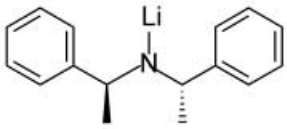
Genealogical tree of chiral bases



Achiral Brønsted bases
*t*BuOH, LDA, KOH
RLi, complex bases etc.

Chiral
lithium amides

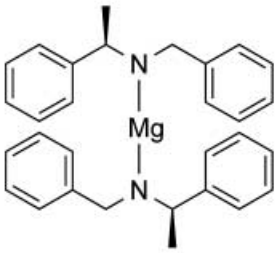
First-generation
of chiral bases
1980's

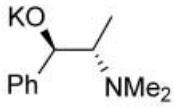
RLi/sparteine

Chiral
magnesium amides

Second-generation
of chiral bases
1990's

Chiral
alkoxides



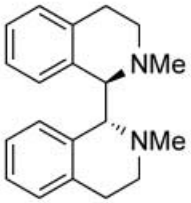


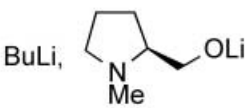
The New generation?
2000's

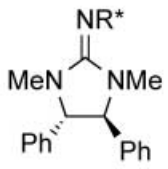
Chiral
proton sponges

Chiral
complex bases

Chiral
guanidiniums







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New Insights in the Search for Chiral Brønsted Bases

Jean-Christophe Plaquevent,* Thierry Perrard, and Dominique Cahard[a]

Abstract: The concept of using chiral bases in asymmetric synthesis appeared with the emergence of the chemistry of chiral lithium amides. In recent years, new classes of chiral bases, such as chiral magnesium bisamides and chiral alkali alkoxides have proven to be highly efficient and easy to handle. This paper highlights recent advances and new concepts in the chemistry of this second generation of chiral bases.

Keywords: asymmetric catalysis · asymmetric synthesis · electrophilic substitution · elimination · enantioselectivity

Introduction

With the exception of some very early attempts to use chiral Brønsted bases in asymmetric synthesis (see Section 2.1.), the true potential of these chiral auxiliaries was only demonstrated at the beginning of the eighties. In 1980, two simultaneous and independent papers appeared exemplifying two aspects of the chemistry of chiral bases.[1, 2] It is worthy of note that the two examples reported focused on the two major strategies to induce an enantioselective reaction by means of these reagents. The first possibility (type 1) is the generation of a prochiral anionic intermediate by means of the chiral base, thus giving its conjugate acid form (Figure 1).

This form can then be a chiral ligand for the metallated prochiral intermediate which can then in turn react enantioselectively with various electrophilic reagents (typically enantioselective protonation, alkylation, and halogenation of enolates). The second possibility (type 2) is to induce enantioselective deprotonation by discrimination of two enantiotopic protons of a prochiral compound (typically enantioselective deprotonation, isomerisation, and elimination).

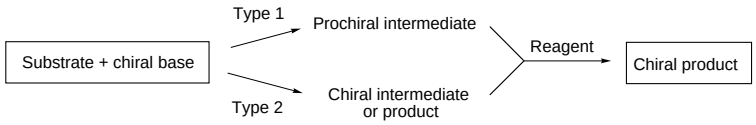
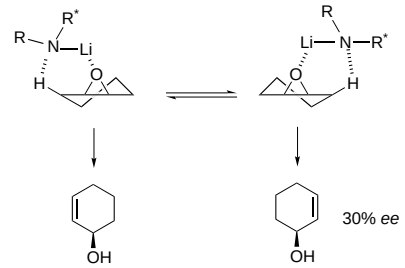


Figure 1. Two types of reaction mediated by chiral bases.

Thus, Whitesell and Felman have shown in their seminal paper on the enantioselective isomerisation of *meso* epoxides that chiral lithium amides derived from phenylethylamine led to isomerisation with an *ee* of about 30% (Scheme 1).[1] An improvement in the enantioselection for this reaction was subsequently achieved by modification of the chiral reagent (for example see Asami).[3]



Scheme 1. Enantioselective isomerisation reaction described by Whitesell and Felman.[1]

At the same time, within our own group, the effect of chiral lithium amides on the deracemization of aminoesters was described. We were able to show that the secondary amine which was liberated during the deprotonation step of the racemic substrate played the role of a chiral ligand for the lithium ion, thus rendering the protonation step enantioselective, even when it was achieved using an achiral or racemic acid (Scheme 2).[2]

The generalization of this observation was then reported for electrophiles other than the proton: enantioselective aldolisations,[4] alkylations[5] and carboxylations[6] were carried out with high selectivity in some cases. Several recent comprehensive reviews have been devoted to modern aspects of the chemistry of chiral lithium amides.[7]

Nevertheless, the use of chiral lithium amides as Brønsted bases has some drawbacks, mainly as a result of their instability and their preparation from alkyllithiums. For

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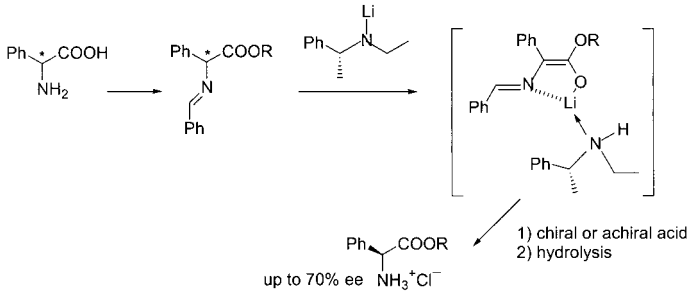


Scheme 2. Effect of chiral lithium amides on the deracemization of aminoesters.

example, as in the case of common lithium amides, the use of an inert atmosphere is required as well as low temperature conditions. In addition, access to large amounts of product is not easy. Finally, most of the chiral lithium amides are not as stable as LDA for example, thus rendering difficult the recovery of the chiral auxiliary and requiring the reaction conditions to be more controlled than with standard lithium amides. These drawbacks incited us to focus our work on the search for new chiral basic reagents which would be easier to prepare, to handle (especially in large amounts), and which could be used under less rigorous conditions. Two classes of reagents were accordingly selected as potential "second-generation" chiral Brønsted bases:

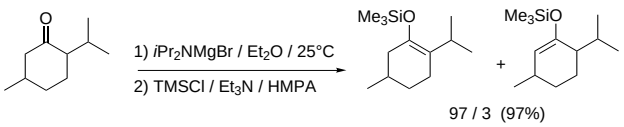
- chiral Hauser bases and magnesium bisamides (Section 1)
- chiral alkali alkoxides (Section 2)

The results highlighted herein describe our own contribution to this chemistry as well as the use of these reagents by other groups.

1. Chiral Hauser Bases and Magnesium Bisamides

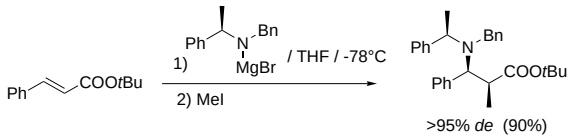
1.1 Chiral Hauser bases—Expectations and disappointments: In addition to the chemistry of lithium amides, some groups have developed the synthetic aspects of magnesium amides. Actually, these reagents were discovered in 1947 and are known as Hauser's bases.[8] Nevertheless their use only emerged in the 70s. Differences in reactivity between lithium and magnesium amides are mainly related to the nature of the cation; with both having a similar ionic radius but with magnesium twice as charged as lithium, Mg^{2+} is a stronger Lewis acid than Li^{+} and also less polarisable thus showing a harder acidic behaviour. One can expect that Hauser bases are less basic than lithium amides. Consequently the use of Hauser bases allows higher temperature reactions. Some interesting differences in behaviour were observed in a comparative study of both types of amides. Krafft and Holton reported that deprotonation of dissymmetric cycloalkanones carried out with Hauser bases lead to the thermodynamic enolate (Scheme 3).[9] According to the authors, Hauser bases are the most effective bases for the preparation of thermodynamic enol ethers.

Other applications such as the deprotonation of cubanes,[10] of substituted cyclopropanes,[10] of *tert*-butyl acetate,[11] of sulfoxides[12] and of aromatic and vinylic systems[13] have also been studied.



Scheme 3. Deprotonation of dissymmetric cycloalkanones carried out with Hauser bases leading to the thermodynamic enolate.

Very few examples of enantioselective reactions carried out by means of chiral Hauser bases are reported in the literature. The first attempt to use chiral Hauser bases in asymmetric synthesis was disclosed by Davies in 1994 in a hetero-Michael reaction (while not used as a deprotonating agent, we think it of interest to cite this work).[14] The 1,4-addition of the chiral Hauser base on *tert*-butyl cinnamate followed by the addition of methyl iodide gives the *syn* product with a diastereomeric excess of 95% (Scheme 4). Noteworthy in this tandem addition-methylation reaction is that the lithium amide provides the *anti* product but only in 30% *de*. The Michael addition step was found to proceed with the same sense of asymmetric induction in both cases whilst the methylation of the β-amino enolate proceeded in a stereodivergent manner thus allowing the production of either the *syn* or the *anti* adduct by a simple change of counterion.



Scheme 4. 1,4-Addition of the chiral Hauser base on *tert*-butyl cinnamate followed by the addition of methyl iodide to give the *syn* product.

In order to get more insight into the chemistry of chiral Hauser bases, we initiated a study on the carboxylation of prochiral imines. The chiral Hauser base was used to generate the magnesium azaallyl intermediate and the chiral amine thus released served as external ligand for the enantiofacial discrimination. This was targeted to the synthesis of amino acids under very mild conditions. Such a strategy was first reported by Duhamel et al. in 1988 using chiral lithium amides at $-78\,^{\circ}C$ to yield amino acids in up to 40% *ee* values.[6b]

Hauser bases were easily prepared from diisopropylamine or 2,2,6,6-tetramethylpiperidine in THF or diethyl ether at ambient temperature by treatment with ethyl magnesium bromide. The carboxylation was run either with carbon dioxide or alkylchloroformates. Unfortunately, all the conditions tested (temperature, solvent, cosolvent, amide structure, imine structure, carboxylating agent) failed to give the expected product. Nevertheless the deprotonation step was evidenced by the change in color due to the azaallyl intermediate. We then investigated the Michael addition of methyl malonate on a 2-substituted cyclopentenone. We thought that a chiral Hauser base could be used to promote an enantioselective 1,4-addition. Many procedures were examined varying experimental parameters such as the addition of a co-solvent (DMPU or HMPA) or of additives (Cu^{+} salts, Mg^{2+} or Li^{+} salts, TMSCl). Again the results were

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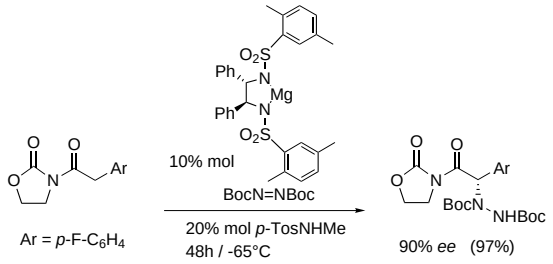
disappointing since the addition product was only obtained in trace amounts.

Our experience in both the carboxylation and the Michael addition led us to conclude that Hauser bases are sufficiently strong Brønsted bases for the deprotonation step. Unfortunately, the intermediate anionic species did not exhibit the required reactivity possibly due to their stabilisation.[15] This drawback then led to examine chiral alkali alkoxides as second generation chiral bases (see Section 2).

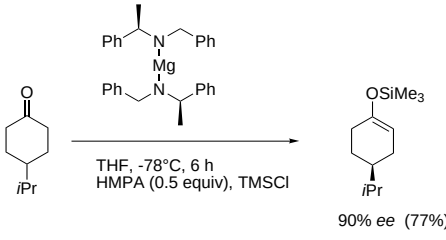
1.2 Chiral magnesium bisamides—Regio and enantioselectivity: In 1997 Evans et al. reported chiral magnesium bis(sulfonimide) complexes as catalysts in the enantioselective amination of enolates (Scheme 5).[16] In this study magnesium bisamides compared favourably with lanthanides and alkali alkoxides stressing the high efficiency of this class of chiral auxiliaries.



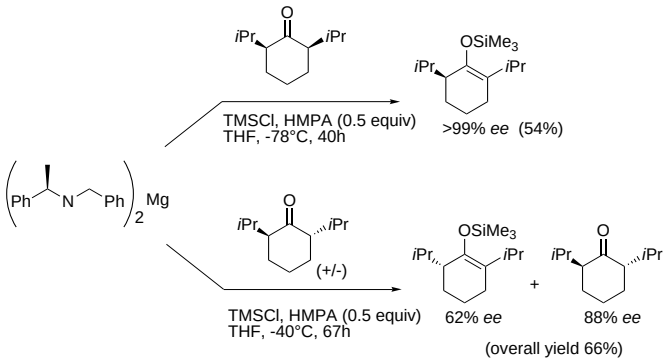
Scheme 5. Chiral magnesium bis(sulfonimide) complexes as catalysts in the enantioselective amination of enolates.[6]

At the end of the nineties, two groups independently examined the potential of magnesium bisamides as chiral bases, with the aim to by-pass the drawbacks of Hauser bases. The first studies were carried out in the achiral series. Henderson and co-workers described aldol additions mediated by bis(hexamethyldisilazido)magnesium,[17] and Bordeau and co-workers proposed the use of $(DA)_2Mg$ (magnesium bis(diisopropylamine)) as an efficient base for regioselective deprotonation of unsymmetrical ketones.[18] These modern approaches led the same two groups to examine the possibility of asymmetric induction by means of chiral magnesium bisamides.[18b, 19] Henderson's group extensively studied chiral bisamides, and observed significant results, with *ee* values as high as 90% obtained in the asymmetric deprotonation of 4-isopropylcyclohexanone (Scheme 6).[19, 20a]

When applied to *meso*-2,5-diisopropylcyclohexanone, enantiomeric ratios were quantitative[20] while kinetic resolution was observed on the *trans* isomer (Scheme 7).



Scheme 6. Asymmetric induction by means of chiral magnesium bisamides.[19, 20a]



Scheme 7. Asymmetric deprotonation of diisopropylcyclohexanone.[20]

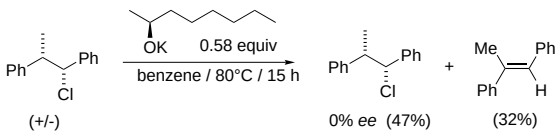
Henderson et al. have recently described the preparation and use of polymer-supported chiral magnesium bisamides for the asymmetric deprotonation of a series of prochiral cyclohexanones, with a selectivity almost equal to that obtained with unsupported reagents.[21] The chemistry of magnesium bisamides as reagents in synthesis has been recently reviewed.[22] The asymmetric inductions reported to date are now in the same range as those previously published in the chemistry of chiral lithium amides.[7]

2. Chiral Alkali Alkoxides: Simplicity and Efficiency

The use of chiral alkali alkoxides as ligands in enantioselective reduction or nucleophilic addition is well documented and will not be discussed herein.[23, 24] Surprisingly, the development of such reagents as Brønsted bases has been neglected as compared to chiral lithium amides. As for the latter reagents, type 1 and type 2 reactions are, of course, well established (see Figure 1).

2.1. Early studies

2.1.1. Cram's kinetic resolution: In the early fifties, Cram had the inspiration to test chiral bases in an enantioselective dehydrohalogenation reaction.[25] As conceived, the organic base, used in a substoichiometric amount, was expected to react faster with one enantiomer of the substrate than with the other; and the resulting kinetic resolution would then yield enantiomerically enriched unchanged starting material (Scheme 8).

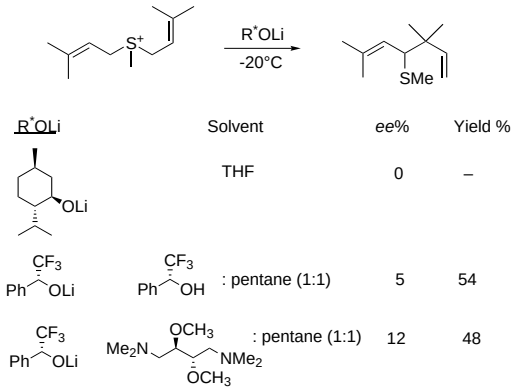


Scheme 8. Kinetic resolution to yield enantiomerically enriched unchanged starting material.[25]

Interestingly, the chiral alkoxide gave the expected dehydrohalogenation, nevertheless the recovered starting material was racemic probably because of the high temperature conditions. Some experiments have also been done using

lithium (2,2-dimethylpropyl)-(*R*)-(1-phenylethyl)-amide, but failed to give elimination (either no reaction or formation of by-products was observed).[25] It is worth noting that in this first trial of using chiral bases in an asymmetric reaction, alkoxides proved to be of higher synthetic efficiency than lithium amides!

2.1.2. Trost's [2,3]-sigmatropic transposition of sulfonium salts: Trost et al. were the first to examine the chiral base initiated [2,3] rearrangement of a sulfonium salt (Scheme 9).[26]



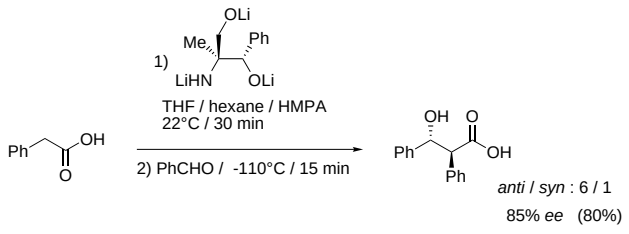
Scheme 9. [2,3]-Sigmatropic transposition of sulfonium salts.[25]

Experiments involving only the chiral alkoxide as chiral auxiliary led to racemic material whilst modest *ee* values were obtained when the chiral alkoxide was also combined with a chiral cosolvent. The authors assumed that the key step for asymmetric induction was the enantioselective deprotonation in the α-position of the sulfonium moiety. Alternatively, one can imagine that the enantioselectivity proceeds through a type 1 system in which the intermediate carbanion could be coordinated by the chiral auxiliary.

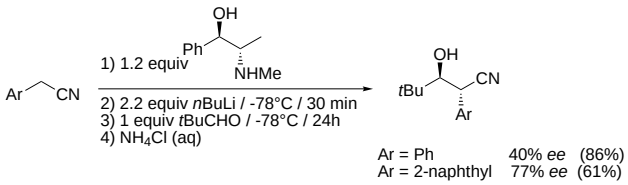
2.2. Type 1 reactions (enantioselective electrophilic addition)

2.2.1. Aldolisation: The earliest example of this class was reported by Mulzer et al. who described the synthesis of a β-hydroxy acid starting from a carboxylic acid and benzaldehyde.[27] The chiral auxiliary was a mixed alkoxide-amide base and both diastereoselectivity and enantioselectivity were fairly good (Scheme 10).

In a recent related study Carlier et al. have shown that an asymmetric transformation occured in the aldol reaction of arylacetonitriles (Scheme 11).[28] Those experiments clearly



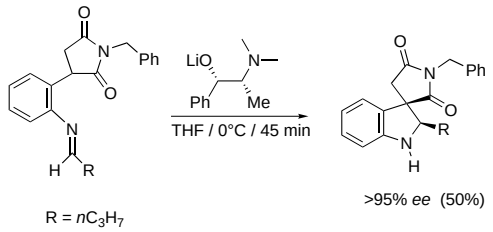
Scheme 10. Enantioselective electrophilic addition.[27]



Scheme 11. Asymmetric transformation in the aldol reaction with arylacetonitriles.[28]

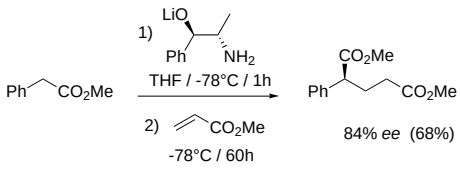
indicated that enantioselectivity was thermodynamically controlled and that the aldol reaction was reversible when the reaction time was long enough. This observation must be taken into account especially when previous reports on enantioselective aldolisation under the influence of chiral alkoxides were considered.[29]

At the same time as the work of Mulzer, a very efficient asymmetric cyclisation was described by Speckamp et al.[30] Thus, lithium *N*-methylephedrinate was used to generate an enolate which added in intramolecular fashion to the imine function of the substrate with creation of two contiguous stereogenic centers (Scheme 12).



Scheme 12. Very efficient asymmetric cyclisation described by Speckamp et al.[30]

2.2.2. Michael addition: In 1994 Koga reported an enantioselective Michael addition mediated by of alkali alkoxides as chiral auxiliaries (Scheme 13).[31] The best results were obtained when using lithium as the counterion and an internal ligation site. The catalytic approach was also effective.



Scheme 13. Enantioselective Michael addition mediated by of alkali alkoxides as chiral auxiliaries.[31]

2.2.3. Olefination: The search for an asymmetric variant of the Horner – Wadsworth – Emmons reaction of a prochiral ketone for the synthesis of an olefin with a chiral axis is the subject of active research.[32] Amongst various approaches, Koga et al. have described such an enantioselective olefination using a chiral alkoxide as a base, with an achiral phosphonate (Scheme 14).[33]

The authors examined the elimination reaction on the racemic aldol intermediates which were individually prepared (Scheme 15). When treated with the same chiral base similar

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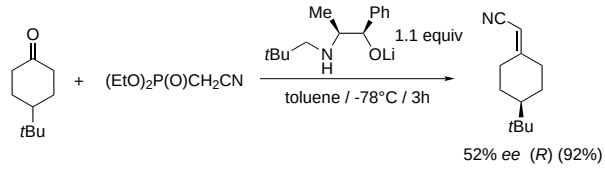
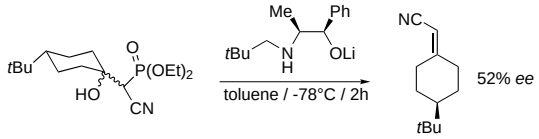


Scheme 14. Enantioselective olefination using a chiral alkoxide as a base.[33]

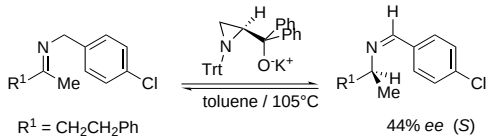


Scheme 15. Elimination reaction on the racemic aldol intermediates.[33]

ee's were obtained thus evidencing an asymmetric transformation similar to that seen in the case of aldol reactions (see 2.2.1).

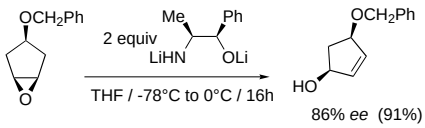
2.3. Type 2 reactions

2.3.1. Isomerisations: A catalytic asymmetric synthesis of chiral amines using a chiral base catalysed [1,3]-proton shift reaction of imines was described by Zwanenburg et al. in 1995 (Scheme 16).[34] This isomerisation reaction proceeded in modest enantioselection and was only promoted with potassium alkoxides.



Scheme 16. Asymmetric synthesis of chiral amines using a chiral base catalysed [1,3]-proton shift reaction of imines.[34]

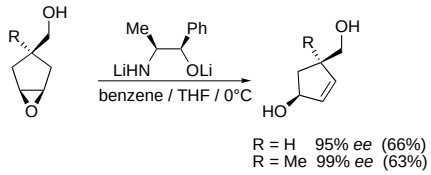
The enantioselective rearrangement of *meso* epoxides to allylic alcohols using chiral lithium amides has been the focus of much research since the seminal paper of Whitesell and Felman.[1] Two groups have examined similar rearrangements by means of dilithiated amino alcohols. Murphy et al. initiated this study in 1993 (Scheme 17).[35]



Scheme 17. Enantioselective rearrangement of *meso* epoxides to allylic alcohols using chiral lithium amides.[35]

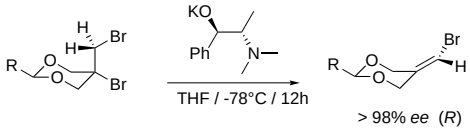
Hodgson et al. have also applied the same reagents in order to induce a similar rearrangement giving access to carbocyclic nucleoside precursors in high *ee* values (Scheme 18).[36]

2.3.2. Eliminations: Since 1993, our group has described the use of chiral alkoxides obtained from ephedrines for enantioselective proton abstraction.[37] These reagents allow the



Scheme 18. Carbocyclic nucleoside precursors obtained by enantioselective rearrangement.[36]

practical synthesis of axially dissymmetric 1,3-dioxanes by highly enantioselective dehydrohalogenation reactions (Scheme 19). We wish to emphasize that chiral lithium amides failed to give the expected elimination. The conditions for catalytic use of these chiral alkoxides have also been defined.[37c, d]



Scheme 19. Highly enantioselective dehydrohalogenation reactions to obtain axially dissymmetric 1,3-dioxanes.[37c, d]

The best results were obtained starting from the prochiral *trans*-dibrominated isomer and using alkali ephedrinates bearing the dimethylamino and the pyrrolidino moieties,respectively, which are the smallest dialkylamino groups. The dramatic role of the steric hindrance of the nitrogen moiety of the base was convincingly demonstrated in this way.

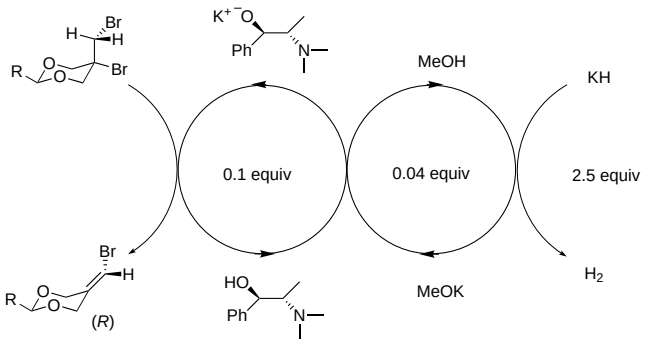
Lithium alkoxides were rejected since they led to very poor conversion into chiral dioxanes. Potassium alkoxides gave higher asymmetric induction than the corresponding sodium bases, and better results were obtained when R was an aryl group.

For a catalytic version of this reaction, the key problem was to design a system consisting of an achiral base (in excess) and the chiral alkoxide (in a substoichiometric amount) in which the achiral component would be able to deprotonate the chiral alcohol but not the prochiral substrate. The following system proved to be successful for the reaction:

1) potassium hydride in excess
2) methanol in substoichiometric amount
3) *N*-methylephedrine in substoichiometric amount

Indeed, potassium hydride was able to generate in situ potassium methylate and the resulting achiral alkoxide reached equilibrium with potassium ephedrinate thereby providing the expected enantioselectivity in the dehydrohalogenation process (Scheme 20).[37c,d]

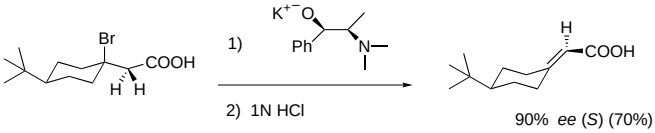
Very high enantioselectivities were obtained, especially for aromatic derivatives, thus giving access to a variety of chirons in the 1,3-dioxane series, which were subsequently used for the synthesis of chiral compounds.[38] Carba-ephedrine analogues of *N*-methyl ephedrines, with a simple change of bridging nitrogen for CH were synthesized and served to probe the role of the nitrogen atom in the discrimination of enantiotopic protons by means of the derived alkoxides.[39]



R = *n*Pr, *i*Pr, *t*Bu, 65<*ee*%<90;
R = Ph, *p*-PhC$_6$H$_4$, *p*-NO$_2$C$_6$H$_4$, *p*-MeOC$_6$H$_4$, 94<*ee*%<99

Scheme 20. Enantioselective dehydrohalogenation reaction using potassium ephedrinate.[37c, d]

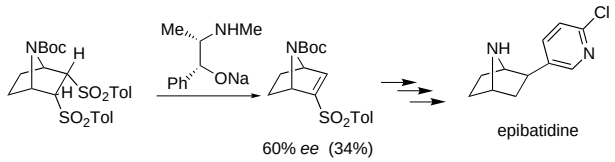
In addition, the application of this type of chiral alkoxide was extended to the asymmetric synthesis of a carbocyclic substrate using the chiral base either in excess[37a] or in substoichiometric amount (Scheme 21).[37d]



Scheme 21. Chiral alkoxides in the asymmetric synthesis of a carbocyclic substrate.[37d]

We are currently interested in the effect of the polymer-attached alkali ephedrinates on the stereochemical course of the dehydrohalogenation of prochiral dioxanes and in the design of new polymers bearing amino alcohol moieties.

Simpkins et al. recently described a stereoselective synthesis of epibatidine in which the key intermediate is accessed through chiral base mediated enantioselective sulfinate elimination. Sodium ephedrinate appeared to be the best auxiliary (Scheme 22).[40] Again, chiral alkoxides appeared more efficient than chiral lithium amides, which suggests that they could be the reagents of choice for elimination reactions.

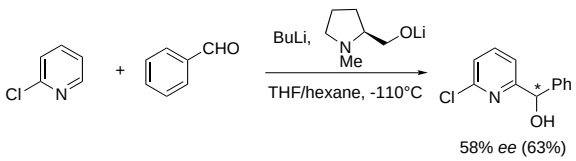


Scheme 22. Stereoselective synthesis of epibatidine.[40]

3. Challenges and Prospects

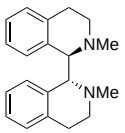
Within this concept we have highlighted new aspects of the chemistry of chiral Brønsted bases. Whilst chiral lithium amides have certainly proven to be highly efficient in various reactions they are not versatile and can have some drawbacks which prevent their use on a large scale. Two "second-generation" classes of chiral bases have been examined. While chiral Hauser bases were not successful to date, the corresponding magnesium bisamides gave promising results. Chiral alkali alkoxides also appear to be a powerful class of chiral basic auxiliaries giving high induction in most cases, and seem to be excellent candidates for future asymmetric syntheses. In 2001, three new approaches were published, and these will probably lead to further developments:

- Chiral superbases: Fort et al. described the first use of BuLi chiral alkoxide for the chemo-, regio-, and enantioselective functionnalisation of pyridine derivatives (Scheme 23).[41]



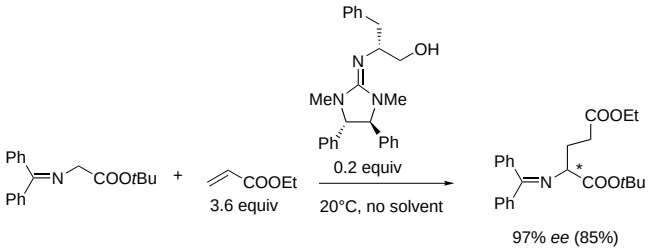
Scheme 23. BuLi chiral alkoxide as chiral superbases.[41]

- Chiral proton sponge: The synthesis and properties of a chiral bis-tetrahydroisoquinoline proton sponge have been reported by Elliott et al. The application in asymmetric synthesis has not been reported to date, but studies are currently underway in author's group (Scheme 24).[42]



Scheme 24. Chiral proton sponges as potential candidates.[42]

- Chiral guanidine bases: Modified guanidines as chiral superbases have been applied in asymmetric Michael reactions with high *ee* values (Scheme 25).[43]



Scheme 25. Chiral guanidine bases as chiral superbases.[42]

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