Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2225–2259

TETRAHEDRON: *ASYMMETRY*

TETRAHEDRON: ASYMMETRY REPORT NUMBER 51

Enantioselective reductions by chirally modified alumino- and borohydrides†

Paola Daverio[a] and Matteo Zanda[b,c,*]

[a]*Honeywell PFC Italiana S.r.l., R&D Department, Bulciago (LC), Italy*
[b]*Dipartimento di Chimica del Politecnico di Milano, via Mancinelli 7, I-20131 Milan, Italy*
[c]*CNR, Centro di Studio sulle Sostanze Organiche Naturali, via Mancinelli 7, I-20131 Milan, Italy*

Received 9 August 2001; accepted 11 September 2001

Abstract—Fifty years after the first report on the reduction of carbonyl compounds using chiral $LiAlH_4$-derived hydrides (Bothner-By, A. A. *J. Am. Chem. Soc.* **1951**, *73*, 846), the field of enantioselective aluminohydride and borohydride reagents modified by chiral additives is reviewed. The first section deals with the preparation, scope, limits, mechanism of action and synthetic applications of chiral aluminohydrides, classified according to the chemical nature of the stereogenic modifier. The second covers the field of chiral borohydrides, which have been further classified according to the boron sources, namely metal borohydrides (via reaction with chiral additives or in the presence of chiral catalysts), or chiral boranes (by reduction with alkyllithiums or metal hydrides).

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* Corresponding author. Fax: +39-02-2399 3080; e-mail: zanda@dept.chem.polimi.it
† This review is dedicated to Valentina, on the very special occasion of her first birthday.

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00395-0

1. Introduction

One of the most important reactions in asymmetric synthesis is the enantioselective reduction of prostereogenic functions, such as C=O, C=N and C=C bonds. A number of methodologies featuring variable degrees of efficiency and generality are now available, spanning (a) hydrogenation over chiral catalysts, (b) the reductions catalysed by enzymes or microorganisms, (c) stoichiometric reactions performed by chiral organic reducing agents (for example boron derivatives), and (d) reductions by inorganic hydrides in the presence of chiral additives, to mention just four of the main classes of reactions. Several general reviews on the topic have been published,[1] but an updated and specific review of inorganic hydrides has not been published for several years.[2] This paper is conceived to fill, at least in part, this gap, by presenting an overview of about 50 years of research aiming at the development of enantioselective alumino- and borohydride reagents modified by chiral additives.

According to E. J. Corey,[3] the use of chirally modified aluminohydride and borohydride reagents in asymmetric synthesis has so far proved disappointing due to the empirical character and limited experimental practicality affecting some of the work in this area, as well as to the often uncertain nature of the reducing species and their mode of action, which together can represent a source of low reliability and lead to poorly reproducible results. Therefore, these reagents have seen relatively limited practical synthetic application for the extensive research efforts and the good levels of stereocontrol obtained in a number of cases. However, we believe that many chiral aluminohydrides and borohydrides have already fully demonstrated their reliability and synthetic effectiveness, playing a key role in a number of routes to important target compounds, as shown in the following sections of this review. Noyori's (BINAL-H) and Sharpless' reagents, complexes between $LiAlH_4$ and Darvon-alcohol (CHIRALD®) or TADDOL, Alpine Hydride®, NB-Enantride™ are examples of these popular reagents, some of them commercially available, which find current widespread use in asymmetric synthesis. Moreover, as often happens in basic research, the studies in the field of enantioselective hydride reducing agents have generated a considerable amount of scientific insight, paving the way for extraordinary achievements. For example, one of the most powerful synthetic weapons currently available in the arsenal of an organic chemist, namely the Corey's chiral oxazaborolidine catalysts,[3] directly stems from the seminal work of Itsuno with mixtures of 1,2-amino alcohols and BH_3,[4] which is correlated with other work employing 1,2-amino alcohol/$NaBH_4$/Lewis acid mixtures (see Ref. 167).

We would like to emphasise that some recent achievements where novel sources of stereoinduction or solid-supported catalysts or reagents are used, show that the field is remarkably vital, and that further breakthroughs might be just around the corner. Finally, one should keep in mind that the ready availability and low cost of starting materials such as $LiAlH_4$ and $NaBH_4$ will continue to boost research by industrial and academic groups in a continuing effort to replace more expensive and less user-friendly reagents.[5]

2. Chirally modified aluminohydrides

Lithium aluminium hydride (LAH)[6] has been extensively used for the preparation of chirally modified enantioselective reducing agents due to its low cost and high reactivity, in combination with a number of different sources of chirality, namely alcohols and diols, amino alcohols, amines and diamines, sulphamides, and porphine-type nickel complexes.

2.1. Alcohols and diols as ligands

The first ligands used as chiral modifiers for LAH were alcohols such as (−)-menthol, (+)-isoborneol, and diols.[7] The chiral reducing agent was generally obtained from LAH and the ligand, according to the following reaction:

$$LiAlH_4 + n\,ROH \rightarrow [LiAlH_{(4-n)}(OR)_n] + n\,H_2$$

This approach gave very poor results because of the tendency of the resulting complex to disproportionate in solution. The consequent formation of several reducing species in the reaction medium, in particular the highly reactive achiral LAH, gave rise to low stereoselectivities.

$$2\ LiAl(OR)H_3 \rightarrow LiAl(OR)_2H_2 + LiAlH_4$$

Good stereochemical results (enantiomeric excesses of up to 95%) using $LiAlH_4$/menthol complexes were obtained only in the reductions of α- and β-amino ketones. The observation that 2-acetylpyridine afforded the corresponding alcohol with 44% optical purity, while 4-acetylpyridine gave a racemic alcohol strongly supports the hypothesis of participation of nitrogen in the transition state.[8]

Yamaguchi and Kabuto came to the same conclusions in 1977.[9] They examined the reduction of several ω-substituted alkyl phenyl ketones [$PhCO(CH_2)_nY$] with LAH/menthol complexes. In fact, if $Y = OCH_3$ or NR_2, product e.e.s were higher than with Y = SMe or Et, even though the steric requirements are expected to be similar. The enantioselectivity was also found to depend on the number of methylene groups (n), the best results being with $n = 2$ or 3. Addition of TMEDA resulted in decreased product e.e., thus supporting participation of Li^+ in the complexation.

In 1966, Landor et al.[10] began a study of LAH/asymmetric cyclic diol complexes. The idea was that cyclic diols should provide more stable complexes than acyclic ones, and therefore be less prone to disproportionation. Monosaccharide derivatives were chosen as chiral ligands because of their low cost and ready availability. In particular, LAH/3-*O*-benzil-1,2-cyclohexylidene-α-D-glucofuranose complex proved to be better than others,

although stereoselectivity was low (e.e.s of 1–10%). The authors were able to suggest a predictive model **1** (Fig. 1) for the reductions, hypothesising a bimolecular mechanism involving the ketone and the complex.[11]

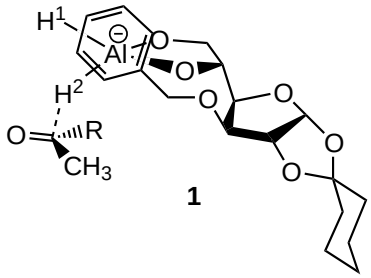


Figure 1.

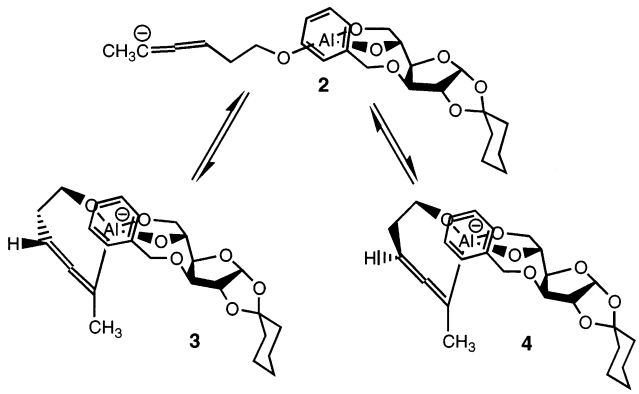
The residual hydrides, H^1 and H^2, on aluminium are not equivalent, because H^1 is shielded by the benzyl protective group. Thus, H^2 is the most reactive hydride. The carbonyl oxygen points away from the oxygens of the aluminium complex. This transition state accounts for the predominant formation of (*S*)-alcohols in the reduction of both methylalkyl ketones and acetophenone. This hypothesis is supported by the observation that, if 1 equiv. of ethanol is added to the complex, (*R*)-configured alcohols are obtained with higher stereoselectivities.[12] The most reactive hydride, H^2, is in fact removed and the reduction is accomplished by H^1. Similar considerations seemed to apply in the reduction of *N*-phenyl imines by the same complex, to give optically active primary amines and also in the reduction of ketoxime-*O*-alkyl ethers.[13] The reduction of unsubstituted ketoximes[14] involves two molecules of substrate. In fact the most reactive hydride, H^2, deprotonates the ketoxime hydroxyl group, but the resulting complex incorporating the ketoxime fragment cannot react intramolecularly because the reactive sites, C=N and H^1, are too far from each other. Thus, the reduction requires the participation of a second LAH–monosaccharide complex with intermolecular hydride transfer, affording (*S*)-configured amines. In agreement with the model, addition of 1 equiv. of primary alcohol provided (*R*)-amines.

Later, the same authors investigated the possibility that the stereoselective reduction with LAH/3-*O*-benzil-1,2-cyclohexylidene-α-D-glucofuranose complex could be piloted by steric and electronic interactions between the benzyl protective group and substituents on the chiral substrate. Thus, the low asymmetric inductions observed in the reduction of aromatic ketones and ketoximes could result from π–π interaction with the aromatic moiety.[15] This hypothesis was checked by replacing the benzyl moiety with a cyclohexyl group. The resulting complex failed to give better results with aromatic ketones, while e.e.s in the reduction of ketoximes were three times higher. This behaviour was explained by supposing that in the intermediate LAH/glucofuranose/ketoxime complex the higher bulk of the cyclohexyl group shields the residual H^1 sterically.

Complex **1** was also used for the stereoselective reduction of enynols to (*R*)-allenic alcohols, giving e.e.s of up to 12%.[16]

$$RC{\equiv}CCH{=}CHCH_2OH \rightarrow RCH{=}C{=}CHCH_2CH_2OH$$

The reduction is thermodynamically controlled and two different diastereomeric complexes **3** and **4** (Scheme 1) are likely formed. The initial hydride transfer produces the delocalised anion **2**, and the allenic system becomes stereogenic only after complexation by the trivalent aluminium. The intermediate complexes **3** and **4** are eventually hydrolysed to the chiral β-allenic alcohols. This hypothesis was confirmed by performing the enynol reduction directly with LAH, followed by addition of the ligand. As expected the stereochemical outcome of the reaction was unchanged.



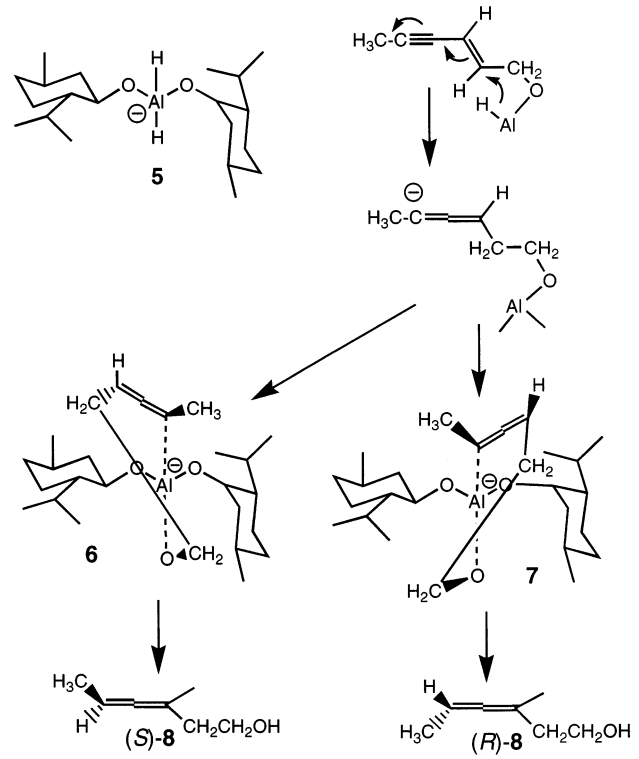
Scheme 1.

An analogous mechanistic hypothesis, involving the formation of diastereomeric seven-membered cyclic transition states in equilibrium (**6** and **7**, Scheme 2), was applied to interpret the outcome of the reduction of enynols with LAH/bismenthyloxy complex **5**. In this case, (*S*)-allenic alcohols **8** were obtained (no e.e. data was provided).[17]

Poor stereoselectivity was obtained with complexes derived from rigid diols such as (+)-1,2,2-trimethyl-1,3-bis(hydroxymethyl)cyclopentane (**9**, Fig. 2), easily prepared in one step from (+)-camphoric acid,[18] and *cis*-2,3-pinanediol **10**.[19]

In both cases, when 1 equiv. of achiral primary alcohol (ethanol, benzyl alcohol or isopropanol) was added to the reducing medium, lower yields but higher stereoselectivities were obtained, due to the removal of one of the diastereotopic hydrogens. Product e.e.s were nevertheless rather low. Low e.e.s were also obtained with LAH/terpenic glycol complexes.[20]

Very high e.e.s were achieved with the reducing complex LAH/1,1′-bi-2-naphthol/primary alcohol **11**, (Fig. 3), published by Noyori in 1979,[21] which represented a breakthrough in this area. In fact, Noyori's complex (also called BINAL-H) provided a solution to some of the problems met with other reducing complexes (dis-



Scheme 2.

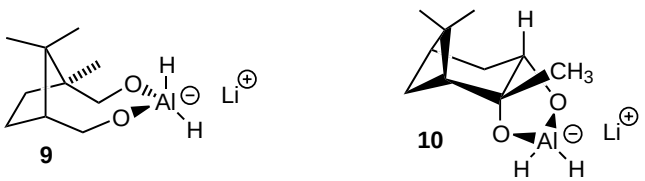
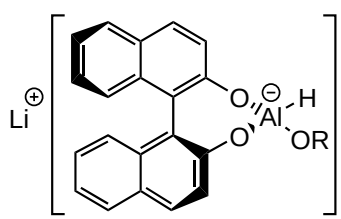


Figure 2.

proportionation, variety of aggregation states, variety of conformations, different reducing agents in solution). The main drawback of the method is probably the high commercial price of the ligand (50–65 Euros per gram), combined with its difficult recovery and recycling. Binaphthol is a bidentate ligand which gives a stable, conformationally mobile complex with LAH. As it belongs to symmetry group C_{2v}, the residual hydrides on aluminium are homotopic.



11 BINAL-H (Noyori's complex)

Figure 3.

The presence of 1 equiv. of alkoxide makes the complex almost completely soluble in THF (a homogeneous reaction medium is considered important in order to obtain a high degree of enantioselectivity) and induces high e.e.s that are also strongly dependent on the nature of the primary alcohol used. Without primary alcohol, enantioselection is low (2% e.e. in the reduction of acetophenone), possibly because of disproportionation or lack of enantioface-differentiating properties.

The complex is a very good reducing agent for alkylphenyl ketones (95% e.e.) (with some exceptions),[22] α-halo ketones and conjugated enones,[23] while it does not give good results with dialkyl ketones. Good results were obtained also with aryl trifluoromethyl ketones, especially those having two *ortho*-substituents.[24] In contrast, 1,1,1-trifluoro-4-phenyl-buten-2-one was reported to undergo reduction by BINAL-H without any stereoselectivity, providing the corresponding allylic alcohol as a racemic mixture.[25] However, a very recent paper by Prakash, Petasis and Olah described the successful reduction of the same substrate by (*S*)-**11** (3 equiv.) to the (*S*)-alcohol with 94% yield and 71 e.e., although better results in terms of enantiocontrol were achieved with Corey's oxazaborolidine catalysts (which gave up to 75% e.e. for the (*S*)-enantiomer).[26]

As a general rule, the direction of stereoselectivity is the same for phenyl, alkenyl and alkynyl ketones, namely (*R*)-binaphthol gives (*R*)-ketones, and vice versa. Interestingly, reversal of enantioselectivity was observed when R = OCH_2CF_3 and R = 2,6-di-*tert*-butylphenoxyl. According to Noyori, the high e.e.s observed for the reduction of conjugated ketones depend not only on steric factors, but also on electronic ones. In fact, the stereodirecting effect has the same sense for a wide range of unsaturated ketones and is independent from the steric requirements of the second substituent on the substrate. In the first step of the reduction, the acidic lithium cation coordinates to and activates the carbonyl group, then intramolecular hydride transfer takes place via a six-membered, quasi-aromatic ring transition state **12A** (Noyori's model, Fig. 4). The alcoholic oxygen RO acts as the bridging atom because, of the three oxygens attached to Al, its basicity is the highest.

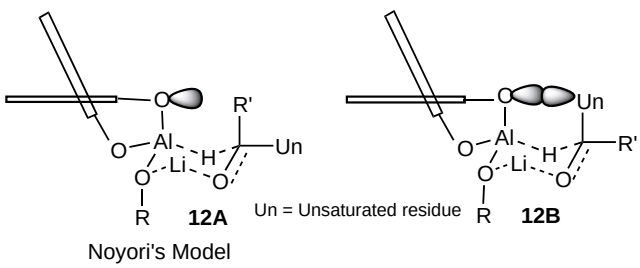


Figure 4.

The two possible transition states in the reduction of an asymmetric ketone are diastereomeric, and the structure **12A** is favoured over **12B**, where a repulsive n–π electronic interaction between an oxygen and the unsaturated carbonyl substituent is extant. The 1,3-diaxial-type steric repulsion between R′ and oxygen

becomes important only by increasing the steric requirements of R′. Interestingly, in the case of methyl ketones, low e.e.s (24% with 2-octanone) and opposite stereoselectivity was observed, i.e. (*R*)-binaphthol gave (*S*)-alcohols. This behaviour, together with the lower e.e.s achieved with methyl ketones as compared to dialkyl ketones with longer chains, might be interpreted in terms of the *pseudo*-π character of the methyl group. In fact, although small in size, the methyl group might compete with the unsaturated groups for the occupation of the equatorial position in order to minimise the interaction with the binaphthol oxygen electron pair. 4-Cyclopentene-1,3-dione is rapidly reduced by (*S*)-BINAL to the (*R*)-hydroxy ketone. In this case, n–π* attractive interactions between oxygen non-bonding orbitals and the LUMO of the enone moiety prevail over repulsive ones in the transition state **13** (Fig. 5). During the last 20 years BINAL-H has found widespread applications in a number of syntheses of natural and/or bioactive molecules, as illustrated below. The enantioselective reduction of both the building blocks 4-cyclopentene-1,3-dione **14** (94% e.e. after acetylation, Scheme 3) and (*E*)-1-iodo-1-octen-3-one **15** with (*S*)-BINAL-H allowed the synthesis of the pyrazole prostacycline II **16**, a more stable prostacyclin analogue.[27]

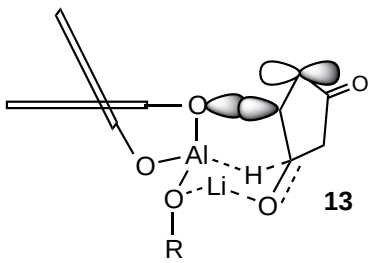


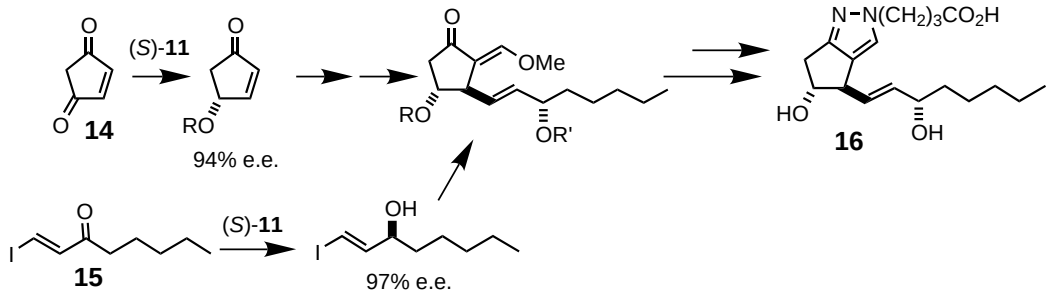
Figure 5.

BINAL-H was extensively exploited for achieving remote diastereocontrol (reagent-control) in the reduction of key chiral intermediates of a number of prostaglandins. Noyori used BINAL-H to improve Corey's synthesis of prostaglandin-ω **17** (Scheme 4), achieving near complete enantiocontrol.[28]

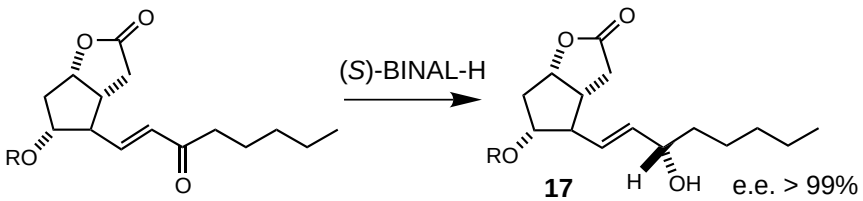
Analogously, a series of saturated prostaglandins **18** (Scheme 5), with nanomolar potency for hFP receptor, were obtained using BINAL-H in the key-reduction step.[29]

Other chiral prostaglandin intermediates were reduced by BINAL-H, with excellent remote diastereocontrol, by the group of Rokach, in the course of their intensive work on the synthesis of isoprostanes $IPF_{2\alpha}$-I,[30] $IPF_{2\alpha}$-III,[31] $IPF_{2\alpha}$-V,[32] 12-*epi*-$PGF_{2\alpha}$,[33] and 8-12-*iso*-$IPF_{2\alpha}$.[34] Good remote diastereocontrol (49–72% d.e.) was also achieved by Nokami et al. during the synthesis of Lipoxin analogues.[35]

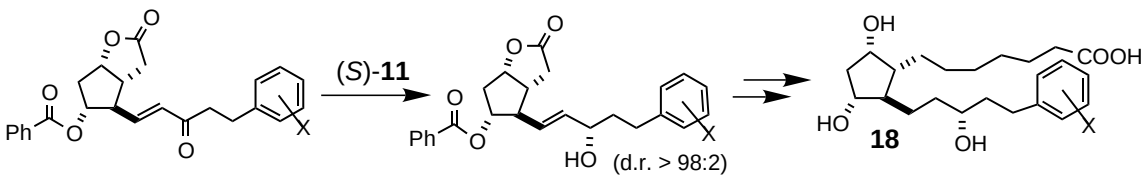
Obviously, the main application of BINAL-H has been in the field of enantioselective reductions of achiral



Scheme 3.

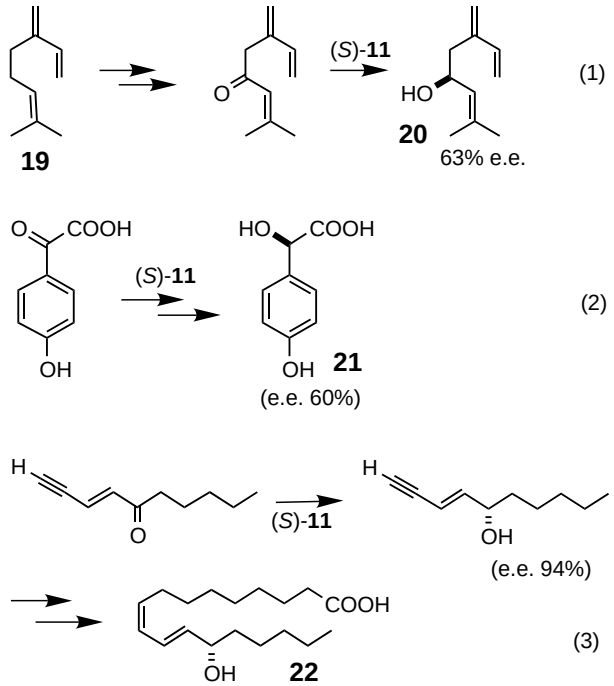


Scheme 4.



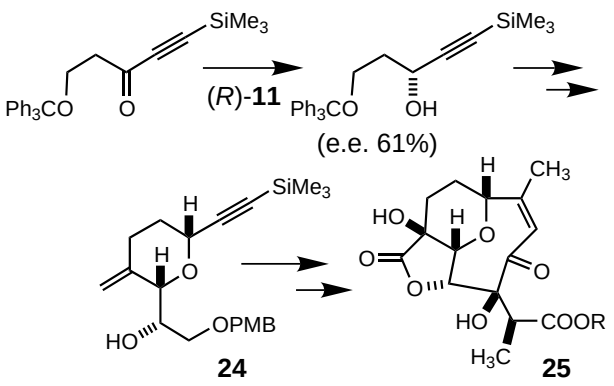
Scheme 5.

substrates. Thus, the optically active pheromone ipsdienol **20** (Scheme 6, Eq. (1)) was obtained by reduction of a ketone derived from myrcene **19**,[36] the antifungal pisolithin B (*p*-hydroxymandelic acid) (**21**, Eq. (2)) from the corresponding ketone,[37] and the natural fatty acid (*S*)-coriolic acid **22** was prepared from the corresponding enynone (Eq. (3)).[38]



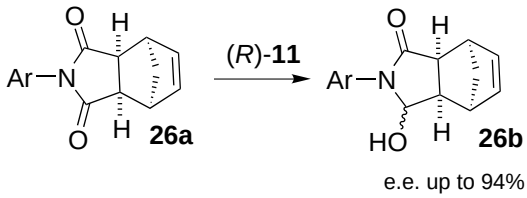
Scheme 6.

The use of (*R*)-BINAL-H **11** for the multi-gram enantioselective reduction of the acetylenic ketone **23** (Scheme 7) allowed for the synthesis of 3-methylenetetrahydropyran building block **24**, intermediate of neoliacinic acid **25**.[39]



Scheme 7.

The reduction of *meso*-cyclic-1,2-dicarboxyamides **26a** (Scheme 8) with (*R*)-**11** afforded optically active 5-hydroxy-2-pyrrolidinones **26b**, versatile intermediates of natural products, with e.e.s as high as 94% and yields of up to 86%.[40]



Scheme 8.

The reaction may proceed through the transition state **27** (Fig. 6), with preferential attack of (*R*)-BINAL-H to the carbonyl attached to the (*R*)-centre of the dicarboximide from its convex face to afford the 5β-hydroxy-2-pyrrolidinone, which then epimerises to the 5α-isomer during work up (epimeric ratios 5α:5β-**26b** depend on the work up conditions).

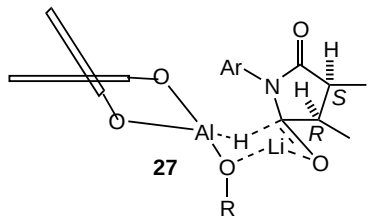
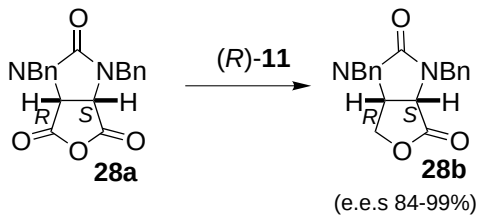


Figure 6.

The same model is applicable to the highly enantioselective reduction of several *meso*-anhydrides (such as **28a**, Scheme 9) to produce the corresponding chiral lactones **28b**.[41,42]

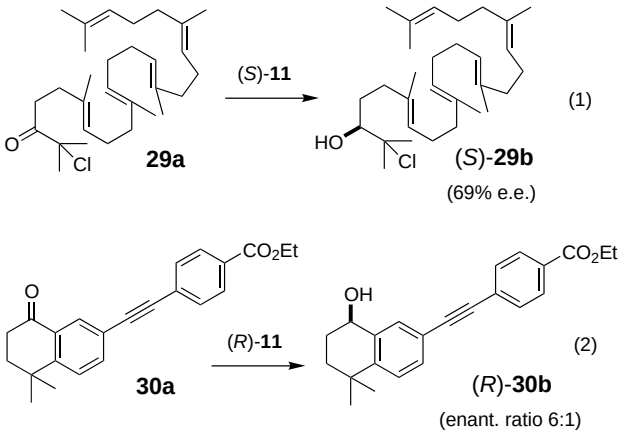


Scheme 9.

Alkyl-2-acylbenzoates were reduced by (*S*)-BINAL-H to the corresponding (*S*)-3-alkylphthalides, which have various pharmacological effects, with good enantiocontrol (e.e.s up to 83%).[43]

(*S*)-BINAL-H **11** was exploited for the enantioselective synthesis of a precursor of (3*S*)-2,3-oxidosqualene.[44] In fact, reduction of the α-chloro ketone **29a** (Scheme 10, Eq. (1)) took place with moderately good enantiocontrol (69% e.e.) providing the intermediate (*S*)-carbinol **29b**.

In the course of studies directed towards the synthesis and the biological evaluation of novel classes of retinoids,[45] (*R*)-BINAL-H was used for the enantioselective reduction of the cyclic ketone **30a** (Eq. (2)) to (*R*)-**30b**, which took place with satisfactory stereocontrol, although the system BH_3/(*S*)-B-methyloxazaborolidine performed slightly better in the same reduction (enantiomeric ratio 7:1).



Scheme 10.

An interesting and original application of BINAL-H is represented by the atropoenantioselective reduction of configurationally unstable biaryl lactones.[46] The reduction took place with dynamic kinetic resolution of the atropoisomers **31a** (Scheme 11), while the enantiomers were not reduced. The resulting atropoisomeric diols **31b**, which are configurationally stable, were formed with e.e.s of up to 92%, which increased to >99% after crystallisation.

Excellent enantioselectivity (98% e.e.) was obtained in the reduction of a saturated stannane ($C_2H_5COSnBu_3$) to the corresponding hydroxystannane, a useful reagent for the synthesis of the pheromones (+)-*endo*- and (−)-*exo*-brevicomine.[47]

It is worth noting that Marshall, supported by analogous unpublished results by Saddler, reported that reduction of several ketones using **11** gave highly variable results (see Ref. 99). This could be solved by

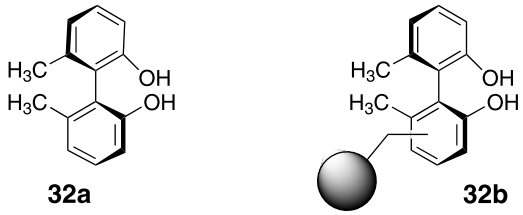


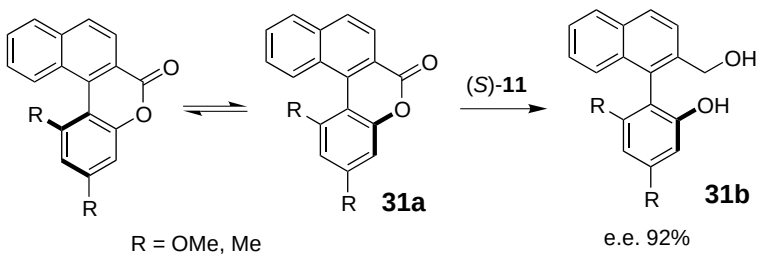
Figure 7.

heating a mixture of binaphthol, LAH and EtOH for a brief period in refluxing THF, which gave a reagent that effected the reductions efficiently and reproducibly with high e.e.s.

The effectiveness of BINAL-H prompted intensive investigations on similar atropoisomeric diols. The reducing agent formed from LAH and the ligand **32a** (Fig. 7) gave e.e.s as high as 89–98%. The polymer-supported ligand **32b** was prepared by Friedel–Crafts alkylation of Merrifield-type resin.[48]

As expected, the supported reagent LAH/**32b** required longer reaction times to afford yields comparable with **32a** and its efficiency increased with decreasing reaction temperature. The presence of an alcohol as additive had a small effect on enantioselectivity, suggesting that the disproportionation of the dihydride complex, which is normally prevented by the addition of an achiral alcohol, is strongly retarded due to the low mobility of the polymer-bound ligand.

There are several other examples of enantioselective reductions on aromatic ketones using LAH complexes with diols having an atropoisomeric structure. For example, the biphenolic complex LAH/**33** (Fig. 8) allowed the reduction of 2-octanone with 76% e.e. and



Scheme 11.

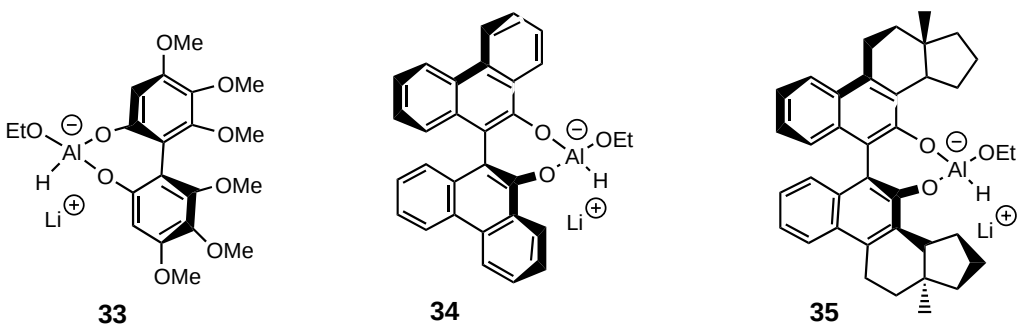
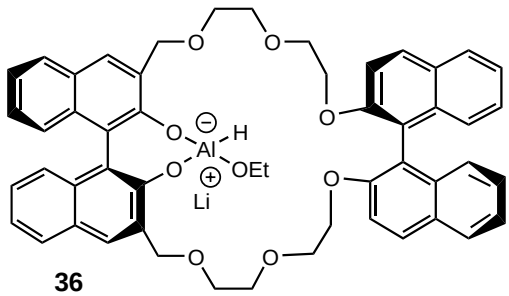


Figure 8.

performed well on several different classes of prochiral ketones.[49] Biphenanthryl complex **34**,[50] and bis-steroidal complex **35**[51] gave up to 98% e.e. in the reduction of arylalkyl ketones. Very recently, novel chiral binaphthols incorporating a hydroxyl group, conceived for providing 'internal' ligation to LAH, gave poor results in the reduction of acetophenone, with maximum e.e. of 58% and modest yields.[52]

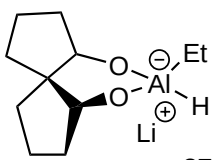
The atropoisomeric complex **36** (Fig. 9) where LAH is modified by a crowned 2,2′-dihydroxy-1,1′-binaphthyl reduced both aromatic and aliphatic ketones to (*S*)-alcohols.[53]



36

Figure 9.

The spiro diol complex **37** (Fig. 10) also belongs to the group of rigid diols and was employed in the reduction of a number of aromatic ketones.[54]



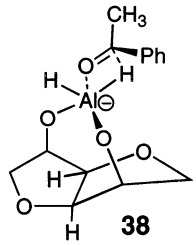
37

Figure 10.

Both complexes **36** and **37** afforded good e.e.s only upon addition of 1 equiv. of ethanol, and the reductions were proposed to take place through a chair-like transition state very similar to the one described by Noyori.

A recent report described the use of complexes similar to **11** formed from $LiGaH_4$ and monothiobinaphthol in highly enantioselective reductions of aromatic, hetero-aromatic and α,β-unsaturated ketones (product e.e.s of 63–93%).[55] However, the structure of the actual reducing complex is not yet fully understood.

Complexes of 1,3:4,6-di-*O*-benzylidene-D-mannitol and 1,4:3,6-dianhydro-D-mannitol with LAH do not have diastereotopic hydrides because the ligands have C_2 symmetry. In spite of this potential advantage, poor enantiocontrol was achieved in both cases with aryl alkyl ketones. (*S*)-Alcohols were obtained with the former complex, while the latter afforded (*R*)-alcohols.[56] This behaviour could be explained by means of the transition states **38** and **39** (Fig. 11), with the formation of a four-membered cycle where the less



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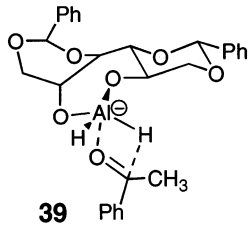
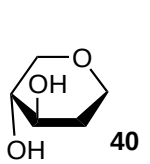


39

Figure 11.

bulky group is placed in the more hindered position. However, the behaviour of the same complexes in the reduction of dialkyl ketones could not be explained with transition states **38** and **39**, because both complexes gave alcohols with configurations opposite to those obtained with arylalkyl ketones. This observation suggests that electronic factors are also likely to play a key role.

Using the chiral diols **40** and **41** (Fig. 12), obtained from D-xylose and D-glucose, enantioselectivities were low. The two residual hydrogens of the corresponding LAH complexes are diastereotopic and might show opposite enantioselectivity, but the small amount of shielding exerted by the tetrahydropyranyl ring does not cause a difference in reactivity.[57]



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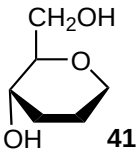
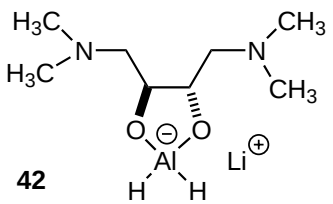


41

Figure 12.

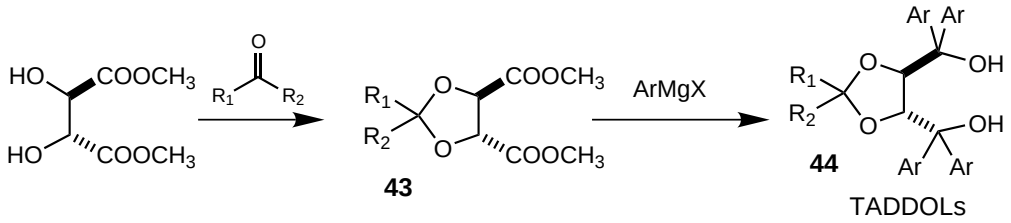
Starting from enantiomerically pure tartaric acid ethyl ester, Seebach obtained different chiral diols, and tested them as LAH ligands.[58] (2*S*,3*S*)-1,4-Bis(dimethylamino)butan-2,3-diol and its enantiomer were obtained from the corresponding amides, and the resulting complex **42** (Fig. 13) was able to reduce dialkyl and arylalkyl ketones to alcohols having e.e.s of up to 75%.



42

Figure 13.

The reaction of diethyltartrate acetals **43** (Scheme 12) with aryl Grignard reagents produced one of the most popular classes of chiral ligands, namely TADDOLs (α,α,α′,α′-*t*etra*a*ryl-1,3-*d*ioxolane-4,5-*d*imethan*ols*) **44**, which have been successfully employed as chiral ligands in different enantioselective reactions.[59] In particular, complexes of TADDOLs/LAH/ethanol have been used to reduce acetophenone, performing well both as soluble complexes[60] and as polymer-bound reagents.[61]



Scheme 12.

As a result of the simple synthesis of these ligands, which allows modification of R_1, R_2 and Ar substituents, many different TADDOLs have been tested in the reduction of acetophenone. After several experiments to set the conditions, Seebach performed the reduction at rt with a 2:1 reductant/substrate ratio. Ligands with large Ar groups (α-naphthyl, β-naphthyl) gave rise to lower selectivities as compared to Ar = Ph (87:13 versus 95:5). Reduction of aryl alkyl ketones showed that stereoselectivities also drop with increasing size of the alkyl group. TADDOLs enantioselectively form inclusion compounds with chiral alcohols that are insoluble in pentane. This peculiar feature allows for an increase of enantiopurity of the alcohols (97.5:2.5) by means of a special work up. It has been possible to link LAH/TADDOL complexes to several polymeric supports producing the resins **45**–**48** (Fig. 14). Reductions were conducted at −75°C in THF, using a LAH/ligand ratio of 2:1. Conversions higher than 75% and (*S*)/(*R*) ratios ranging from 78:22 to 88:12 were obtained with all of the ligands, except with the 'branched-type' **48**. It has been shown that it is possible to re-use the polymers without significant modifications of stereoselectivity.

The soluble complex LAH/(+)-**44** (Ar = Ph, $R_1 = R_2 =$ Me) has been recently employed in the synthesis of (−)-bifurcadiol (**49**, Scheme 13), that shows high cytotoxicity against cultured human tumour cells.[62] Interestingly, the use of Corey's oxazaborolidine was not effective in this case.

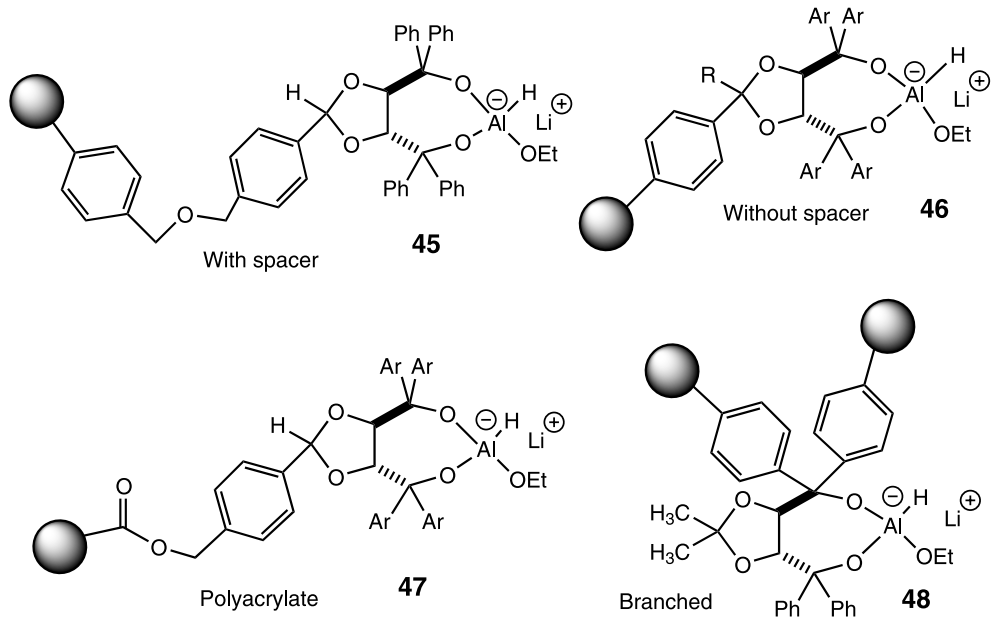
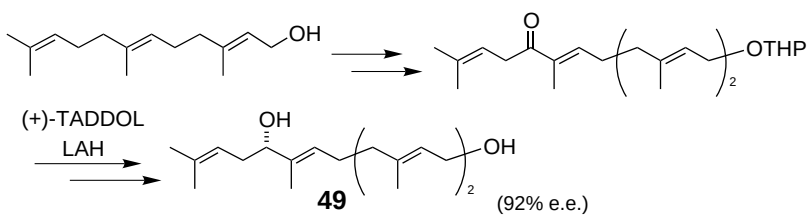


Figure 14.



Scheme 13.

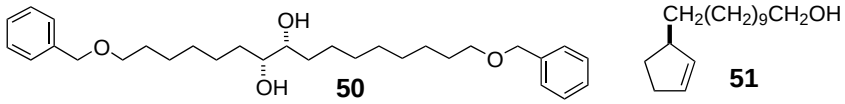


Figure 15.

Some exotic alcohols have also been used in prochiral ketones reduction, with the aim of finding the ideal and 'universal' reducing LAH complex. An example is the diol **50** (Fig. 15), obtained from (+)-*threo*-(9*R*,10*R*)-9,10,16-trihydroxy hexadecanoic acid (aleuritic acid),[63] a polyhydroxy fatty acid present in lac resin. The long alkyl substituents around the vicinal hydroxyl groups were hypothesised to provide steric hindrance and thus contribute to the selectivity.

It was shown that the complex gives good results ((*R*)-alcohols with 70% e.e.) only in the presence of 1 equiv. of (*R*)-hydnocarpic alcohol **51** or alcohols with long alkyl chains. The chain length influences the free rotation of the hydride species, and reduces the number of hydride species present in the reaction mixture. Enantioselectivity was high with aryl ketones, while when one or more methylene groups are present to separate the phenyl and the carbonyl groups, low e.e.s were observed. The preferential formation of (*R*)-alcohols can be explained according to the transition state **52** (Fig. 16), similar to the one proposed by Noyori.

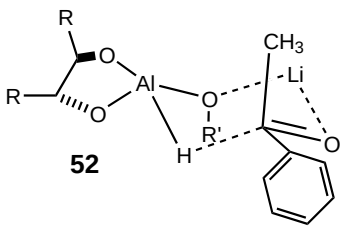


Figure 16.

Complexes prepared from LAH and (1*R*,2*S*,3*S*,5*R*)-(−)-10-methoxypinanediol, obtained from myrtenol, gave good chemical yield but rather poor e.e.s (8–72%).[64]

Recently, the use of chiral reducing agents obtained from $NaAlH_4$ and chiral diols was reported; 1,3- and 1,4-diols were found to give complexes with greater stereoinduction properties than those formed from 1,2-diols.[65]

2.2. Amino alcohols as ligands

The earliest studies into LAH–amino alcohol complexes, in particular alkaloids, date back to the 1960s. Reduction of acetophenone with LAH–quinine complex gave phenylethan-1-ol with 48% e.e.,[66] diaryl ketones such as phenylmesityl ketone gave 39.5% e.e.,[67] *p*-alkylacetophenones afforded a maximum e.e. of 51.4%.[68] More recently, a procedure was reported to increase the enantiomeric purity of aryl ethanols (obtained from the reduction of methylaryl ketones with LAH/(−)-quinine complexes) by recrystallisation of the corresponding 3,5-dinitrobenzoate derivatives.[69] The same complex has been applied to the reduction of *N*-(diphenylphosphinyl)ketimines **53** (Scheme 14) to give (*R*)-amines **54** with e.e. lower than 36%.[70]

Good levels of stereoselectivity were achieved using optically active 2-oxazolines.[71] The reaction of 2 equiv. of ligand with LAH formed a dihydride reducing species **55** (Fig. 17), whose structure was not described in detail.

The highest stereoselectivity was obtained with R = Et, which also gave a completely soluble complex in the whole range of temperatures examined. E.e.s increased on lowering the reaction temperature. With arylalkyl ketones e.e.s were in the range 8–65%, whereas dialkyl ketones were reduced with very low e.e. (<6%). The dihydride complex was able to react with a third oxazoline molecule, but the resulting species was unable to reduce ketones, probably because of high steric shielding of the residual hydride.

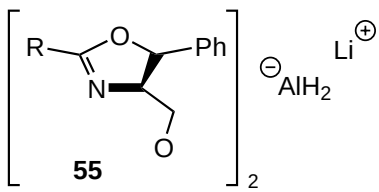
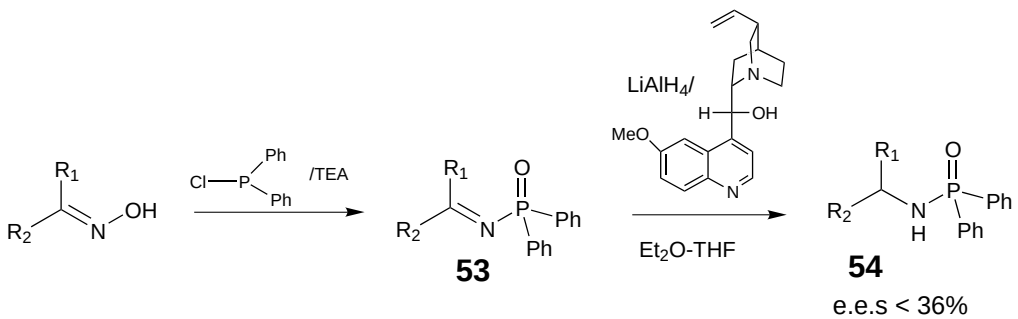


Figure 17.



Scheme 14.

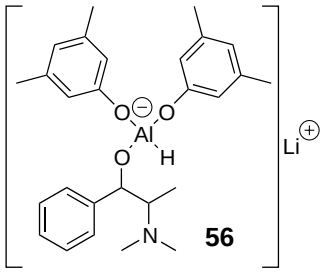


Figure 18.

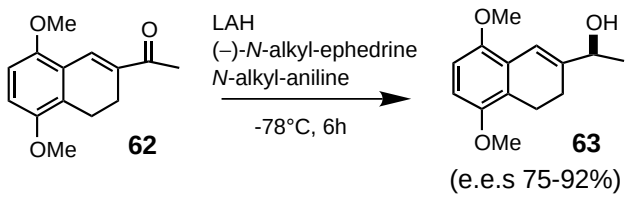
A very useful reducing complex **56** (Fig. 18) was first obtained by Vigneron and Jacquet from LAH/*N*-methylephedrine in the presence of phenols.[72]

The complex, which is soluble in many solvents from ether to benzene, can be obtained by sequential addition of 1 equiv. of ephedrine and 2 equiv. of a phenol to LAH. The resulting species can reduce acetophenone and other arylalkyl ketones to alcohols having (*R*)-configuration. Enantiomeric purities are in the range 14–80% depending on the achiral alcohol used. 3,5-Dimethylphenol was selected from 25 different alcohols and phenols as the one that gave the highest asymmetric induction. Temperature, which probably influences the complex's aggregation state in solution (15°C was the ideal reduction temperature), reaction time, substrate structure and the solvent all influence the stereochemical outcome of the reduction. Arylalkyl ketones having linear aliphatic chains were reduced with e.e.s higher than those with α-branched chains. Stereoselectivity was lower with methyl alkyl ketones, and in this case branching seems to improve enantioselectivity. The complex **56** is very interesting because it combines good synthetic performance with ready availability (as it can be produced from commercial ephedrine). Moreover, the ligand can be recovered from the reaction mixture without racemisation by acidic washing. Complex **56** gave very high e.e.s and good yields in the reduction of α-acetylenic ketones to propargylic alcohols without affecting the triple bond. This behaviour has been explained considering that the electronic properties of the acetylenic group are similar to those of the aryl group, thus producing a similar stereochemical outcome.[73]

Complex **56** was also successfully applied in the asymmetric reduction of 2-alkyl-1,3,4-cyclopentantriones **57** (Scheme 15) to give optically active cyclopentane **58** in 50% yield and 55% e.e. Compounds of the type **58** are useful in the synthesis of prostaglandins such as **59**.[74]

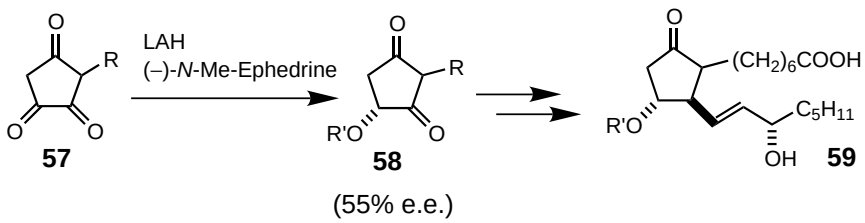
β-Hydroxy ketones **61** (Scheme 16) can be obtained in several steps by the enantioselective reduction of 2,2-disubstituted-1,3-dithioacetals of the type **60** (51–78% e.e.) using complex **56**.[75]

Reduction of 2-acetyl-5,8-dimethoxy-3,4-dihydro-2-naphthalene **62** (Scheme 17) with a slightly different reducing complex, obtained from (–)-*N*-alkylephedrines and an achiral amine (*N*-alkylanilines, in particular *N*-ethyl aniline), gave an optically active allylic alcohol **63**, precursor of anthracyclinones, with 100% yield and e.e. ranging from 75 to 92% depending on reaction conditions (temperature, solvent and substituents on the ephedrine ligand).[76]

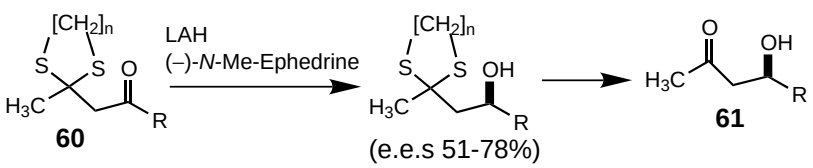


Scheme 17.

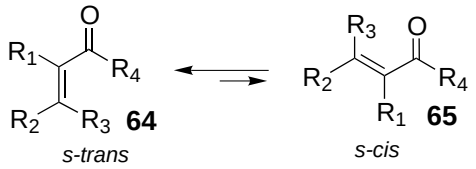
The same complex was successfully applied to the reduction of aromatic ketones (but not aliphatic ones)[77] and several enones.[78] Open chain enones gave higher e.e.s in comparison to cyclic ones. This behaviour was explained by considering that an open chain enone can exist in an equilibrium of *s-trans* **64** and *s-cis* **65** conformers (Scheme 18), where the former should predominate. Cyclic enones, on the other hand, are fixed in an *s-trans* conformation. Enones that can adopt an *s-cis* conformation in the transition state are reduced with higher yields and e.e.s.[79]



Scheme 15.



Scheme 16.



Scheme 18.

The transition state **66** proposed by the authors (Fig. 19) which features a regular octahedral Al centre, accounts for the preferential formation of (*S*)-alcohols. The presence of a lithium cation is essential to achieve high asymmetric induction, in fact addition of TMEDA lowers the e.e. Its role is likely to provide coordination to the *N*-atoms of the ligands. Smaller steric differences between the substituents of the ketone and/or lack of electronic interactions might be the reason why cyclic enones and aliphatic ketones are reduced with lower enantioselectivity.

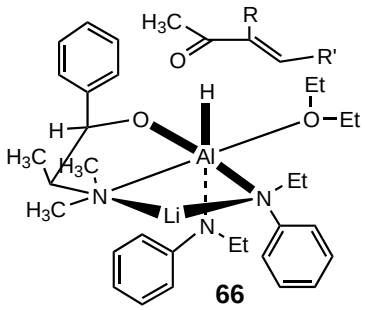
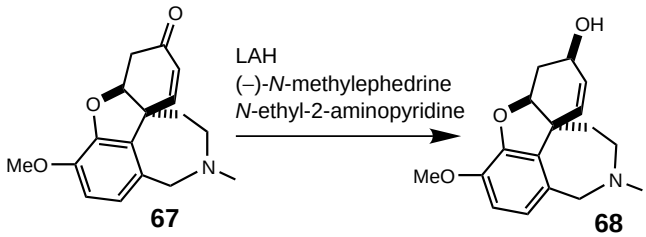


Figure 19.

LAH/(–) - *N* - methylephedrine/2 - alkylaminopyridine complexes allowed for the reduction of cyclic prochiral ketones, while linear ketones underwent reduction with lower stereoselectivity.[80] For example, 2-cyclohexen-1-one was reduced to (*R*)-2-cyclohexen-1-ol at −78°C in 81% yield and 98% e.e. The LAH/(–)-*N*-methylephedrine/*N*-ethyl-2-aminopyridine complex was applied in a successful tandem enantioselective reduction/kinetic resolution. In practice, the reduction of (–)-narwedine **67** to (–)-galanthamine **68** (Scheme 19), which is used in the treatment of Alzheimer's disease, could also be performed starting from racemic narwedine, because the (+)-form is not reduced under the reaction conditions and may be racemised and recycled.[81]



Scheme 19.

The same complex was exploited for the asymmetric synthesis of (2*R*)-2-hydroxy-2-[2-(*Z*)-octenyl]-1-cyclopentanone **69** (Scheme 20).[82]

Recently, the LAH/(–)-*N*-Me-ephedrine system was also used for performing the chemoselective reduction of a functionalised cyclohexenone to the corresponding cyclohexanol, with a remarkable 83% e.e.[83,†]

Further work on LAH/*N*-alkylephedrine complexes has led to the polymer bound complex **70** (Fig. 20).[84] This supported reducing agent was prepared by treatment of LAH with 2 equiv. of 3,5-dimethylphenol and, after a period of equilibration, 1 mol of Merrifield-type resin. Acetophenone was reduced with e.e.s in the range 5–43% depending on several experimental factors, with best results at −15°C.

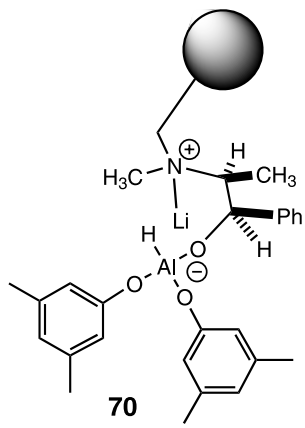
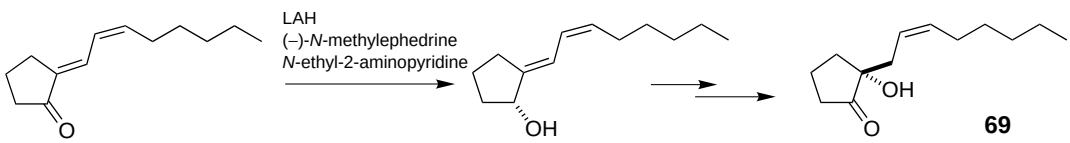


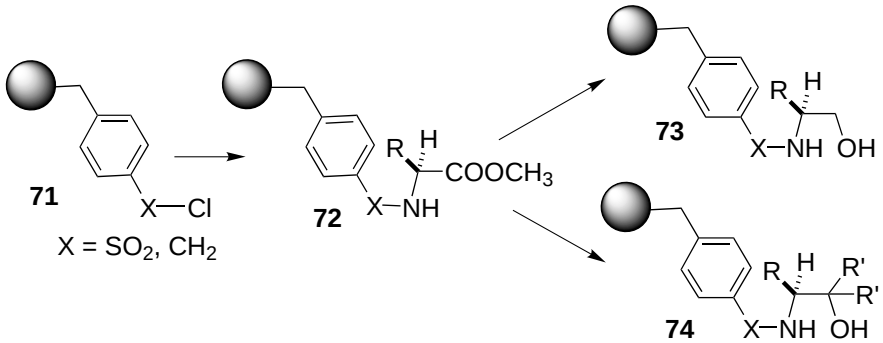
Figure 20.

Recently, a new polymer-supported chiral amino alcohol and its use in enantioselective reductions were reported.[85] Chlorosulphonated polymers **71** (Scheme



Scheme 20.

† *Note added in proof*: Very recently, the first example of enantioselective reductions of esters to (*S*)-hemiacetals by means of $NaAlH_4$/(–)-ephedrine reagent, followed by *O*-acetylation, has been described (Rychnovsky, S. D.; Bax, B. M. *Tetrahedron Lett*. **2000**, *41*, 3593–3596). The reaction works quite well (e.e.s of up to 83%, yields <60%) only with α-benzyloxyacetates. Other ligands, such as TADDOL and binaphthol, gave modest results.



Scheme 21.

21), obtained by controlled chlorosulphonation of polystyrene at 40°C, were converted into polymeric sulphonamides **72** by reaction with several methyl α-amino esters. Reduction with LAH or reaction with RMgX gave the resins **73** and **74**. E.e.s in the reduction of acetophenone with **73**/LAH or **74**/LAH did not exceed 43%.

In another work, after resolution by fractional crystallisation, optically active 2-amino-1,2-diphenylethanol was converted into the corresponding *N*,*N*-dimethyl derivative and tested as a chiral ligand in the reduction of alkylphenyl ketones providing e.e.s of 26–72%. The results showed that the configuration of the product was influenced by the configuration of the C(2) stereogenic centre of the ligand, which bears the amino function.[86]

LAH has been modified with (1*S*,2*S*)-2-(1-phenylethyl)-amino-1-phenylethanol and its (1*S*,2*R*)-diastereomer, to give the complexes **75** (Fig. 21),[87] but in both cases reductions provided e.e.s lower then 25%, and the former diastereomeric complex was more stereoselective than the latter.

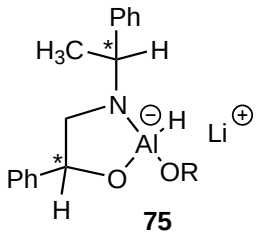
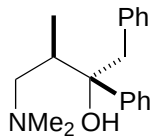


Figure 21.

An interesting study was reported by Soai et al., who studied the asymmetric auto-inductive reduction of α-amino ketones by LAH modified with a chiral 1,2-amino alcohol and an achiral additive.[88] Amino alcohols with the same configuration of the ligand were obtained. As an example 2-morpholinoacetophenone was reduced with LAH/(*S*)-2-morpholino-1-phenyl-ethanol/*N*-ethylaniline complexes, and the same (*S*)-1,2-amino alcohol was obtained with 95.8% e.e.

(2*S*,3*R*)-(+)-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol (Darvon alcohol or CHIRALD®, which is the commercial name of **76**, Fig. 22) has been one of the first amino alcohols to give a highly stereoselective complex with LAH without addition of a third achiral complexing agent.[89] The LAH/CHIRALD® complex is undoubtedly one of the most important and widely used chirally modified aluminohydrides.



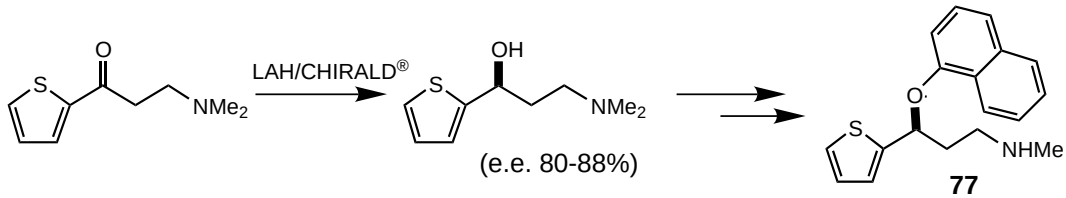
76

Darvon alcohol (CHIRALD®)

Figure 22.

Reduction of acetophenone gave phenylethan-1-ol with e.e.s ranging from 40 to 75%, but it has been noticed that stereoselectivity depends on whether the reagent is used immediately after preparation, after storage overnight, or if it is heated under reflux for a few minutes. In the former case, the complex is insoluble in the ethereal reaction mixture, and the reduction gives high yield of (*R*)-alcohol, whereas in the latter the complex is completely soluble in ether and (*S*)-phenylethanol is obtained, although in low yields. This behaviour, which is quite general with the exception of phenyl trifluoromethyl ketone, accounts for the rather low stability of the complex, and suggests the presence in solution of several reducing species, differing either for aggregation state or stoichiometry. Although the authors do not fully explain the reduction mechanism and the complex's instability, the kinetic complex (the one obtained without ageing, also called Mosher's reagent) was used for the reduction of several aromatic (e.e.s 50–97%) and heteroaromatic ketones,[90] such as 3-dimethylamino-1-thiophen-2-yl-propan-1-one (Scheme 22), an intermediate in the synthesis of the serotonin/norepinephrin uptake inhibitor LY248686 **77**.[91]

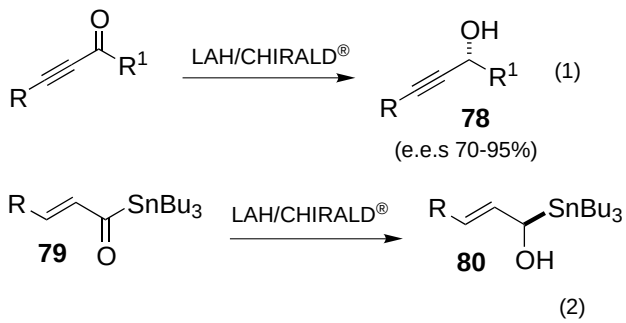
An important and general application of the complex LAH/CHIRALD® is represented by the reduction of



Scheme 22.

acetylenic ketones to (*R*)-propargylic alcohols, which usually takes place with enantioselectivities in the range 70–95%.[92] The direction of stereoselectivity is the same as for aromatic ketones, because the π-electron system of the acetylenic bond appears to have similar effect to that of the aromatic moiety, as already seen with other complexes (for example **56**).

The reduction of acetylenic ketones has been often applied in order to prepare optically active propargylic alcohols (**78**, Scheme 23, Eq. (1)), which represent important synthetic intermediates.[93] An impressive amount of work was accomplished by Marshall et al., who exploited extensively the LAH/CHIRALD® system for the enantioselective reduction of a huge variety of acetylenic ketones with good to excellent stereochemical control.[94] Several other groups have exploited the potential of LAH/CHIRALD® in the enantioselectively reduction of acetylenic ketones,[95] with a particular mention for the syntheses of Brefeldin-A[96] and the total synthesis of the macrocycle 506BD (a ligand for Immunophilin FKBP).[97] There is also an example of LAH/CHIRALD® reduction of a chiral acetylenic ketone, having a stereocentre α to the carbonyl group; the observed stereoselection was opposite to that usually seen, which is probably a result of substrate-based diastereocontrol.[98]



Scheme 23.

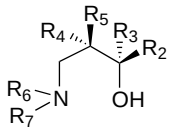
α-(Hydroxy)allylstannanes **80** (Scheme 23, Eq. (2)) have been prepared by reduction of the corresponding stannyl enones **79** with LAH/CHIRALD® or (*S*)-Binal-H, with better results for the latter in terms of enantioselectivity (ca. 95% e.e.), but less problems of reproducibility for the former (ca. 65% e.e.).[99] LAH/CHIRALD® complexes also reduced 3-bromo-2-cyclohexenone to the corresponding (*R*)-alcohol (50–60% e.e.s). The opposite enantiomer was also obtained by using *ent*-**76**/LAH complex.[100] Reduction of *N*-Cbz-3-indolyl-methyl ketone by LAH/CHIRALD® produced the expected alcohol with high enantiocontrol (e.e. > 80%).[101]

The LAH/CHIRALD® complex was also used for achieving the desired diastereocontrol (reagent-control) during the synthesis of the antibiotic Herbimycin,[102] where reduction of an open chain ketone having six stereogenic centres (of which one was α to the carbonyl) delivered the desired (*S*)-configured carbinol with 70.0:17.5 ratio, whereas LAH-reduction of analogous substrates was reported to occur without stereocontrol. On this basis, during the total synthesis of vitamin E, Cohen et al. took into account the possibility of reducing acetylenic ketones to propargylic alcohols by modification of LAH with Darvon alcohol analogues **81** (Fig. 23).[103] The aim of the study was two-fold: on one hand it was interesting to evaluate the possibility to use low cost, easily accessible alcohols in order to obtain higher asymmetric induction, additionally it was an opportunity to establish the influence of the various stereocentres in the ligand. Some of the alcohols that were synthesised from chiral β-hydroxy acids and tested as LAH modifiers are portrayed in Fig. 23.

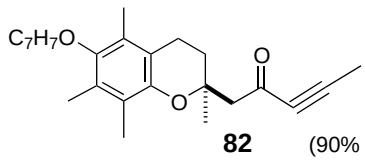
Reductions were conducted at −70°C and yields were in the range 60–99%. (*R*)-Alcohols were formed preferentially and e.e.s varied from a minimum of 64% to the highest value of 90% obtained in the reduction of the vitamin E precursor **82** with the complex LAH/*ent*-**76**, as a result of matching double stereoselection. Interestingly, and surprisingly, ligands **81a** and **81e** gave alcohols with opposite configuration to that observed using Darvon alcohol **76**. It is clear that the secondary stereogenic centre, although far from the site of complexation, exerts some influence on the stereochemical outcome of the reduction.

More recently other Darvon alcohol analogues having just one stereocentre and different nitrogen substituents have been synthesised, such as **83** and **84** (Fig. 24).[104]

Ligand **84**, which is available as both (*R*)- and (*S*)-enantiomers, is the most stereoselective. In particular, it is able to reduce several *o*-substituted benzophenones[105] and α-aminophenones with high e.e.s.[106]

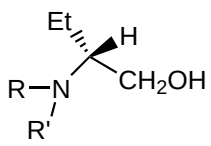


	R_2	R_3	R_4	R_5	R_6	R_7
76	$PhCH_2$	Ph	CH_3	H	CH_3	CH_3
ent-**76**	Ph	$PhCH_2$	H	CH_3	CH_3	CH_3
81a	H	H	CH_3	H	CH_3	CH_3
81b	H	H	CH_3	H	CH_3	(*S*)-$CH(CH_3)Ph$
81c	H	H	H	CH_3	CH_3	(*S*)-$CH(CH_3)Ph$
81d	H	H	CH_3	H	$PhCH_2$	$PhCH_2$
81e	H	H	CH_3	H	$-(CH_2)_4-$	

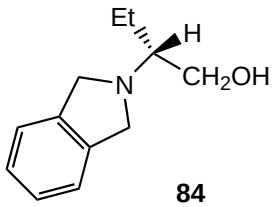


82 (90% e.e.)

Figure 23.



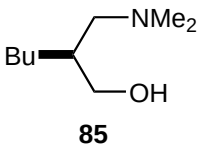
83



84

Figure 24.

Other bidentate and tridentate chiral amino alcohols similar to those used by Cohen were synthesised and the corresponding LAH complexes were examined in the reduction of acetophenone, giving erratic and unpredictable results.[107] For example, **85** (Fig. 25) gave 22% e.e., in comparison with the 60% e.e. obtained with the Cohen-like structure **86**. Moreover, in spite of the fact that the stereocentres have opposite configuration, the products are always (*S*)-alcohols. Better stereoselectivities were obtained when BH_3 was used as the reducing agent.



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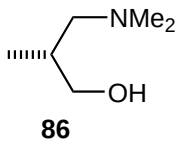
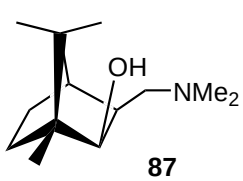


86

Figure 25.

Mosher's activity in the field of LAH/amino alcohol complexes led to the synthesis of the amino alcohols **87** and **88** (Fig. 26), obtained from camphor, but their stereoselectivity in ketone reductions was disappointing (e.e <30%).[108]



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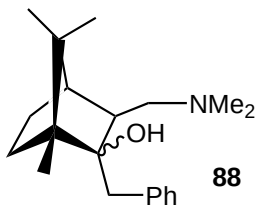
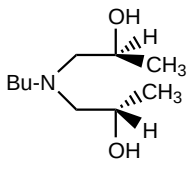


88

Figure 26.

By reaction of a primary amine with (*S*)-propylene oxide or ethylene oxide, Morrison prepared chiral tridentate aminodiols **89**–**92** (Fig. 27) bearing a tertiary nitrogen in a 1,2-relationship with each of the two hydroxyl groups.[109]

Morrison's results were in agreement with Cohen's observation, namely that both the carbinolic stereocentres and the stereogenic carbon on nitrogen contribute to the stereoselective properties of the complex. In fact, reduction with the LAH/**90** complex gave only 10% e.e. in acetophenone and propiophenone reductions, while



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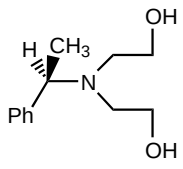

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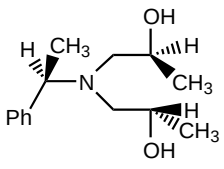
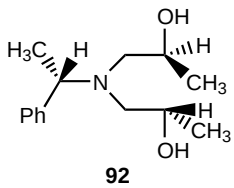


91



92

Figure 27.

the LAH/**89** complex gave the corresponding (*R*)-alcohols with moderate e.e.s (44 and 57%, respectively). Addition of an (*S*)-stereogenic centre on nitrogen (ligand **92**) raised the e.e. to 82%, while with ligand **91**, the e.e. falls to 35%. It is apparent that the three stereocentres work together in determining the direction of stereoinduction.

The structure **93** (Fig. 28) was proposed for the transition state. The nitrogen does not coordinate to the aluminium centre, but to Li^+, which also activates the carbonyl oxygen by coordination.

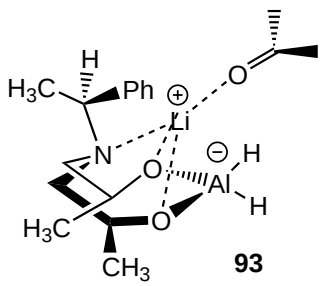
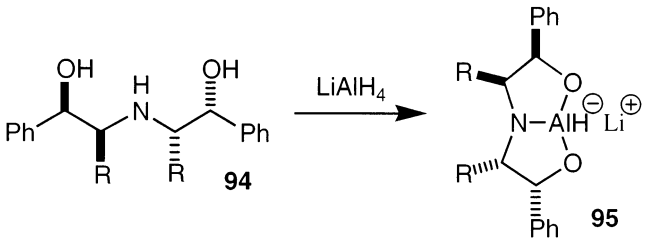


Figure 28.

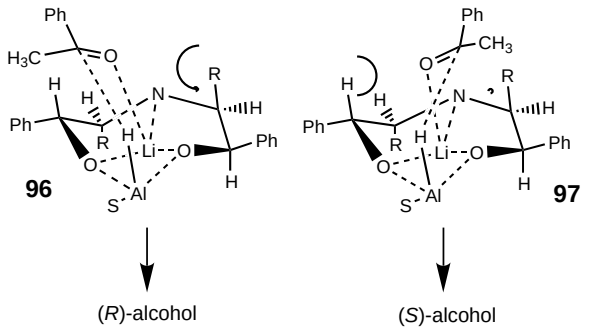
Similar monohydride complexes (LAH/diethanolamines) having C_2 symmetry of the type **95** (Scheme 24) differing only in the substituents attached to carbon atoms α to nitrogen, were used for the reduction of substituted acetophenones. Systematic variation of these substituents provided information about the nature of the transition state.[110]



Scheme 24.

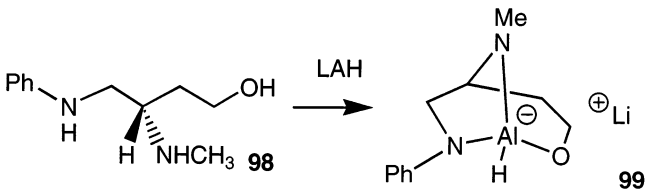
Stereoselectivities were found to depend both on the reaction temperature of the reduction and on the conditions under which the chiral reagent is formed from the chiral amino alcohol **94**. Increasing the reduction temperature resulted in lower asymmetric induction. The formation of the complex was complete only after heating the mixture in refluxing THF for 30 min. Heating under reflux was necessary for complete deprotonation of the amine function, but longer refluxing times provided lower asymmetric induction, probably because of disproportionation of the complex.

The study of the influence of the R substituent on the stereoselectivity of the reaction revealed the following order of enantioselectivity: H>Me>Et=*n*-Pr. Surprisingly, auxiliaries where R=H gave the (*S*)-enantiomer, while the (*R*)-enantiomer predominated when R=alkyl. Substrate screening showed that higher e.e.s were obtained with aromatic ketones (86% e.e. with a *p*-OMe substituent) carrying electron-donating substituents, which were reduced more selectively than aromatic ketones with electron-withdrawing groups (67–70% e.e.). Tetralone and analogues were also reduced with high enantioselectivity (e.e. 72–94%). All these observations were rationalised through the transition state **96** (Scheme 25), where lithium instead of the aluminium centre is coordinated to both oxygen and nitrogen atom of diethanolamine. The bicyclic transition state adopts a conformation in which both phenyl groups occupy a *pseudo*-equatorial position and the R group a *pseudo*-axial one. If R=alkyl, then the alkyl group of the ketone points in the direction of the benzylic proton of the diethanolamine to avoid steric interactions with these R substituents, thereby leading to the formation of (*R*)-alcohols. If R=H, a different transition state, **97**, leading to (*S*)-alcohols, is preferred.



Scheme 25.

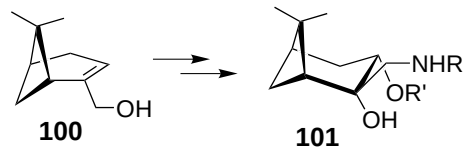
Complexation of LAH with (*S*)-4-anilino-3-methylamino-1-butanol **98** (Scheme 26), derived from aspartic acid, gave the rigid chiral reducing agent **99**.[111]



Scheme 26.

In reductions using complex **99** yields varied between 84 and 93%, (*S*)-alcohols were obtained with e.e.s ranging from 33% for aliphatic ketones, to 86–88% for ketones possessing a bulky alkyl group, such as *tert*-butyl phenyl ketone and α-tetralone. The ligand could be recovered from the reaction medium without racemisation by acidic aqueous extraction. Higher stereocontrol was observed in the reduction of α,β-unsaturated ketones to optically active (*S*)-allylic alcohols with the same complex **99**.[112] Cyclohexenone was reduced with complete stereoselectivity (100% e.e.) to (*S*)-cyclohexenol. The use of (*S*)-4-(2,6-xylidino)-3-methylamino-1-butanol gave (*R*)-alcohols with the same stereoselectivity.

Rigid complexes were obtained from LAH and aminodiols such as **101** (Scheme 27), prepared from commercially available (−)-myrtenol **100**.[113]



Scheme 27.

The ligand **101** with R = Ph and R′ = Et was selected from several analogues as the one affording the highest enantioselectivity. Reduction of several substituted acetophenones in Et_2O–THF 1:10 gave (*R*)-phenylethan-1-ols with e.e.s ranging from 50 to 91%. The ligand was recovered in 96% yield by silica-gel chromatography. Addition of LiI to the reaction mixture led to a small increase of e.e.s.

The proposed transition state **102** for reductions of acetophenones with **101** is shown in Fig. 29.

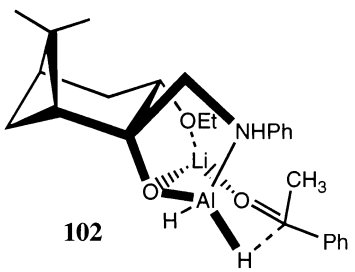


Figure 29.

The low stereoselectivity observed when R′ = H is probably due to competition between hydroxyl groups in coordinating to aluminium.

Amino diols obtained from tartaric acid and malic acid were found to be poor chiral ligands (30% e.e. in the reduction of acetophenone).[114]

2.3. Amines and diamines as ligands

In the first seminal work dealing with LAH/chiral amine complexes,[115] dating back to 1973, several classes of chiral reducing agents obtained from the reaction of LAH and hydrochlorides of chiral amines, such as (*S*)-methyl-1-(phenyl)ethyl amine, and identified as chiral alanes having formula RR*$NAlH_2$, were reported to reduce acetophenone with e.e.s of up to 85% (when the reaction was performed in ether at −71°C) to (*S*)-phenylethan-1-ol, and other phenylalkyl-, as well as dialkyl ketones with lower enantioselectivity.

In 1977, several *ortho*-substituted optically active benzylamines **103** (Fig. 30) were synthesised and tested as LAH ligands with the aim of finding a 'better' ligand as compared to those available at that time.[116]

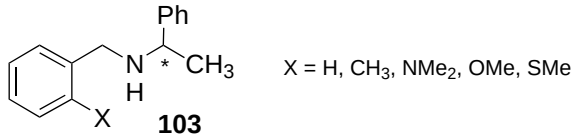


Figure 30.

The corresponding complexes with LAH were soluble in toluene even at −78°C and reduction yields were good both on acetophenone and propiophenone. However, e.e.s were negligible if X = H, CH_3, i.e. when the molecule has just one chelation site. The highest stereoselectivities were observed when X = NMe_2, because nitrogen has a strong affinity for lithium and can thus lead to stable complexation. In fact, if TMEDA was added to the reaction mixture, then asymmetric induction was lost. Surprisingly, if X = SMe, which should not effectively coordinate to lithium, e.e.s were still good. A possible transition state **104** for these reactions is depicted in Fig. 31.

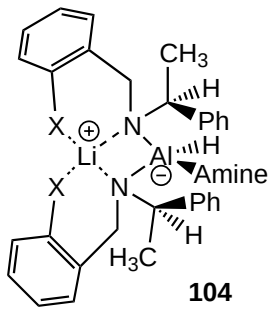


Figure 31.

Not only biphenols (see Section 2.1), but also atropoisomeric diaminobiphenyls, like **105** and **106** (Fig. 32), having C_2 symmetry have been used as chiral LAH modifiers.

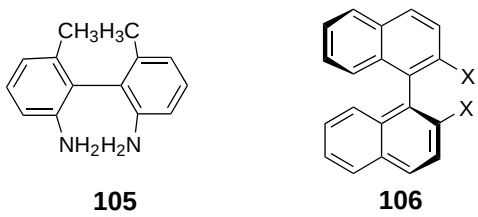


Figure 32.

Ligand **105** was prepared in 33% yield from *o*-toluidine, and recovered from the reaction mixture by extractive work up.[117] E.e.s for the reductions of different aromatic ketones were lower than 60%. Both the order of addition of the reactants and the reaction temperature affected the e.e. of the final products, suggesting that a different complex reagent is formed in each case.

Complexes obtained from ligands **106** displayed different reactivity depending on the steric bulk of the alkyl

group.[118] In the case of (*R*)-2,2′-diamino-1,1′-binaphthyl, (*R*)-alcohols were obtained (e.e.s 1–9%). When the amine was alkylated, better enantioselectivity (23–82% e.e.s) and a reversal of stereoselectivity were observed. Surprisingly, addition of 1 equiv. of EtOH lowered the stereocontrol. The steric requirements of the alkyl substituents on both the amino group and the substrate (aromatic ketones were used) also affected the stereoinduction. The best ligand was obtained when X = NHEt, and the corresponding ligand gave the highest enantioselectivity in the reduction of isopropylphenyl ketone (82% e.e.).

Reaction of LAH with (*S*)-2-(*N*-aryl aminomethyl)-pyrrolidines, prepared in four steps from (*S*)-proline, gave rise to evolution of 2 mol of hydrogen, leading to the formation of a dihydride complex **107** (Fig. 33), which is insoluble both in toluene and ether but soluble in THF. This complex reduced aromatic ketones to (*S*)-alcohols, with enantiomeric purities strongly depending on the reduction conditions (solvent, temperature, additives).[119]

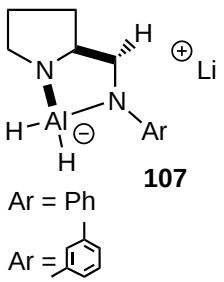
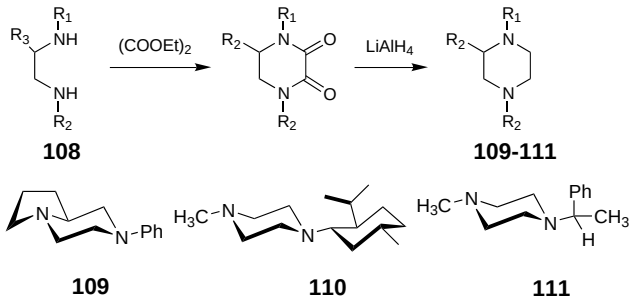


Figure 33.

The two residual hydrides on aluminium have different reactivity, because one is shielded both by the aromatic ring and the pyrrolidine moiety and remains unreacted. It has been observed that an increase in steric requirements of the aromatic ring, i.e. introduction of two methyl substituents *ortho* to the nitrogen atom, brings about a remarkable increase of e.e.s (acetophenone, 95% e.e.; propiophenone, 96% e.e.), while electron-donating or electron-withdrawing groups do not affect the stereoselectivity.[120] The direction of asymmetric induction is probably a result of formation of the rigid *cis*-fused five-membered ring of **107**, which creates an additional stereogenic centre on the nitrogen atom in the pyrrolidine ring. The lithium ion coordinates to the nitrogen atoms and restricts the direction of approach by the ketone. As usual, addition of TMEDA or dimethoxyethane produced a decrease of enantioselectivity because the lithium ion was prevented from coordination.

Substantial modification of the amine structure by addition of a stereogenic *N*-substituent provided worse results.[121] For example, *N*-methyl-*N*′-[(*R*)-menthyl]-1,2-diaminoethane and 2-[*N*-(*R*)-menthylaminomethyl]-pyrrolidine were prepared and tested as chiral ligands for the reduction of aromatic ketones with LAH but e.e.s lower than 59% were obtained.

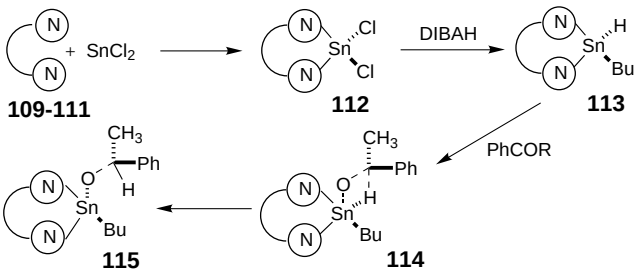
More recently the same authors reported the synthesis of the chiral piperazines **109**–**111** (Scheme 28) from chiral 1,2-diaminoethanes **108**, with a procedure that did not involve the formation of new stereogenic centres.



Scheme 28.

Treatment of the chiral piperazines with $SnCl_2$ and DIBAH produced the reducing agent. Reductions were performed on aromatic or propargylic ketones, in CH_2Cl_2 or in ether, giving up to 85% e.e. with ligand **109**.[122,123] E.e.s were dependent not only on the ligand and the steric requirements of the substrate, but mainly on the temperature at which the final hydrolysis takes place. Each time the reaction was not complete at −100°C, the change of hydrolysis conditions from low to room temperature modified the enantiocontrol. Thus, the presence of residual unreacted ketone in the reaction mixture at room temperature influences the stereochemical outcome of the reduction.

It is likely that the actual reducing species is not an aluminium hydride, but a chiral tin hydride (**113**, Scheme 29). Formation of the initial complex **112** is supported by ^1H NMR analysis. The complex is then transmetallated by DIBAH, giving **113**, which coordinates the carbonyl oxygen of the substrate. Hydride transfer occurs via a four-membered transition state **114**. If the temperature is raised above −100°C, the resulting tin alkoxide **115** can act as a reducing agent towards a second molecule of ketone through a Meerwein–Pondorff–Verley mechanism, thus altering the e.e. of the resulting carbinols.



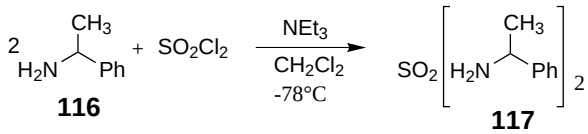
Scheme 29.

The idea of using the chiral-diamine/$SnCl_2$/DIBAH system was not new, since Mukaiyama et al. had previously achieved very good results using diamines derived from (*S*)-proline as the source of stereoinduction in the reduction of several prochiral ketones (methyl benzyl ketone, acetophenone, etc.)[124] and α-, β- and γ-keto esters,[125] with e.e.s in the range 40–78% for simple ketones and 35–89% for keto esters.

Similar considerations are applicable to the chiral reducing agent prepared from $ZnCl_2$ or $MgCl_2$, optically active 1,2-diaminoethane and DIBAH.[126] Both the stereochemistry of the reduction process and the configuration of the resulting carbinol depend also on the metal halide, $ZnCl_2$ generally leading to the highest e.e.s.

2.4. Sulphamides as ligands

Partial decomposition of LAH with 1 equiv. of *N*,*N*′-bis(α-methylbenzyl)sulphamide **117** (Scheme 30), prepared from α-methylbenzylamine **116** and SO_2Cl_2, and an achiral amine gives the so-called Sharpless reagent.[127]



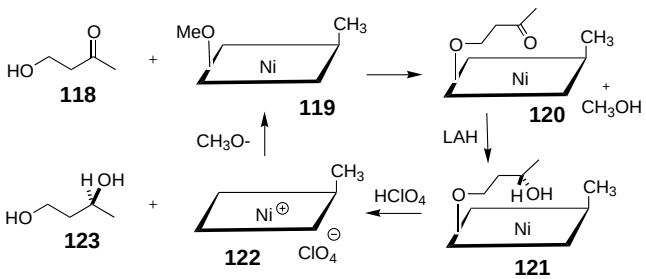
116 **117**

Scheme 30.

N-Benzylamine is preferred to ethanol and other secondary amines as the achiral ligand, because the corresponding complex is the most reactive and stereoselective. The highest enantioselectivities were obtained with *n*-butyl-2-naphthyl ketone and in general for the reduction of arylalkyl ketones, but also cyclohexylmethyl ketone is reduced with good results (71% e.e.). The reagent is notable because the chiral sulphamide is readily available in both enantiomeric forms, and very low temperatures or high pressures are not required.

2.5. Porphin-type nickel complexes as chiral matrix

Porphin-type nickel complexes **119** (Scheme 31) can act as a chiral matrix to perform the enantioselective reduction of keto alcohols of the type **118** to give diols **123**.[128]



118 **119** **120** **123** **122** **121**

Scheme 31.

The alcohol must have a functional group that can react with the derivative **119** obtained from porphine-perchlorate **122**. Addition gave exclusively the corresponding *cis*-1,11-disubstituted porphinoid **120**, which was reduced diastereoselectively to **121** by LAH thanks to an interaction between the Ni centre and the carbonyl group. This interaction was not detectable by IR analysis, but the recovered alcohol was formed in 20% e.e., thus supporting its existence. The nickel complex was recovered in 97% yield.

2.6. Magnetic field as a catalyst?

The enantioselective reduction of ketones in a static magnetic field deserves a particular mention. In 1994, Breitmeier et al. reported that the reduction of different phenones with LAH within a magnetic field of 1.2 T yielded (*R*)- or (*S*)-arylethanols with enantioselectivities ranging from 55 to 98%.[129] Lower e.e.s were achieved in the reduction of 2-butanone. E.e.s were claimed to increase steadily with the magnetic flux density B_o, although it was usually impossible to predict which enantiomer would predominate. However, following a brief season of general excitement in the scientific community, many groups failed to reproduce the results of Breitmeier, obtaining just racemic mixtures.[130] Thus, the main author admitted that the results had been manipulated by the main experimentalist G. Zadel,[131] and that the paper was the result of scientific fraud.

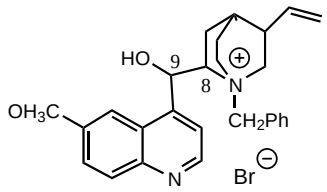
3. Chirally modified borohydrides

Two main strategies have been used to prepare chirally modified borohydrides, namely (1) the reaction of chiral additives with metal borohydrides, in particular sodium borohydride (NBH) but also lithium borohydride (LBH), and (2) the reduction of chiral boranes. The former strategy is very attractive due to the user-friendly properties and ready availability of NBH.[132] The second approach is somewhat more elaborate, but generally more effective, reliable and much less empirical, due to the fact that single reducing species, having well determined structure, can be prepared and used.

3.1. Chiral borohydrides from metal borohydrides

3.1.1. Chiral ammonium salts as PTC catalysts. As the solubility of NBH in water is high, the earliest studies concentrated on ketone reductions under phase transfer conditions (PTC) using chiral ammonium salts[133] or phosphonium salts[134] as catalysts. The e.e.s achieved were low (e.e. <32%). Among the chiral phase transfer catalysts, *N*,*N*-dialkylephedrinium bromide,[135] and the rigid benzylquinium bromide **124** (Fig. 34)[136] gave the best results.

In the asymmetric PTC borohydride reduction with chiral ammonium catalysts, the hydroxy group β to the cation (such as in the case of **124**) seems to have a major role, interacting with the carbonyl group of the substrate and favouring one of the possible diastereomeric transition states. γ-Hydroxy groups have



124

Figure 34.

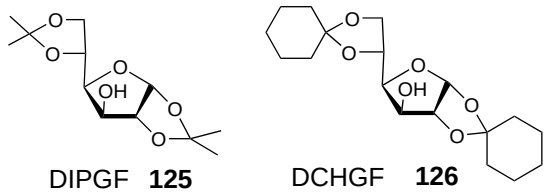


Figure 35.

a less relevant effect. It has also been shown that stereoselectivity depends on the configuration at C(8) and C(9),[137] while other stereogenic carbon atoms do not play any role. Other chiral ammonium salts combining a flat aromatic region with spatially close polar groups were prepared, but results were not satisfactory, with maximum e.e.s of 40%.[138] The degradation of quinine and quinidine allowed the synthesis of other chiral ammonium salts, which have also been tested in PTC conditions achieving poor results (e.e. <32%).[139]

Montmorillonite-supported (–)-*N*-dodecyl-*N*-methylephedrinium borohydride under PTC conditions enhanced the activation of the carbonyl group towards reduction by complexation with Lewis acid sites on clay.[140] E.e.s were very low (<10%), but it is interesting to note that the use of clay as a support seems to impart an asymmetric environment to the catalyst. In fact, as claimed by the authors, in the reduction of acetophenone using just NBH and sodium montmorillonite e.e.s of 1.2–1.5% were observed.

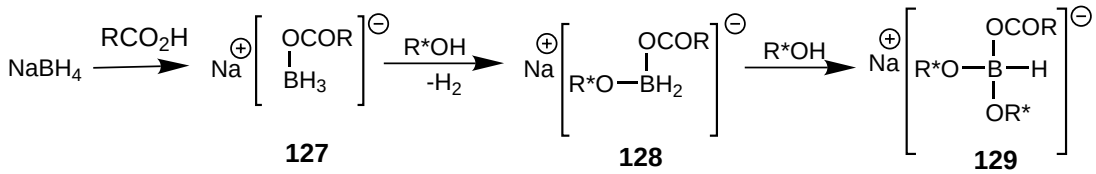
3.1.2. Monosaccharides as ligands. NBH complexes with glucose and fructose reduced ketones with moderate asymmetric induction.[141] Reductions were performed in aprotic solvents such as benzene or THF in order to maximise interactions between NBH and the ligand. Under these conditions NBH is soluble both in benzene and THF. Yields were quantitative, e.e.s were moderate (<40%), and an increase in steric requirements of the ketone substituents brought about a decrease in asymmetric induction.

The addition of 1 equiv. of carboxylic acid in the preparation of the NBH complex afforded higher stereoselectivities in the reduction step, as shown in the following examples. Reduction of propiophenone to the (*R*)-alcohol in THF with the ternary complexes obtained from NBH, 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (DIPGF) **125** (Fig. 35) or 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose (DCHGF) **126**, and a carboxylic acid gave e.e.s ranging from 40 to 83% depending on the reaction conditions.[142]

According to the authors of these papers, reaction of NBH with a carboxylic acid forms an (acyloxy)-borohydride of the type **127** (Scheme 32), which is soluble in THF. Addition of the monosaccharide (2 equiv.) results in the evolution, within 2 h, of 1 equiv. of hydrogen and formation of a monoalkoxy(acyloxy)borohydride **128**, which is then slowly transformed into a bis(alkoxy)acyloxyborohydride **129**, with evolution of a second equivalent of hydrogen.

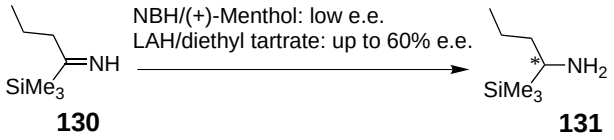
This system is even more complex because the reduction product can coordinate to boron and generate a fourth hydride species. It was observed, in fact, that high yields and low e.e.s were obtained if the substrate was added within 2 h from the formation of the complex **129**, while the opposite trend was observed when the reduction was performed after longer times. Both Morrison and Hirao suggested the rapidly formed monoacyloxyalkoxy borohydride **128** to be the most reactive species, while the bis(alkoxy)acyloxyborohydride **129** gave rise to higher enantioselectivity and lower yields. The use of chiral carboxylic acids did not bring significant variations in enantioselectivity, which indicates that the stereochemical induction depends only on the sugar portion. Chiral alcohols such as $PhCH(OH)CH_2OH$ did not give any asymmetric induction.

The reduction of aromatic ketones with NBH/**125** in the presence of Lewis acids (metal chlorides) gave modest e.e.s.[143] Under these conditions the corresponding metal borohydride was probably the dominant species. $AlCl_3$ and $ZnCl_2$ gave the highest stereoselectivities and, curiously, $ZnCl_2$ was the only one to give (*S*)-alcohols. The reducing agent obtained from $ZnCl_2$/NBH/**125** demonstrated higher enantioselectivity than the others, and was studied in detail (ratio, temperature, solvents were varied).[144]



127 **128** **129**

Scheme 32.



Scheme 33.

3.1.3. Alcohols as ligands. Recently, the reduction of an imine **130** (Scheme 33) using diethyl L-tartrate/metal hydride complexes was reported. E.e.s were not high (40% using NBH, 60% with LBH) but the reagent was selected from others (LAH/(+)-borneol, NBH/(−)-menthol, NBH/bisacetonide of α-D-glucofuranoside) as the only way to obtain **131** by enantioselective reduction.[145]

3.1.4. Amino acids as ligands. Chiral sodium salts of α-amino acid/borane complexes **132** (Fig. 36) were prepared from equimolar amounts of NBH and optically active amino acids in THF at room temperature. These complexes reduced aromatic and aliphatic ketones with e.e.s of <50%.[146]

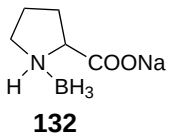
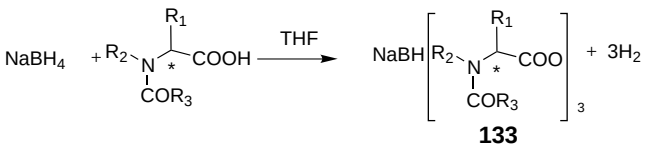


Figure 36.

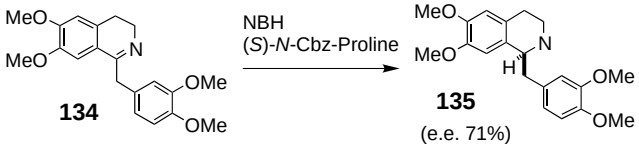
Acyloxyborohydrides of the type **133** (Scheme 34) obtained from reaction of NBH with 3 equiv. of optically active *N*-acylamino acid (for example (*S*)-*N*-acylproline) were employed successfully to produce chiral amines from cyclic imines (e.e. 60–80%).[147]



Scheme 34.

An imine–borane complex, which is formed after substitution of one ligand as the carboxylate, was probably the effective reducing agent.

Reduction of 3,4-dihydropapaverine **134** (Scheme 35) to (*S*)-norlaudandine **135** with NBH/(*S*)-*N*-Cbz-proline was achieved in 6 h (−30°C, CH_2Cl_2, yield 70%, e.e. 71%). The reduction was applicable also to the corresponding hydrochloride, thus preventing the otherwise ready oxidation of the imine free base to the corresponding 1-benzoyl derivative.[148]



Scheme 35.

NBH/*N*-acylproline complexes were applied to the synthesis of an intermediate (**136**, Scheme 36) of the antibacterial agent (*S*)-(−)-Ofloxacine **137**.[149] The best results in this C=N bond reduction were achieved with the NBH/(*S*)-*N*-($CO_2CH_2CHMe_2$)proline complex, which provided an outstanding 95% e.e.

Recently, good e.e.s have been achieved in the reductions of cyclic imines using sodium *N*,*N*-phthaloylamino acyloxy borohydrides **138** (Fig. 37). These reactions afforded alkaloid derivatives of the type **139**.[150]

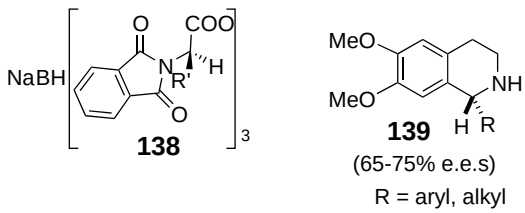
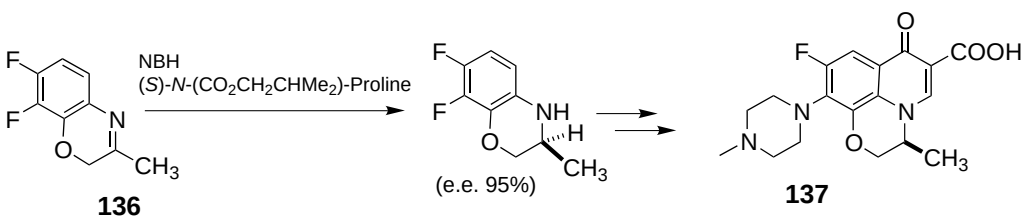


Figure 37.

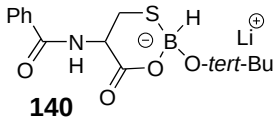
Yields were 75–80%, and (*S*)-amines **139** were formed with 65–75% e.e.s (determined by NMR studies). Addition of $ZnCl_2$ improved the asymmetric induction, and e.e.s reached 80%. The same complex was also used in an alumina-supported form, giving excellent chemical yields and very high enantioselectivities (80–92% and 93–100%, respectively).

LBH complexes **140** (Fig. 38), obtained from *N*-benzoylcysteine and *tert*-butanol[151] represented the first examples of sulphur-containing chiral reducing agents. *N*-Benzoylcysteine can be easily obtained in optically pure form from commercial cysteine. The sulphur atom is believed to stabilise the anionic complex and prevent disproportionation. Reductions were performed at −78°C, and the achiral alcohol was found to be highly important in order to increase enantioselectivity (e.e.s



Scheme 36.

varied between 87 and 92% on arylalkyl ketones). *N*-Benzoylcysteine could be recovered by aqueous alkali extraction.



140

Figure 38.

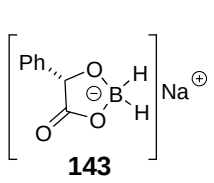
Similar results were obtained with the (*S*,*S*)-*N*,*N*′-dibenzoylcystine/LBH complex in the reduction of aromatic ketones, α,β-unsaturated aromatic ketones,[152] β-arylketo esters,[153] acetylpyridines, α- and β-amino ketones,[154] and α-halo ketones to the corresponding optically active halohydrins, then converted to oxiranes.[155] The same complex was also successfully applied to the enantioselective reduction of acetylfuran to (*S*)-1-(2-furyl)ethanol (95% e.e.), an intermediate in the synthesis of daunosamine.[156]

In 1996, a synthesis of Diltiazem **142** (Scheme 37) by asymmetric reduction of a prochiral ketone intermediate **141** using NBH/(*S*)-amino acids complexes was reported.[157] Enantioselectivity was observed only when α-amino acids possessing hydrocarbon side chains were used, in particular amino acids having long straight or γ-branched chains. (*S*)-*tert*-Leucine was selected as the best ligand. Several additives and reaction temperatures were tested, and the procedure that gave the highest selectivities employed AcOH as auxiliary at −30°C for 60 h. The reduction seems to occur via dynamic kinetic resolution, so that only one isomer out of four was produced with 98% conversion and 91% stereoselectivity for the wanted (2*S*,3*S*)-isomer.

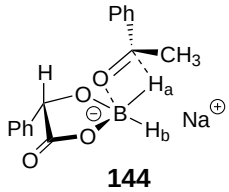
3.1.5. Carboxylic acids as ligands. The modification of NBH with organic acids has not provided very important results in asymmetric reductions. Itsuno prepared chirally modified acyloxyborohydrides using several different acids such as D-camphoric acid, L-malic acid, D-tartaric acid and so on, and used them for the reduction aromatic ketones, obtaining e.e.s lower than 50%.[158]

The NBH/(*S*)-mandelic acid complex, to which the structure **143** (Fig. 39) was assigned, was described in 1982.[159]

The reagent **143** is slightly less reactive than NBH and reduction of acetophenone occurred with low enantioselection providing (*R*)-methylphenylcarbinol with



143



144

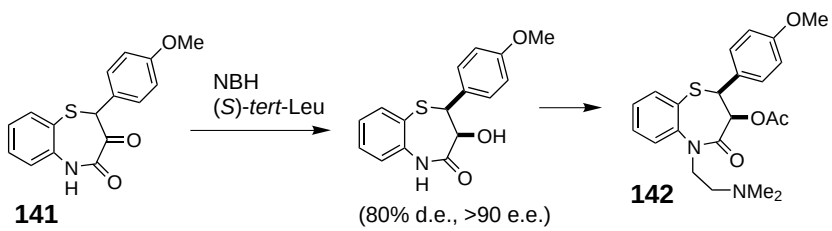
Figure 39.

11.5% e.e. The proposed transition state **144** has two diastereotopic hydrides, H_a being less hindered than H_b, and therefore more reactive.

In 1988, Bianchi et al.[160] described the reduction of acetophenone in benzene or THF with NBH/(*S*)-ethyl lactate, NBH/L-2-acetoxypropionic acid, and NBH/2-L-acetoxypropionic acid/L-ethyl lactate complexes. The formation of the reducing complexes was investigated by NMR spectroscopy. The best results were obtained with the 'mixed' complex in benzene, however e.e.s did not exceed 38%.

More recently, a similar approach using NBH/organic acid complexes [(−)-lactic, -malic, -mandelic, -tartaric, -camphanic acids] was used to reduce acetoacetic esters, but e.e.s were lower than 20%.[161] Reduction of non-functionalised ketones with NBH/L-tartaric acid complex provided low enantioselectivity, while α- or β-functionalised ketones were reduced with high e.e.s.[162] α-Methoxyacetophenone underwent reduction to give α-methoxyphenylethan-1-ol in 87% yield with 84% e.e. It is clear that the possibility to have chelation between the α- or β-positions of the carbonyl compound and the boron or sodium is, once again, important to the observed stereoselectivity. This is confirmed by the high enantioselectivity observed in the reduction of keto esters. For example, ethyl phenylglyoxylate was reduced with 86% e.e., while α-hydroxy and α-chloro acetophenone showed lower enantioselectivity. If chelation with the γ position is weaker, then stereoselectivity was lower. A further application of NBH/L-tartaric acid complex allowed the reduction of an aryl-α-keto ester to the corresponding alcohol, as an intermediate in the synthesis of chiral α-(aminooxy)arylacetic esters.[163] A screening of reducing agents demonstrated that this complex was superior to a number of other NBH/chiral acid complexes, giving rise to a product with 70% e.e.

NBH/L-Tartaric acid complex was also used for preparing (*R*)-*p*-pentadecyl ethyl mandelate from the corresponding α-keto ester. Although the enantioselection



141

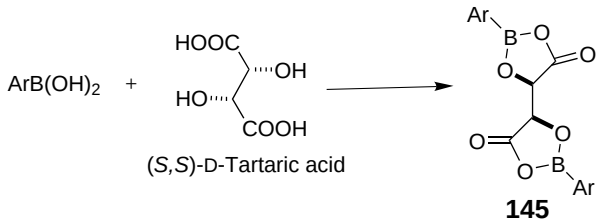
(80% d.e., >90 e.e.)

142

Scheme 37.

was not reported, the enantiopure product (e.e. >95%) was obtained after crystallisation with (*R*)-phenylethylamine.[164] The same complex was used in an interesting example of remote diastereocontrol (reagent control) for the preparation of an advanced intermediate in the synthesis of the potent mycotoxin (+)-verrucosidin (diastereomeric ratio ca. 5:1).[165]

Recently a new chiral reducing system involving a bimetallic Lewis acid complex, derived from the L-tartaric acid/boronic acid derivative **145** (Scheme 38) and LBH, was described.[166]



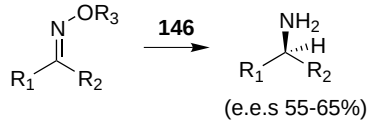
Scheme 38.

E.e.s were in the range 2–99% with substituted acetophenones, depending on the reaction conditions, and LBH was the reagent of choice. Benzophenones underwent reduction with final e.e.s spanning from 30 to 85%. Trifluoromethyl ketones were reduced with very low e.e.s (3–11%). In the optimised procedure, LBH was added to a premixed solution of substrate and Lewis acid (which suggests the formation of a complex between the latter). In the hypothetical model, which is supported by NMR studies, the Lewis basic sites, namely the carbonyl groups, coordinate the counterion (Li^+), and, at the same time, the boron centres interact with the carbonyl groups of the ketone. The method is advantageous, because although not catalytic, inexpensive tartaric acid is used, and boronic acid can be recovered by extraction from the acidic aqueous phase.

3.1.6. Amino alcohols as ligands. This field was pioneered by Itsuno, who reported that NBH reacts with chiral amino alcohols in the presence of Lewis acids such as $ZrCl_4$, producing H_2 and a chiral reducing complex,[167] which is probably a mixture of zirconium aminoacyloxy borohydrides **146** (Scheme 39).

This chiral complex reduces oxime-*O*-alkyl ethers (Scheme 40) to chiral primary amines.[168]

Reduction of a number of oximes in THF at 20°C, using (*S*)-aminovalinol as chiral ligand, gave yields in



Scheme 40.

the range 78–95%, and e.e.s between 55 and 65%. A small improvement in enantioselectivity was observed when benzyl-oximes were used instead of methyl-oximes. Different Lewis acids such as $ZnCl_2$, $ZnBr_2$, $AlCl_3$ were not effective, while the mixture $ZnCl_2/AlCl_3$ gave very high e.e.s (95%) but the difficult removal of Zn and Al salts caused a decrease in the yield. The amino alcohol **147** (Fig. 40) was selected as the best complex in terms of enantioselectivity. Advantageously, the hydrochloride salt of **147** is insoluble in water and hence is easily recovered after the reaction.

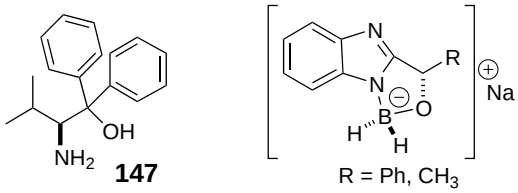
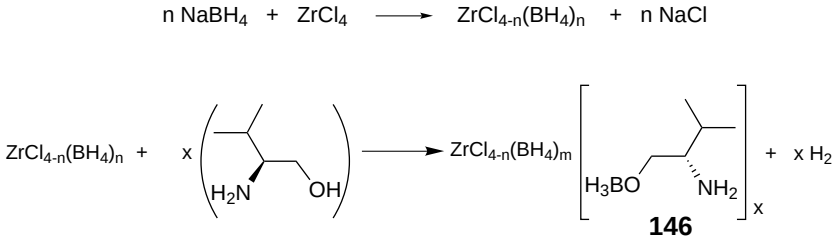


Figure 40.

Recently, NMR studies on NBH complexes with (*S*)-2-(α-hydroxybenzyl)benzimidazole or (*S*)-2-benzimidazole-1-ethanol as ligands[169] demonstrated the formation of the complex **148** (Fig. 40). It is worth noting that, as recognised by Corey, Itsuno's studies on BH_3/amino alcohol and NBH/amino alcohol complexes paved the way to the discovery of oxazaborolidine catalysts.[3]

An interesting piece of work on enantioselective heterogeneous reductions by NBH supported on chiral amino alcohols bound to polymers was performed by Caze et al.[170] Porous- or gel-type polystyrene supports (**149**, Fig. 41) loaded with amino alcohols were prepared in enantiopure form by polymerisation of vinylbenzene precursors, or via nucleophilic chlorine displacement by L-Serine on Merrifield resin. Polymers **150** were obtained with e.e.s of >90% via reduction of polystyrene carbonyl resin precursors with Ipc_2BCl. Reduction of acetophenone by NBH/**149** took place with remarkable enantiocontrol (up to 75% e.e., conversions 15–75%), whereas the system NBH/**150** was less selective (e.e.s 38–60%, conversions 50–87%). The



Scheme 39.

texture of the support had remarkable impact on the yield but not on enantioselectivity, in particular gel-type polymers were more efficient, probably as a result of better site accessibility by the substrate.

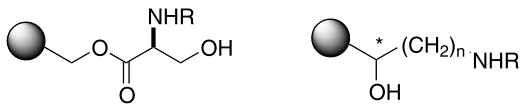


Figure 41.

Recently, the synthesis of several optically active lithium dialkoxyaminoborohydrides from chiral diethanolamines and borane was described.[171] However, the stereoselectivities observed in the reduction of acetophenone were very low (e.e.<10%).

3.1.7. Semicorrin and oxoaldimine metal complexes as catalysts. Chiral semicorrins of the type **151** (Fig. 42), which are vinylogous amidine systems having C_2 symmetry, form chiral metal complexes. The complexes have been applied to the NBH reduction of the C=C bond of α,β-unsaturated carboxylic esters and amides.[172]

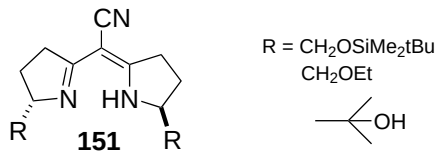


Figure 42.

Both enantiomers of the ligand can be synthesised from pyroglutamic acid, and the stereoselectivity can be modulated by varying the nature of the R group. The complex was prepared in situ by treatment of the ligand with $CoCl_2$ and used in catalytic amount (<1% mol) in EtOH–DMF or diglyme as solvent at 25°C. Yields were quantitative, e.e.s were higher than 95% and the reduction system was selective for conjugated double bonds. (*E*)- or (*Z*)-Geometric isomers were reduced to opposite enantiomers. The reduction path can be explained by the model **152** (Fig. 43).[173]

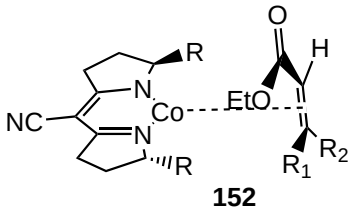


Figure 43.

An alkyl–cobalt complex, with the metal centre coordinated to the π-bond of the α,β-unsaturated ester, is formed. Hydride transfer from NBH to the Co centre of the complex, is followed by H-shift from Co to the β-position of the substrate, which leads to a cobalt enolate that is eventually protonated by the solvent. Indeed, labelling experiments showed that the proton in the β-position comes from NBH, while the one in the α-position comes from the solvent.

This method was also employed during the synthesis of key intermediates of (+)-strigol and sorgolactone, but the reduction of a series of α,β-unsaturated-γ-lactones to the corresponding saturated lactones proceeded with low enantiocontrol (e.e.s of 39–45%), while acyclic α,β-unsaturated esters gave rise to slightly better results (e.e.s of 50–60%).[174]

Yamada and Mukaiyama reported the enantioselective reduction by NBH in the presence of catalytic amounts of Co(II)-β-oxoaldimines complexes **153**–**155** (Fig. 44). The corresponding chiral cobalt hydrides, which are very effective and enantioselective with prochiral ketones, were thus formed.[175] Complexes **153**–**155** were prepared by heating the corresponding ligands with NaOH and $CoCl_2 \cdot H_2O$ in water–methanol at 60°C.

Reduction of 2,2-dimethylchroman-4-one with the system NBH/**155** (Ar = 3,5-dimethylphenyl) at −20°C, in the presence of a small amount of ethanol, which is necessary in order to achieve high enantioselectivity, gave the corresponding alcohol in 92% e.e. Several cyclic aromatic ketones were reduced, mainly chromanone derivatives having alkyl groups in the 2-position. In some cases the use of different hydrides, for example KBH_4, allowed higher enantioselectivity as

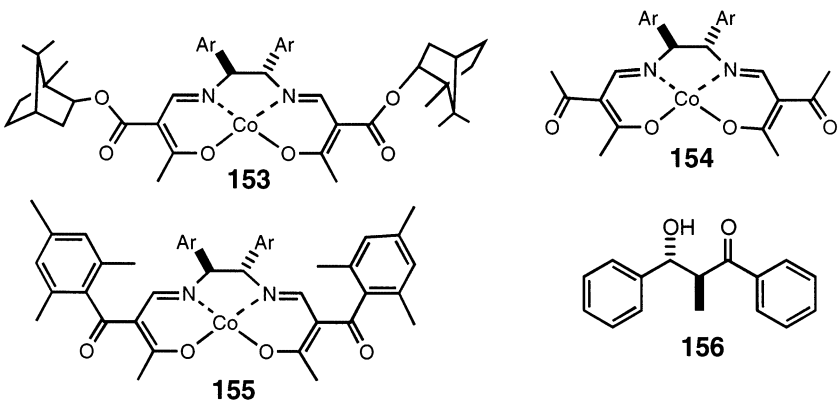
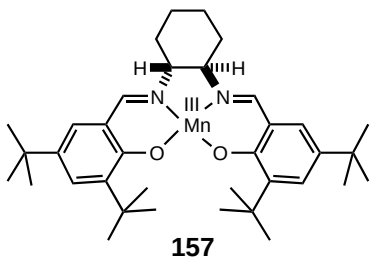


Figure 44.

compared with NBH. It is worth noting that both enantiomeric diarylethylenediamines are commercially available. Subsequently, the systems NBH/**154** and NBH/**155** proved to give extremely enantioselective reductions of a number of ketones,[176] imines,[177] and, very recently, even in the desymmetrisation of 2-alkyl-1,3-diketones, which was performed with e.e.s of up to 99% and 93–99% *anti*-diastereoselectivity to the corresponding β-hydroxy ketones, such as **156** (Fig. 44).[178] The very high stereoselectivity of the method, combined with its catalytic nature, demonstrate its great synthetic potential.

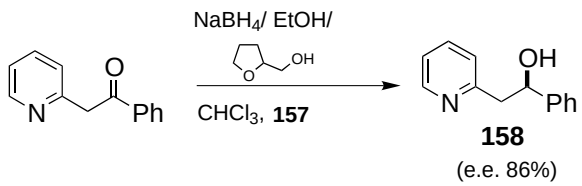
Recently 2-phenacylpyridine has been converted to the corresponding (*S*)-alcohol using Jacobsen's catalyst **157** (Fig. 45).[179]



157

Figure 45.

The best reducing species selected after screening was NBH/ethanol/tetrahydrofurfurylalcohol, (−20°C) which afforded the pyridyl alcohol **158** in 76% yield and 86% e.e. (Scheme 41).

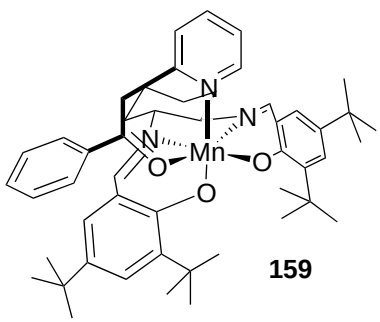


158

(e.e. 86%)

Scheme 41.

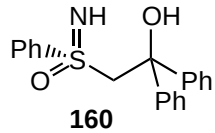
The metal centre of complex **157** is a Lewis acid, therefore it is likely to coordinate the substrate, forming an intermediate complex **159** (Fig. 46) having enantiotopic faces, which is preferentially attacked by NBH at the open *Re* face.



159

Figure 46.

Asymmetric reduction of acetophenone with a mixture of NBH/Me_3SiCl with 10% mol of ligand **160** (Fig. 47) afforded (*R*)-phenylethanol in 92% yield and 84% e.e. Even better results were obtained with other aromatic ketones (90% e.e.).[180] The ligand could be recovered from the reaction mixture with yields of >70%.



160

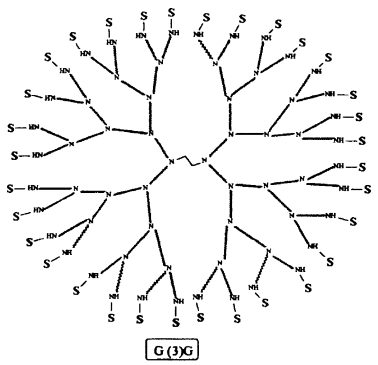
Figure 47.

The mixture of NBH/Me_3SiCl is likely to form BH_3, which should be the actual reducing agent.

$$NaBH_4+Me_3SiCl \rightarrow NaCl+Me_3SiH+BH_3$$

3.1.8. Cyclodextrins and chiral dendrimers as catalysts. Alkyl(2-furyl), alkyl(2-thienyl) and methylpyridyl ketones are able to form stoichiometric inclusion complexes with cyclodextrins. Reduction of these complexes with NBH gave the corresponding alcohols with e.e.s up to 27%.[181]

Reduction of simple aromatic ketones with NBH in water or THF using chiral dendrimers like **161** (Fig. 48) as ligands allowed e.e.s as high as 100%.[182] These dendrimers carry polyhydroxylated groups derived from glucose, and can be considered as rigid unimolecular micelles able to solubilise hydrophobic ketones in aqueous solution. Reduction then takes place at the chiral interface. THF was shown to be a better reaction medium as compared to water. The complex between NBH and the dendrimer was insoluble, so the reaction was performed using heterogeneous conditions and the dendrimer could be recovered by filtration.



161

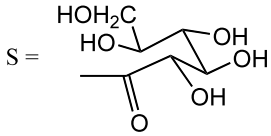
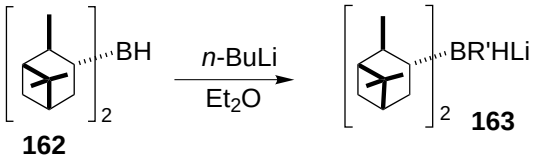


Figure 48.

3.2. Chiral borohydrides by reduction of boranes

In the 1970s several optically active boranes were studied as reducing agents, and the good results achieved by this strategy suggested the possibility to obtain new chiral borohydrides from the corresponding boranes. In 1971, Grundon studied the stereoselectivity of lithium trialkylborohydrides **163** (Scheme 42), whose synthesis from α-pinene by hydroboration to **162** and subsequent reaction of the resulting intermediate with an alkyllithium was already known,[183] in the reduction of imines and ketones.[184]



Scheme 42.

Low enantiomeric purities were obtained (e.e. 7–58% for aryl alkyl ketones). The complex was used for the asymmetric reduction of cyclic imines, useful intermediates in the synthesis of optically active alkaloids. Starting from α-pinene (*R*)-amines were obtained, but with low enantioselectivity (e.e. 4–25%). The authors suggested the structure **164** (Fig. 49) for the complex, where the two bulky pinanyl substituents are mutually at right angles.

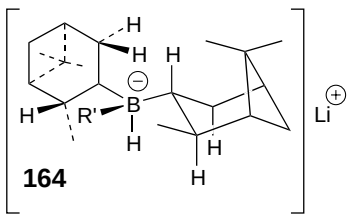


Figure 49.

The imine approaches the complex on the same side of R′ as shown in the model **165** (Fig. 50), thus minimising the interactions between the methylene groups on the ring and the boron substituents. In fact, it was observed that when R′ = *tert*-Bu reduction does not take place.

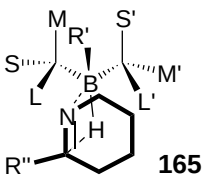
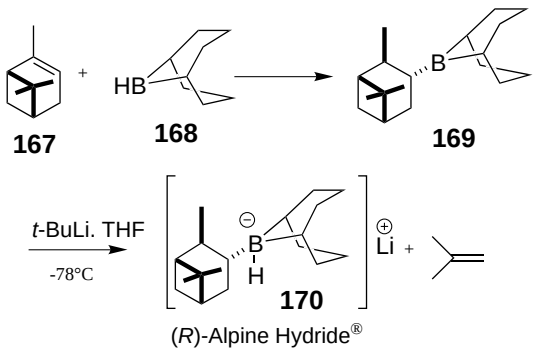


Figure 50.

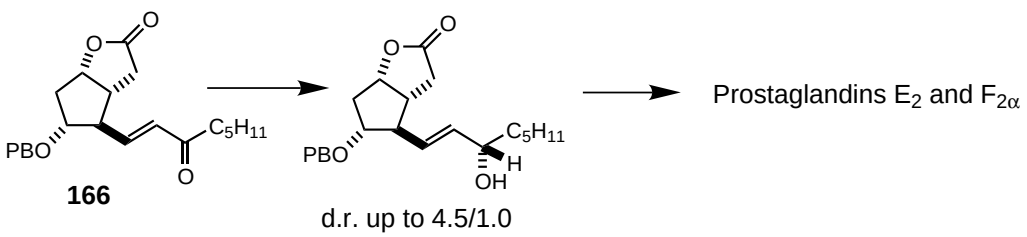
Reaction of isopinocamphenylborane, or a borane derived from (+)-limonene and thexylborane, with *tert*-BuLi or MeLi gave the corresponding chiral borohydrides, which proved to be highly chemoselective and rather stereoselective in the reduction of prostaglandin precursors such as **166** (Scheme 43), allowing Corey to improve the synthetic path to primary prostaglandins.[185]

The analogous lithium B-isopinocamphenyl-9-borabycyclo[3.3.1]nonyl hydride (which is a popular reagent, commercially available in both enantiomeric forms with the name of Alpine Hydride®) **170** (Scheme 44) was obtained by Brown via hydroboration of α-pinene **167** with 9-BBN **168** and reduction of the resulting borane **169** with RLi.[186]



Scheme 44.

The resulting species, a trialkylboro analogue of Selectrides®, is very reactive even in the reduction of highly hindered ketones such as 3,3-dimethyl-2-butanone, which is reduced at −78°C in THF in less than 1 h. The mechanism of action of **170** is uncertain. Stereoselectivity is generally not very high (enantiomeric purities range from 3 to 37%), and for this reason it has found synthetic applications mainly in the diastereoselective reduction of chiral compounds. For example, Alpine Hydride® **170** was used by Maryanoff et al. who achieved very good remote diastereocontrol with chiral acyclic hydroxy ketones bearing a protected amino function.[187] The level of 1,5-*anti*-diastereocontrol was 10:1, while even better *anti*-diastereoselectivity (12:1) was achieved for 1,6-hydroxy carbonyl systems. Moderate 1,7-*anti*-selectivity was also obtained. A chelation controlled mechanism involving the hydroxyl of the substrates was invoked to rationalise the high *anti*-remote diastereocontrol.

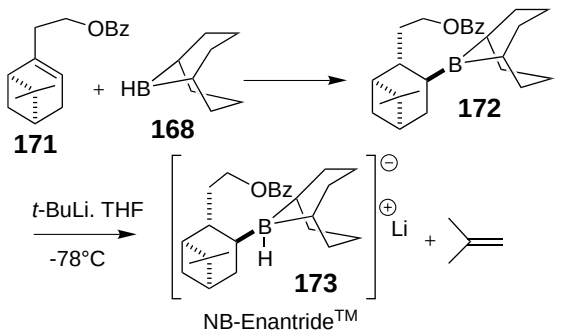


Scheme 43.

(–)-15-Hexadecanolide was synthesised via a key reduction of a chiral macrocyclic ketone by (*S*)-**170** with good remote diastereoselection (final e.e. 74%).[188] Analogous strategy allowed for the synthesis of another macrocyclic lactone, (*R*)- and (*S*)-phoracantolide. In that case, (*R*)-**170** performed the reduction of 2-(2-oxo-4-butyl)-2-nitrocyclohexanone to the (*R*)-carbinol (47% e.e.).[189]

Alpine Hydride® was also applied in the reduction of cyclic ketones. Thus, the reduction of keto-carbohydrates allowed to obtain the corresponding hydroxy-derivatives with moderate to good control,[190] and the reduction of a tricyclic triketone allowed Kishi to prepare the all-axial triol with reasonable selectivity (3:1).[191]

A few years later, Midland reported the similar hydride **173** (Scheme 45), nowadays commercially available as NB-Enantride™ and having chelating properties as well, prepared starting from commercial nopol benzyl ether **171** and 9-BBN **168**, followed by reduction of the resulting NB-Enantrane™ **172** with *tert*-BuLi.[192]



Scheme 45.

This reagent is very interesting because it can reduce both aromatic and aliphatic ketones with high enantioselectivity. 2-Butanone and 2-octanone were reduced to the corresponding alcohols with, respectively, 76 and 79% e.e. On the other hand, 3,3-dimethyl-2-butanone was reduced with only 2% e.e., because asymmetric induction decreased with increasing steric requirements of the ketone. The best results were obtained when purified **171** was used as starting material.

The intriguing chemical behaviour of NB-Enantride™ **173** and the parameters that influence asymmetric induction were investigated in detail. For this purpose, several modified analogues of **173** were tested. Midland proposed a ten-membered cyclic transition state, where the lithium ion coordinates both the ethereal oxygen of nopol and the carbonyl oxygen of the substrate,[193] on the basis of the following experimental observations.

1. Substitution of lithium by other cations shows, in each case [$KB(O\text{-}i\text{-}Pr)_3H$, $ZnCl_2$, $MgCl_2$, $Ti(OPr)_4$] decreased asymmetric induction and no reaction at temperatures below –65°C.
2. Analogues having an additional carbon atom or lacking a carbon atom on the side chain that carries the ethereal oxygen show decreased enantioselectivity. The same behaviour is observed if the protective groups on oxygen are changed.
3. If the protective group carries a second site of coordination, the e.e. falls rapidly.
4. Substitution of the oxygen atom for nitrogen or sulphur results in lower e.e.
5. The analogues of nopol benzyl ether **173** and **174** showed a different reactivity, namely **174** failed to react with 9-BBN **168**, while hydroboration of **173** occurred at different rate on the two epimers (Fig. 51). The corresponding hydrides exhibited low asymmetric induction, probably because of steric considerations.
6. Hydrides obtained from analogues having non-oxygenated side chains as in 2 above (e.g. 2-benzylapopinene **175** and 2-ethylapopinene **176**) display a stereoselectivity similar to NB-Enantride™, thus indicating that a steric effect predominates over a complexation effect, a conclusion which is supported also by Ramachandran and Brown.[194]

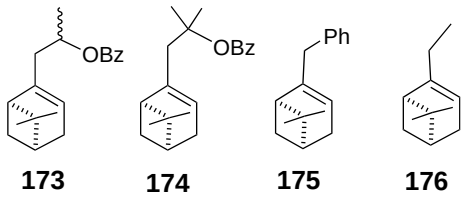


Figure 51.

Recently, the chiral borohydride **177** (Fig. 52) was proposed by Ramachandran et al. The reagent was synthesised from *N*,*N*-diethylnopilamine and 9-BBN **168**, which allowed the achievement of the highest e.e.s ever obtained in aliphatic ketones reduction (82% on 2-octanone).[195]

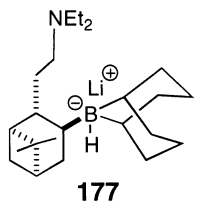
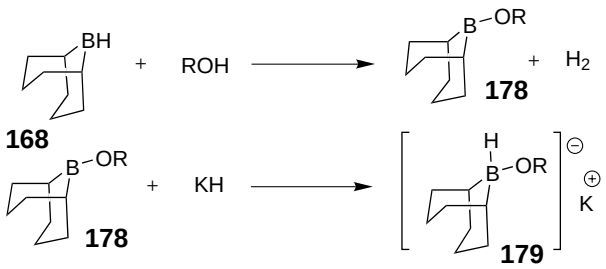


Figure 52.

Brown described the synthesis of borinic esters **178** (Scheme 46) starting from a borane such as **168** and an alcohol, and their conversion into borohydrides **179** using KH.[196] The transfer of hydride takes place at temperatures between 0 and 25°C and the products are generally stable in an inert atmosphere in THF solution and in the presence of an excess of KH. The borohydrides containing the 9-BBN substructure are particularly stable towards disproportionation. For this reason, **168** was selected as starting product for further work on the subject, and for the synthesis of other chiral borohydrides as well. Analogous chemistry was carried out starting from boronic esters $RB(OR')_2$,

providing the corresponding dialkoxymonoalkylborohydrides.



Scheme 46.

The chiral alcohols that were employed include (+)-menthol, (−)-isopinocamphenol, (+)-*trans*-2-methylcyclopentanol. In about 2 h at 25°C the corresponding borinic esters **178**, identified by the highly diagnostic ^{11}B NMR ($\delta = 55$–56.3) were obtained. The corresponding hydrides **179** were also recognised by means of NMR spectroscopic analysis, because they showed a signal at −1.7 to 1.1 ppm. Stability towards disproportionation was established monitoring the evolution of H_2. Reduction of acetophenone occurred with high yields (>90%) at −78°C, but e.e.s were highly variable (3–78%).

The same authors also described a chiral boronic ester and the corresponding hydride **180** (Fig. 53), whose chirality depends on the starting borane and not on the alcohol. Unfortunately, it showed poor stereoselectivity. The reagent is interesting because it is stable even though it does not contain the 9-BBN group.[197]

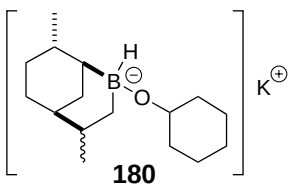


Figure 53.

Among the others, the borohydride deriving from 9-BBN **168** and thexyl alcohol (2,3-dimethyl-2-butanol) gave very good results in the reduction of cyclic ketones.[198] The most stereoselective species in the reduction of aromatic ketones represents the first example of a complex between a metal hydride and a monosaccharide whose structure has been fully assigned. This reagent is potassium-9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo-[3.3.1]nonane (9-*O*-DIPGF-9-BBN or K-Glucoride) **181** (Fig. 54).[199]

The complex, which was synthesised by treating the corresponding borane with KH in excess, is stable to disproportionation and it contains just one hydride per molecule, an important feature for high stereocontrol, as well as for the comprehension of the stereochemical outcome and the mechanism of reduction. Hindered aromatic ketones were reduced with very high e.e.s, up

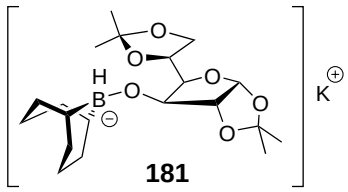


Figure 54.

to 97–100% with pivalophenone, 78% with acetophenone, 87% with isobutyrylphenone. In general, (*R*)-alcohols were formed preferentially, but aliphatic ketones allowed modest results. If some chelating functions were present on the substrate, then the degree of asymmetric induction was higher. In fact, K-Glucoride **181** reduced α-keto esters to (*S*)-α-hydroxy esters with yields of about 80% and e.e.s in the range 89–100%.[200] Aromatic α-amino ketones gave (*S*)-β-aminoalcohols with 44–73% e.e.s.[201]

The same hydride **181**, together with the analogous potassium 9-isopinocamphenyloxy-9-boratabicyclo[3.3.1]nonane, were compared to the reducing system represented by the mixture of the corresponding boranes and KH.[202] These four systems were used in the reduction of some epoxides. While the chiral boranes react via coordination to the epoxy oxygen followed by reduction by KH (model **182**, Fig. 55), the potassium borohydrides (having no vacant orbitals for oxygen coordination) directly attack the epoxide ring (model **183**). The constantly higher e.e.s obtained with the borane/KH systems, as compared to the hydrides, seem to indicate that the borane coordination step is very important to stereocontrol.

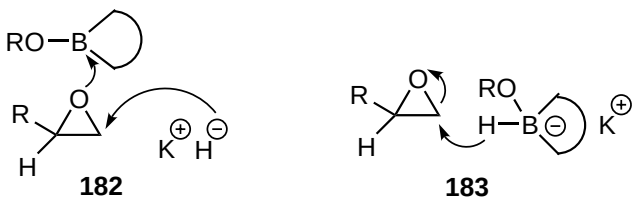


Figure 55.

In an attempt to improve the stereoselectivity in the reduction of aliphatic ketones, and to understand the factors governing the stereoselectivity, 9-*O*-DIPGF-9-BBN analogues **184**–**186** (Fig. 56) bearing different monosaccharide moieties were synthesised.[203]

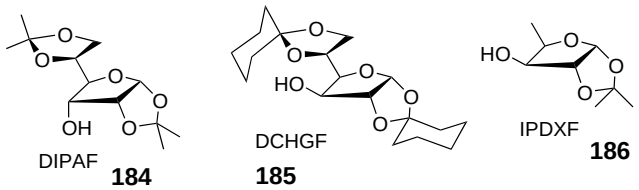
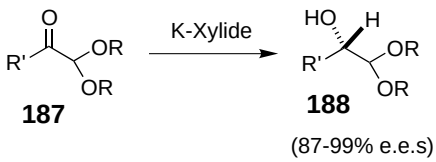


Figure 56.

DIPAF **184** is the C(3) epimer of DIPGF **125**, and the corresponding hydride showed opposite stereoselectivity as compared to DIPGF, but low e.e.s (57% on

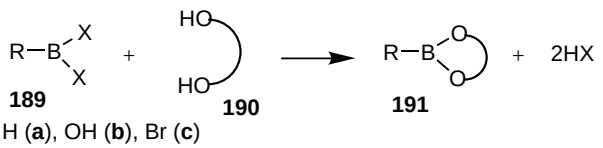
acetophenone). DCHGF **185** carries a protective group with higher steric requirements as compared to DIPGF **125** but stereoselectivity was comparable. IPDXF **186** carries a methyl group in position 4, and the corresponding potassium hydride (K-Xylide) reduced acyclic aliphatic ketones to (*R*)-alcohols with a slightly higher stereoselectivity than DIPAF **184** and DCHGF **185** (76% on 3,3-dimethylbutan-2-one compared to 70 and 58%, respectively), and aromatic ketones with the same excellent stereoselectivity, thus indicating that the steric effect of substituents at C(4) has a weak influence on asymmetric induction.

The same reducing agent (K-Xylide) was used for the reduction of α-keto acetals **187** to **188** with very high e.e.s (from 87–99%, depending on the substrate)[204] (Scheme 47). The best results were obtained with cyclic acetals (R = $(CH_2)_3$, R′ = Me, Ph).



Scheme 47.

Brown also studied the synthesis of chiral dialkoxymonoalkylboranes (boronic esters) and the corresponding hydrides.[205] The boronic esters **191** (Scheme 48) were obtained by reaction of boranes **189a**, boronic acids **189b** or monoalkyldibromoboranes **189c**, with the corresponding diols **190**. Boronic esters **191** having stereogenic groups both on the borane and the diol fragments were prepared.



Scheme 48.

A number of derivatives having R = methyl, thexyl, (−)-monoisopinocamphenyl and the alcohol part = diethyleneglycol, (2*R*,3*R*)-butanediol, (1*S*,2*S*,3*R*,5*S*)-pinanediol and 1,2:5,6-di-*O*-isopropylidene-D-mannitol **192** (Fig. 57) was synthesised.

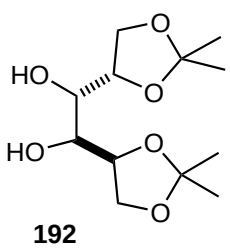


Figure 57.

Model reductions were performed on acetophenone and 3-methyl-2-butanone. Once again yields were high, while the sense of asymmetric induction and e.e.s were extremely variable. The best results were obtained with the borohydride derived from **192**, having C_2 symmetry, and texylborane. This reagent reduced cyclohexenone to cyclohexenol in 71% e.e. without affecting the double bond. Examples of very sterically hindered chiral boronic esters whose chirality depends both on the borane and on the glycol moiety failed to react with KH or *tert*-BuLi and therefore were unable to give the corresponding hydride.

4. Conclusions: which is the 'best' enantioselective reducing agent?

Of course, the above is a provocative question, because it is evident that a universal, 'best' enantioselective reducing agent is not (or not yet) available. In fact, the choice of the most appropriate reagent is strongly dependent on the substrate, as clearly demonstrated by the following works aimed at finding an answer to this intriguing question, in which different reducing agents were compared in order to define the features of the 'best' one.

In 1987, Brown[206] compared six different groups of reducing agents, i.e. aluminium hydrides, borohydrides, boranes and even an enzymatic reducing agent and studied their behaviour in the reduction of ten different classes of ketones (cyclic, acyclic, aryl alkyl ketones, conjugated ketones, and so on). The comparison was performed by taking into account the data available both from the literature and from repetition of known reducing procedures on the different substrates. The result was a list of the best reducing agents for each class of ketones (Table 1).

A more limited selection was conducted on the reduction of prochiral diphenylphosphinyl imines to the corresponding phosphinyl amines, then hydrolysed to amines. Three reducing agents, namely Binal-H, Darvon alcohol/LAH and K-Glucoride were studied.[207] Surprisingly, stereoselectivity was higher with dialkyl substrates than with aryl alkyl ones, and the e.e. seemed to depend on steric rather than electronic factors. The highest asymmetric inductions (50–84% e.e.) were obtained with K-Glucoride.

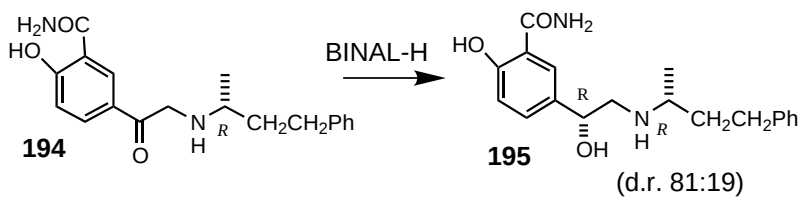
The asymmetric reduction of *N*-phenyl imines to chiral amines was continued by Cho and Chun, who, in 1992, compared the following reducing agents: Itsuno's reagent, Corey's reagent (both use BH_3 as reducing agent), K-Glucoride, Sharpless' reagent and Darvon alcohol/LAH. Itsuno's reagent was claimed to be the best for these compounds.[208]

An interesting study has been completed in Schering–Plough's laboratories. In the optimisation of the synthesis of Dilevalol **195** (Scheme 49), the aim was to find the ideal reagent for the reduction of α-amino ketones such as **194** to β-amino alcohols with high enantioselectivity. Noyori's reagent (BINAL-H) was the best among a huge number of reducing agents and conditions tested, giving a diastereomeric ratio (*RR*:*SR*) of 81:19.[209]

Table 1. Preferred asymmetric reducing agents

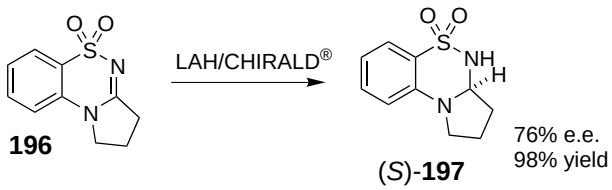
Classes of ketones	Features	Preferred reagents (in order of effectiveness)
1. Acyclic	(a) Unhindered	2,5-Dimethylborolane *B*-Ipc-9-BBN, 6 kbar TBADH enzyme NB-Enantride
	(b) Hindered	2,5-Dimethylborolane Ipc_2BCl BH_3-AMDPB
2. Cyclic		Ipc_2BCl BH_3-AMDPB K-Glucoride
3. Arylalkyl	(a) Unhindered	*B*-Ipc-9-BBN, 6 kbar Ipc_2BCl LAH-DBP-EtOH Binal-H LAH-diamine BH_3-AMDPB
	(b) Hindered	K-Glucoride LAH-diamine Ipc_2BCl
4. Heterocyclic		*B*-Ipc-9-BBN, 6 kbar *B*-Ipc-9-BBN, neat Ipc_2BCl
5. α-Halo		*B*-Ipc-9-BBN, neat BH_3-AMDPB Ipc_2BCl Binal-H
6. α-Keto esters		K-Glucoride *B*-Ipc-9-BBN, neat
7. β-Keto esters		LBH-DBC-*tert*BuOH Ipc_2BCl
8. Acyclic conjugated enones		Binal-H LAH-MEP-NEA LBH-DBC-*tert*BuOH LAH-aminobutanol
9. Cyclic conjugated enones		LAH-aminobutanol LAH-MEP-EAP
10. Conjugated ynones		Binal-H NB-Enantrane LAH-MEP-ArOH *B*-Ipc-9-BBN, THF

A similar updated list was compiled by Noyori in a review.[1a]



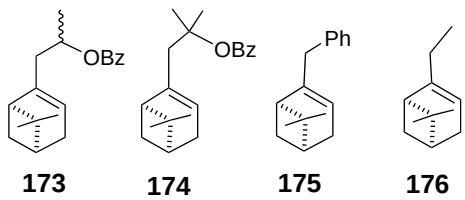
Scheme 49.

Another interesting comparative work was performed in order to find the best reducing agent for transforming **196** (Scheme 50) into (*S*)-**197**, an AMPA receptor positive modulator. Six reagents, namely NBH/(*S*)-*N*-Cbz-proline (see **133**, Scheme 34), LAH/(−)-*N*-Me-ephedrine/PhNHEt, LAH/(*S*)-2-(anilomethyl)pyrrolidine (**107**, Fig. 33), BH_3/oxazaborolidine, (*R*)-BINAL-H (**11**, Fig. 3), LAH/CHIRALD®. The best results were achieved with the latter, at 0°C in Et_2O, which provided 76% e.e. and 98% yield. No reaction, or very low yields and e.e.s were observed with the former, with the BH_3/oxazaborolidine system, and with BINAL-H as well. Low e.e.s were obtained with LAH/(−)-*N*-Me-ephedrine/PhNHEt and LAH/(*S*)-2-(anilinomethyl)-pyrrolidine.



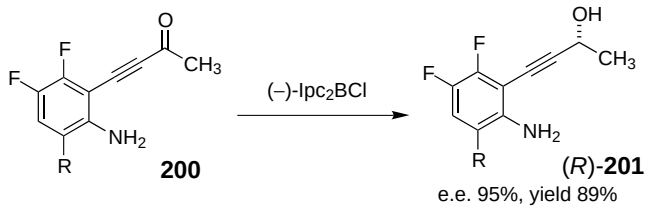
Scheme 50.

Chamberlin and Miller studied the enantioselective reduction of a *meso*-*N*-benzyl tartrimide **198** (Scheme 51) in order to prepare the reduced derivative (+)-**199**, as an intermediate of glycosidase inhibitors (−)-Swainsonine and (+)-Castanospermine. At least ten different reducing agents, such as NB-Enantride®, BINAL-H, LAH/CHIRALD®, the Sharpless reagent, etc. were examined, and the best result was obtained using the complex LAH/(*S*)-2-(2,6-xylidinomethyl)pyrrolidine (see **107**, Fig. 33) which afforded 56% e.e. and 79% yield.[210]



Scheme 51.

During their synthesis of the anti-microbial (*S*)-Nadifloxacin, Morita et al. explored the reduction of propargylic ketones **200** (Scheme 52) to the corresponding alcohols (*R*)-**201**, using five different enantioselective reagents, namely LAH/CHIRALD®, catecholborane/and BH_3/Corey's oxazaborolidine, (−)-Ipc_2BCl, (*R*)-Alpine Borane®, under different experimental conditions.[211] Although the former complex is usually very effective in reducing enantioselectively propargylic



Scheme 52.

ketones, in this case it scored a rather modest 61% e.e. The best results in terms of enantiocontrol (95% e.e.) were achieved with both (–)-Ipc_2BCl and (*R*)-Alpine Borane®, but the former gave a better yield (89% in THF at 4°C).

We believe that the examples above, and many others throughout this review, confirm that the choice of the 'best' enantioselective reducing agent is strongly depending on the substrate, and that we are still far from a 'universal' reagent, able to solve alone all the problems connected with an enantioselective reduction.

In conclusion, we would like to express our hope that this review will serve not only as a source of information for the choice of the best asymmetric hydride reagent, but also as a source of inspiration for promoting further innovative and useful research with chirally modified alumino- and borohydride reagents. Although we have tried our best to provide a comprehensive review of the field, it is more than likely that some contributions have been regrettably and unintentionally omitted. For this reason we would like to apologise in advance to authors whose names and articles are missing from the list of references.

Acknowledgements

MURST Cofin-2000 and CNR-CSSON are gratefully acknowledged for financial support.

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