JOC Article

A Straightforward Enantioselective Route to Dialkyl Sulfoxides Based upon Two Carbon-for-Carbon Substitution Reactions on the Sulfinyl Group

Maria Annunziata M. Capozzi,[†,‡] Cosimo Cardellicchio,[§] Francesco Naso,*[,†,§] and Valerio Rosito[†]

Consiglio Nazionale delle Ricerche, Istituto di Chimica dei Composti OrganoMetallici, Sezione di Bari and Dipartimento di Chimica, Università di Bari, via Orabona 4, 70126 Bari, Italy

naso@area.ba.cnr.it

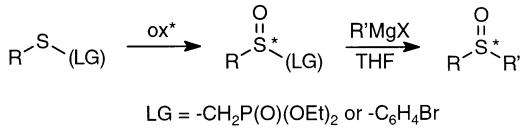
Received May 27, 2002

Benzyl *p*-bromophenyl sulfoxide **1** was obtained on a multigram scale and in an enantiomerically pure form by an enantioselective catalytic oxidation, using *tert*-butyl hydroperoxide in the presence of chiral titanium complexes. Some mechanistic and stereochemical features of interest were studied in this process. Compound **1** was then subjected to two different substitution reactions with Grignard reagents, which caused two sequentially stereocontrolled carbon-for-carbon displacements, leading to chiral nonracemic dialkyl sulfoxides.

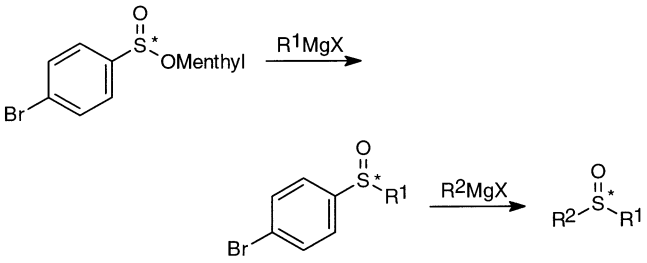
Chiral nonracemic sulfoxides are valuable intermediates[1] and have relevant applications in asymmetric synthesis.[1,2] In our recent work,[3−5] we have reported a synthetic useful route to sulfoxides in high enantiomeric purity by using the stereocontrolled reaction between Grignard reagents and suitable sulfinyl compounds, with the displacement of a carbanionic moiety. This approach was especially convenient for the preparation of dialkyl sulfoxides, a class of compounds for which a general and straightforward route appeared particularly needed. Our work was characterized by two significant moments: in a first approach,[3,4] we synthesized aryl alkyl or dialkyl sulfoxides by a two-step procedure involving the preparation of the chiral sulfinyl precursor by an enantioselective oxidation, followed by the synthesis of the final sulfoxide through a Grignard reagent promoted stereocontrolled substitution of a carbanionic leaving group (LG) (Scheme 1).

In a second approach,[5] we obtained various chiral nonracemic dialkyl sulfoxides by a two-displacement sequence starting from menthyl (*S*)-*p*-bromobenzenesulfinate. In particular, alkyl Grignard reagents promoted the stereocontrolled displacement of the menthoxide ion in the first step, which was then followed by the displacement of the *p*-bromophenyl leaving group on the resulting *p*-bromophenyl sulfoxide.

SCHEME 1



SCHEME 2



The procedure of Scheme 2 represents a useful synthetic route to dialkyl sulfoxides based upon a carbon-for-oxygen substitution, followed by a carbon-for-carbon substitution. In principle, since the sulfinate was obtained through a diastereomeric separation by crystallization, it appeared that the importance of our procedure could be significantly increased by finding a suitable starting compound, accessible by a direct enantioselective oxidation and susceptible to transformation into the final sulfoxide by two consecutive displacements of carbanionic leaving groups (Scheme 3).

Since the first carbanionic leaving group was already at hand (i.e., the *p*-bromophenyl group), the attention had to be focused on the second one, which had to show either

[†] Dipartimento di Chimica, Università di Bari.

[‡] Present address: Istituto di "Produzioni e Preparazioni Alimentari", Facoltà di Agraria, Università degli Studi di Foggia, via Napoli 25, 71100 Foggia.

[§] Consiglio Nazionale delle Ricerche, Istituto di Chimica dei Composti OrganoMetallici.

(1) Drabowicz, J.; Kiełbasinski, P.; Mikołajczyk, M. Synthesis of Sulphoxides. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C., Eds.; John Wiley and Sons: New York, 1988; pp 233−378. Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961−998.

(2) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760.

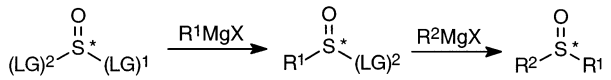
(3) (a) Cardellicchio, C.; Fracchiolla, G.; Naso, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 525−532. (b) Capozzi, M. A. M.; Cardellicchio, C.; Fracchiolla, G.; Naso, F.; Tortorella, P. *J. Am. Chem. Soc.* **1999**, *121*, 1, 4708−4709.

(4) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Tortorella, P. *J. Org. Chem.* **2000**, *65*, 2843−2846.

(5) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Spina, G.; Tortorella, P. *J. Org. Chem.* **2001**, *66*, 5933−5936.

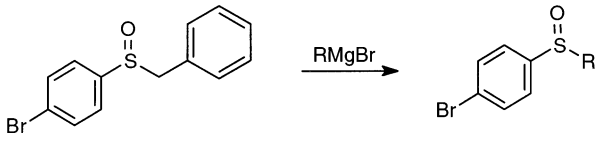
10.1021/jo025974j CCC: $22.00
Published on Web 09/18/2002

SCHEME 3



LG = carbanionic leaving group

SCHEME 4



1

a higher or a lower leaving group ability in respect to the *p*-bromophenyl moiety. The difficulty of finding a second carbanionic leaving group with this peculiar feature was coupled with the need of obtaining the suitable starting sulfoxide, once found, by an enantioselective oxidation.

Now, we wish to report our successful experimental execution of this synthetic plan together with several relevant aspects which emerged during our efforts for the production of the appropriate starting material with special reference to the enantioselective oxidation step.

Results and Discussion

The Search for the Substrate. Upon scanning the literature background on possible candidates as carbanionic leaving groups for a carbon-for-carbon substitution, it appeared to us that a carbanionic leaving group worth testing was the benzyl moiety. Indeed, a ligand exchange process was observed by Durst et al.[6] when *n*- or *tert*-butyllithium was reacted with benzyl phenyl sulfoxide to give *n*- or *tert*-butyl phenyl sulfoxide (yield 40−50%). The stereochemical course of the benzyl group displacement was not reported. Another relevant result derived from our previous investigations[3−5] was represented by the observation that synthetically useful ligand exchange processes, as a general rule, required Grignard reagents, instead of organolithium compounds. Under these particular conditions, the reactions could be driven toward a complete displacement of a carbanionic leaving group, with limited amounts of side products and full stereochemical control.

With this background, we assumed that benzyl *p*-bromophenyl sulfoxide **1**[7] could be a feasible substrate on which two different carbanionic leaving groups could be sequentially substituted. Indeed, in preliminary experiments, we observed that the reaction of **1** with 1.5 equiv of alkyl Grignard reagent in THF at room temperature caused the displacement of only the benzyl group, yielding the alkyl *p*-bromophenyl sulfoxide, without the displacement of the *p*-bromophenyl moiety (Scheme 4).

Since we had already shown that alkyl *p*-bromophenyl sulfoxides could be also subjected to a stereocontrolled reaction with alkyl Grignard reagents to displace the *p*-bromophenyl moiety,[4,5] we inferred that **1** could be a substrate especially suitable for obtaining dialkyl sulfoxides by a two-step substitution procedure. At this point we had to face the production of **1** through an enantioselective oxidation of the benzyl *p*-bromophenyl sulfide.

Oxidation of Benzyl *p*-Bromophenyl Sulfide. Synthetic, Mechanistic, and Stereochemical Aspects. Among the various types of enantioselective oxidation of sulfides,[8] we focused our attention on the reaction with hydroperoxides in the presence of a catalytic amount of chiral titanium complexes, a procedure originally introduced by Modena et al.[9] and by Kagan et al.[10] Summing up the information now available on this process, we can distinguish two main classes of reactions:

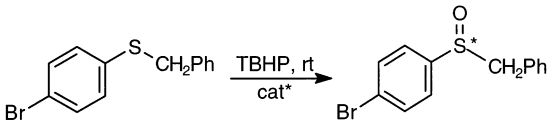
(A) The sulfoxide is produced in high enantiomeric purity with the formation of only low amounts of the corresponding sulfone. Examples of these truly enantioselective oxidations were described by Modena,[9] Kagan,[10] Bolm,[11] and their co-workers, and by us.[3b]

(B) High amounts of sulfone are produced in the oxidation process. Examples of these processes were reported by Uemura[12] and Imamoto.[13] The oxidation with a chiral hydroperoxide, reported by Adam,[14] was also accompanied by a large quantity of sulfone. In these papers, it was proved that a kinetic resolution process occurred during the oxidation of the sulfoxide to sulfone, with the enrichment of the enantiomeric purity of the remaining sulfoxide. High levels of sulfone were required in order to recover a sulfoxide with high enantiomeric purity. As a consequence of this overoxidation, the isolated yield of sulfoxide could not be high.

Keeping in mind this mechanistic dichotomy, we undertook the series of oxidation experiments reported in Table 1, with the aim of obtaining the sulfoxide **1**, possibly through a reaction following the type-A mechanism. At the outset, we oxidized benzyl *p*-bromophenyl sulfide with *tert*-butyl hydroperoxide (TBHP) in the presence of a complex between Ti(O-*i*-Pr)$_4$, water and (*R*)-1,1′-bi-2-naphthol (BINOL) as a chiral ligand (Table 1, entries 1−4), at room temperature according to our previously reported procedure,[3b] which works particularly well in the oxidation of (alkylthio)- or (arylthio)methylphosphonates. In contrast with the results obtained with these substrates, after 29 h, we obtained the benzyl *p*-bromophenyl sulfoxide **1** in high ee (up to 95%), but in low isolated yield (34%), due to the formation of a large amount of sulfone (Table 1, entry 1). On the other hand, decreasing the reaction time led to low amounts of sulfone, but the corresponding sulfoxide was produced in low ee (Table 1, entry 2). Furthermore, we found a depletion of ee upon changing the solvent from carbon

(6) Durst, T.; LeBelle, M. J.; Van Der Elzen, R.; Tin, K.-C. *Can. J. Chem.* **1974**, *52*, 761−766.
(7) Degani, J.; Tiecco, M.; Tundo, A. *Gazz. Chim. Ital.* **1962**, *92*, 1213−1220.
(8) Bolm, C.; Muñiz, K.; Hildebrand, J. P. Oxidations of Sulfides. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 697−710.
(9) Bortolini, O.; Di Furia, F.; Licini, G.; Modena, G.; Rossi, M. *Tetrahedron Lett.* **1986**, *27*, 6257−6260. Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325−327.
(10) Brunel, J. M.; Kagan, H. B. *Synlett* **1996**, 404−406. Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135−5144. Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188−8193.
(11) Bolm, C.; Dabard, O. A. G. *Synlett* **1999**, 360−362.
(12) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 7624−7626. Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529−4533.
(13) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1997**, *62*, 8560−8564.
(14) Adam, W.; Korb, M. N.; Roschmann, K. J.; Saha-Möller, C. R. *J. Org. Chem.* **1998**, *63*, 3423−3428.

TABLE 1. Enantioselective Oxidation of Benzyl *p*-Bromophenyl Sulfide by Hydroperoxides in the Presence of Chiral Titanium Catalysts



(*R*)- or (*S*)-**1**

Molar ratio Ti(O-*i*-Pr)$_4$:chiral ligand:substrate: oxidant 1:2:40:44

entry	ligand	water[a]	solvent	oxidant	time (h)	yield[b] (%)	ee[c] (%) (config)
1	(*R*)-BINOL	0.5	CCl_4	TBHP	29	34	95 (*R*)
2	(*R*)-BINOL	0.5	CCl_4	TBHP	6	42	46 (*R*)
3	(*R*)-BINOL	0.5	CH_2Cl_2	TBHP	24	33	47 (*R*)
4	(*R*)-BINOL	0	CCl_4	TBHP	22	69	0
5[d]	(*R*,*R*)-DET	0	CH_2Cl_2	CHP	22	46	58 (*R*)
6	(*S*,*S*)-HB	0.5	CCl_4	TBHP	13	63	96 (*R*)
7	(*S*,*S*)-HB	0.5	CH_2Cl_2	TBHP	22	76	73 (*R*)
8	(*S*,*S*)-HB	0.5	toluene	TBHP	84	74	89 (*R*)
9	(*S*,*S*)-HB	0.5	*n*-hexane	TBHP	72	81[e]	>98 (*R*)
10	(*S*,*S*)-HB	0	CCl_4	TBHP	17	77	>98 (*R*)
11	(*S*,*S*)-HB	0	*n*-hexane	TBHP	48	85[f]	>98 (*R*)
12	(*R*,*R*)-HB	0	*n*-hexane	TBHP	48	84	>98 (*S*)
13	5 (*S*,*S*)-HB + 1 (*R*,*R*)-HB	0	*n*-hexane	TBHP	48	63	88 (*R*)
14	3 (*S*,*S*)-HB + 1 (*R*,*R*)-HB	0	*n*-hexane	TBHP	49	71	69 (*R*)
15	2 (*S*,*S*)-HB + 1 (*R*,*R*)-HB	0	*n*-hexane	TBHP	48	66	48 (*R*)
16	(*R*,*S*)-HB	0	*n*-hexane	TBHP	48	45[g]	- -
17	1 (*S*,*S*)-HB + 1 (*R*,*S*)-HB	0	*n*-hexane	TBHP	72	51[h]	58 (*R*)

[a] Water/sulfide molar ratio. [b] Yields refer to pure isolated sulfoxide **1**. [c] Determined by HPLC (see text). [d] Reagents ratio: Ti(O-*i*-Pr)$_4$: DET: *i*-Pr$_2$NEt: substrate: oxidant 3:6:3:10:9.5. Reaction temperature for this entry −20 °C. [e] Isolated sulfone 7%. [f] Isolated sulfone 5%. [g] Isolated sulfone 31%. [h] Isolated sulfone 28%.

tetrachloride to methylene chloride (Table 1, entry 3), and a racemic sulfoxide was obtained when no water was added (Table 1, entry 4). All these aspects showed a close similarity with the results reported by others[12] for a type-B enantioselective oxidation with the same chiral ligand, even if different reaction conditions were used. Thus, considering all the results obtained with BINOL as a chiral ligand, only the experiment of entry 1 appeared to be of some synthetic interest, which increased significantly when we found that the product **1** having a 95% ee could be easily recrystallized to yield the enantiomerically pure compound.

The absolute configuration of **1** was determined with NMR techniques, by adding (*R*)-(methoxy)phenylacetic acid, and analyzing the pattern of the methylene signals of an enantiomerically enriched mixture.[5] The configuration of the enantiomer, which was obtained in the reaction with the (*R*)-BINOL as a chiral ligand, was found to be (*R*).

Then, we investigated the oxidation of the same sulfide with cumene hydroperoxide (CHP) in the presence of a complex between Ti(O-*i*-Pr)$_4$ and (+)-diethyl tartrate (DET) in several reaction conditions. The best results (Table 1, entry 5, 46% yield, 58% ee) were obtained in conditions similar to those reported in a recent paper.[15] Ti(O-*i*-Pr)$_4$, DET and the sulfide were heated to 40 °C and then the mixture was cooled to −20 °C and *i*-Pr$_2$-NEt and CHP were added.

The subsequent chiral ligand tested in our investigation was represented by (*S*,*S*)- or (*R*,*R*)-1,2-diphenyl-1,2-ethanediol (stilbene diol, or hydrobenzoin, HB). This compound, which could be obtained in high enantiomeric purity by an enantioselective dihydroxylation,[16] is currently commercially available. Diols structurally related to HB had been used as ligands in a hydroperoxide oxidation of sulfide,[17] catalyzed by a stoichiometric amount of a titanium complex (55−81% yields, 43−84% ee). Recently, Rosini et al.[18] have reported an enantioselective TBHP-oxidation of aryl alkyl sulfides in the presence of 5% of a 1:2 complex between Ti(O-*i*-Pr)$_4$ and HB (55−74% yields and 22→99% ee). The reaction was performed at 0 °C, in CCl_4 and in the presence of a large amount of water (1:1 molar ratio with the substrate). A 2:1 molar ratio of oxidant/sulfide was added, and the reaction was quenched after 2 h, to prevent overoxidation of both the sulfide and the chiral ligand. This system was used also to oxidize benzyl aryl sulfide (aryl = phenyl, *p*-tolyl, *p*-anisyl, 60−73% yields; 92→99% ee).

In our experiments, we used a 2.5% molar ratio of a 1:2 catalyst prepared from Ti(O-*i*-Pr)$_4$ and HB, in the presence of water. The substrate was in a 2:1 molar ratio in respect to water and 1.1 to 1 molar ratio in respect to the oxidant. After 13 h at room temperature, using CCl_4 as solvent, **1** was obtained in moderate yields and in high enantiomeric excess (96% ee, Table 1, entry 6).

Lower enantiomeric purities (73−89% ee) were obtained when toluene or methylene chloride were employed as solvents (Table 1, entries 7 and 8), whereas the use of *n*-hexane gave the best results (Table 1, entry 9). During the reaction performed in this solvent, a white crystalline solid was observed to separate. After 3 days at room temperature, the white solid, collected and analyzed, was found to be enantiopure **1**, with a small

(15) Cotton, H.; Elebring, T.; Larsson, M.; Li, L.; Sorensen. H.; von Unge, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3819−3825.

(16) McKee, B. H.; Gilheany, D. G.; Sharpless, K. B. *Org. Synth.* **1991**, *70*, 47−53.

(17) Yamamoto, K.; Ando, H.; Shuetake, T.; Chikamatsu, H. *J. Chem. Soc., Chem. Commun.* **1989**, 754−755.

(18) Donnoli, M. I.; Superchi, S.; Rosini, C. *J. Org. Chem.* **1998**, *63*, 9392−9395.

amount of sulfone. A simple recrystallization (ethanol) yielded the desired compound in high yield (81%). Also for these reactions, when the (*S*,*S*)-HB was used as a chiral ligand, the absolute configuration of **1** was found to be (*R*). Surprisingly, the addition of water, whose role was crucial in almost every oxidation procedures of sulfides,[3b,9−12] did not affect the enantioselectivity of our reaction with HB as a chiral ligand. Indeed, similar high enantiomeric purities were obtained both in the presence or in the absence of water (Table 1, entries 6, 9−11). Since Rosini et al.[18] had demonstrated the need for water in the oxidation of methyl *p*-tolyl sulfide in the presence of a Ti(O-*i*-Pr)$_4$/HB complex, a different mechanism should be considered operating in the oxidation leading to **1**. The reaction in *n*-hexane was also used for the oxidation of 25 g of benzyl *p*-bromophenyl sulfide (see Experimental Section). A 24.06 g amount of white solid precipitated from the reaction mixture. After a recrystallization (ethanol), 22.5 g (85% yield) of enantiopure **1** could be obtained. No particular difficulty should arise performing the oxidation on a larger scale.

The oxidation procedure was tested also with (*R*,*R*)-HB (entry 12). Also in this case, a white solid precipitated, which, after recrystallization, yielded (*S*)-**1** having the usual high ee values (>98%).

We are inclined to consider that this process is a type-A oxidation. Such a conclusion is based first of all upon the fact that the amount of sulfone produced was rather small (5−7%). Furthermore, when the white solid obtained during the reaction performed in *n*-hexane was analyzed at the early stages of oxidation (4 h), it was found to present already a high enantiomeric purity (ee 93%). This observation suggests that mainly the direct oxidation of the sulfide is the responsible for the high degree of enantioselectivity, whereas the kinetic resolution in the subsequent oxidation of the sulfoxide to sulfone, if any, plays a minor role.

In an attempt to gain further insight into the mechanism, the formation of the titanium complexes in the enantioselective oxidation reactions was also monitored by ^{1}H NMR. In this respect, it is worth noting that, when the spectra of the catalyst used in the Kagan−Modena oxidation had been recorded,[19] several signals were detected, which could be associated to a large number of different titanium/diethyl tartrate species in solution. Our NMR analysis was conducted by performing the reaction in CCl_4. A sample of the reaction mixture was taken, C_6D_6 (0.1 mL) was added as an internal reference, and ^{1}H NMR spectra of the resulting mixture were recorded. When the Ti(O-*i*-Pr)$_4$/BINOL catalyst was used, the NMR spectra revealed the presence of a dominant complex among the others, but some signals had a different chemical shift depending upon the presence or the absence of water. These spectra could suggest that different catalytic species were operating in the two cases. On the other hand, when the complex between Ti(O-*i*-Pr)$_4$ and HB was used, the spectra were simple and sharp. The signals of the isopropoxy moiety shifted upfield, as in free 2-propanol, whereas the HB signals moved downfield with respect to the signals of the free HB. The presence or absence of water had no significant effect on the chemical shift of the above signals. This result could suggest a catalytic species with the HB directly bound to the metallic center and without any significant participation of water molecules.

From a mechanistic point of view, nonlinear effects (NLEs) connecting the enantiomeric purity of the chiral ligands and the enantiomeric purity of the products have been also considered important.[20] For example, the oxidation with formation of high amounts of sulfone was characterized by a positive NLE,[12] i.e. asymmetric amplification, whereas Modena oxidation had a negative NLE,[20] i.e. an asymmetric depletion. On the other hand, the Kagan procedures showed mainly a negative or a negligible NLE, but also cases of slightly positive values were observed, due to the different ways of producing the catalyst.[20]

In the TBHP-oxidation of benzyl *p*-bromophenyl sulfide in the presence of the complex Ti(O-*i*-Pr)$_4$/HB, we found a positive NLE (Table 1, entries 13−15) after 2 days. Indeed, HB of lower enantiomeric purity could drive the formation of a sulfoxide toward higher values of enantiomeric excess.

Different results were found by using *meso*-HB, either pure or mixed with (*S*,*S*)-HB. When the reaction was performed only with *meso*-HB (Table 1, entry 16), large amounts of sulfone were produced after 2 days (31%) and racemic **1** was isolated in a 45% yield. When a 1:1 mixture of (*S*,*S*)-HB and (*R*,*S*)-HB was used, a sulfoxide of 58% ee was obtained, once again with a large amount of sulfone (isolated yield 51% for the sulfoxide **1** and 28% for the corresponding sulfone, Table 1, entry 17). In contrast with the results of entry 11, in these conditions, the ee of the sulfoxide was found to increase during the reaction. The values observed were 8% after 3 h and 17% after 6 h. The final value (51%) was measured after 3 days. The high amount of sulfone and the evolution of the ee during the reaction time suggest that a kinetic resolution step is also operating as a consequence of the addition of the *meso*-ligand.

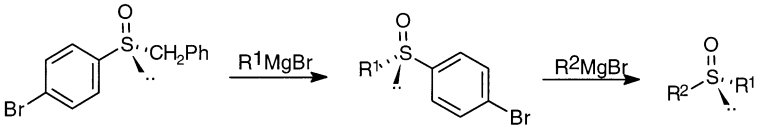
On the basis of the results presented above, we can conclude that using (*S*,*S*)- or (*R*,*R*)-HB as a chiral ligand, in conditions largely different from those reported by others,[18] high ee values and high yields can be obtained in the production of **1**. Furthermore, the mechanistically important conclusion that can be reached is that the enantioselection is only due to the sulfoxide oxidation step, without any significant contribution of the kinetic resolution of the resulting sulfoxide. However, the latter process appears always impending, as shown by the significant changes observed upon addition of *meso*-HB. Undoubtedly, further work is required to better clarify the various factors influencing the two mechanisms, including the role of the water and the significance of the sign of the NLE. However, due to the main aim of the present work, i.e. the synthesis of dialkyl sulfoxides from a general precursor, for the moment it was not considered of interest to expand further the mechanistic study.

Reaction between Benzyl *p*-Bromophenyl Sulfoxide (1) and Grignard Reagents. The substitution of the benzyl group in the benzyl *p*-bromophenyl sulfoxide

(19) Potvin, P. G.; Fieldhouse, B. G. *Tetrahedron: Asymmetry* **1999**, *10*, 1661−1672.

(20) Brunel, J.-M.; Luukas, T. O.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 1941−1946.

TABLE 2. Stereospecific Substitution of Carbanionic Leaving Groups by Grignard Reagents on Sulfinyl Compounds



1 **2-5** **6-7**

entry	substrate	R^1	R^2	solvent[a]	*T* (°C)	product[b,c]	yield (%)[d]	ee (%)[e]
1	**1** (*R*)	*n*-dodecyl		THF	−30	**4** (*S*)[c]	53	87
2	**1** (*R*)	*n*-pentyl		benzene	5	**3** (*S*)[b]	62	95
3	**1** (*R*)	ethyl		toluene	−30	**2** (*S*)[b]	67	>98
4	**1** (*R*)	*n*-pentyl		toluene	−30	**3** (*S*)[b]	69	>98
5	**1** (*R*)	*n*-dodecyl		toluene	−30	**4** (*S*)[c]	87	>98
6	**1** (*R*)	cyclohexyl		toluene	−30	**5** (*S*)[b]	70	>98
7	**3** (*S*)	*n*-pentyl	*n*-dodecyl	THF	−30	**6** (*R*)[c]	62	>98
8	**4** (*S*)	*n*-dodecyl	*n*-pentyl	THF	−30	**6** (*S*)[c]	69	>98
9	**4** (*S*)	*n*-dodecyl	*i*-propyl	THF	−30	**7** (*R*)[c]	91	>98

[a] Solvent for the substrate. Grignard reagents were prepared in THF and used in a 1.5:1 molar ratio in respect to the substrate. [b] The configuration was established by correlation with the known configuration of sulfoxides obtained in previous work. [c] Configuration attributed assuming a stereochemical outcome of inversion of configuration as found in similar cases (see text). [d] Isolated yield. [e] Determined by HPLC (see text).

1 by 1.5 equiv of *n*-dodecylmagnesium bromide in THF was found to occur with an 87% ee, even at low temperature (Table 2, entry 1). Better results were obtained in the reaction of the *n*-pentylmagnesium bromide in benzene (Table 2, entry 2). A complete stereochemical control of this carbon-for-carbon displacement was achieved performing the reaction in toluene, at −30 °C (Table 2, entry 3−6). The sulfoxides obtained from (*R*)-**1** had negative optical rotations. The absolute configurations of the sulfoxides (−)-**2** and (−)-**5** were then found to be (*S*), since (+)-**2** and (+)-**5** are known to have the (*R*)-configuration.[5] It is also worth noting that sulfoxide (+)-**3** was obtained[21] in the reaction between menthyl (*S*)-*p*-bromobenzenesulfinate and pentylmagnesium bromide, a reaction which we have shown to occur with inversion of configuration.[5] Consequently, the (*R*)-configuration could be attributed to sulfoxide (+)-**3** and the (*S*)-configuration to the counterpart (−)-**3**. The overall pattern observed is then consistent with the expected inversion of configuration in the displacement of the benzyl moiety. On the basis of such a pattern, it seems correct to attribute the (*S*)-configuration to the sulfoxide (−)-**4**.

Reactions between Alkyl *p*-Bromophenyl Sulfoxides and Grignard Reagents. The displacement of the bromobenzene anion moiety with Grignard reagents was already described in a previous work.[4,5] However, for the sake of completeness and also with the aim of presenting here the full execution of the synthetic plan, in Table 2 we have added three further cases involving a primary and a secondary alkyl group, leading to **6** and **7**, respectively (Table 2, entries 7−9), to which the configuration was assigned on the basis of previous work.[5] Both enantiomers of **6** were obtained by choosing the suitable sequence of substitution (Table 2, entries 7 and 8).

Conclusion

In the present work, we have shown that benzyl *p*-bromophenyl sulfoxide can act as a general precursor of dialkyl sulfoxides through a two carbon-for-carbon substitution sequence. The starting compound can be easily obtained in an optically pure form and on a multigram scale by an enantioselective oxidation followed by a simple crystallization. The method compares very favorably with other procedures since it offers the advantage of the high enantioselectivity of the steps upon which it is based without presenting any problem connected with separations of stereoisomers. A parallel outcome of our investigation is represented by a series of observations which are of relevance for the mechanistic picture of the oxidation process occurring in the first step of the procedure.

Experimental Section

The purified reaction products were characterized by their ^{1}H and ^{13}C NMR spectra, recorded in $CDCl_3$ at 500 and 125 MHz, respectively, and their mass spectra were determined by GC/MS analysis (70 eV), when they did not decompose. The ee values of the sulfoxides were determined by HPLC (Chiralcel OB-H or OD-H).

Synthesis of Benzyl *p*-Bromophenyl Sulfoxide (1) by Enantioselective Oxidation of Benzyl *p*-Bromophenyl Sulfide with *tert*-Butyl Hydroperoxide in the Presence of a Ti Catalyst (general procedure). A solution of Ti(O-*i*-Pr)$_4$ (7.7 mg, 0.027 mmol) in 4 mL of the specified solvent was added to a solution of the ligand (0.054 mmol) in 8 mL of the solvent under a nitrogen atmosphere. If present, water (0.54 mmol) was added at this stage. The mixture was stirred for 1 h at room temperature. Benzyl *p*-bromophenyl sulfide (0.3 g, 1.07 mmol) was then added, and the mixture was stirred for 30 min. After this time, 0.15 mL of a commercial 80% solution of *tert*-butyl hydroperoxide (1.18 mmol) was added, and the stirring was continued for the time specified in the Table. Then, the solvent was removed in vacuo, and the evaporated mixture was subjected to column chromatography (eluent ethyl acetate/petroleum ether 3:7) to yield benzyl *p*-bromophenyl sulfoxide **1**.

(*R*)-Benzyl *p*-bromophenyl sulfoxide (1): mp 170−172 °C (ethanol) (lit.[7] mp 141−142 for racemic **1**). $[\alpha]_D = +79.2$ (*c* = 1, $CHCl_3$). **(*S*)-Benzyl *p*-bromophenyl sulfoxide 1**: mp 170−172 °C (ethanol). $[\alpha]_D = -80.0$ (*c* = 1.6, $CHCl_3$). The ee value was measured by HPLC (Chiralcel OD-H, hexane/2-propanol 90:10).

Large Scale Preparation of (*R*)-Benzyl *p*-Bromophenyl Sulfoxide (1). A solution of Ti(O-*i*-Pr)$_4$ (0.64 g, 2.25

(21) Nishide, K.; Nakayama, A.; Kusumoto, T.; Hiyama, T.; Takehara, S.; Shoji, T.; Osawa, M.; Kuriyama, T.; Nakamura, K.; Fujisawa, T. *Chem. Lett.* **1990**, 623−626.

mmol) in 30 mL of *n*-hexane was added to a solution of (*S*,*S*)-hydrobenzoin (0.963 g, 4.5 mmol) in 130 mL of *n*-hexane. The mixture was stirred for 1 h at room temperature, under a nitrogen atmosphere. Benzyl *p*-bromophenyl sulfide (25 g, 89.54 mmol) was then added, and the stirring was continued for 30 min. The mixture was diluted with additional 230 mL of *n*-hexane. At this stage, 12.5 mL of a commercial 80% solution of *tert*-butyl hydroperoxide was added. The mixture was stirred at room temperature for 48 h, and after this time, it was subjected to centrifugation to recover 24.06 g of a precipitated white solid. The solid collected by centrifugation was crystallized (ethanol), obtaining 22.5 g of pure **1** (85% yield, >98% ee).

Reaction of Alkyl Grignard Reagents with (*R*)-Benzyl *p*-Bromophenyl Sulfoxide (1). A solution of 6.3 mmol of Grignard reagent in THF was dropped into a solution of 4.2 mmol of **1** in 25 mL of toluene at −30 °C and under N_2. After 1.5 h, the reaction mixture was quenched with a saturated solution of NH_4Cl. The usual workup yielded a residue which was purified by column chromatography and crystallization (hexane).

(*S*)-*p*-Bromophenyl ethyl sulfoxide (2): mp 53−54 °C (hexane) (lit.[5] 53−55 °C). $[\alpha]_D = -162.1$ ($c = 1$, $CHCl_3$) (lit.[5] $[\alpha]_D = +162.0$ ($c = 1$, $CHCl_3$) for the (*R*)-configuration). The ee value, measured by HPLC (Chiralcel OB-H, hexane/2-propanol 70:30), was >98%.

(*S*)-*p*-Bromophenyl *n*-pentyl sulfoxide (3): mp 46−48 °C (hexane) (lit.[21] 44−45 °C). $[\alpha]_D = -169.4$ ($c = 1$, $CHCl_3$) and $[\alpha]_D = -152.7$ ($c = 1$, CH_3OH) (lit.[21] $[\alpha]_D = +148$ ($c = 1.01$, CH_3OH) for a sulfoxide having the (*R*)-configuration and 98% ee, see text). The ee value, measured by HPLC (Chiralcel OB-H, hexane/2-propanol 90:10), was >98%.

(*S*)-*p*-Bromophenyl *n*-dodecyl sulfoxide (4): mp 66−68 °C (hexane). $[\alpha]_D = -109.5$ ($c = 1$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) 7.67−7.65 (m, 2 H), 7.50−7.45 (m, 2 H), 2.76 (t, J = 7.8 Hz, 2 H), 1.78−1.69 (m, 1 H), 1.63−1.53 (m, 1 H), 1.45−1.18 (m, 18 H), 0.88 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) 143.23, 132.39, 125.64, 125.29, 57.33, 31.88, 29.57, 29.48, 29.30, 29.12, 28.62, 22.66, 21.99, 14.09. Anal. Calcd for $C_{18}H_{29}BrOS$: C, 57.90; H, 7.83. Found: C, 58.26; H, 8.18. The ee value, measured by HPLC (Chiralcel OD-H, hexane/2-propanol 90:10), was >98%.

(*S*)-*p*-Bromophenyl cyclohexyl sulfoxide (5): mp = 119−121 °C (hexane) (lit.[5] 119−120 °C). $[\alpha]_D = -158.4$ ($c = 1$, $CHCl_3$) (lit.[5] $[\alpha]_D = +156.3$ ($c = 1$, $CHCl_3$) for the (*R*)-configuration). The ee value, measured by HPLC (Chiralcel OB-H, hexane/2-propanol 80:20), was >98%.

The reactions of alkyl Grignard reagents with *p*-bromophenyl *n*-dodecyl sulfoxide **4** were performed according to our previous work.[5]

***n*-Dodecyl *n*-pentyl sulfoxide (6)**: mp = 70−72 °C (pentane). $[\alpha]_D = -0.93$ ($c = 1$, $CHCl_3$) for the (*R*)-configuration). mp = 71−73 °C (pentane). $[\alpha]_D = +0.73$ ($c = 2.5$, $CHCl_3$) for the (*S*)-configuration. ^{1}H NMR (500 MHz, $CDCl_3$) 2.74−2.69 (m, 2 H), 2.67−2.59 (m, 2 H), 1.81−1.71 (m, 4 H), 1.50−1.20 (m, 22 H), 0.92 (t, J = 7.1 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) 52.40, 52.35, 31.89, 31.00, 29.59 (2 carbons), 29.52, 29.35, 29.32, 29.19, 28.87, 22.67, 22.60, 22.29 (2 carbons), 14.10, 13.82. Anal. Calcd for $C_{17}H_{36}OS$: C, 70.77; H, 12.58. Found: C, 70.35; H, 12.42. The ee value, measured by HPLC (Chiralcel OB−H, hexane/2-propanol 99:1), was >98%.

(*R*)-*n*-Dodecyl 2-propyl sulfoxide (7): mp = 54−56 °C (pentane). $[\alpha]_D = +47.5$ ($c = 1$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) 2.78 (heptet, J = 7.1 Hz, 1 H), 2.65−2.53 (m, 2 H), 1.83−1.73 (m, 2 H), 1.50−1.21 (m, 24 H), 0.88 (t, J = 6.9 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) 50.11, 48.72, 31.90, 29.59, 29.52, 29.37, 29.32, 29.22, 28.97, 22.89, 22.66, 16.09, 14.65, 14.08. Anal. Calcd for $C_{15}H_{32}OS$: C, 69.16; H, 12.38. Found: C, 69.36; H, 12.04. The ee value, measured by HPLC (Chiralcel OD-H, hexane/2-propanol 99:1), was >98%.

Acknowledgment. This work was financially supported in part by the Ministero dell'Istruzione, Università e Ricerca, Rome (National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni") and by the University of Bari.

Supporting Information Available: Additional relevant spectral data for compounds **1**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025974J