Substituted Benzene Anions as Leaving Groups in the Reaction of Sulfinyl Derivatives with Grignard Reagents: A New and Convenient Route to Dialkyl Sulfoxides in High Enantiomeric Purity

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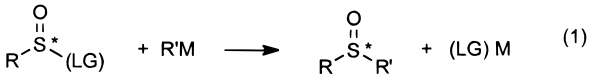
Carbanionic leaving groups (LG) can be displaced in the reaction of organometallic reagents with suitable sulfinyl compounds.[1−9] The substitution occurs with full inversion of configuration at the sulfur stereogenic center (eq 1).[1−6]



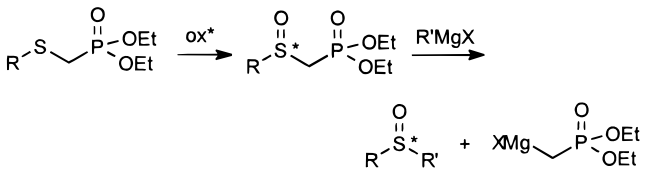
(1)

Recently, special interest has grown about the stereochemistry of this process[1−4] and the fate of the leaving group.[8,9]

In previous work,[1] we have investigated mechanistic and stereochemical aspects of the displacement of the halovinyl group in the reaction represented in eq 1. Our attention was then driven toward the use of the anions of dialkyl methylphosphonates as leaving groups.[2−4] The results obtained were used as the basis of a new easy and straightforward two-step route to chiral nonracemic sulfoxides. In fact, we have devised a catalytic, simple, and high-yield oxidation of commercially available (arylthio)- or (alkylthio)methylphosphonates to (arylsulfinyl)- or (alkylsulfinyl)methylphosphonates in high enantiomeric purity (91 to >98% ee).[4] These easily obtained sulfinyl compounds were converted into the corresponding sulfoxides by Grignard reagents, with the release of the anion of the diethyl methylphosphonate (Scheme).[4]

The second step of the procedure occurs with full inversion of configuration. Several chiral dialkyl sulfoxides, a type of sulfoxide that has attracted considerable synthetic interest,[10−13] now can be considered easily available by using our approach. In particular, methyl alkyl sulfoxides can be obtained in high enantiomeric purity (>98% ee).[4] The method was also suitable for the preparation of ethyl sulfoxides or phenyl sulfoxides in a lower enantiomeric purity (ee values 91−94%). Metalation of the substrate is a side reaction that causes the incomplete conversion of the substrate and has to be avoided by using a variation of the strategy.[4]

Scheme 1



The displacement of an aryl carbanion from a sulfinyl derivative by means of organometallic reagents has various precedents in the literature.[5−7] However, in no case was the synthetic potential of this displacement adequately considered for the synthesis of sulfoxides. With this background, the evaluation of the possibility of extending our two-step strategy (enantioselective oxidation and carbon for carbon substitution)[1−4] to aryl-substituted systems appeared as an interesting procedure to convert *one* readily available starting compound into *a series* of chiral nonracemic sulfoxides.

Results and Discussion

Our synthetic scheme required a preliminary choice of the candidate for the displacement. Therefore, several types of sulfoxides were investigated. Preliminary results, obtained by using methyl phenyl sulfoxide, were totally unsatisfactory. Indeed, the main reaction observed was the reduction of the sulfinyl group and the formation of a mixture of sulfides, a result that had been reported also by other workers[14] for the reaction of the same sulfoxide with Grignard reagents in the presence of magnesium amides. An analogous behavior was also shown by using *p*-nitrophenyl methyl sulfoxide. Better results and a different course were observed for the reaction between aryl methyl sulfoxides **1**−**8** with alkylmagnesium bromides. Alkyl methyl sulfoxides **9**−**14** were obtained (eq 2).

The reaction of *o*-, *m*-, and *p*-anisyl methyl sulfoxides **1**−**3** with *n*-decylmagnesium bromide gave low isolated yields (up to 48%) of *n*-decyl methyl sulfoxide (Table 1, entries 1−3) due to the concurrent formation of reduction products.

On the other hand, *o*-, *m*-, and *p*-halophenyl methyl sulfoxides **4**−**8** yielded satisfactory isolated yields (64−

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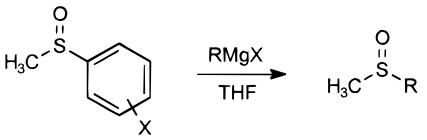
Table 1. Reaction of Substituted Aryl Methyl Sulfoxides with Grignard Reagents



entry	substrate	X	R	product	yield[a] (%)
1	**1**	2-OCH_3	*n*-decyl	**10**	42
2	**2**	3-OCH_3	*n*-decyl	**10**	48
3	**3**	4-OCH_3	*n*-decyl	**10**	22
4	**4**	2-Cl	*n*-octyl	**9**	72
5	**5**	4-Cl	*n*-hexadecyl	**13**	64
6	**6**	2-Br	*n*-decyl	**10**	71
7	**7**	3-Br	*n*-decyl	**10**	82
8	**8**	4-Br	*n*-decyl	**10**	69

[a] Yields refer to pure isolated products.

(2)

X=CH_3O, Cl, Br

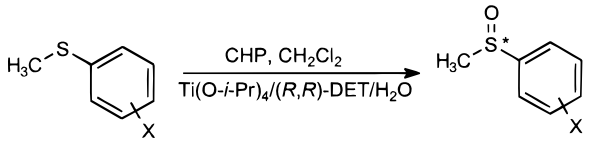
1-8 **9-14**

82%) of the alkyl methyl sulfoxide (Table 1, entries 4−8) and were used for further studies. For evaluation of the reactivity order between the halophenyl methyl sulfoxides, two substrates (in a 1:1 ratio) were treated with a deficiency of Grignard reagent. The reactivity ratios were evaluated from the composition of the recovered unchanged material, by assuming simple kinetic behavior. *p*-Chloro- and *p*-bromophenyl methyl sulfoxides **5** and **8** showed no significant reactivity difference. The same conclusion was reached in the case of the comparison between *m*-bromophenyl methyl sulfoxide **7** and *p*-bromophenyl methyl sulfoxide **8**, whereas the reactivity ratio between *o*-bromophenyl methyl sulfoxide **6** and *m*- or *p*-bromophenyl compounds **7** or **8** was found to be ca. 2.

To prepare chiral nonracemic dialkyl sulfoxides with the carbon for carbon substitution strategy, optically active starting alkyl aryl sulfoxides were required. These substrates can be obtained by an enantioselective hydroperoxide oxidation of the prochiral sulfides in the presence of chiral titanium complexes.[15−17] The procedure represents indeed a simple and straightforward access to these chiral substrates. Unfortunately, the ee values are not generally high, and peak values are obtained only for certain substrates.[15−17]

The oxidation of the prochiral sulfides with *tert*-butyl hydroperoxide in the presence of a complex Ti(O-*i*-Pr)$_4$/(*R*)-BINOL, according to our previous reported procedure,[4] gave low enantioselectivity (1−18% ee). On the other hand, it is known that the cumene hydroperoxide

Table 2. Enantioselective Cumene Hydroperoxide Oxidation of Substituted Aryl Methyl Sulfides Mediated by a (*R*,*R*)-Diethyl Tartrate Titanium Complex



Reaction ratios: Ti(O-*i*-Pr)$_4$/DET/H_2O/CHP1:2:0.5:1.1

entry	X	yield[a] (%)	product	ee[b] (%)
1	2-OCH_3	86	(*R*)-**1**	88
2	3-OCH_3	70	**2**[d]	93
3	4-OCH_3	72	(*R*)-**3**	92
4	2-Cl	94	(*R*)-**4**	80
5	4-Cl	76	(*R*)-**5**	91[c]
6	2-Br	77	(*R*)-**6**	83[c]
7	3-Br	67	**7**[d]	97
8	4-Br	88	(*R*)-**8**	95 (>98)[e]

[a] Yields refer to pure isolated products. [b] Determined by HPLC (see text). [c] Determined by NMR (see text). [d] The absolute configuration has not been reported, but it should be *R* (see footnote *c* in Table 3). [e] After one recrystallization (see text).

(CHP) oxidation of the prochiral sulfides in the presence of a complex Ti(O-*i*-Pr)$_4$/(diethyl (*R*,*R*)-tartrate) gives higher ee values.[15,16] In our hands, the best results were obtained by adopting a modification of the reported reaction conditions,[15,16] according to our previous work.[3] The modification, which consists of the use of a lower amount of oxidizing agent and water, gave both high enantioselectivity (Table 2, 80-97% ee) and satisfactory yields (67−94%) of the chiral sulfoxides **1**−**8**. In particular (Table 2, entry 8), *p*-bromophenyl methyl sulfoxide **8** with a high ee value was easily obtained by enantioselective oxidation (95% ee) followed by one recrystallization (>98% ee).

The substituted enantiomerically enriched aryl methyl sulfoxides **1**−**8** were reacted with alkyl Grignard reagents (Table 3). The reaction occurred with inversion of configuration, and the enantiomeric excess of the resulting sulfoxides was found to be very close to the value measured for the starting material (±2%).

Due to the higher ee value of the *p*-bromophenyl methyl sulfoxide **8**, further reactions were performed with this compound (Table 3, entries 8−12). We focused in particular on long-chain alkyl methyl sulfoxides (Table 3, entries 8−11), since we are currently investigating these compounds as components of chiral metallomesogens. The dialkyl sulfoxides were obtained in the same enantiomeric purity (>98%) and in satisfactory isolated yields (72−90%). The reaction appeared to be not restricted to primary alkyl Grignard reagents. Indeed, the use of a secondary alkyl Grignard reagents, i.e., cyclohexylmagnesium bromide (Table 3, entry 12), gave cyclohexyl methyl sulfoxide **14** in good isolated yields (72%) and in high enantiomeric purity (>98%). However, a low conversion was obtained in the reaction of *tert*-butylmagnesium bromide with substrate **8**, and this reaction was not investigated further.

Conclusions

Our work has shown that a variety of aryl methyl sulfoxides could be subjected to a displacement at the sulfur center. The most satisfactory substrate appears to be the halo-derivatives, among which the *p*-bromo

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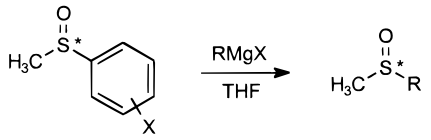
Table 3. Reaction of Chiral Substituted Aryl Methyl Sulfoxides with Grignard Reagents



entry	substrate	X	ee substrate (%)	R	product	yield[a] (%)	ee product[b] (%)
1	(*R*)-**1**	2-OCH_3	88	*n*-decyl	(*S*)-**10**	40	86
2	(*R*)-**2**[c]	3-OCH_3	93	*n*-decyl	(*S*)-**10**	56	91
3	(*R*)-**3**	4-OCH_3	92	*n*-decyl	(*S*)-**10**	24	92
4	(*R*)-**4**	2-Cl	80	*n*-octyl	(*S*)-**9**	65	81
5	(*R*)-**5**	4-Cl	91	*n*-decyl	(*S*)-**10**	73	89
6	(*R*)-**6**	2-Br	83	*n*-octyl	(*S*)-**9**	68	85[d]
7	(*R*)-**7**[c]	3-Br	96	*n*-decyl	(*S*)-**10**	81	96
8	(*R*)-**8**	4-Br	>98	*n*-octyl	(*S*)-**9**	84	>98
9	(*R*)-**8**	4-Br	>98	*n*-tridecyl	**11**[e]	74	>98
10	(*R*)-**8**	4-Br	>98	*n*-tetradecyl	**12**[e]	90	>98
11	(*R*)-**8**	4-Br	>98	*n*-hexadecyl	**13**[e]	77	>98
12	(*R*)-**8**	4-Br	>98	cyclohexyl	(*S*)-**14**	72	>98

[a] Yield refer to pure isolated products. [b] Determined by HPLC (see text). [c] The configuration has not been reported previously, but it should be *R* because the reaction with *n*-decylmagnesium bromide yielded (*S*)-**10** as in the case of other sulfoxides of known configuration, and it seems reasonable to assume that also this reaction occurred with inversion of configuration. [d] Determined by NMR (see text). [e] The configuration has not been reported previously, but it should be *S*, provided that the reaction with Grignard reagents occurred with full inversion of configuration also in this case.

sulfoxide has to be considered the starting compound of choice due both to higher yields in the coupling and to the very easy possibility to prepare it in an optically pure form. The use of Grignard reagents appears to avoid the partial or complete racemization reported in earlier works[5−7] for reactions with organolithium compounds. Finally, a comparison between the present procedure and the approach based upon the use of the anion of dialkyl methylphosphonates as leaving group[4] reveals that the two methodologies are complementary for the synthesis of alkyl methyl sulfoxides. In fact, whereas the use of the latter can be considered of more general scope, but to a certain extent affected by the metalation of the substrate, this competing process does not afflict the reaction of the aryl derivatives used in the present investigation.

Experimental Section

The purified reaction products were characterized by their ^1H and ^{13}C NMR spectra, recorded in $CDCl_3$ at 500 and 125 MHz, respectively, and their mass spectra determined by GC/MS analysis (SE30, 30 m, capillary columns and mass selective detector, 70 eV). Substituted aryl methyl sulfides were obtained from the corresponding commercially available thiols and methyl iodide. The ee values of the products were determined by ^1H NMR techniques (addition of (*R*)-(−)-3,5-dinitro-*N*-(1-phenylethyl)benzamide as a chiral solvating agent) or HPLC (Chiralcel OB-H or OD-H). Only HPLC determinations were used for substrates and products of high enantiomeric purity (>98%).

Substrates. Racemic aryl methyl sulfoxides **1**−**8** were obtained by standard oxidation of the corresponding sulfides.

Preparation of Chiral Aryl Methyl Sulfoxides (1−8) by CHP Enantioselective Oxidation of Sulfides in the Presence of a Chiral Titanium Complex. A solution of Ti(O-*i*-Pr)$_4$ (1.48 mmol) in 3 mL of anhydrous CH_2Cl_2 was added to a solution of diethyl tartrate (2.95 mmol) in 5 mL of anhydrous CH_2Cl_2. After 2 min, 13 μL of water was added. The mixture was stirred at room temperature for 20 min and then cooled to −20 °C. After 20 min, 1.48 mmol of thioether in 3 mL of anhydrous CH_2Cl_2 and 1.63 mmol of CHP were added. The reaction mixture was stirred at −20 °C for 3 h and quenched with a saturated solution of NH_4Cl. The solids were removed by filtration, and the organic layer was extracted with CH_2Cl_2. The organic extracts were dried over anhydrous sodium sulfate and then evaporated in vacuo. The obtained sulfinyl compound was separated by column chromatography (eluent petroleum ether/ethyl acetate 3:7). **(*R*)-(+)-*o*-Anisyl methyl sulfoxide (1):** Kugelrohr oven temperature 90 °C, $p = 5 \times 10^{-2}$ mbar; $[\alpha]_D = +295$ ($c = 1$, acetone) for an 88% ee (lit.[18] $[\alpha]_D = +340$ ($c = 1$, acetone)). **(+)-*m*-Anisyl methyl sulfoxide (2):**[19] Kugelrohr oven temperature 110 °C, $p = 5 \times 10^{-2}$ mbar; $[\alpha]_D = +127.8$ ($c = 1.5$, chloroform) for a 93% ee. **(*R*)-(+)-*p*-Anisyl methyl sulfoxide (3):** Kugelrohr oven temperature 100 °C, $p = 10^{-2}$ mbar; $[\alpha]_D = +161.7$ ($c = 2$, chloroform) for a 92% ee (lit.[20] $[\alpha]_D = +165.9$ ($c = 0.38$, chloroform)). **(*R*)-(+)-*o*-Chlorophenyl methyl sulfoxide (4):** Kugelrohr oven temperature 80 °C, $p = 10^{-2}$ mbar; $[\alpha]_D = +204$ ($c = 1.5$, THF) for an 80% ee (lit.[21] $[\alpha]_D = +139$ ($c = 1$, THF)). **(*R*)-(+)-*p*-Chlorophenyl methyl sulfoxide (5):** Kugelrohr oven temperature 90 °C, $p = 10^{-2}$ mbar; $[\alpha]_D = +153$ ($c = 1$, chloroform) for a 91% ee (lit.[22] $[\alpha]_D = -158$ ($c = 0.95$, chloroform)) for the *S* configuration. **(*R*)-(+)-*o*-Bromophenyl methyl sulfoxide (6):** Kugelrohr oven temperature 110 °C; $p = 5 \times 10^{-2}$ mbar; $[\alpha]_D = +207$ ($c = 1.3$, THF) for a 83% ee (lit.[21] $[\alpha]_D = +251$ ($c = 1$, THF)). **(+)-*m*-Bromophenyl methyl sulfoxide (7):**[23] Kugelrohr oven temperature 110 °C, $p = 5 \times 10^{-2}$ mbar; $[\alpha]_D = +116.3$ (1.2, acetone) for a 97% ee. **(*R*)-(+)-*p*-Bromophenyl methyl sulfoxide (8):** mp 75−77 °C (hexane); $[\alpha]_D = +98.3$ ($c = 2.5$, acetone) (lit.[15c] $[\alpha]_D = +77$ ($c = 1.8$, acetone)) for a 80% ee.

Reaction of Grignard Reagents with Racemic or Enantiomeric Sulfoxides 1−8. A solution of 2.1 mmol of Grignard reagents in THF was added to a solution of 1.4 mmol of sulfoxide in 10 mL of THF at 0 °C and under N_2. After 1.5 h, the reaction mixture was quenched with a saturated solution of NH_4Cl. After the usual workup, the reaction mixture was separated by column chromatography and recrystallized (hexane) or distilled.

(*S*)-(+)-Methyl *n*-octyl sulfoxide (9): mp 35−37 °C (hexane); $[\alpha]_D = +77.3$ ($c = 1$, acetone) (lit.[13] $[\alpha]_D = +62.5$ (acetone); lit.[4] $[\alpha]_D = -83.6$ ($c = 1$, acetone)) for the *R* configuration. **(*S*)-(+)-Methyl *n*-decyl sulfoxide (10):** mp 48−51 °C (hexane); $[\alpha]_D = +54.0$ (c=1, chloroform) (lit.[4] $[\alpha]_D = -52.7$ ($c = 1$, chloroform)) for the *R* configuration. **(+)-Methyl *n*-tridecyl sulfoxide (11):**[24] mp 63−65 °C (hexane); $[\alpha]_D = +52.9$ ($c = 1$, chloroform).

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(+)-Methyl *n*-tetradecyl sulfoxide (12):[25] mp 70−72 °C (hexane); $[\alpha]_D = +49.4$ ($c = 1$, chloroform); **(+)-*n*-Hexadecyl methyl sulfoxide (13):**[26] mp 78−79 °C (hexane); $[\alpha]_D = +43.7$ ($c = 1.5$, chloroform). **(*S*)-(+)-Cyclohexyl methyl sulfoxide (14):** Kugelrohr oven temperature 135 °C; $p = 10$ mbar; $[\alpha]_D = +67.7$ ($c = 1$, acetone) (lit.[4] $[\alpha]_D = -69.5$ ($c = 1$, acetone)) for the (*R*) configuration.

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Supporting Information Available: Relevant spectral data for compounds **1**−**14**; data concerning HPLC determination of the ee values. This material is available free of charge via the Internet at http://pubs.acs.org.

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