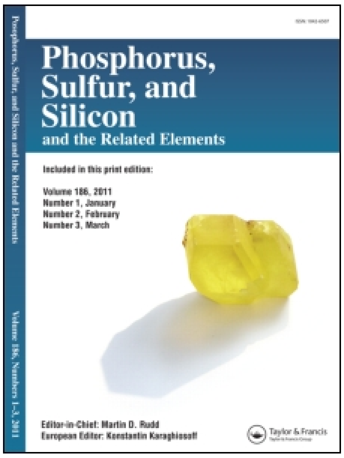

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SOME APPLICATIONS OF CHIRAL β-KETOSULFOXIDES IN ASYMMETRIC SYNTHESIS

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Abstract The addition reactions of three different tricoordinates aluminium reagents (DIBAL, $AlMe_3$ and Et_2AlCN) on chiral β-ketosulfoxides are discussed

This lecture concerns some reactions that we have developed related to the addition of tricoordinated aluminium reagents on chiral β-ketosulfoxides and β-iminosulfoxides and their applications in asymmetric synthesis. Four topics will be discussed: a) Synthesis of the starting sulfoxides; b) DIBAL and DIBAL/ZnX_2 reductions; c) Methylation reactions with Me_3Al; d) Hydrocyanation reactions with Et_2AlCN.

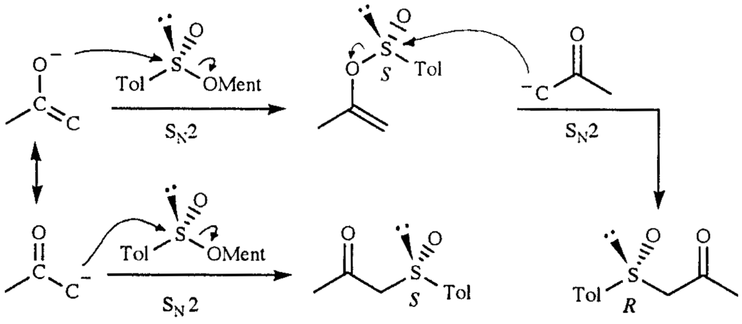
a) SYNTHESIS OF β-KETO AND β-IMINOSULFOXIDES

Our contribution to the synthesis of these compounds has been centered in the following aspects:

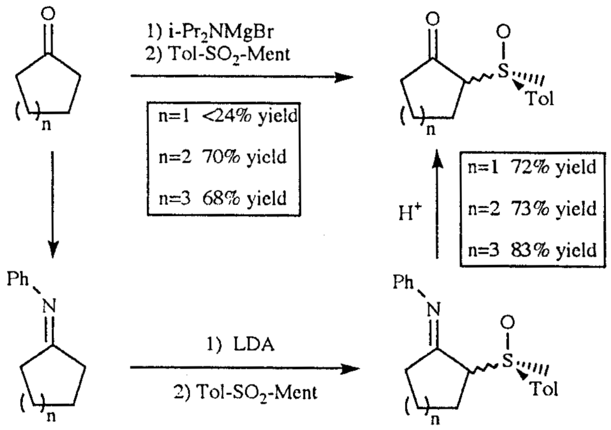
1) Preparation of optically pure cyclic β-ketosulfoxides

The Andersen-type synthesis, using cycloalkanone enolates as nucleophiles, appeared as the most obvious method to obtain these substrates. However, it had been reported that the reaction of alkali acyclic enolates with (-)-menthyl (S)-p-tolylsulfinate results in partial racemization at sulfur, which precludes the use of this method to obtain optically pure β-ketosulfoxides. This conclusion was checked by us in the case of the cyclohexanone. Its reaction with LDA and further treatment with menthyl sulfinate yielded a 75:25 mixture of the C-α epimers, being very poor (17%) the ee measured for the major one.[1]

We concluded that it was the ambident nucleophilic character of the enolate which was responsible for the partial racemization. Thus, the direct C-sulfinylation of the enolate would yield the (S)-β-ketosulfoxide, whereas the O-sulfinylation followed by the C-sulfinylation of the resulting vinyl sulfinate would afford the (R)-enantiomer.



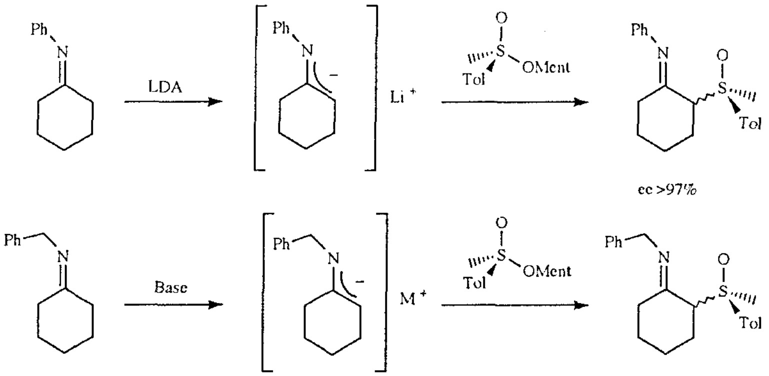
This assumption suggested to us that the use of bases derived from metals able to provide stronger association with the enolic oxygen would avoid the O-sulfinylation. This was realized in the reaction of the magnesium cyclohexanone enolate with menthyl (S)-p-tolylsulfinate which afforded a mixture of the enantiomerically pure (ee>97%) epimers.[1] This method was extended to the five and seven membered rings.[2]



To minimize autocondensation, the main product obtained with cyclopentanone in this reaction, we carried out the sulfinylation of its N-phenylimine derivative. This method was also succesfully used for other cyclic ketones. The β-iminosulfoxides were easily hydrolyzed to their corresponding ketosulfoxides during their chromatographic purification without affecting its optical purity.[2]

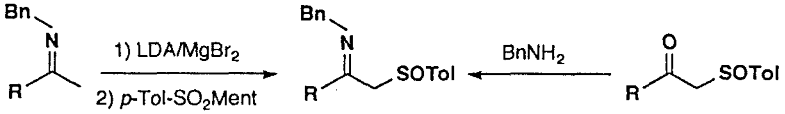
2) Preparation of the optically pure β-iminosulfoxides

The above method could be adapted to the synthesis of the optically pure N-1-(2-p-tolylsulfinyl)cyclohexylidene phenyl amines, avoiding their hydrolysis during the last chromatographic step by using an eluent containing Et_3N.[3] When this reaction was carried out on the N-benzylimine the ee of the obtained β-iminosulfoxide was only 7%. The different nucleophilic power of the nitrogen in both imines (much lower in the N-phenylderivative due to delocalization of the lone electron pair at nitrogen over the ring) satisfactorily explain the observed behaviour differences. The use of a magnesium base slightly improves the enantiomeric excess (11%) but cannot avoid the partial epimerization at sulfur. The epimerization was totally suppressed when the reaction was carried out with LDA in the presence of $MgBr_2$.[3]



Base	
LDA	ee ≈ 7%
i-Pr_2NMgBr	ee = 11%
LDA / $MgBr_2$ (excess)	ee > 97%

Finally, we have found the experimental conditions allowing the syntheses of enantiomerically pure acyclic β-ketiminosulfoxides. The reactions of the β-ketosulfoxides with benzylamine afforded the desired products without sulfur epimerization.[4] The same results were achieved when the lithium enolates obtained from the N-benzylketimines reacted with menthyl (S)-2-p-tolylsulfinate in the presence of $MgBr_2$ (excess).[4]



Yield (%)	R	Yield (%)
83	Me	94
75	n-Pr	90
81	i-Pr	55
40	t-Bu	55
92	Ph	65

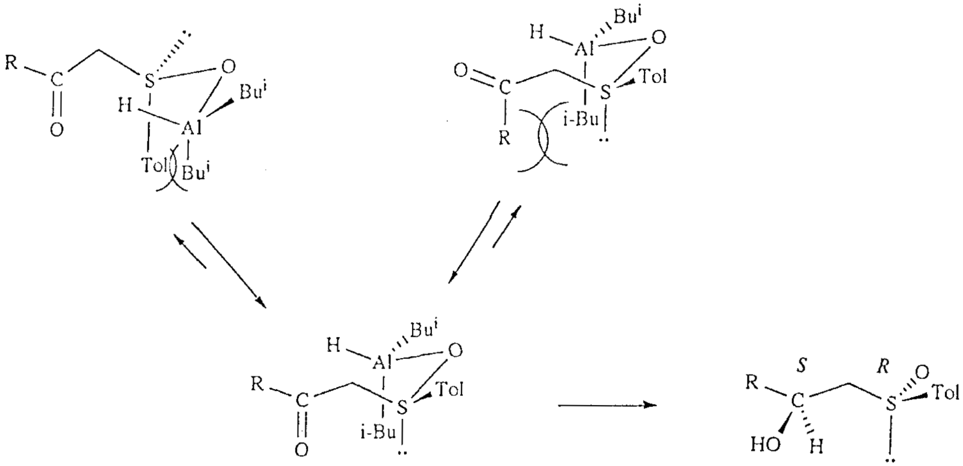
b) DIBAL AND DIBAL/ZnX_2 REDUCTIONS.

With respect to these reactions we have mainly worked in three different subjects.

1) Mechanistic models.

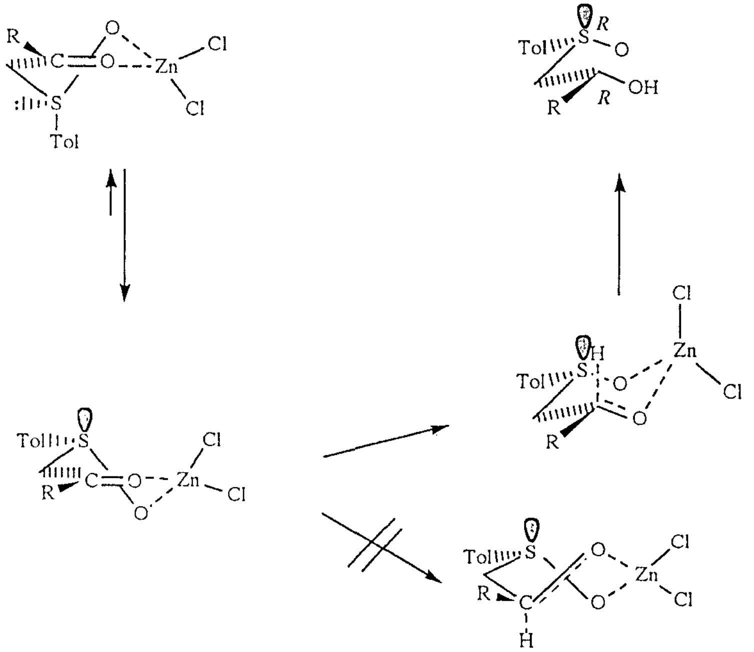
Our interest was initially centered in the models proposed to explain the stereochemical course of these reductions. In 1985 Solladie proposed two different models to justify the stereochemistry of the β-hydroxysulfoxides obtained by reduction of the β-ketosulfoxides with DIBAL and DIBAL/$ZnCl_2$.[5] Although they satisfactorily predicted the configuration of the favoured epimer in each case, there were several experimental facts that questioned their validity. Essentially, both models assumed an exclusive steric control for the hydride approach, differing under the nature of the favoured conformation for the substrate in both conditions. The different and even opposite stereochemical results observed for other similar sized reducing agents, such $NaBH_4$ and $LiAlH_4$, seriously questioned these models.

On the basis of the studies made on rigid cyclic α-sulfinylcyclohexanones and other acyclic substrates, we proposed that the electronic interactions between substrate and reagent are as least as important as the steric ones to control the relative stability of the transition states involved in the different hydride appoaches. Thus, the electrophilic character of the DIBAL allows the metal becames associated to the sulfinyl oxygen as a previous stage of the intramolecular hydride transfer, which will take place thorought the most stable chair-like transition state. Such association is not possible with nucleophilic hydrides.[6]



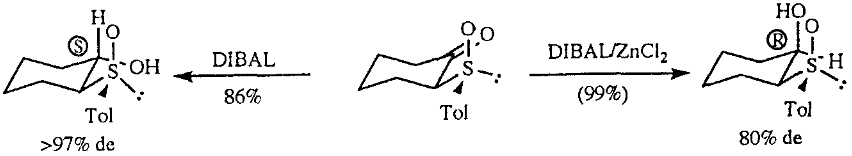
In the presence of $ZnCl_2$, the attack of the hydride in the more stable half-chair conformation of the chelated β-ketosulfoxide occurs from the upper face of the carbonyl group due to steric effects (a chair-like transition state is more stable than a twist-like transition state). This tendency will be modulated (reinforced in the case of DIBAL and decreased in those of the nucleophilic hydrides) by the electronic interactions of the hydride with the lone electron pair at sulfur, which will be stabilizing for DIBAL and destabilizing for negatively charged hydrides.

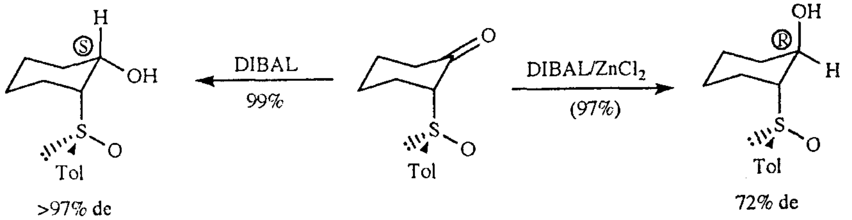
The lower stereoselectivity observed in the evolution of some substrates exhibiting decreased basicity at the carbonyl oxygen must be a consequence of the lower stability of the chelated species, which determines that only some of the β-ketosulfoxide molecules be chelated.[7]



2) Synthetic applications

From a synthetic point of view, we have taken advantage of the highly stereoselective reduction of β-ketosulfoxides with DIBAL and DIBAL/$ZnCl_2$ in the syntheses of several interesting natural products containing a methylcarbinol moiety in their structure.[8] Nevertheless, our most significant contribution has been centered in extending the "Solladie's methodology", which had so far only been used for the synthesis of secondary methylcarbinols. Thus, we first studied the reduction of 2-p-tolylsulfinyl cyclohexanones with DIBAL and DIBAL/$ZnCl_2$. The stereochemical course was identical to that observed in acyclic molecules allowing us to synthesize all the β-sulfinylcyclohexanols in high optical purity.[1] Similar results have been recently obtained with cyclopentanone and cycloheptanone derivatives.[9]

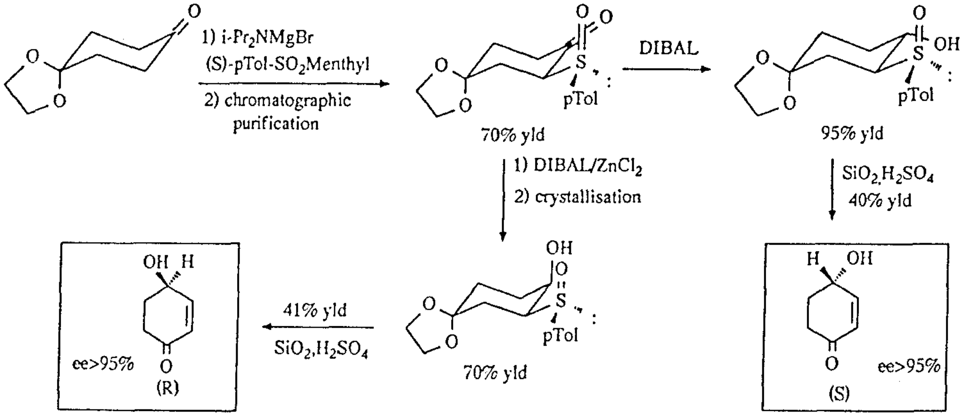




One of the most interesting points about the evolution of these substrates containing two chiral centers, is the fact that the stereoselectivity control is mainly governed by the sulfur configuration (1,3-induction). Less important is the influence of the chiral carbon (1,2-induction) despite its greater proximity to the reaction center. This fact reinforced our mechanistic proposal and demonstrated that the electronic interactions could be even more important that the steric ones.

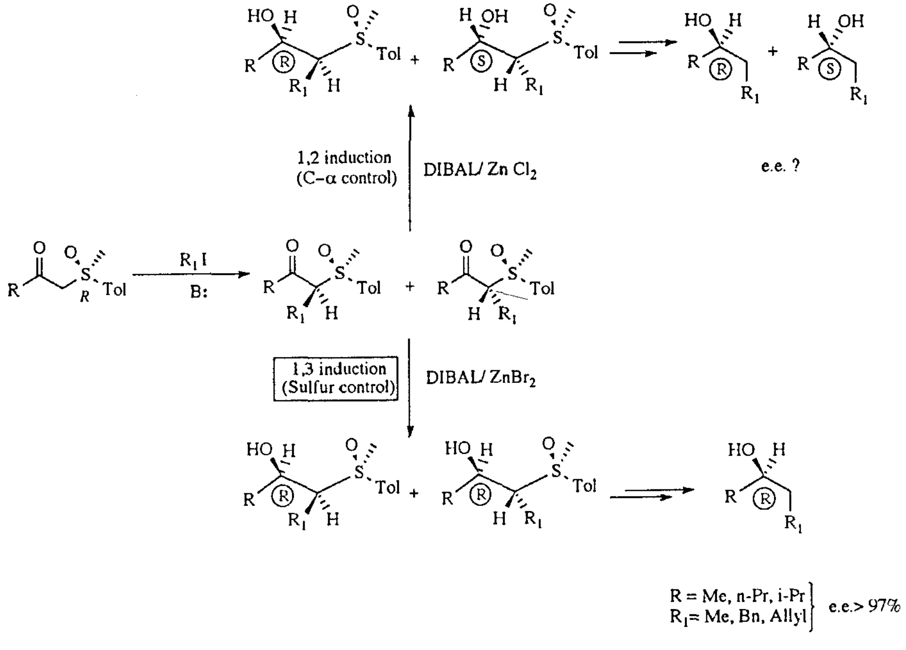
We took advantage of this behaviour in the syntheses of both enantiomers of 4-hydroxy-2-cyclohexenone, which had been used as the starting material in the syntheses of the compound ML-236 and compactine.

The reaction of 1,4-cyclohexanedione ethylenemonoketal with menthyl (S)-2-p-tolylsulfinate and i-Pr_2NMgBr yielded an epimeric mixture of β-ketosulfoxides, and it was possible to isolate the major product by chromatography in 70% yield. The reduction of this compound with DIBAL and DIBAL/$ZnCl_2$ mainly afforded two hydroxysulfoxides which were easily transformed in the desired enantiomers by hydrolysis of the acetal group and simultaneous pyrolysis of the sulfinyl one.[10]



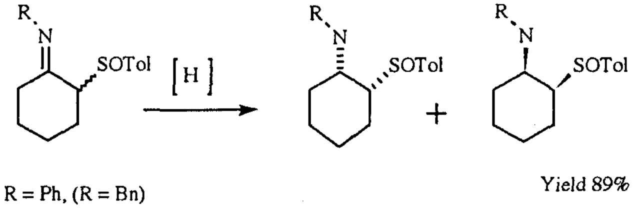
Finally, we have investigated the competence between the 1,2- and the 1,3-induction during the reduction of acyclic β-ketosulfoxides α-alkylsubstituted.[11] These substrates are always obtained as mixtures of C-α epimers, which are quite difficult to separate. On the other hand it had been reported that the stereoselectivity of their DIBAL and DIBAL/ZnCl$_2$ reductions was mainly controled by the configuration at C-α[12] (the opposite to that observed by us on cyclic substrates). Both observations limited the use to the Solladie's methodology to the syntheses of the optically pure acyclic secondary methyl carbinols.

We prepared different epimeric mixtures of α-alkyl,β-ketosulfoxides. Their reactions with DIBAL/ZnCl$_2$ are quite stereoselective yielding new epimeric mixture of the β-hydroxysulfoxides exhibiting the same configuration at hydroxylic carbon and the opposite one at C-α. This showed that their stereochemical evolution is governed by the sulfur configuration (1,3-induction) and not by that of the C-α (1,2-induction) as it had been previously reported.[12] Deviations of this rule are a consequence of an imperfect chelation of the substrate. In these cases, the use of ZnBr$_2$ instead ZnCl$_2$ and the increase of the molar ratio catalyst:substrate improve the stereoselectivity in the expected sense. These results considerably extend the scope of the Solladie's methodology to synthesize optically pure secondary carbinols.



3) Reduction of β-iminosulfoxides

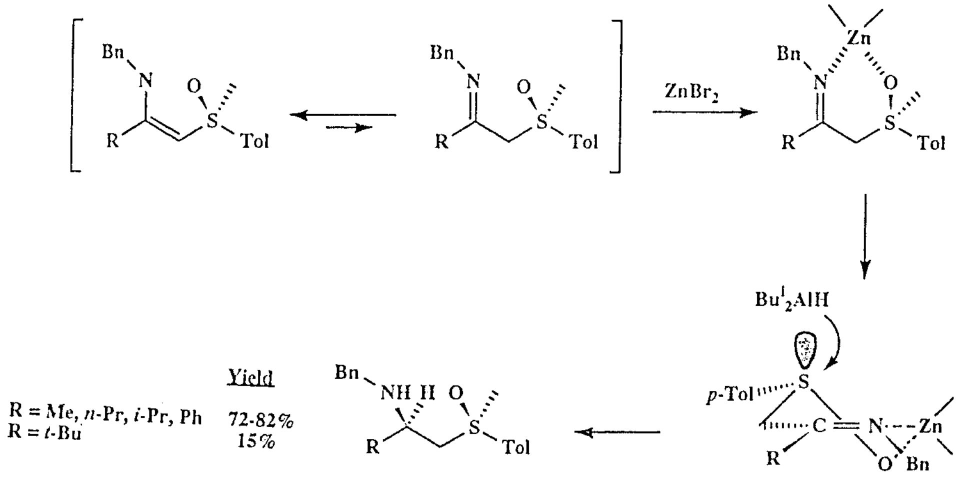
The usefulness of the β-ketosulfoxide reduction to the asymmetric synthesis of secondary alcohols suggested the use of the β-iminosulfoxides as starting products to synthesize optically pure amines. The reduction of chiral N-(2-p-tolylsulfinyl)cyclohexylidene phenyl (and benzyl) amines with different hydrides are highly stereoselective, only yielding the cis-aminosulfoxides.



DIBAL	0 (0)	100 (100)
DIBAL/ $ZnCl_2$	0	100
$LiAlH_4$	0	100

Despite the synthetic interest of this reaction its stereochemical course is not as clear as that observed for the corresponding ketosulfoxides. It seems that the steric effects are much more important than the electrophilic or nucleophilic character of the reducing agents.[3] In the case of the N-phenylimines, the addition of $ZnCl_2$ has no influence since the chelated species is not formed.

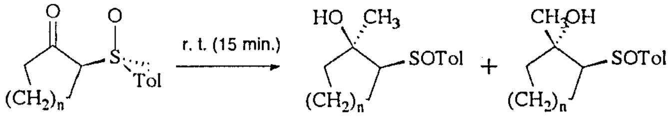
The acyclic β-iminosulfoxides usually adopt the enaminic form which makes more difficult their reduction. The study of different reducing agents allowed us to conclude that the highest stereoselectivities and the best yields could be obtained with DIBAL/$ZnBr_2$, whereas with DIBAL alone the reduction is not observed. We have shown by nmr that $ZnBr_2$ chelates the iminic forms. This chelation increases the reactivity of the substrates and thus DIBAL is able to reduce them. The stereochemical course of these reactions can be explained as that of the corresponding β-ketosulfoxides.[4]



d.e.> 97%

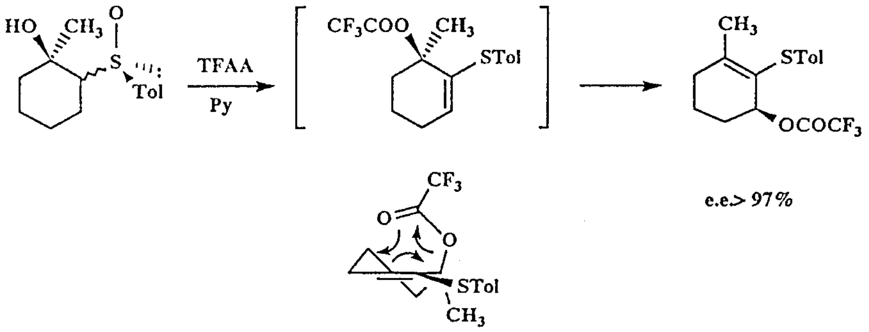
c) METHYLATION REACTIONS WITH Me_3Al

Taking into account that the DIBAL and Me_3Al structures are very similar, we thought that reactions of the latter with β-ketosulfoxides could also take place following the same stereochemical course as those of the DIBAL, making possible the asymmetric synthesis of the tertiary methylcarbinols. The first reactions were carried out on the cyclic substrates. The treatment of the 2-p-tolylsulfinylcyclohexanones with $Me_3Al/ZnCl_2$ only yielded the methylcarbinols with (R) configuration at the hydroxylic carbon, decreasing the stereoselectivity in the absence of the Lewis acid.[13] Starting from the cyclopentanone derivatives, the highest stereoselectivity was achieved with Me_3Al. All these results can be explained by using the same models as in the DIBAL reductions, taking into account that the different size of the methylide and hydride transferring groups determines that the relative influence of the steric factors be more important in the methylation reactions.



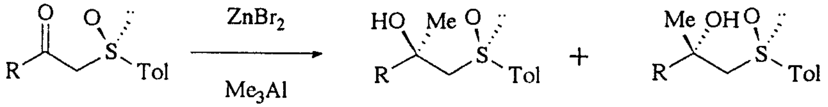
				Yield (de)
n= 2	$AlMe_3$	80	20	95 (**60**)
	$AlMe_3/ZnCl_2$	100	0	94 (**>97**)
n= 1	$AlMe_3$	100	0	98 (**>97**)
	$AlMe_3/ZnCl_2$	complex mixture		88

On the other hand, when the optically pure tertiary alcohols obtained from α-sulfinylcyclohexanones were treated under the Pummerer reaction conditions, they evolved according to a highly stereoselective hetero-Claisen rearrangement.[14]



e.e.> 97%

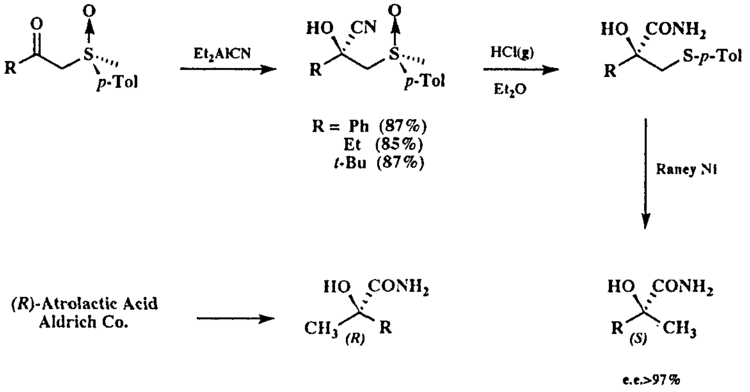
Selectivities only moderated (de<60%) and low chemical yields (45%) were obtained in the reactions of acyclic β-ketosulfoxides with Me_3Al, but the addition of $ZnBr_2$ improved both of them, allowing us to synthesize several acyclic tertiary methylcarbinols.[9]



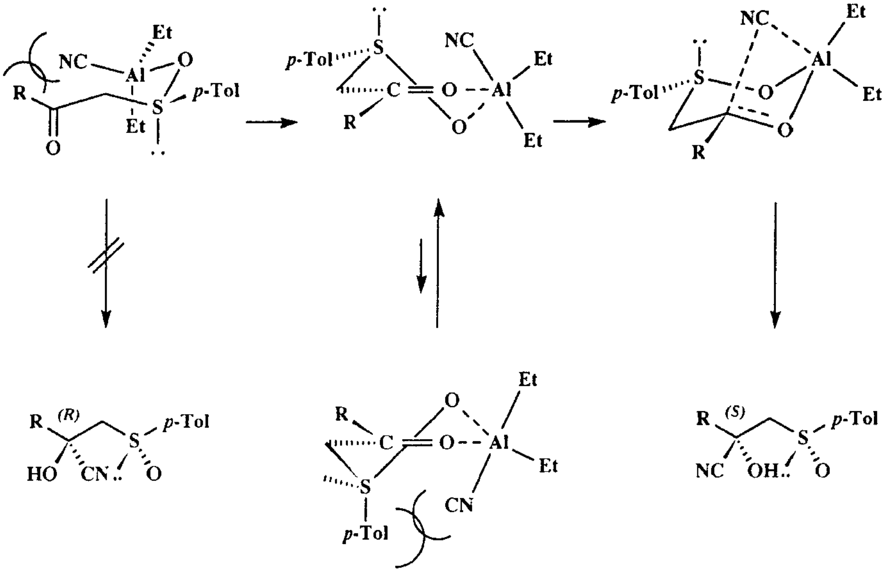
R	Yield (%)			
Ph	96	86	:	14
Et	98	87	:	13
i-Pr	89	87	:	13
t-Bu	83	98	:	2

d) HYDROCYANATION REACTIONS WITH Et_2AlCN

The good results obtained in reactions of β-ketosulfoxides with DIBAL and Me_3Al prompted us to study the behaviour of these substrates in the presence of Et_2AlCN, in order to get stereoselective cyanide transfer. The reactions of the acyclic substrates with Et_2AlCN yielded the sulfinyl cyanohydrins with d.e. higher than 97%. The presence of the $ZnCl_2$ does not affect the stereochemical results. The obtained cyanohydrins can easily be transformed in optically pure α-hydroxycarboxamides.[15]

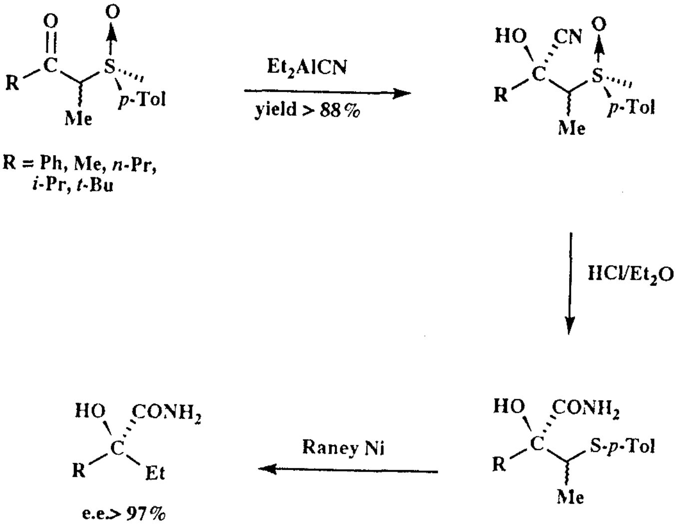


The configurational assignment at the hydroxylic carbon could be established by chemical correlation. The strong Lewis acid character of the Et_2AlCN suggests its association with the sulfinyl oxygen to form a tetracoordinated species, like that postulated in the DIBAL reductions. Nevertheless, the intramolecular cyanide transfer from such species would lead to the opposite configuration to that experimentally observed. Therefore, we postulate the formation of a pentacoordinated aluminium species with a trigonal bipyramidal structure around the metal, where the cyanide group is in an apical position (the NC-Al bond being longer and weaker than usual) which facilitates its intramolecular transfer. The stronger Lewis acid character of the Et_2AlCN with respect to the DIBAL, due to the presence of the withdrawing-electron group CN, could explain the observed differences in the behaviour of both compounds.



The stereochemical results obtained in the study of the evolution of the cyclic ketosulfoxides with Et_2AlCN strongly support the propossed mechanism.[9]

We have also studied the hydrocyanation of the α-alkyl,β-ketosulfoxides. All of them evolved with very high stereoselectivity which is exclusively governed by the sulfur configuration (1,3-induction). It allows the hydrocyanation on the α-epimeric mixtures without previous separation and increases the synthetic usefulness of this reaction.[16]



The interest of these reactions is related to the chemical versatility of the cyanohydrins, which are valuable intermediates to the synthesis of biologically and pharmaceutically interesting organic groupings. So far, we have used it to prepare α-hydroxyacid derivatives and 2-alkylglycidic acid derivatives. The latter was prepared by reaction of the thioethers resulting in the hydrolysis of the cyanohydrins with $Me_3O^+BF_4^-$ and further treatment with a weak base.[9]

Currently we are working in the reaction of the β-iminosulfoxides with Et_2AlCN in order to obtain α-alkylsubstituted α-aminoacids. Preliminary results indicate that the stereoselectivity is also very high.

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