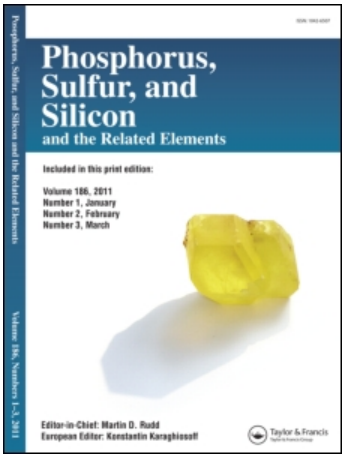


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# Enantioselective Routes to Sulfoxides Based upon Carbon-for-Carbon Substitution Reactions on the Sulfinyl Group

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*Grignard reagents were found to displace carbanionic leaving groups from suitable sulfinyl compounds. Because the process occurred with full inversion at the sulfinyl group, it was possible to set up an easy and straightforward route to chiral nonracemic sulfoxides. The starting compounds were easily produced, mainly by enantioselective oxidation of prochiral sulfides, and then the carbon-for-carbon displacement was effected with formation of a variety of new enantiopure sulfoxides.*

**Keywords** Carbanions; Grignard reagents; leaving groups; sulfoxides

## INTRODUCTION

Chiral nonracemic sulfoxides are key compounds in organic synthesis, because they are widely used as chiral auxiliaries in relevant asymmetric transformations.[1–3] Furthermore, some of them have also an important biological activity.[3]

The synthesis of enantiopure sulfoxides is based upon two main approaches: (i) the displacement strategy and (ii) the oxidation strategy.

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In the first type of approach,[3–14] an organometallic reagent displaces an oxygen or a nitrogen leaving group from an *S*-resolved sulfinate[3–8] or sulfinyloxazolidinone.[9] The reaction occurs with full inversion of configuration. A variety of systems are also available in which two equal (two oxygens)[10] or different (oxygen and nitrogen)[11,12] leaving groups can be displaced by organometallic reagents. Very recently, a significant progress in this type of strategy has been reported by the groups of Garcia-Ruano[13] and Senanayake.[14] Obviously, the success of the displacement procedure depends upon the possibility of preparing in a ready manner the enantiopure substrate and upon the regio- and stereoselectivity of the displacements.

In the second approach,[15] an enantioselective oxidation of a prochiral sulfide, most frequently performed in the presence of transition metal complexes with chiral ligands, yields the corresponding sulfoxide. However, the enantiomeric excess (ee) values are not systematically high.

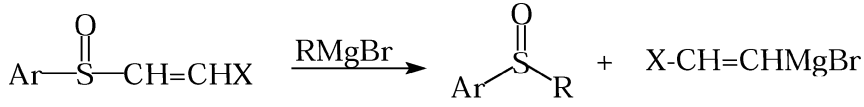
Finally, alkyl *tert*-butyl sulfoxides have been obtained by a procedure which couples the two types of strategies (*i.e.*, oxidation and heteroatom substitution).[16] In particular, di-*tert*-butyl sulfide was subjected to enantioselective oxidation and the resulting enantiopure *tert*-butyl *tert*-butanethiosulfinate was allowed to react with organometallic reagents, thus producing alkyl or aryl *tert*-butyl sulfoxides.



## THE CARBANIONIC LEAVING GROUP STRATEGY

### One Carbon-for-Carbon Substitution

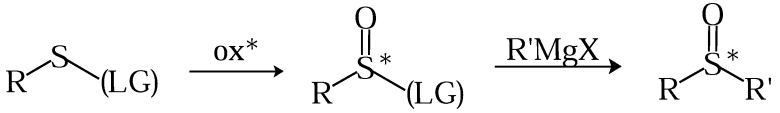
During the course of our work on the reactions between 2-halovinyl sulfoxides and organometallic reagents,[17] we observed that the halovinyl moiety could be displaced by Grignard reagents according to Scheme 1.




**SCHEME 1**

Furthermore, starting with 1-halovinyl aryl sulfoxides,[18] it was possible to establish that a stereochemical course of full inversion occurred. The possibility of displacing carbanions leaving group from sulfoxides

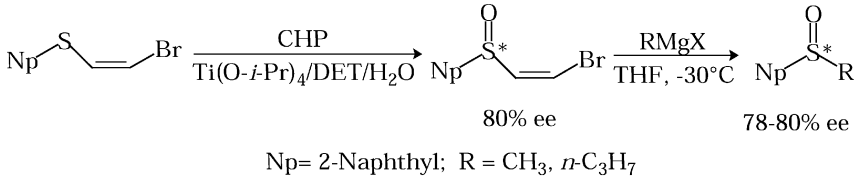
had been previously reported in a few cases, in particular by the groups of Johnson,[19] Durst,[20] Hojo,[21] and Furukawa.[22] The clean stereospecific displacement of carbanionic leaving groups observed in our reactions suggested to us the possibility of setting up a novel approach to enantiopure sulfoxides.[23] The principle that we wanted to subject to experimental evaluation is represented in Scheme 2, where a prochiral sulfide, bearing a suitable carbanionic leaving group, is oxidized to the corresponding sulfoxide, which in turn reacted with organometallic reagents to give the final sulfoxide.




**SCHEME 2**



On the basis of our experience on halovinyl sulfoxides, the first application of this principle was made by starting with 2-halovinyl 2-naphthyl sulfoxide. In particular, alkyl naphthyl sulfoxides with an 80% ee value were prepared according to Scheme 3.[18]




Np= 2-Naphthyl; R = $CH_3$, $n$-$C_3H_7$

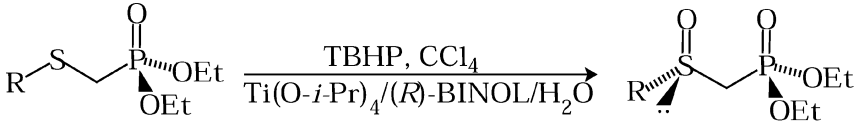
**SCHEME 3**

After these preliminary experiments, to improve the ee values of the starting sulfinyl compounds we turned our attention to the evaluation of suitable systems containing different carbanionic leaving groups.

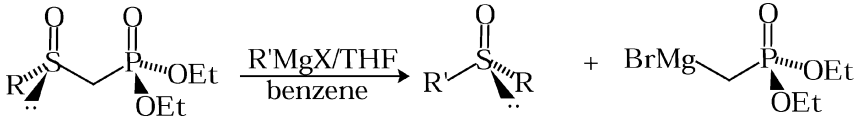
Studies performed on sulfinylmethylphosphonates[24] suggested to us the possibility of displacing the anion of dimethyl methylphosphonate as a new carbanionic leaving group. Whereas in the preliminary experiments an optically active sulfinylmethylphosphonate obtained through the Andersen procedure had been used, we were able to oxidize commercially available diethyl (arylthio)- or (alkylthio)methylphosphonates with *tert*-butyl hydroperoxide in the presence of a titanium/(*R*)-1,1′-Bi-2-naphthol (BINOL) complex (Scheme 4).[25]

The diethyl sulfinylmethylphosphonates were then allowed to react with a variety of Grignard reagents according to Scheme 5.[25]

The measured ee values were high (91−>98% ee) but the yields were only moderate (43–50%). This was due to the competing metalation of




**SCHEME 4**




R= methyl, ethyl, phenyl
R' = *n*-octyl, *n*-decyl, *n*-octadecyl, cyclohexyl, *tert*-butyl, (*E*)-2-styryl, phenyl, *p*-tolyl

**SCHEME 5**

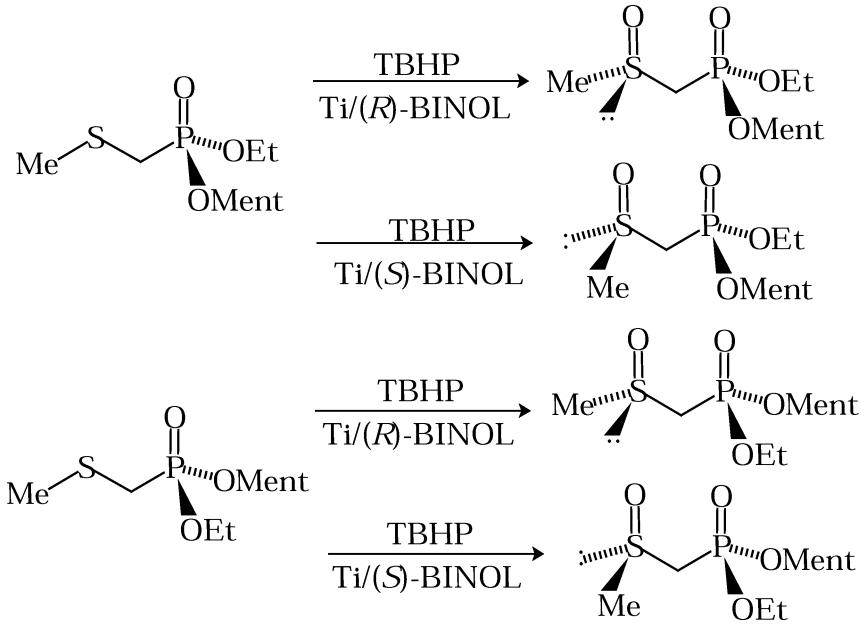


the starting material by the organometallic reagent. However, by using a procedure that allowed us to recover the metalated species, in the case of the reactions of (methylsulfinyl)methylphosphonate, we were able to increase the yields of the reactions (61–86%).[25]

The ready access to these sulfoxides allowed the preparation of platinum complexes with stilbazoles and enantiopure alkyl methyl sulfoxides.[26] These complexes are the first example of a metallomesogen in which the stereogenic center is directly bound to the metal.

Furthermore, it is also worth noting that (methylsulfinyl)methylphosphonates, independent their use for the synthesis of other sulfoxides, are compounds of interest from a pharmacological point of view. Platinum complexes with diethyl (methylsulfinyl)methylphosphonates have been prepared to influence the antitumor activities of the metal.[27] Furthermore, a mixture of the stereoisomers of the ethyl menthyl (methylsulfinyl)methylphosphonate[28] was preliminarily tested as anticancer for activity. Therefore, it appeared of interest to prepare all the four sulfur and phosphorus stereoisomers for a deeper pharmacological investigation. The oxidation that led to products with high distereomeric excess (de) values was performed according to Scheme 6, starting from ethyl menthyl ($S_P$)- or ($R_P$)-(methylthio)methylphosphonate.[29]

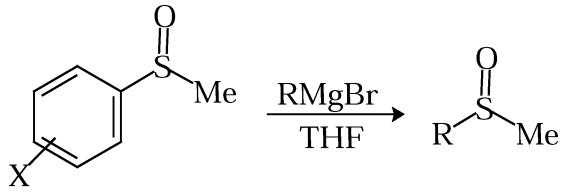
A systematic study on substituted aryl methyl sulfoxides[30] showed that *o*-, *m*-, and *p*-halophenyl methyl sulfoxides could react with alkyl Grignard reagents with the displacement of the whole aryl




**SCHEME 6**



moiety and the formation of alkyl methyl sulfoxides (64–82% isolated yields) (Scheme 7).



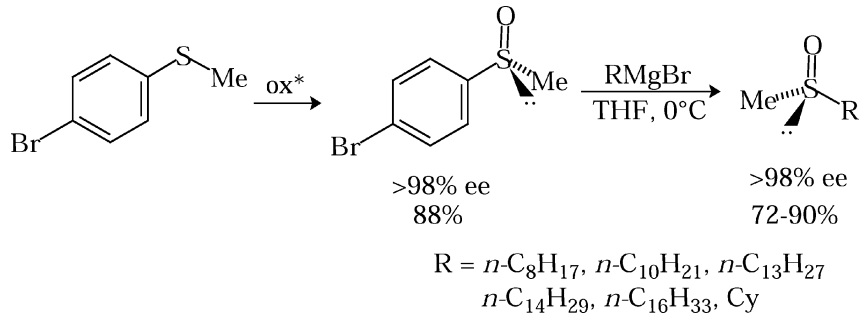

R = *n*-octyl, *n*-decyl, *n*-hexadecyl
X = Cl, Br

**SCHEME 7**

The starting (*R*)-, *o*-, *m*-, and *p*-halophenyl methyl sulfoxides were synthesized in good yields (67–94%) and in high ee values (80–97% ee) by a cumene hydroperoxide oxidation of the corresponding sulfides in the presence of titanium/diethyl (*R*, *R*)-tartrate complexes.[30] In particular, *p*-bromophenyl methyl sulfoxide was obtained in a 95% ee and

was crystallized with formation of an enantiomerically pure sulfoxide (>98%).

When the prepared aryl methyl sulfoxides were reacted with alkyl Grignard reagents, the substitution of the halophenyl moiety occurred also in this case with inversion of configuration.[30] (*R*)-*p*-Bromophenyl methyl sulfoxide upon treatment with alkyl Grignard reagents yielded (*S*)-alkyl methyl sulfoxides in good isolated yield (72–90%) (Scheme 8).

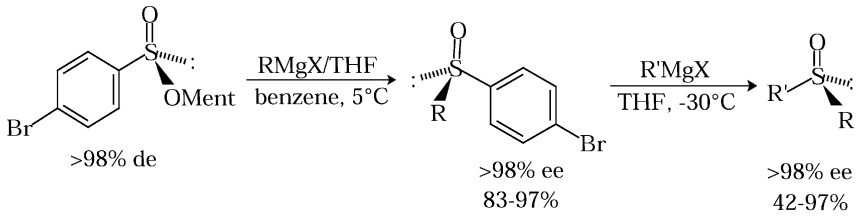



**SCHEME 8**

## One Carbon-for-Oxygen Displacement Coupled with a Carbon-for-Carbon Displacement

As an extension of our procedure, we turned our attention toward suitable substrates bearing two different leaving groups, which could be chemoselectively substituted. With this aim, we decided to combine our carbanionic leaving group approach with the classical displacement of the menthoxide anion from a suitable menthyl sulfinate. After preliminary tests, menthyl *p*-bromobenzenesulfinate appeared as a valid substrate for a two-step synthesis of chiral sulfoxides.[31] This sulfinate was prepared on a multigram scale as a mixture of diastereomers by reacting menthol and *p*-bromophenylsulfonyl chloride, using trimethyl phosphite as a reducing agent. Satisfactory yields of the (*S*)-stereoisomer could be obtained by crystallization (57% overall yield).

Menthyl (*S*)-*p*-bromobenzenesulfinate was reacted with alkyl Grignard reagents, with formation of alkyl *p*-bromophenyl sulfoxides (83–97%) and substitution of the menthoxide moiety. The obtained alkyl *p*-bromophenyl sulfoxides were separated and reacted with alkyl Grignard reagents, thus producing dialkyl sulfoxides in good yields and in a high enantiomeric purity (>98% ee) (Scheme 9).[31]

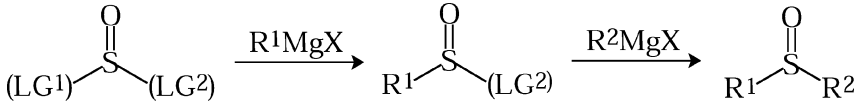



R, R' = ethyl, *n*-decyl, *i*-propyl, cyclohexyl

**SCHEME 9**

## Two Carbon-for-Carbon Displacements

In principle, the carbon-for-carbon displacement strategy could be extended to a system containing two carbanionic leaving groups according to Scheme 10.

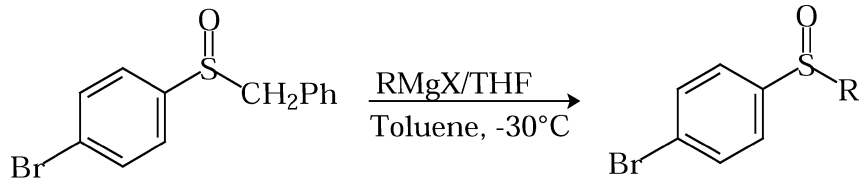



$LG^1$, $LG^2$ = carbanionic leaving groups

**SCHEME 10**

Because the *p*-bromophenyl moiety has been already successfully used, we needed only to search for another carbanionic leaving group that could be displaced at a sufficiently different rate with respect to the halophenyl group. After a preliminary survey, the benzyl group appeared as a suitable group. Indeed, the displacement of the two groups occurred sequentially, with the benzyl group being displaced first by alkyl Grignard reagents to give alkyl *p*-bromophenyl sulfoxides (Scheme 11).[32]

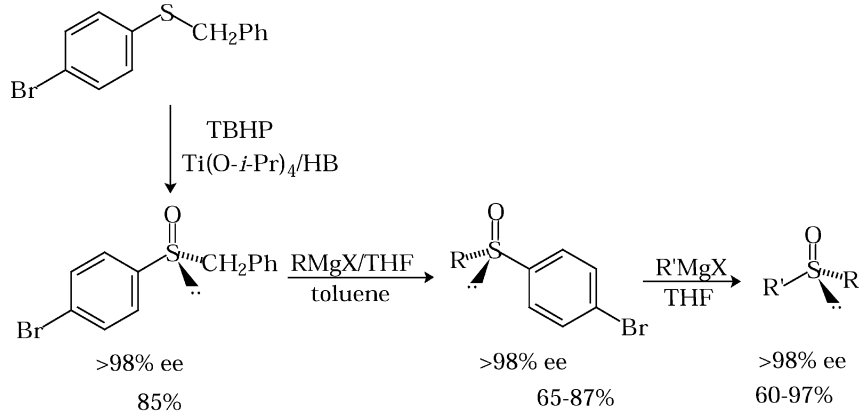
The problem of obtaining the required benzyl *p*-bromophenyl sulfoxide with an easy oxidation procedure was successfully solved by oxidizing benzyl *p*-bromophenyl sulfide with *tert*-butyl hydroperoxide in the presence of the complex resulting from titanium tetraisopropoxide and (*S*, *S*)-hydrobenzoin (HB) in *n*-hexane at room temperature. The procedure yielded the required sulfoxide in 85% yield with a >98% ee value. The procedure was very simple from an experimental point of view, because the sulfoxide was found to precipitate from the reaction solution. Therefore, it was rather easy to perform the reaction on a multigram scale (up to 25 g).[32]




R= ethyl, *n*-pentyl, *n*-dodecyl, cyclohexyl.

**SCHEME 11**

Benzyl *p*-bromophenyl sulfoxide was then subjected to reaction with alkyl Grignard reagents to displace first the benzyl group with the formation of alkyl *p*-bromophenyl sulfoxide, which, after isolation, could be subjected to the second displacement, according to the procedure presented previously. For the sake of clarity, the full sequence is shown in Scheme 12.




R, R' = ethyl, *n*-pentyl, *n*-dodecyl, *i*-propyl, cyclohexyl

**SCHEME 12**

It is worth noting that it is possible to obtain both enantiomers of the required sulfoxide by choosing the appropriate order of introduction of alkyl substituents.

## CONCLUSIONS

The carbanionic leaving group strategy opens a viable route to enantiopure sulfoxides. Although dialkyl sulfoxides were produced in most

of our reactions, the work performed with the phosphonates has shown the possibility of applying the same strategy to alkyl aryl sulfoxides and to diaryl sulfoxides. The synthetic potential of our approach will increase upon discovering other suitable carbanionic leaving groups. It is also worth noting that the possibility of an extension of the carbanionic leaving group strategy to the synthesis of chiral non racemic phosphine oxides has been already reported.[33]

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