b**).[226, 227]



162 **163a**,**b** **165a**,**b**

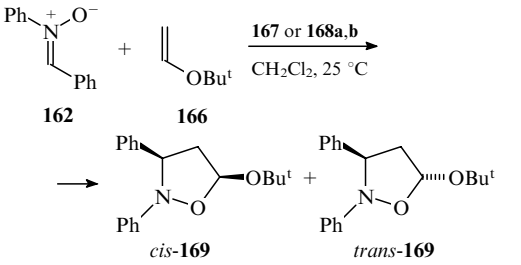
R^1 = H (**163a**, **165a**), Me (**163b**, **165b**);

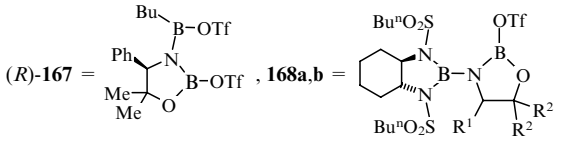
164a,**b** =  [R^2 = H (**164a**), Bu (**164b**)].

The 1,3-dipolar cycloaddition of the nitrone **162** to the electron-enriched alkene **163** is an example of a reaction with reverse electronic requirements. In this reaction, the catalyst **164** was used for the enantioselectivity control, since it was believed that a prominent role in such reactions is played by the donor–acceptor π–π interactions of the catalyst and the reagent in the transition state. The benzyloxy group of the catalyst **164** meets this requirement, since it interacts with the phenyl groups of the nitrone **162**.[227]

The enantioselectivity of this reaction drops drastically with an increase in temperature: at −78 °C, compound **165b** is formed with *ee* 62%, while at 25 °C *ee* is 38%. The product yields and reaction stereoselectivity also depend on the solvent.[227] Thus the reaction in THF catalysed by compound **164a** yields the isomer (−)-**165b** with *ee* 62%, whereas the reaction carried out in diphenyl ether, nitrobenzene or nitroethane gives the isomer (+)-**165b** with *ee* 79%. The yields of (−)- and (+)-**165b** are 33% and 60%, respectively.

The 1,3-dipolar cycloaddition of the nitrone **162** to the enal **166** in the presence of the catalyst (*R*)-**167** or **168a**,**b**[230] yields a mixture of isomers *cis*-**169** and *trans*-**169** in the *cis* : *trans* ratio of 1 : (8–9). In this case, the product yields are 44%–67%. The enantioselectivity of this reaction is rather low: the enantiomeric excess of *cis*-**169** in the reaction catalysed by (*R*)-**167** is 57%, while *ee* of *trans*-**169** in the presence of catalysts **168a** and **168b** are 8% and 19%, respectively.





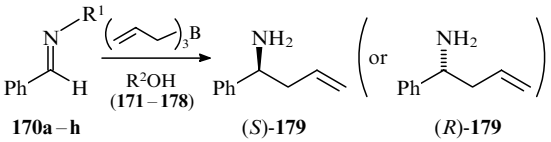
R^1 = Ph, R^2 = Me (**168a**);
R^1 = Bu^t, R^2 = H (**168b**).

The catalysis of the Diels–Alder reaction by 1,3,2-oxazaborolidines covalently bound to a polymeric matrix is also possible.[231, 232]

5. Miscellaneous reactions

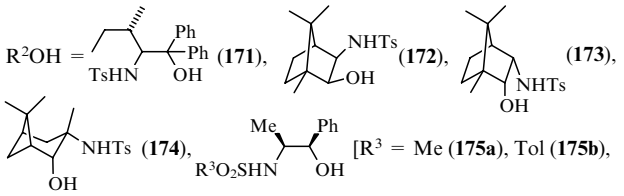
The asymmetric allylation of imines **170a**–**h** by triallylborane in the presence of chiral amino alcohols R^2OH (**171**–**178**) has been described by Itsuno *et al.*[233]

The yields of 1-phenylbut-3-enylamine (**179**) vary from 12% to 90%. Depending on the nature of the imine used, either the (*S*)- or the (*R*)-isomer **179** with *ee* 10%–72% is formed. The best yields of (*S*)-phenylbut-3-enylamine (**179**) (64%–93%, *ee* 78%–96%) were obtained if (1*R*,2*S*)-norephedrine derivatives

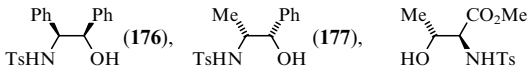


170a–**h** (*S*)-**179** (*R*)-**179**

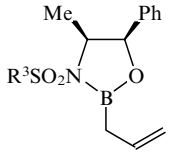
R^1 = *p*-MeOC$_6$H$_4$ (**170a**), Tr (**170b**), OMe (**170c**), OAc (**170d**), SPh (**170e**), Ts (**170f**), P(O)Ph$_2$ (**170g**), SiMe$_3$ (**170h**);



o-NO$_2$C$_6$H$_4$ (**175c**), 1-naphthyl (**175d**), 2-naphthyl (**175e**)],

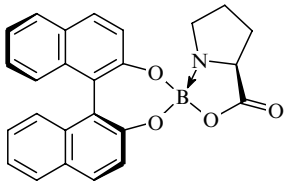


175a–**d** were used as catalysts. In the authors' opinion, this reaction occurs *via* the intermediate 2-allyloxazaborolidines of the type **180**.

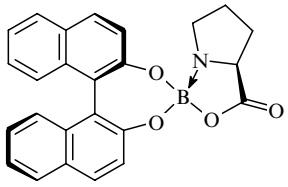


180

The chelate compounds **181** and **182** based on borates incorporating (*S*)-Pro were used for effective resolution of racemic 1,1′-bi-2-naphthol into enantiomers.[234]



181



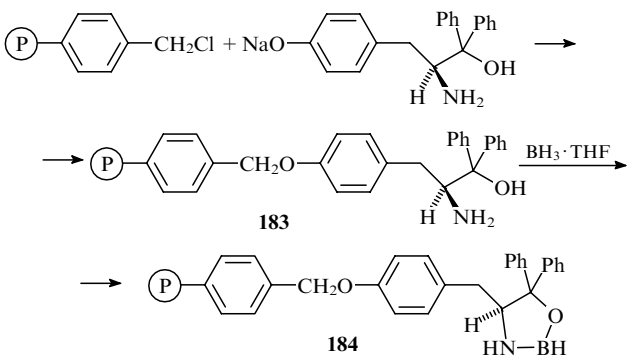
182

The use of oxazaborolidines for enantiomeric cleavage of epoxides by amines has been described.[235]

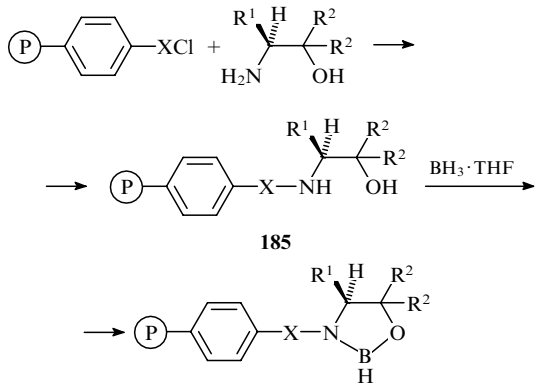
V. Reduction by immobilised 1,3,2-oxazaborolidines

Immobilised (polymer-bound or solid-phase) catalysts have a number of advantages over homogeneous catalysts, *e.g.*, they are easily separated from the reaction mass and can be used repeatedly.[158]

Several approaches to the synthesis of immobilised oxazaborolidines are known. First, the reaction of chloromethylated cross-linked polystyrene with amino alcohols containing phenol-type linkers (particularly, with tyrosine derivatives [156, 231, 236, 237]) yields the immobilised amino alcohol **183**, its reaction with $BH_3 \cdot THF$ affords the immobilised oxazaborolidine **184**.



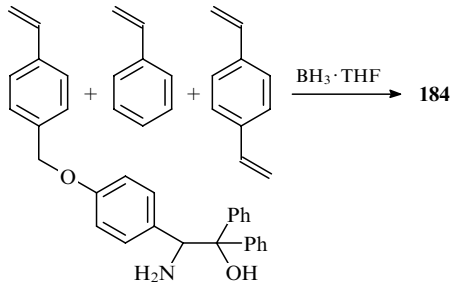
Second is *N*-alkylation or *N*-acylation of chiral amino alcohols by a reactive polymeric reagent with subsequent reaction of the intermediate **185** formed with $BH_3 \cdot THF$.[231, 232, 237–241]



185

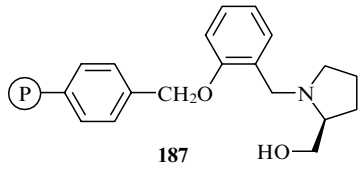
X = CH_2, SO_2; R^1 = Alk; R^2 = H, Alk, Ar.

The third approach entails suspension radical copolymerisation of the chiral monomer **186**, containing an amino alcohol fragment with styrene and divinylbenzene[156, 231, 242–244] in the presence of $BH_3 \cdot THF$.



186

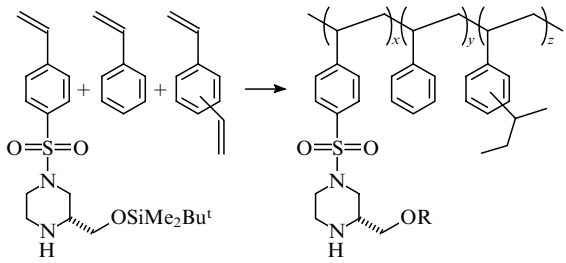
The enantiomeric excess in the reduction of butyrophenone by $BH_3 \cdot THF$ to (*R*)-1-phenylbutan-1-ol in the presence of the system **183** was 88%. The best results (*ee* 92% – 97%) were achieved in the reduction of acetophenone in the presence of the catalyst **187**.[156]



187

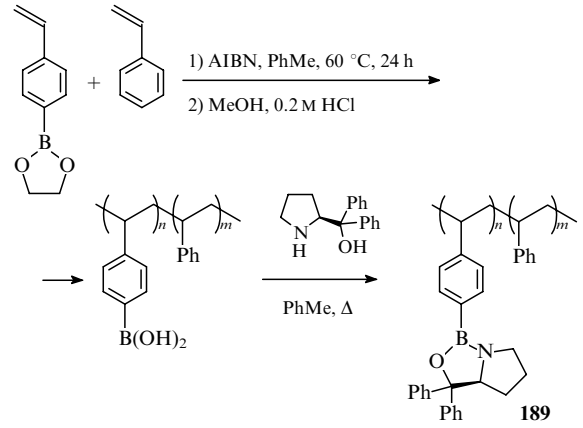
The immobilised reagent **184** was also used in the reduction of ketoxime ethers;[156] however, in this case the optical yields did not exceed 26%. The addition of Lewis acids ($AlCl_3$, $ZnCl_2$, $BF_3 \cdot OEt_2$) accelerated the reduction and increased the optical yields to 42% – 67%.[158]

Later,[158] a copolymer of a chiral monomer **188** with styrene and divinylbenzene was synthesised. With the molar content of the chiral ligand of 20% and of divinylbenzene of 10% (or 2%) (the degree of cross-linking), this compound catalysed the asymmetric reduction of acetophenone *O*-methyloxime to (*R*)-2-phenylethylamine by $BH_3 \cdot THF$ in 60% (or 65%) yield and *ee* 82% (or 96%). Repeated (5 times) use of the catalyst is possible without any loss of stereoselectivity (*ee* ~ 95%) for the divinylbenzene content of 2%.



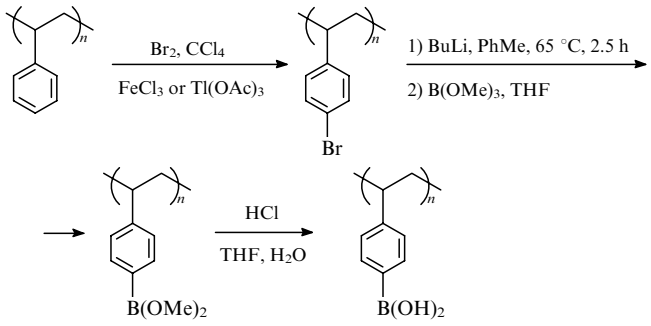
188 (R = $SiMe_2Bu^t$, H)

Immobilised 1,3,2-oxazaborolidines **189** can also be prepared from immobilised boronic acid.[237, 245–247]



AIBN is azobisisobutyronitrile.

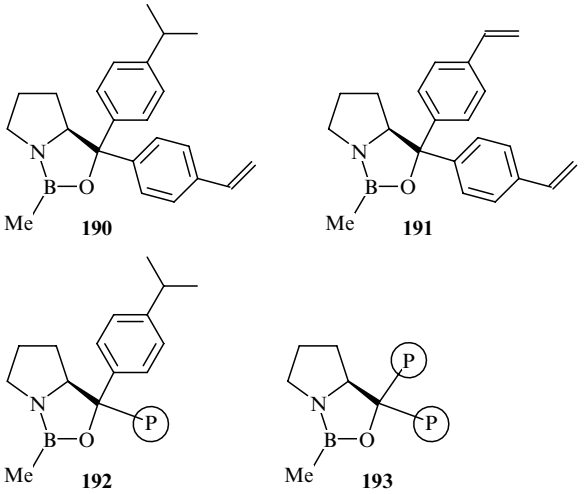
The boronic acid residue can be introduced into polystyrene using the following reaction sequence:[245–247]



Copolymerisation of a mixture of 2-vinylthiophene, styrene and *p*-divinylbenzene is also used for the synthesis of immobilised boronic acid.[247, 248] The resulting thiophene-containing polymer reacts smoothly with n-butyllithium to give the corresponding thiophene-lithiated product, which makes the bromination step unnecessary and increases the final yield of the catalyst. Subsequent synthesis of the polymer containing oxazaborolidine groups can be carried out *in situ* using the system $NaBH_4$ – Me_3SiCl (or $BF_3 \cdot OEt_2$).[239] Reduction of ketones in the presence of this catalytic system is carried out in THF[239–241, 247] or in toluene[241] (the optimum temperatures are 60 – 110 °C, the amount of the catalyst is 0.1 – 0.2 equiv. per equiv. of the substrate; the yields of the secondary alcohols are 87% – 98%, the optical purity is 86% – 96%).[240, 249] The reduction by heterogeneous polymeric catalysts is usually carried out in flow reactors; otherwise, the separation of the catalyst by filtration is necessary. Repeated use[250] and fivefold regeneration[241] of the catalyst with an insignificant (up to 5% *ee*) loss of enantioselectivity are possible.

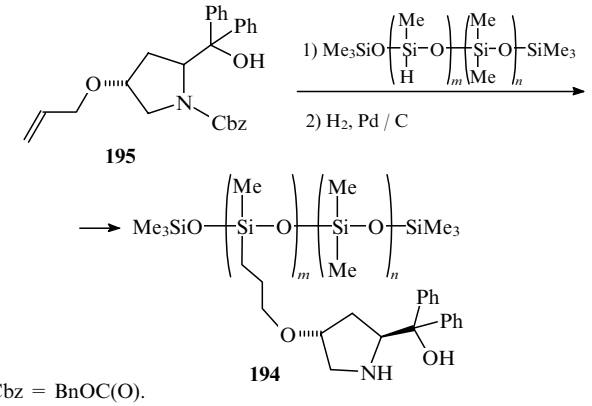
The synthesis of immobilised 1,3,2-oxazaborolidines by copolymerisation of compounds **190** or **191** with styrene and

p-divinylbenzene resulting in the polymeric catalysts **192** and **193** has recently been described.[249] The reduction of acetophenone by the $BH_3 \cdot THF$ complex in the presence of the catalyst **193** gave (*R*)-1-phenylethanol in 100% yield and with *ee* 84.8%, whereas the reduction of pinacoline affords the (*R*)-isomer of the corresponding secondary alcohol with *ee* 88.4%.



190 **191** **192** **193**

These data suggest that in some cases heterogeneous polymer-bound 1,3,2-oxazaborolidines compare well with homogeneous catalysts in efficiency.[240,245] It should be noted, however, that high values of *ee* were obtained only for polymers with a low (up to 2%) degree of cross-linking, *i.e.*, with low mechanical stability, which limits their industrial application.[238,241] An increase in the extent of cross-links hampers the diffusion of the substrate and the reducing agent within the polymer and thus increases the contribution of competitive non-catalytic reduction of the substrate and decreases its enantioselectivity.[245] This may account for the low selectivity of the reduction carried out in the presence of heterogeneous catalysts prepared by suspension copolymerisation.[245] This has prompted an idea to use homogeneous microgels soluble in organic solvents (THF, toluene) as carriers for oxazaborolidines.[237,245,251,252] To this end, the polymer **194** was prepared, which can be converted *in situ* into homogeneous immobilised oxazaborolidine manifesting a strong catalytic effect. The polymer **194** is formed upon palladium-catalysed hydrosilylation of the allyloxyprolinol derivative (2*S*,4*R*)-**195** by a copolymer of methylhydrosiloxane with dimethylsiloxane. In the presence of this catalyst, aromatic ketones are reduced to secondary alcohols with *ee* 89% – 98% (yields 83% – 89%).[251]



195 **194**

Cbz = BnOC(O).

Reaction products are separated from polymeric catalysts by nanofiltration in a membrane reactor.[237,252] Since the conversion of the ketone reaches ~ 100%, the solvent is distilled off at the outlet of the reactor; the reaction products are isolated by vacuum distillation.[252] The catalyst remains in the reactor and can be used in the next conversion cycle.

The preparation of a homogeneous polymeric microgel, which contains an oxazaborolidine fragment based on cheap (*S*)-diphenylalaninol, is a remarkable achievement of the Wulff group.[245] The radical polymerisation was carried out in strongly dilute solutions to prevent macrogel formation; ethylene dimethacrylate was used as a cross-linking agent. The reduction of aromatic ketones in the presence of this catalyst gives alcohols with *ee* 87% – 94%.[245] The weak spot of the given technology is the low activity of the microgels prepared using this method [the number of moles of the product per mole of the catalyst (turnover number) is 10 – 50]. The Kragl group[237] have succeeded in increasing the turnover number of the catalyst to 560. Later, the productivity of the membrane reactor was increased to 1.4 kg litre^{-1} day^{-1}; the deactivation rate of the catalyst was 1.8% per hour.[252] The efficiency of this catalytic system can be judged from the fact that the efficiency of enzymatic reduction of the same ketones by alcohol dehydrogenase is significantly lower (88 g litre^{-1} day^{-1}), which is attributed to low solubility of the enzyme in water.[252] On the whole, the use of homogeneous microgels in asymmetric catalysis is becoming more and more popular; considerable progress in this area should be expected in the near future.

A heterogeneous catalyst based on nickel boride nanoparticles coated with oxazaborolidine has been developed[253] aimed at combination of the advantages of a heterogeneous (easy separation of the catalyst) and homogeneous (high efficiency) catalysis. The catalyst with the formula $NiB_{2-0.1}$ (oxazaborolidine)$_{0.1}$ was synthesised *in situ* from (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol or (1*R*,2*S*)-(−)-norephedrine and nickel salts $NiI_2 \cdot 6\ H_2O$ or $NiCl_2 \cdot 6\ H_2O$. This catalyst reduces acetophenone rapidly and with high enantioselectivity (*ee* of the alcohol is 90%) and can be used repeatedly. To ensure good selectivity, the ketone should be added to a catalyst – $BH_3 \cdot THF$ mixture at a very slow rate.

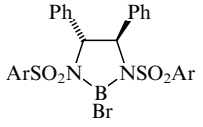
Catalytic reduction of aromatic ketones by the complex $BH_3 \cdot SMe_2$ in the presence of 0.1 equiv. of a chiral dendrimer based on 3,5-dihydroxybenzyl alcohol or 4,4-bis(4-hydroxyphenyl)pentanol with (*S*)-2-amino-3-(4-hydroxyphenyl)-1,1-diphenylpropan-1-ol linked through the phenolic group has been described.[254] The yields of the alcohols are 75% – 82%, *ee* is 82% – 96%. Homogeneous dendrimeric catalysts seem promising, since their application gives higher values of *ee* than the heterogeneous polymeric systems.[254]

The use of immobilised catalysts of the type **187** in enantioselective Diels – Alder reactions,[231,232] aldol condensation[242] and for addition of diethylzinc to aldehydes has been described.[247]

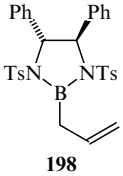
VI. 1,3,2-Oxazaborolidine analogues

1. 1,3,2-Diazaborolidines

1,3,2-Oxazaborolidine analogues, particularly diazaborolidines **196** – **198** recommended by Corey,[255,256] are widely used in asymmetric synthesis.



196, **197**

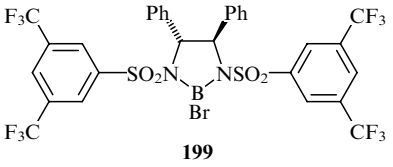


198

Ar = *p*-MeC_6H_4 (**196**), *p*-$NO_2C_6H_4$ (**197**)

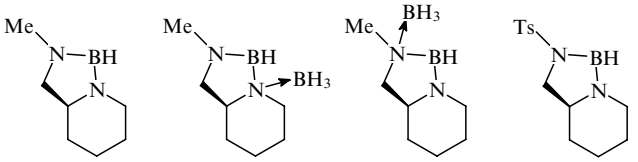
Compounds **196** and **197** catalyse stereoselective aldol condensation,[255] whereas compound **198** is a highly efficient enantioselective allylating reagent for the synthesis of chiral allylic alcohols with *ee* > 90%.[256]

It is known that the introduction of a trifluoromethyl group into the aromatic ring of the arylsulfonyl residue increases the Lewis acidity of the boron atom. This fact was used in the design of an effective catalyst of aldol condensation, **199**. Corey *et al.* used compound **199** for the enantioselective synthesis of aldehydes [257, 258] and D-*threo*-*N*-acetylsphingosine.[259]



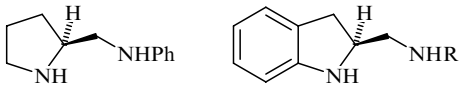
199

1,3,2-Diazaborolidine **200** was recommended as a catalyst for enantioselective reduction of prochiral ketones by boranes,[260] however, the *ee* in the reduction of acetophenone was low (40%). Two types of complexes of compound **200** with borane, *viz.*, **201a** and **201b**, were detected in THF by ^{11}B NMR spectroscopy; their competition accounts for low optical yields of the alcohol in this reaction. The use of compound **202** as a catalyst with a tosyl group at the nitrogen atom has made it possible to increase the enantioselectivity [the yield of (*S*)-1-phenylethanol was 95%, *ee* was 72%].



200 **201a** **201b** **202**

Chiral diamines **203**–**205** were recommended as an alternative to amino alcohols in the enantioselective reduction of prochiral ketones.[261]

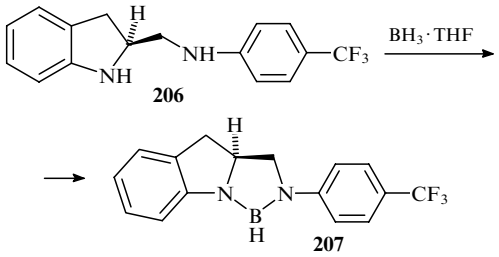


203 **204**, **205**

R = Ph (**204**), cyclo-C_6H_{11} (**205**).

Compound **204** appeared to be the most efficient of them.

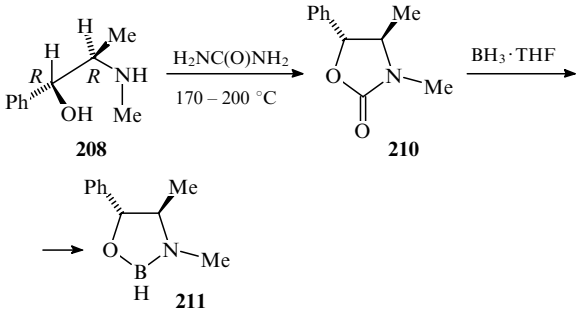
The introduction of electron-withdrawing groups (*e.g.*, CF_3) into the aromatic ring has led to more efficient catalysts; of those, compound **206** appeared to be the best in the reduction of acetophenone [the yield of (*S*)-1-phenylethanol was 88%, *ee* was 92%].



206 **207**

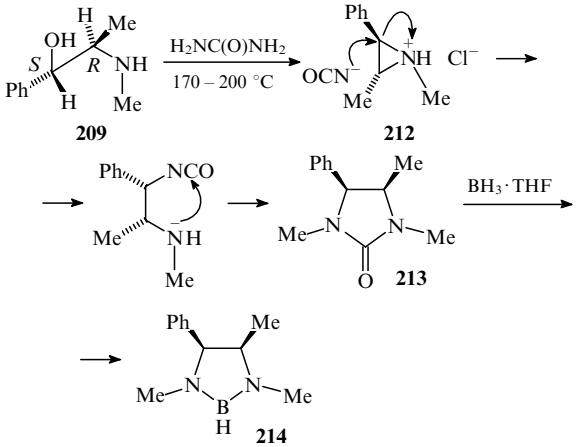
This reduction was carried out in THF at −15 °C in the presence of 0.15 equiv. of the chiral diamine and 1 equiv. of $BH_3 \cdot THF$, the reaction time was 2 h. This reaction is believed to proceed *via* 1,3,2-diazaborolidine **207** formed *in situ*. Other aromatic ketones were reduced in 88%–96% yields and with *ee* 82%–92%.[261] Thus, the electron-withdrawing groups increase the acidity of the boron atom, which results in its better coordination to the ketone carbonyl and, as a consequence, increases the optical yield of the final product.

Synthesis of heteroborolidines from pseudoephedrine (**208**) and ephedrine (**209**) has been described.[262–264] It was found that pseudoephedrine reacts with urea to give oxazolidinone **210**, which is converted into 1,3,2-oxazaborolidine **211** upon subsequent treatment with borane (this reaction is yet another method for the synthesis of 1,3,2-oxazaborolidines).

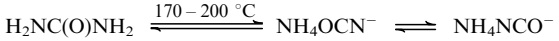


208 **210** **211**

Ephedrine reacts with urea in a different way. Intramolecular cyclisation of ephedrine **209** and subsequent nucleophilic attack by the cyanate ion formed from urea at 170–200 °C on the intermediate **212** gives *cis*-imidazolidinone **213** which yields 1,3,2-diazaborolidine **214** after reduction with borane.[262] The stereochemistry of compounds **212** and **214** was established by heteronuclear $^1H/^{13}C$ NMR and that of compound **213**, by X-ray diffraction analysis.

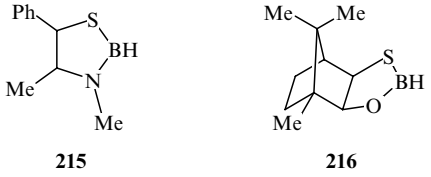


209 **212** **213** **214**



2. 1,3,2-Oxathia- and 1,3,2-azathiaborolidines

1,3,2-Azathiaborolidines (*e.g.*, **215**) [263, 264] and 1,3,2-oxathiaborolidines (*e.g.*, **216**) can be used, along with 1,3,2-oxazaborolidines, as catalysts in enantioselective ketone reduction reactions.[265, 266] 1,3,2-Azathiaborolidine **215** was synthesised from pseudoephedrine.[263, 264]



215 **216**

Compound **216** catalyses the reduction of acetophenone by the complex $BH_3 \cdot SMe_2$ to (*S*)-1-phenylethanol with *ee* 92%.

* * *

The present review demonstrates that chiral 1,3,2-oxazaborolidines occupy a prominent place in the arsenal of modern reagents for asymmetric synthesis owing to their high efficiency in enantioselective reduction of prochiral ketones, imines and oxime ethers. Being representatives of chiral Lewis acids, 1,3,2-oxazaborolidines can also be used as effective catalysts in stereoselective Diels–Alder reactions, aldol condensation, cleavage of acetals and atroposelective resolution of spatially hindered lactones. This trend has been developing especially intensively in the past decade and entails a search for novel highly efficient catalysts, their application in the production of enantiomerically pure drugs, their modification by immobilisation on polymers and dendrimers and broadening of the range of reactions catalysed by them.

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