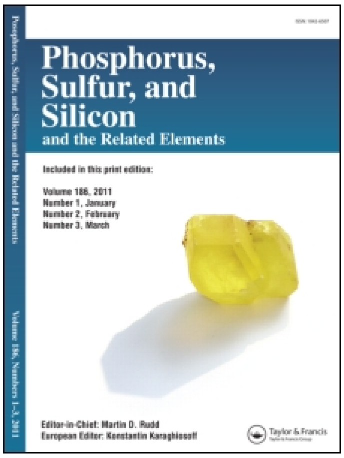

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C-C Asymmetric Bond Formation Mediated by Optically Active Sulfoxides

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C-C ASYMMETRIC BOND FORMATION MEDIATED BY OPTICALLY ACTIVE SULFOXIDES

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Abstract. Highly stereoselective C-C bond forming reactions can be performed with a variety of optically active sulfinyl derivatives to afford, after desulfurization, optically active sulfur-free products.

Optically active sulfoxides have been known since a long time, but a general route to these compounds of high or complete enantiomeric purity was developed only in the early sixties via the Andersen synthesis [1-3], starting from easily available, diastereomerically pure sulfinate esters.

Only in the last decade sulfoxides have been extensively used as chiral synthons in a variety of processes [1-3] to afford sulfur-free, enantiomerically enriched compounds.

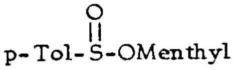
The peculiar features of the sulfinyl group, *i.e.* the marked stereoelectronic differences among the ligands at sulfur together with its generally high optical stability, account for the excellent degrees of chiral discrimination observed in those reactions where a sulfinyl moiety represents the chirality source. A further advantage is represented by the easy insertion and smooth removal of the sulfoxide group. Finally it must be pointed out that usually optically active sulfoxides are obtained from (-) menthyl sulfinates and that the original source of chirality, (-)-menthol, is a cheap and easily available starting material, which can be recovered during the sequence of reactions.

By far the most general route to optically active sulfoxides involves, as mentioned above, the reaction of diastereomerically pure sulfinate esters with organometallic species, usually magnesium or lithium derivatives [1-3].

These reactions are, with a few exceptions [3], stereospecific, and involve inversion of chirality at the sulfur atom, as demonstrated in a variety of cases, so that the absolute configuration at the sulfoxide group can directly be inferred from that of the starting sulfinate.

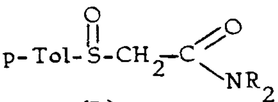
Another possible route to functionalized sulfoxides consists in the reaction of α-metallated sulfoxides with electrophiles such as esters, nitriles, nitrile-oxides, nitrones ..... [1-3].

By the first method we prepared, inter alia, α-sulfinyl-amides [4], -thioamides [5], -hydrazones [6-7], and sulfinyl-oxazolines [8], starting from the appropriate lithium enolate. In every case the absolute configuration of the products is (R)[4-8] if the starting material is (-)-(S)-menthyl toluene-p-sulfinate.

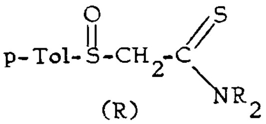


$\text{p-Tol-}\overset{\overset{\displaystyle O}{\|}}{S}\text{-OMenthyl}$

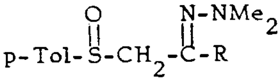
(-)-(S)



(R)

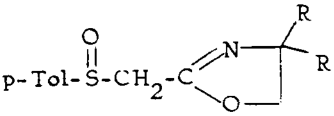


(R)



$\text{p-Tol-}\overset{\overset{\displaystyle O}{\|}}{S}\text{-CH}_2\text{-}\overset{\overset{\displaystyle N\text{-}NMe_2}{\|}}{C}\text{-R}$

(R)



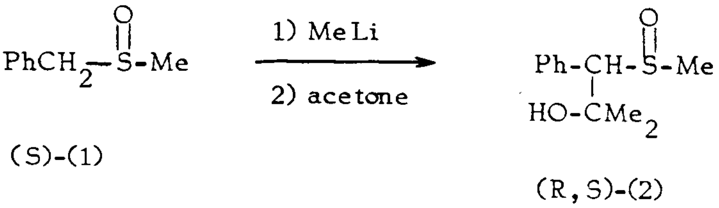
(R)

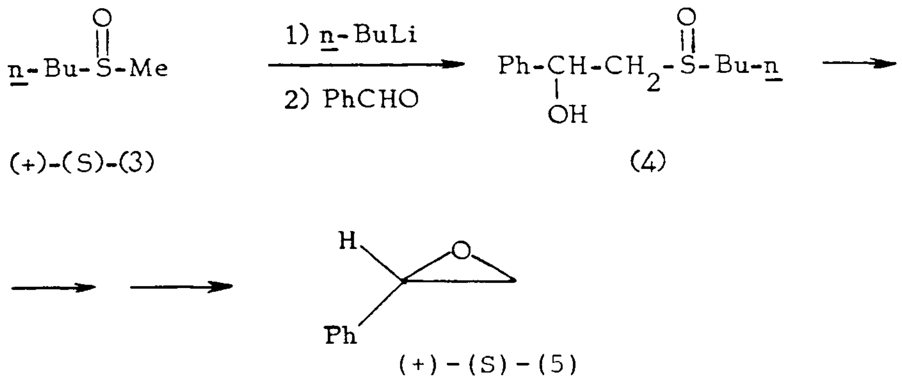
A variety of differently functionalized sulfoxides have been prepared by similar procedures by other research groups active in this area [1-3].

A first hint of the possibilities of the sulfinyl group to promote high levels of stereoselection (in reactions occurring at the carbons α and β to the sulfur atom) was given by Wolfe in 1965 in the H/D exchange reaction of benzyl methyl sulfoxide [1-3]. Since then, good to excellent levels of chiral discrimination have been achieved in sulfoxide-mediated C-H, C-heteroatom and C-C bond formations [1-3,9]. This paper will be (mainly) restricted to asymmetric C-C bond formation in aldol-type reactions.

In the pioneering works by Johnson [10] and Durst [11] (1971) it was shown that α-metallated sulfoxides react with carbonyl compounds to afford optically active sulfur-free products. In the process one or two stereocenters are formed, depending on the nature of the carbonyl derivative and of the sulfoxide.

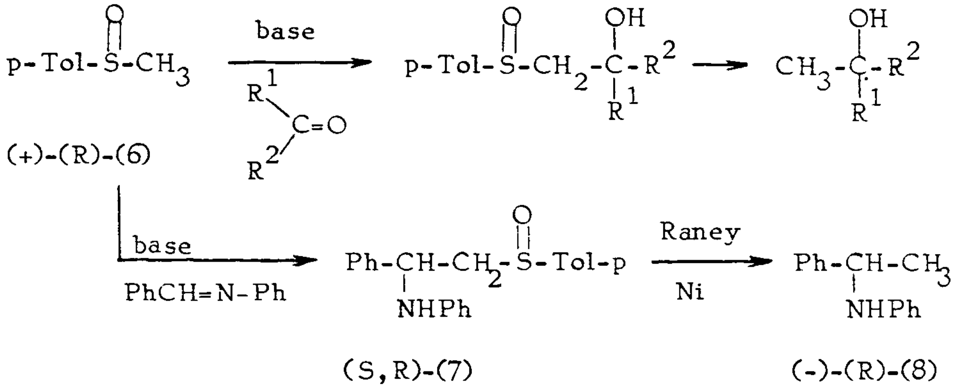
Metallation of optically pure (S)-benzyl methyl sulfoxide (1) followed by addition of acetone afforded <u>via</u> an α-asymmetric induction a 15:1 mixture of the corresponding β-hydroxy sulfoxides the major diastereomer (2) having the (R) configuration at carbon [11].





Johnson's approach[10] exploited a β-asymmetric induction, i.e. the reaction of metallated (+)-(S)-n-butyl methyl sulfoxide (3) with benzaldehyde. The major diastereomer (4), obtained pure by fractional recrystallization, was converted into 90% enantiomerically pure (+)-(S) styrene oxide (5).

Tsuchihashi[12] extended the scope of this reaction to the synthesis of optically active alcohols by reaction of enantiomerically pure p-tolyl methyl sulfoxide (6) with prochiral aldehydes or ketones followed by separation of the β-hydroxy sulfoxides (produced in 1:1/2:1 diastereomeric ratios) and reductive desulfurization by Raney-nickel.



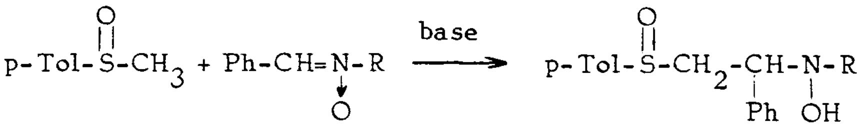
Only one example of addition of α-sulfinyl carbanions, namely α-lithio(+)-(R)-(6), to a Schiff base has been reported[13].

The reaction is more stereoselective if compared to the conceptually related addition to C=O double bonds. Indeed, (S,R)-(7) is the only diastereomer produced. Subsequent desulfurization leads to optically pure amine (-)-(R)-(8).

A high degree of stereoselectivity was also observed in the reaction of (+)-(R)-(6) with nitrones (9)[14] to give optically active sulfinyl hydroxylamines (10).

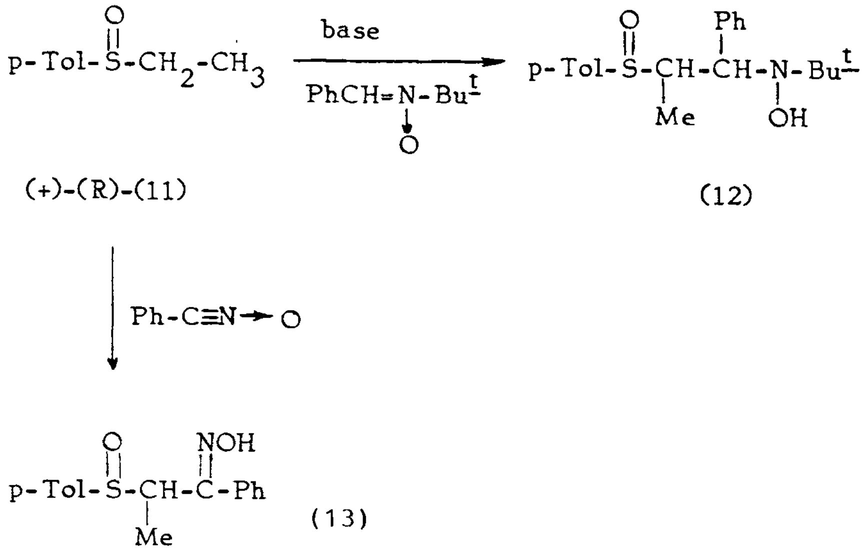
In the formation of the new stereocenter (β-asymmetric induction) the chiral discrimination is very high and increases with increasing bulkiness of the R residue (diastereomeric ratio 75:25, 82:18, 100:0 for R = Me, Ph, Bu^{t}, respectively).

In the reaction of the anion derived from (+)-(R) *p*-tolyl ethyl sulfoxide (11) with (9) (R=Bu^{t}) two stereocenters are concomitantly formed. Hydroxylamino sulfoxide (12) was obtained as a 6:1 mixture of epimers at the carbon α to the sulfur moiety, the β-carbon being presumably enantiomerically pure.



(+)-(R)-(6) (9) (10)

R = Me, Ph, Bu^{t}



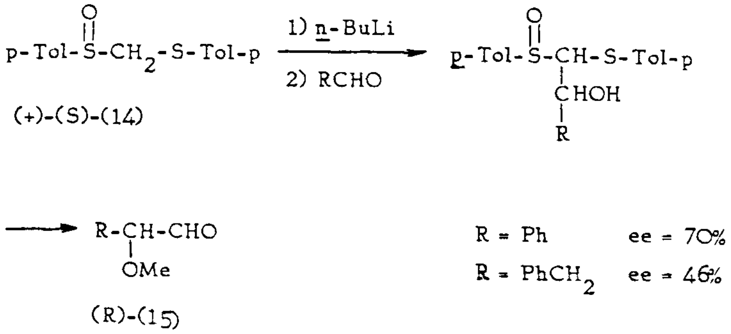
(+)-(R)-(11)

(12)

(13)

A good extent of α-induction was also observed when (+)-(R)-(11) was reacted with phenyl nitrile oxide to afford β-oximino sulfoxide (13) as a mixture of isomers in 13:1 ratio [14].

While only low to moderate stereoselections are observed at the β-carbon in reactions of simple sulfoxides with carbonyl derivatives, functionalized sulfoxides can afford noticeable levels of chiral discrimination. For example the dithioacetal mono-S-oxide (+)-(S)-(14), a chiral acyl anion equivalent, was used by Scolastico [15,16] to develop an efficient asymmetric synthesis of α-methoxy aldehydes (15).

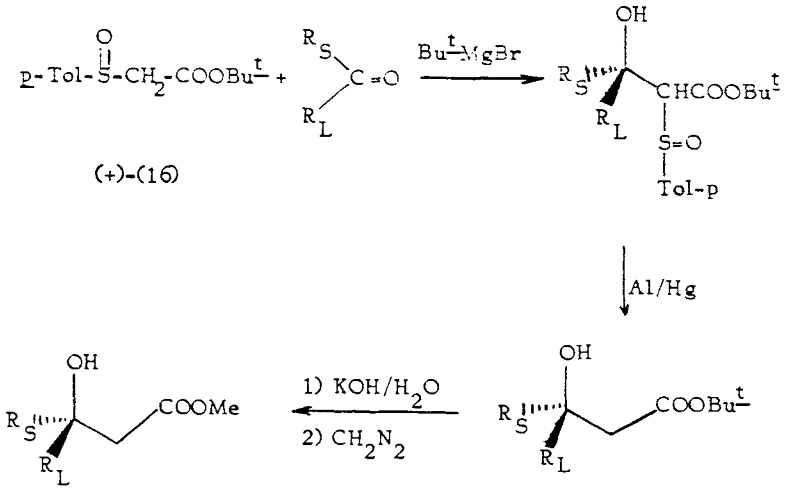


(+)-(S)-(14)

(R)-(15)

R = Ph ee = 70%

R = $PhCH_2$ ee = 46%



(+)-(16)

Kunieda and co-workers [17-19] were the first to report an aldol-type reaction performed on a sulfoxide containing synthon, namely ethyl-α-phenyl sulfinyl acetate. However, only three years later Solladie [20] using the chirality of (+)-(R)-(16) developed an asymmetric synthesis of β-hydroxy acids from aldehydes and ketones (R_S and R_L are small and large groups, respectively). Enantiomeric excesses were in the range 20-95% [20-24]. The nature of the base is crucial, since lithium or sodium enolates did not afford any condensation products.

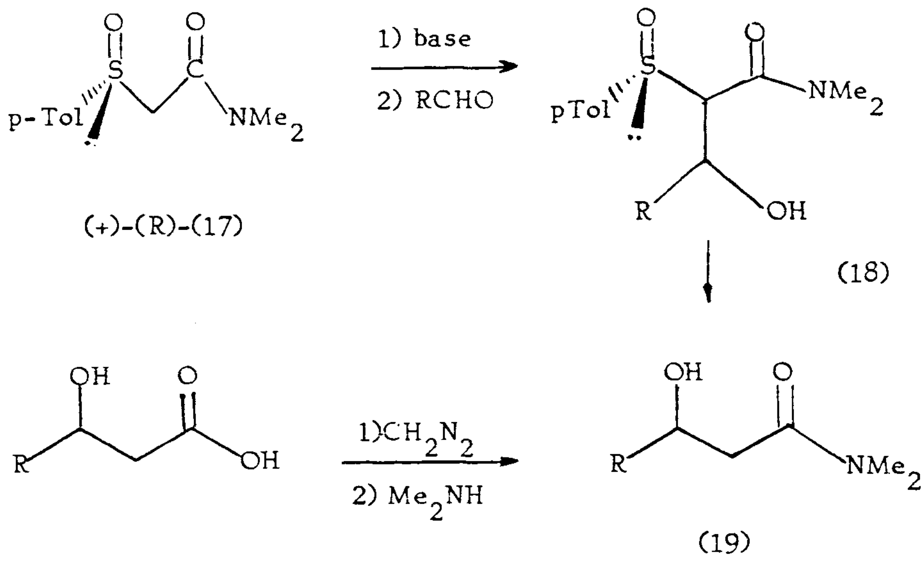
Our interest in aldol-type condensations derived from the observation that while exceptional levels of both diastereo- and enantio-selectivity were achieved by Evans [24] in this type of reactions using boro-enolates of suitably chiralized propionyl imides, the corresponding acetyl imides did not behave so well, to the point than an easily removable methylsulfide group was inserted to restore high stereoselections.

In principle the introduction of a sulfoxide moiety could simultaneously secure the necessary substitution in the enolate, and provide the source of chirality.

To this end we prepared [4] enantiomerically pure (+)-(R)-α-sulfinyl-N,N-dimethylacetamide (17). α-Metallation of (+)-(R)-(17), condensation with aldehydes and desulfurization (Na/Hg, NaH_2PO_4 buffer) gave optically active β-hydroxy-amides (19).

The importance of the nature of the base is evident from the fact that i) low to medium levels of chiral discrimination were observed in the case of lithium enolates; ii) with magnesium enolates excellent degrees of stereoselection were achieved and, even more strikingly, its sense was reversed.

In other words (+)-(R) and (-)-(S) β-hydroxy amides (19) were obtained by working with $Bu^{\underline{n}}Li$ and $Bu^{\underline{t}}MgBr$, respectively, starting from the same chiral precursor. The absolute configuration of the products was firmly establi-



(+)-(R)-(17)

(18)

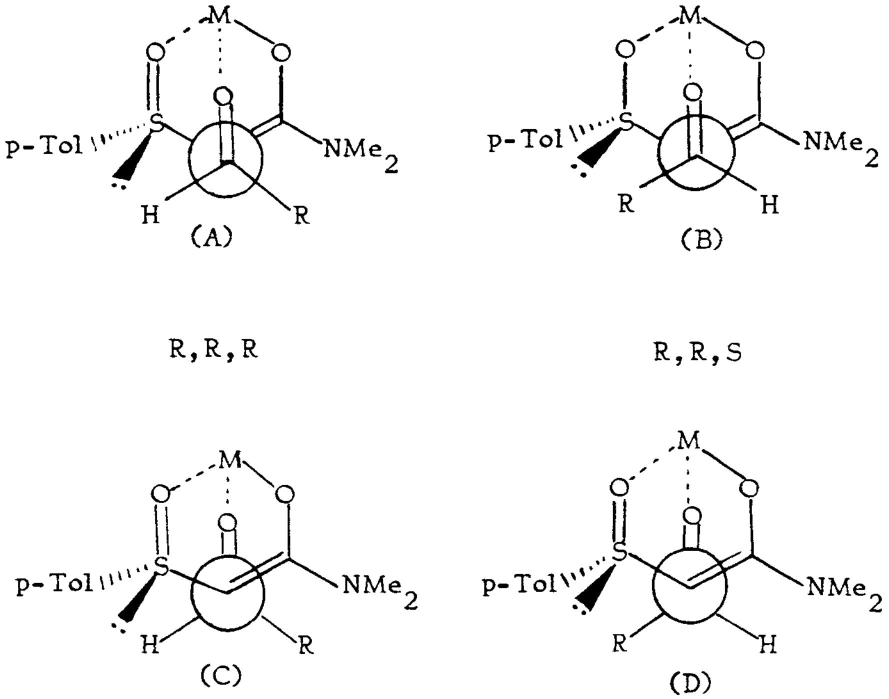
(19)

$R = Me, Bu^i, Pr^i, Bu^t$ e.e. 8-47% Base: $Bu^n Li$
e.e. 85-100% Base: $Bu^t MgBr$

shed by chemical correlation with β-hydroxy-acids of known chirality.

The extent of asymmetric synthesis observed in the case of magnesium enolates is sufficiently high to warrant a correct indication of the transition state involved in the process.

We propose a rigid chelated model, where the aldehyde approaches from the top-side with the aldehydic hydrogen towards the sulfur lone pair. This attack accounts for the absolute configuration of the products. We believe that the other equivalent attack, with the aldehyde R group facing the aromatic residue, can be disregarded on steric grounds.



(A) R,R,R

(B) R,R,S

(C) R,S,S

(D) R,S,R

	A	B	C	D
M = MgBr	97	-	3	-
M = Li	32	12	56	-

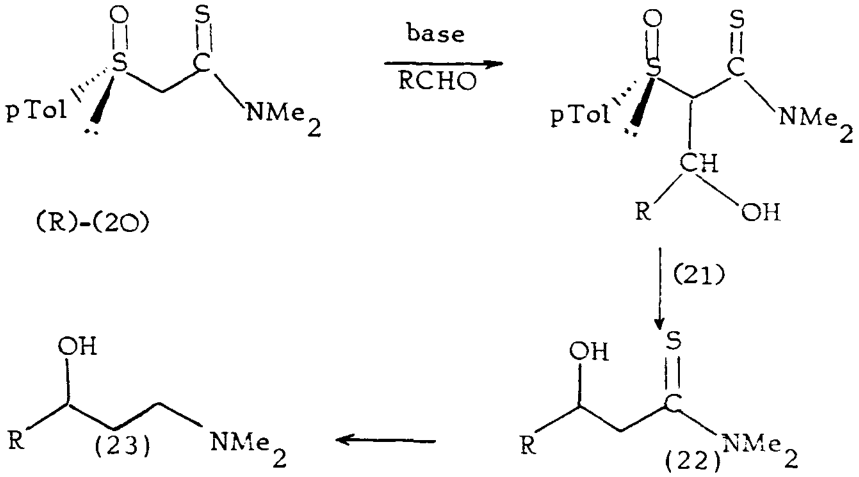
FIGURE 1.

Furthermore the model is substantiated by i) chelation of magnesium by the sulfinyl oxygen which should favor the Z geometry commonly accepted for amide enolates; ii) the model is in agreement with the decrease in stereoselection observed on increasing the steric demand of the aldehyde R residue; iii) other factors being equal, an increase in steric bulkiness of the groups bonded to the amide nitrogen largely decreases the amount of chiral discrimination [25].

A further insight in the stereochemistry of the reaction was given by the isolation of the condensation adducts of sulfoxide (17) with isobutyraldehyde. The reaction of amide (17) with $Bu^{\underline{t}}MgBr$ as base affords only two of the four possible diastereomeric hydroxy-sulfoxides (18) in 35 : 1 ratio , $[\alpha]_D$ + 288° and $[\alpha]_D$ + 54°, respectively, while the use of $Bu^{\underline{n}}Li$ as base leads to three diastereomeric products $[\alpha]_D$ + 55°, $[\alpha]_D$ + 142° and $[\alpha]_D$ + 288° in ~ 4.7 : 1 : 2.7 ratio [25].

By comparison of the spectroscopic properties, optical rotations and relative amount of the adducts and consideration of the enantiomeric excesses and absolute configurations of the final products (19), the R R R and R S S absolute configurations could be assigned to the major and minor products (18) deriving from the magnesium enolate, and the R S S, R R S, and R R R absolute configurations to the products (18) deriving from the lithium enolate. The stereochemical path for the magnesium and lithium enolates are indicated in figure 1.

A different situation was met with in the case of α-sulfinyl thioamides [5]. Condensation of (R)-(20) with aldehydes at -90° by using $Bu^{\underline{t}}MgBr$ as base, and subsequent desulfurization affords β-hydroxy thioamides (22) in 55-90% e.e. In this case the effect of a variation of the R group of the aldehyde on the extent of stereoselection is more difficult to account for. PhCHO and Pr^{i}CHO giving higher e.e. than MeCHO and Bu^{t}CHO.



R=Me, Pr^{i}, Ph, Bu^{t} e.e 55-90%

Reaction of (R)-(20) with Pr^{i}CHO afforded adducts (21) as a mixture of only two of the four possible diastereoisomers in 95 : 5 ratio. From the mixture the major isomer could be isolated by flash chromatography and converted into the corresponding optically pure derivative (22), R = Pr^{i}. Similarly reaction of (R)-(20) with PhCHO afforded adducts (21) as a mixture of only two diastereoisomers in 9:1 ratio. Unfortunately in this latter case desulfurization is accompanied by extensive retro-aldolization.

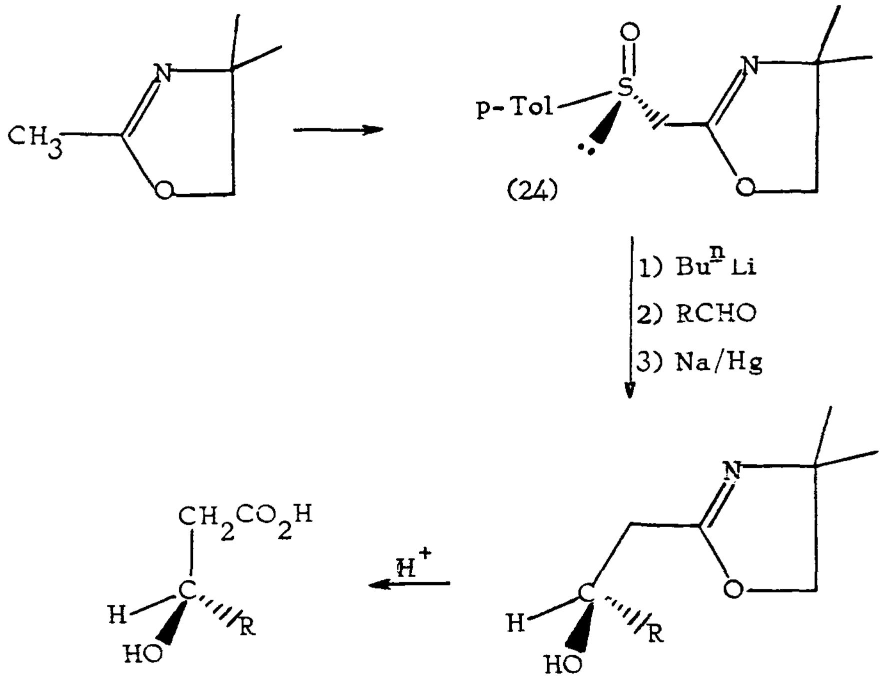
Alkylation of (22) with $Me_3O^+BF_4^-$ and subsequent borohydride reduction allowed conversion of β-hydroxy thioamides (22) into γ-amino alcohols (23). Thus sulphinyl thioamides behave as chiral synthons of β-amino carbanions.

The fact that even apparently minor variations in the system dramatically affect the behaviour of sulfinyl derivatives in aldol-type reactions was confirmed in the case of (-)-(R)-2-(p-tolylsulfinyl methyl)-oxazoline (24), easily available from commercial 2,4,4-trimethyl-2-oxazoline.

α-Metallation of (24) with $Bu^{\underline{n}}Li$, condensation with aldehydes and reductive breaking of the C-S bond afforded β-hydroxyalkyloxazolines (25), which can be unmasked by acid treatment to give the corresponding optically active β-hydroxy acids (26) of predictable absolute configuration, as shown in the scheme, in excellent overall yield (6o-85%). In this case i) the degree of chiral discrimination, although generally satisfactory, is lower than that found in the amide case (see above); ii) it decreases when the R residue of the aldehyde is sterically very demanding; iii) the use of a more chelating and bulky counterion of the azaenolate of (24), such as magnesium bromide, leads to a decrease of optical yields. In other words better stereoselection is achieved by working with $Bu^{\underline{n}}Li$ than $Bu^{\underline{t}}MgBr$ as base. This points out that a different preferential transition state is involved in this case and that reaction conditions must be carefully selected depending on the nature of the substrate.

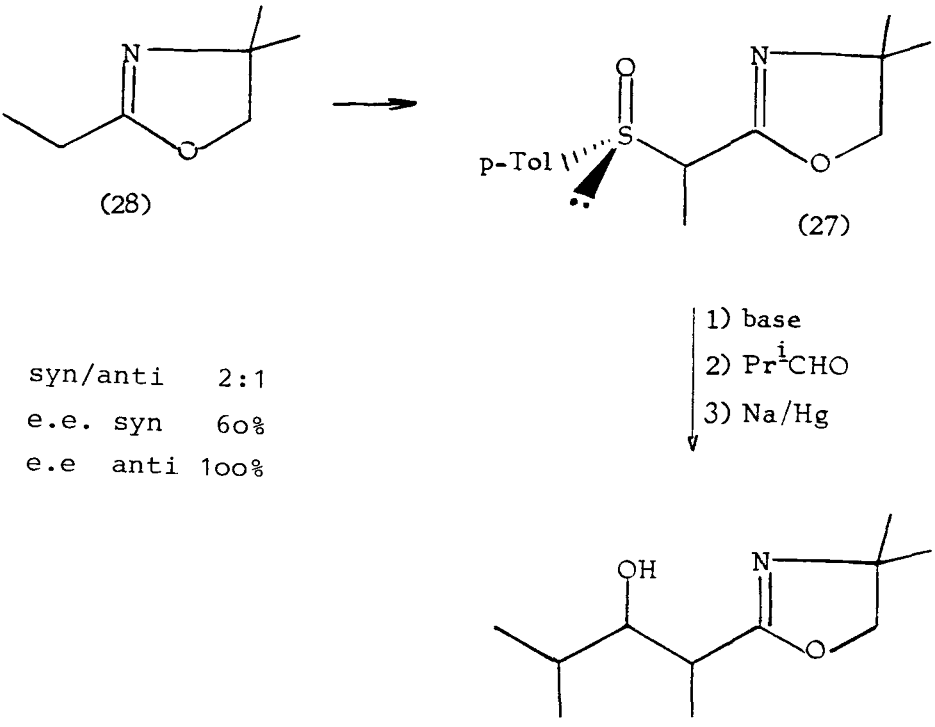
We examined briefly the behaviour of 2-(1'-p-tolylsulfinylethyl)-oxazoline (27). This was obtained as a mixture of epimers at carbon by reaction of metallated oxazoline (28) with (-)-(S)-p-toluene-menthylsulfinate.

Reaction with iso-butyraldehyde and subsequent desulfurization afforded the two diastereoisomeric syn and anti



R = Me, Pr^n, Bu^i, Pr^i e.e. 53-36%
R = Bu^t e.e. 26%

hydroxy oxalines (29) in 2 : 1 ratio. The enantiomeric excesses are respectively 60 and 100% for the syn and anti isomer, higher than those found in the case of (24). It must be noted that identical results were obtained when a single diastereoisomeric sulfoxide (27) was reacted with Pr^iCHO, so that the stereochemistry at the carbon α to the sulfur atom in (27) is immaterial to the



(28)

(27)

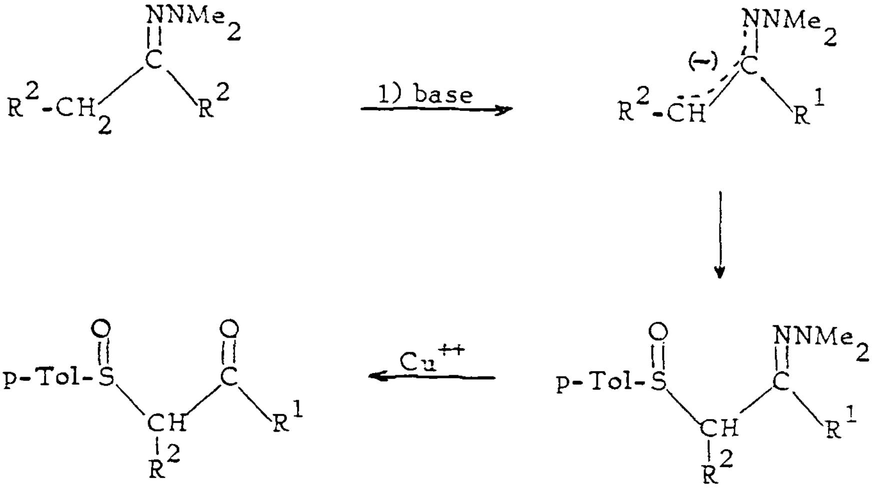
(29)

syn/anti 2:1
e.e. syn 60%
e.e anti 100%

stereoselectivity of the process [25].

Another class of sulfinyl derivatives that we investigated in stereoselective aldol-type reactions is constituted by α-sulfinyl-hydrazones (R)-(30), which can be obtained from (-)-(S)-toluene-p-sulfinate and α-metallated N,N-dimethylhydrazones [7].

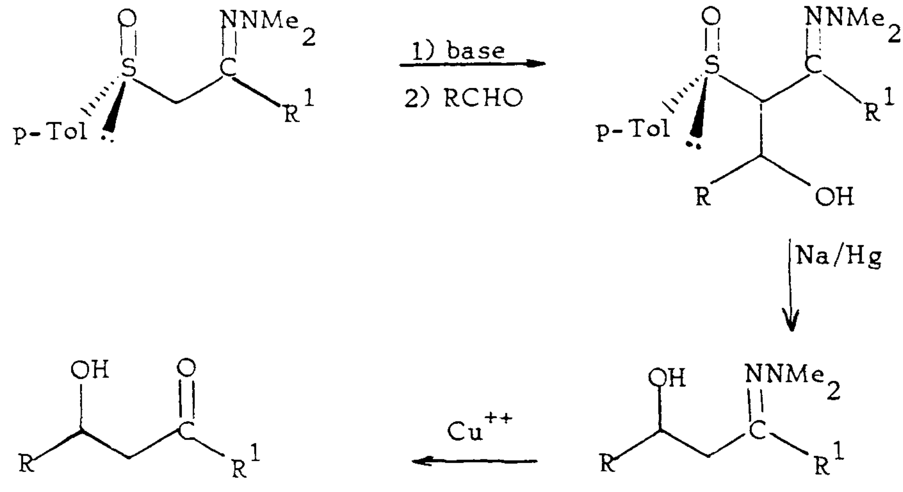
They were obtained as mixtures of E and Z isomers, the E/Z ratios at the C-N double bond ranging from 15 : 85 to 100 : 1, the Z being predominant when R^1 is sterically demanding. The epimer ratios at the α-carbon go from 55 : 45 for R^1 = H, R^2 = Me to 100 : 0 for R^1 = Me, R^2 = Ph. Cupric ion catalyzed hydrolysis of (R)-(30) produced β-oxosulfoxides (+)-(R)-(31), which are not available in optically active form through the Claisen-type condensation of ketone enolates with sulfinates



R^1,R^2 = H, Alkyl, Aryl.

By the usual sequence, α-sulfinyl hydrazones can be converted into optically active β-hydroxy hydrazones, and the latter into β-hydroxy ketones by copper(II)ion promoted hydrolysis [7,26].

Condensation of magnesium enolates is in this case sluggish, and offers no definite advantage; lithium enolates in the presence of HMPA were generally used.



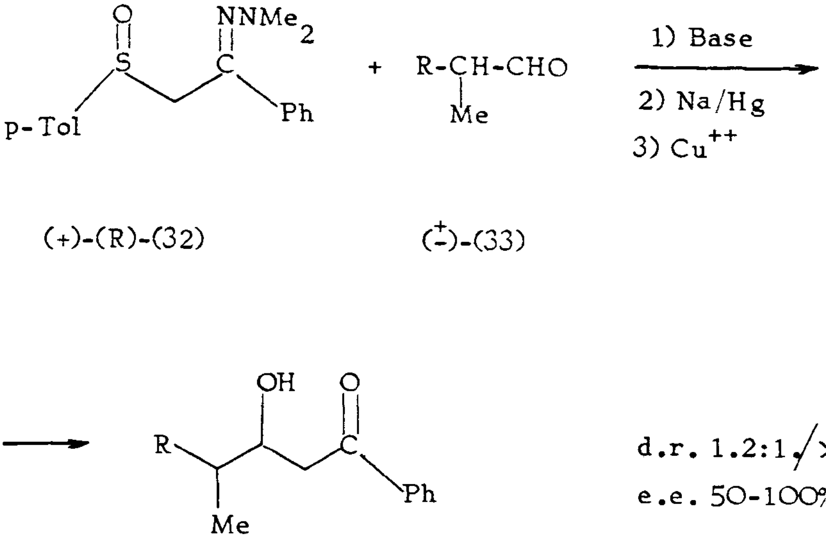
R=Ph, Et, Pr^i, R^1=H, Me, Ph

e.e. ≤88%

The stereochemical outcome of the process strongly depends on the experimental conditions: variations of the amount of the base and of metallation and condensation times and temperatures strongly affect the extent and even the sense of chiral discrimination, to the point that in a few instances both enantiomers of β-hydroxy ketones could be obtained from a single chiral precursor.

In a given set of conditions, some general trends can be pointed out. i) An increase in the bulk of the aldehyde R residue is reflected in an enhanced stereoselection. ii) Higher stereoselections (up to 88%) are achieved when the R^1 residue of the starting sulfoxide is sterically demanding. This is likely related to the different E/Z isomer ratio, which should be reflected at same extent in the geometrical preference of the corresponding aza-allyl anion. In other words a more crowded transition state (bulky R and R^1 groups, Z geometry) is capable of higher enantioface differentiation. On this background we examined the problem of diastereoface discrimination in the condensation of phenylsulfinyl hydrazone (32).

When (+)-(R)-(32) was reacted with an excess of a chiral but racemic aldehyde (33), both asymmetric synthesis and kinetic resolution were obtained.



(+)-(R)-(32)

($\pm$)-(33)

d.r. 1.2:1/>30:1
e.e. 50-100%

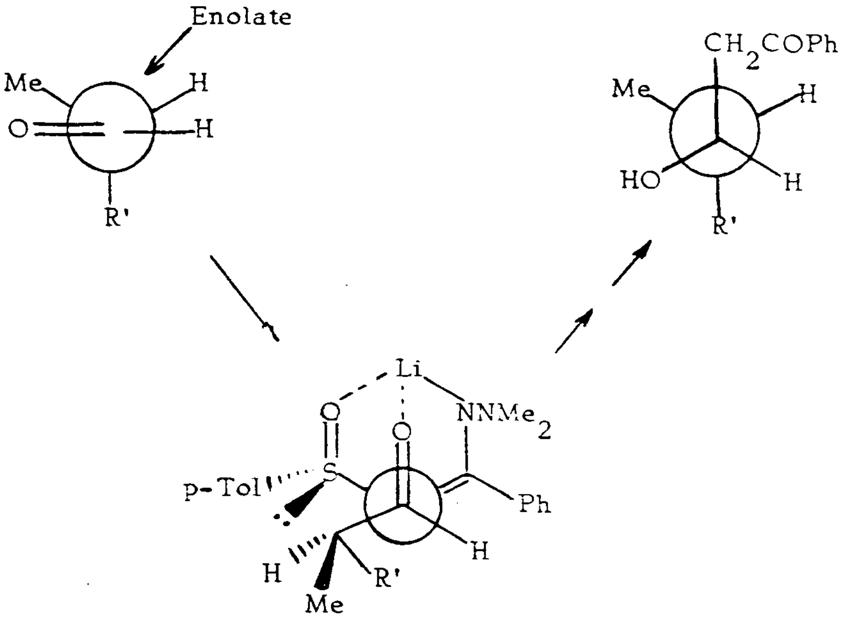
R=Et, PhCH$_2$, Pr^i, Ph.

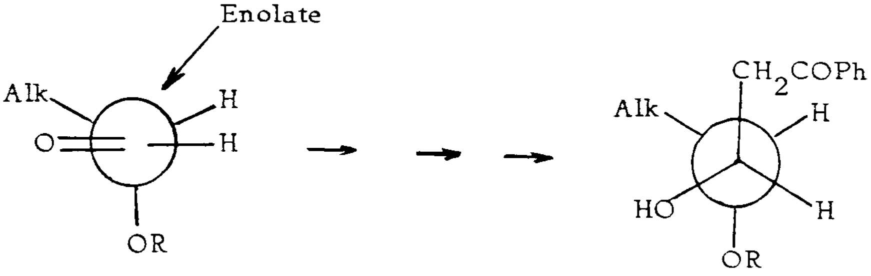
The diastereomeric ratio in the final products reflects the combination of the diastereoface selectivities of the starting enolate and aldehyde (Cram vs anti Cram attack), while the enantiomeric excess within each diastereoisomer reflects the enantioface discrimination of the chiral enolate, namely sulfoxide (32). As expected on the basis of the excellent degree of chiral recognition observed in the condensation of (32) with Pr^{i}CHO, an achiral equivalent of (33), the optical purity of the product was always excellent (5o-1oo% e.e.). Diastereoisomeric ratios are related to the relative size of R _vs_ CH$_3$ in (33), and excellent stereoselectivities were only achieved when R is sterically demanding, to the point that only one out of four stereoisomers was produced when R = Ph [25].

Recovery of the unreacted (S)hydratropaldehyde, and Cram's rule, allow to assign tentatively the (R,R) absolute configuration to ketols (34) and to propose, for the condensation, the transition state depicted in figure. A more complex situation was met with in the case of chiral but racemic α-alkoxy-aldehydes, where a noticeable temperature dependence effect was observed in the condensation both on the extent and sense of stereoselection, making predictions based on Cram's or Felkin's models more difficult. However good to excellent degrees of chiral discrimination could be achieved by careful choice of the reaction conditions. Thus α-sulfinyl hydrazones proved to be effective synthons also if enantio- and diastereo-selectivity must be achieved simultaneously with a variety of aldehydes [26].

In conventional aldol strategy the key C-C bond forming reaction involves addition to the carbonyl group, for example reaction with enolates or with allyl metallic species [24].

A conceptually different approach to control the relative stereochemistry of a sequence of asymmetrically substituted carbon atoms consist in the use of isoxazolines [28-31], which can be obtained by [3+2] dipolar cycloaddition of olefins to nitrile oxides, generated in situ by nitroalkane dehydration (Mukayama's method) or base-promoted HCl elimination from hydroximidoyl chlorides (Huisgen's method).





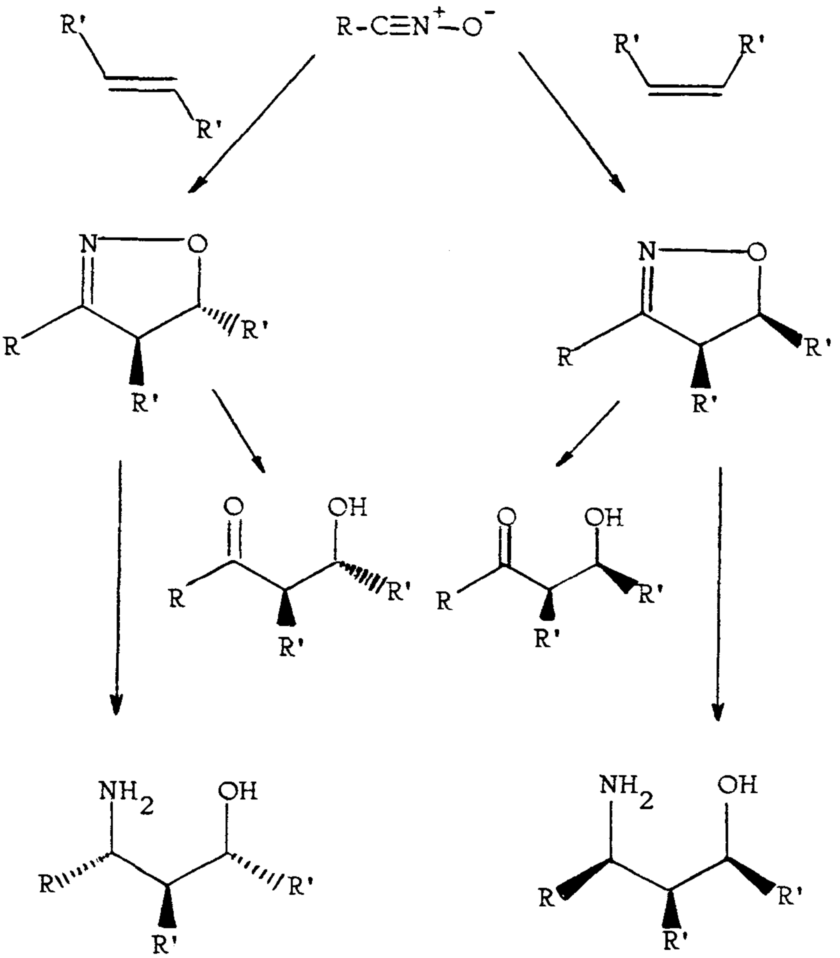
$R = Me,\ CH_2OCH_2Ph$

$Alk = \underline{n}\text{-}C_6H_{13},\ Me$

In this case the key C-C bond forming reaction is the cycloaddition, which tolerates a variety of functional groups, so that a wide array of structures can be assembled starting from acyclic or cyclic alkenes, cumulated or 1,3-dienes, enol ethers or enol acetates, and so on, as evidenced by the brilliant works by Jäger [28], Kozikowski [3o,31], and Curran [29].

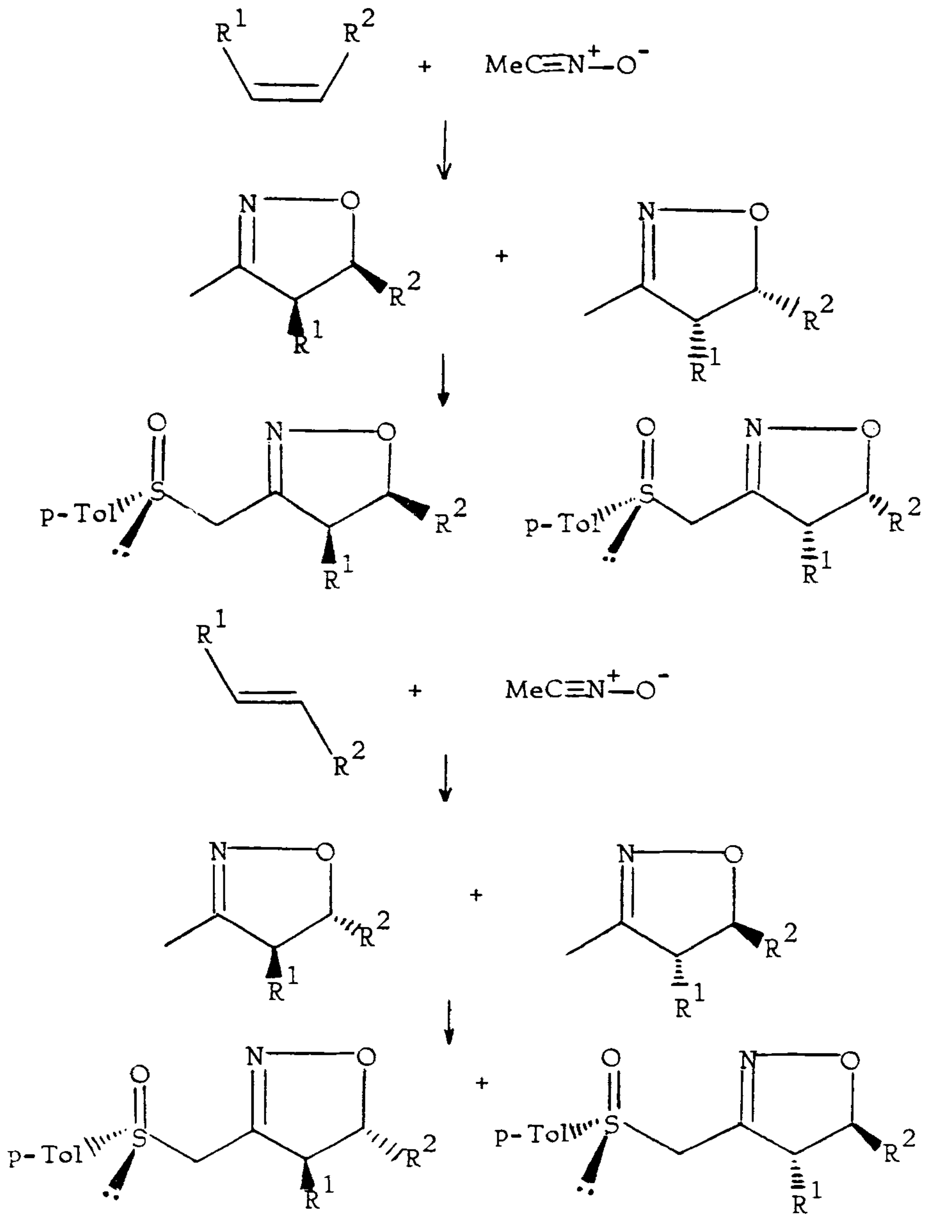
Advantages of isoxazoline-based aldol strategy are the availability of the starting materials, the mildness of the high yielding ring closure, its noticeable regioselectivity, and its stereospecificity, which secures complete control of the relative stereochemistry at C_4 and C_5 of the heterocycle, pre-determined at will by the configuration of the olefin. Moreover the 4-position can be functionalized by treatment with base (LDA or PhLi) and subsequent quenching with reactive electrophiles [RHal, $B(OR)_3/H_2O_2$] to afford alkylated or hydroxylated products in a stereocontrolled fashion [28,29]. Isoxazolines have been shown [28] to be remarkably stable vs acids, bases, oxidizing agents, however the latent functionalities embedded in the heterocyclic ring can be cleanly unmasked [28-31] at appropriate time to afford, inter alia β-ketols or γ-amino alcohols. By careful choice of reaction conditions, [28-31] unmasking preserves the stereochemical integrity at the stereocenters in the ring.

Furthermore high levels of stereoselection can be achieved in the creation of the new stereocenter at the N-bearing carbon in the reduction to β-amino alcohols[28,29]. Thus cycloaddition, modification at the nucleus or in its side chain, and cleavage steps allow the control of relative stereochemistry at a number of functionalized stereocenters.



Unfortunately up to now various attempts to achieve not only diastereo- but also enantio-selections, for instance by using chiral nitrile oxides or chiral olefins, resulted in moderate success [28-3o].

Our approach to optically active isoxazolines involved the use of chiral sulfur derivatives. Exo-metallation of racemic 3-methyl-Δ^2-isoxazolines and subsequent reaction with (-)-(S)-menthyl toluene-p-sulfinate afforded (R)-3-(tolylsulfinylmethyl)-4,5-dihydroisoxazolines with complete inversion of chirality at sulfur, and without

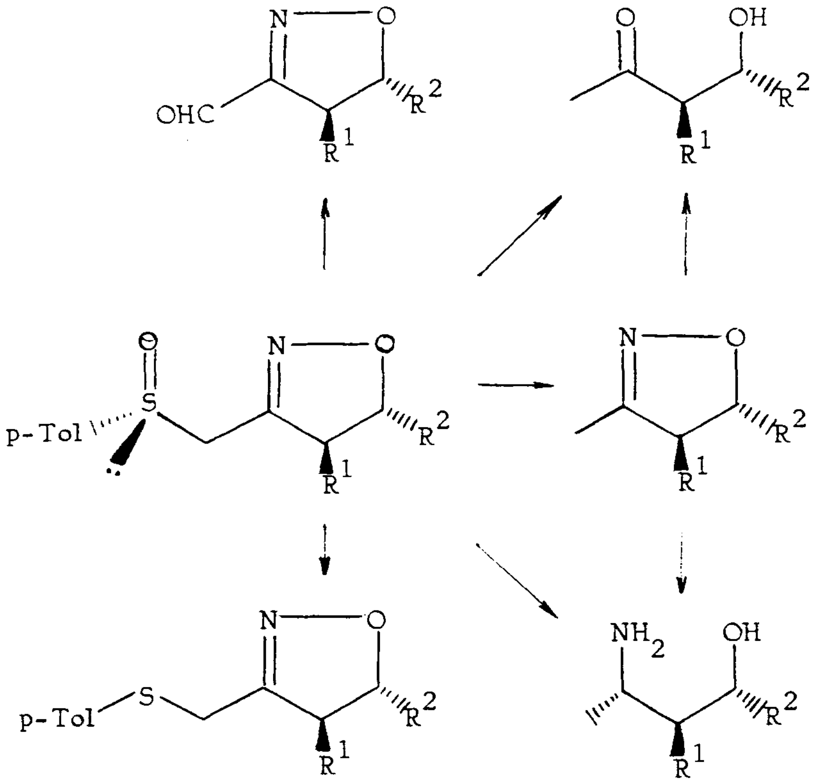

R1
R2
MeC≡N+–O-
N
O
p-Tol
S
R1
R2

racemization at the stereocenter (s) in the ring. Therefore the reaction generates only two diastereoisomers. Albeit the extent of chiral discrimination in this reaction is, not unexpectedly, low, ranging from 8 to 2o%, the individual stereoisomers can be easily separated (by chromatography or fractional crystallization) to give enantiomerically pure compounds. These can be converted by the desulfurization (Na/Hg) into stereoisomerically pure Δ^2-isoxazolines in almost quantitative yields, and the latter transformed by known methods [29] into optically pure β-ketols. Alternatively sulfinyl isoxazolines can be directly converted by Raney nickel-catalysed hydrogenation into β-hydroxy ketones, by simultaneous ring-opening and C-S bond cleavage.

Furthermore borohydride reduction of sulfinyl-isoxazolines in the presence of Ni(II) salts allows an easy entry to γ-amino alcohols by ring-opening, reduction and desulfurization, excellent degrees of chiral discrimination being achieved in the formation of the new stereocenter [25].

Alternatively Na/Hg desulfurization and $LiAlH_4$ reduction [28] of the resulting enantiomerically homogeneous isoxazolines can be used to afford γ-aminoalkohols of high optical purity.

Finally Pummerer rearrangement (TFAA) and uncovering of the carbonyl group open access to an oxidative removal of the sulfur moiety and thus to 3-formylisoxazolines [25]. In the latter three different functionalities, two of them masked, are available for elaboration.



A further advantage of sulfinyl isoxazolines is that the properties of the sulfoxide group, e.g. inter-alia its ability to stabilize α-carbanions and its capacity to promote asymmetric induction, can be exploited before its smooth removal by a variety of methods. Thus metallation of optically pure (R, S)-(35), alkylation with the appropriate benzylic bromide[+], and catalytic hydro-

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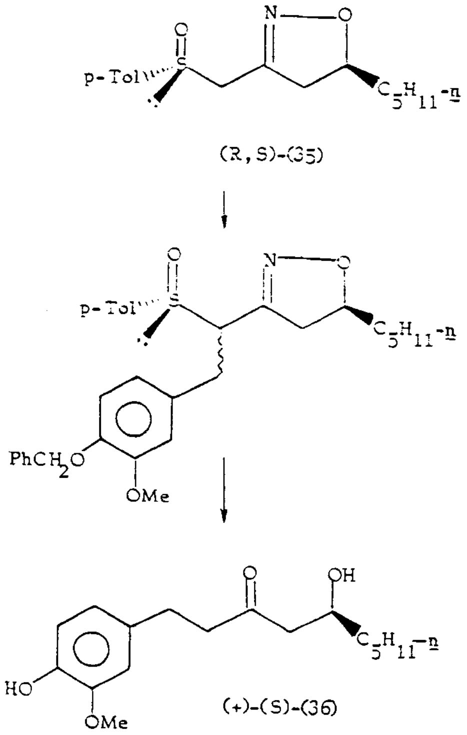
[+] Alkylation produces a 6:4 mixture of epimers at the carbon α to sulfur. No attempt was made to separate them, since this stereochemical information is immaterial to the final product.

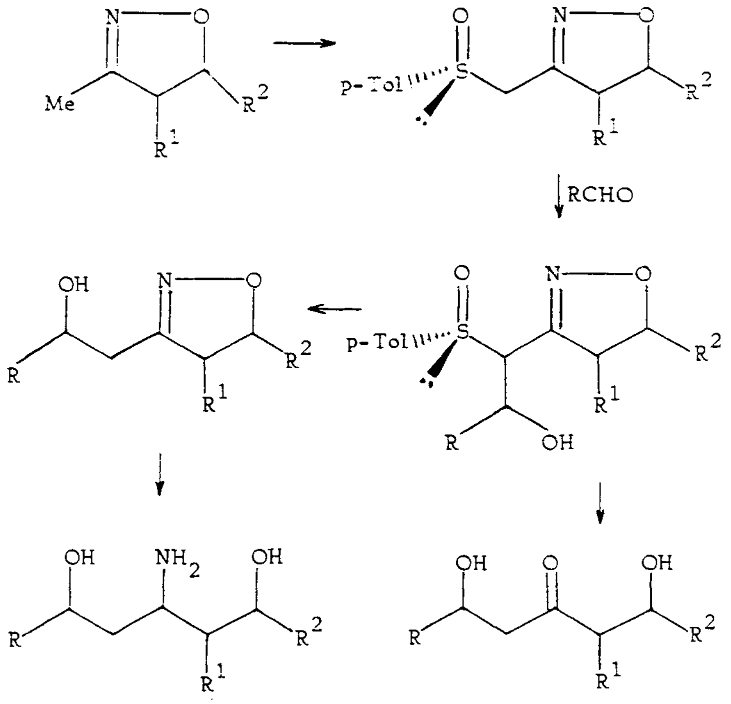
genation (Ni-Raney/then Pd/C) allow an efficient synthesis of optically pure natural (+)-(S)-gingerol (36) in 75% overall yield [32].



The possibility of creating new stereocenters outside of the heterocyclic ring before removal of the sulfoxide group was investigated in the aldol-type condensation of sulfinyl isoxazolines.

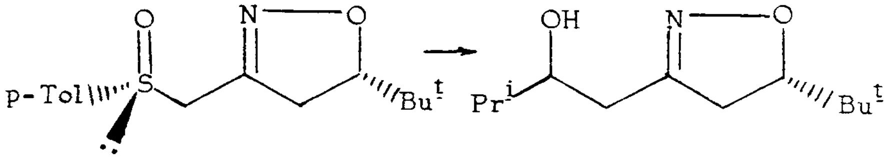
Reaction of stereoisomerically pure sulfinyl-isoxazolines with aldehydes affords, after desulfurization, either the hydroxy-isoxazoline (Na/Hg) or the β,β'-dihydroxy ketone (H_2, Ni-Raney). These are the masked and unmasked products of a formal regiospecific "double aldol" condensation of a ketone with two different aldehydes.

Furthermore hydroxy isoxazolines can be reduced ($LiAlH_4$) to the corresponding amino diols. Good to excellent degrees of stereoselection in the C-C bond formation in the aldol step were achieved [25].

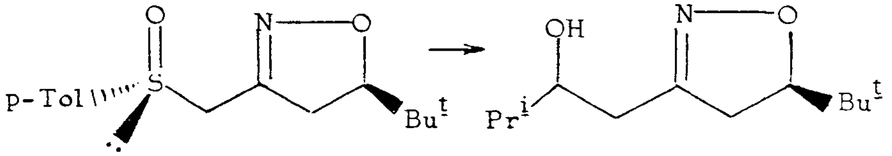


Starting from the two t-butyl isoxazolines (37) and (38) which have the same (R) absolute configuration at sulfur and are epimeric at C_5 it was shown that bulky magnesium bases such as $Bu^t MgBr$ and Pr^i_2NMgBr gave higher stereoselections than lithium bases or less bulky magnesium bases, the former giving higher chiral discrimination although somewhat lower chemical yields with respect to the latter.

Condensation of the magnesium enolate with $Pr^i CHO$ and subsequent desulfurization afforded mixtures of diastereoisomeric hydroxyoxazolines. The predominant isomers produced from (37) and (38) are epimeric and not enantiomeric, in other words they have the same configuration at the aldol center, thus showing that the sulfoxide plays a dominant role in determining the sense of chiral discrimination. The stereocenter at C_5 can cooperate or have an effect opposite to that of the sulfoxide. Indeed, as expected, in comparable conditions



(R,S)-(37) 8:1

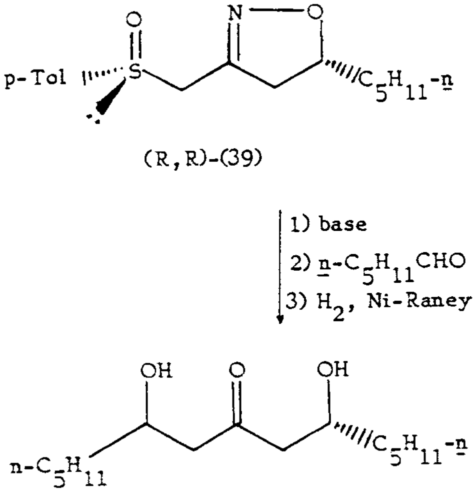


(R,R)-(38) 1:4

one of the two isoxazolines gives better stereoselection (8 : 1 versus 1 : 4). On the assumption that the isomer having the lone pair of the sulfur atom anti to the t-butyl group should give higher chiral discrimination (see below), the absolute configuration (R, S) and (R, R) can be tentatively assigned to (37), $[\alpha]^{25}_D + 337.5^o$ and (38), $[\alpha]^{25}_D + 140.3^o$, respectively.
The absolute configuration of the new stereocenter was firmly established by working with a sulfinylisoxazoline of known absolute configuration at sulfur and $C_{(5)}$, namely (R, R)-(39), $[\alpha]^{25}_D + 297.5^o$.

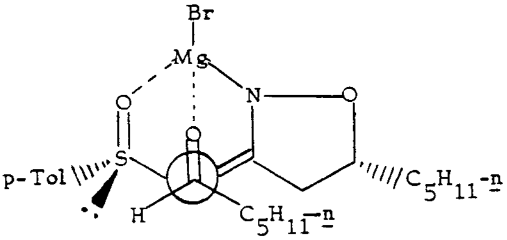
Condensation with n-hexanal afforded two stereoisomeric adducts in 3 : 1 ratio. They were separated and individually converted into the corresponding ketols. Only one of them, namely the one derived from the predominant adduct, was optically active and diastereoisomerically pure, as shown by n.m.r. spectroscopy. To this product the (R,R) absolute configuration is therefore assigned. As expected, the minor adduct afforded the meso ketol.

To account for the predominant stereochemical outcome, we tentatively propose a transition state in which a rigid, sulfinyl chelated enolate is approached top-side by the aldehyde with its proton facing the sulfoxide lone pair and the R group facing the isoxazoline ring, in agreement with the different stereoselectivities observed with isoxazolines (37) and (38), epimeric at $C_{(5)}$ (see above). This mode of attack is in agreement with our previous results obtained with sulfinyl amides. Obviously another approach would lead to the same result, the one from the other side of the enolate with the aldehydic hydrogen facing the heterocyclic ring, but this should be prevented by the aldehyde R group/p-tolyl group steric interaction.



(R,R)-(39)

(R,R)/(S,R) 3:1



We then turned our attention to aldol condensations of sulfinyl isoxazolines having two stereocenters at $C_{(4)}$ and $C_{(5)}$. Once again we choosed systems displaying the same (R) absolute configuration at sulfur, and opposite (but not known) absolute configuration at both C_4 and C_5, the relative configurations at this two stereocenter being anti in both cases. The results of the condensations of (4oa), $[\alpha]_d$ +83.2°, and (4ob), $[\alpha]_D$ + 262.2°, with various aldehydes are reported in Table 1.

A few points deserve a comment. First of all it must be noted that also in this case the sulfoxide group is dominant in directing the sense of chiral discrimination.

Indeed reaction of (4oa) and of (4ob) with the same aldehyde produces the same absolute configuration at the newly formed stereocenter. Furthermore aldol condensations carried out with optically active desulfurized isooxazoline gave poor stereoselections. Secondly both (4oa) and (4ob) gave lower chiral discrimination with increasing bulkiness of the aldehyde R residue, the ef-

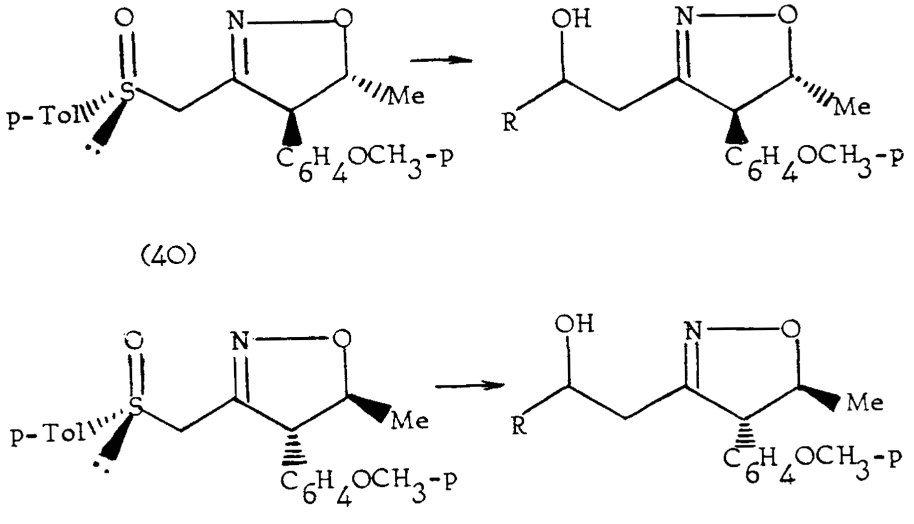


TABLE I Stereoselective condensation of sulfoxide (4o) with RCHO.

Sulfoxide	R	Base	Diastereomeric ratio
(4oa)	Et	MgDA	5o : 1
(4oa)	Pr^i	$Bu^t MgBr$	2o : 1
(4oa)	Pr^i	MgDA	9 : 1
(4oa)	Bu^t	MgDA	14 : 1
(4ob)	Et	MgDA	1 : 5o
(4ob)	Pr^i	$Bu^t MgBr$	1 : 5o
(4ob)	Pr^i	MgDA	1 : 2o
(4ob)	Bu^t	MgDA	1 : 1.1

fect being much more pronounced in one of the two cases. Even if further work is needed to fully clarify the mechanism of the reaction, and especially the relative importance on the extent of stereoselection of the nature and spatial disposition of the substituents at C_4 and C_5, it must be noted that chiral discrimination is generally very high, so that easy access to a variety of functionalized carbon skeletons with a number of stereocenters having definite relative and absolute configuration is in hand.

In conclusion our work as well as that of other research groups has shown that sulfoxide mediated asymmetric C-C bond formation is generally succesfull: sulfinyl derivatives can be used as chiral enolate equivalents to afford variously substituted optically active sulfur-free products.

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