



The search for exceptions in the highly enantioselective titanium catalysed oxidation of aryl benzyl sulfides



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ABSTRACT

After the discovery of a few cases of lower enantioselectivity in the oxidation of aryl benzyl sulfides with hydroperoxides in the presence of a complex between titanium isopropoxide and (*S,S*)-hydrobenzoin, a screening of the oxidation of new substrates that are related to the structures that gave low ee values, was performed. From this screening, we confirmed that only a few sulfides remain as exceptions within a framework of exceptionally high stereoselectivity of the oxidation reaction. Moreover, the exceptions are clearly identified and are connected to particular coordinating moieties present on the aryl groups.

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1. Introduction

The synthesis of enantiopure sulfoxides, relevant intermediates in asymmetric organic synthesis and very useful in medicinal chemistry,¹ is an interesting research topic, as witnessed by the numerous recent literature papers.¹ In the past years, our work focused on different enantioselective oxidation reactions of sulfides.^{2–4} Some of the sulfoxides that were obtained with this route were also transformed into other useful sulfinyl compounds with our strategy based upon a displacement of carbanionic leaving groups, resulting in a carbon for carbon substitution.^{2–5} A large chemical library of enantiopure sulfoxides was synthesised by us by using these two strategies.⁵ Our more recent research^{6–12} has focused on the application of the asymmetric sulfide oxidation reaction with *tert*-butyl hydroperoxide as the oxidant in the presence of a catalytic amount of a 1:2 complex between titanium *i*-propoxide and (*S,S*)- or (*R,R*)-hydrobenzoin, a chiral ligand that is employed in many enantioselective processes.¹³

After the application of this oxidation protocol to the asymmetric synthesis of valuable intermediates, such as Sulindac alkyl esters,⁶ or β -keto-sulfoxides,⁷ we turned our attention to the

enantioselective oxidation of aryl benzyl sulfides.^{4,8–12} The corresponding sulfoxides were obtained with good yields (57–92%, with a single exception) and high ee values (81–>98% ee). In a favourable stereochemical framework, these high ee values can be increased with a crystallisation step, thus allowing us to obtain a large number of enantiopure aryl benzyl sulfoxides.^{8,9} This high asymmetric induction pattern is invariably obtained regardless of the presence of a variety of substituents (such as halogen atoms, methoxy, nitro, carbomethoxy and even bulky aryl or alkyl groups) on both the phenyl moieties on the starting sulfides.^{8,9} In a subsequent step of our research,^{9,10} some fluorinated aryl benzyl sulfides were oxidised with the formation of the corresponding sulfoxides always in an enantiopure form (>98% ee value) and even with higher average isolated yields (81–96%) with respect to the non-fluorinated starting materials. A theoretical calculation was able to account for the high enantioselectivity of the oxidation process, both for non-fluorinated⁸ and for fluorinated substrates.¹⁰

Surprisingly,¹⁰ after the synthesis of several enantiopure aryl benzyl sulfoxides, the oxidation of 2,3,4,5,6-pentafluorobenzyl pentafluorophenyl sulfide emerged as an exception. The ee value of the obtained sulfoxide lowered to 61% ee, whereas the isolated yield dropped to 19%.¹⁰ Nevertheless, our theoretical mechanism was able to account also for this unsatisfactory result. The rationale for this uncommon reaction path was found in a different approach mode of the sulfide to be oxidised towards the titanium complex,

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an approach that was stabilised by weak interactions involving the fluorine atoms.¹⁰

At this point, we considered it of interest to single out further exceptions of this stereochemical framework, to better define scope and limitations of the procedure. On the basis of the results of our calculations, the investigation addressed the modifications of the approach modes of the sulfide to the titanium catalyst, due, for example, to coordinating moieties present on the phenyl groups of the substrates.

We performed a first series of tests,¹¹ studying the oxidation of aminophenyl or pyridyl benzyl sulfides, i.e. aryl benzyl sulfides bearing coordinating nitrogen moieties, different from the nitro-group previously investigated.⁸ Actually, a decrease of the ee values of the produced sulfoxides was observed for the aminophenyl benzyl sulfide (43% ee value) and the 4-pyridyl benzyl sulfide (21% ee value).¹¹ Another oxidation test was performed with 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfide,¹² that is a highly halogenated substrate similar to the 2,3,4,5,6-pentafluorobenzyl pentafluorophenyl sulfide. However, in this case, the usual high yields (91 and 96%, according to different reaction conditions) of the enantiopure 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (>98% ee value) were obtained.¹²

At this point, we decided to perform a further screening of the oxidation of other aryl benzyl sulfides that could have different approach modes to the titanium catalyst, thus leading to other exceptions to the highly favourable stereochemical outcome described so far.

2. Results and discussion

2.1. Enantioselective synthesis of aryl benzyl sulfoxides

Aryl benzyl sulfides **1a**–**12a** were asymmetrically oxidised on a 1 mmol scale to the corresponding sulfoxides **1b**–**12b** with *tert*-butyl hydroperoxide in the presence of 5% of a 1:2 complex formed in situ by mixing titanium *i*-propoxide and (*S,S*)-hydrobenzoin (Table 1).

As can be deduced from the experimental section, the operating procedure of this asymmetric oxidation reaction is simple and convenient, because it is just a ‘mix-and-wait’ procedure, without utilising complicated manipulations. In this respect, it is worth mentioning that our protocol is also insensitive to the presence or

absence of small amounts of water.^{4–8} In all the oxidation reactions collected in Table 1, the corresponding sulfone is generally absent, or present in low amounts (<5%). This evidence is useful to exclude a further enrichment of the ee values through kinetic resolution during the over-oxidation of the sulfoxide to sulfone.⁹

The present research started with the oxidation of 2,3,4,5,6-pentafluorobenzyl sulfides **1a**¹⁴–**3a** that have methyl, nitro–or methoxy-groups in the *para*-position of the phenyl groups. This choice was determined by the partial similarity of these substrates with the problematic 2,3,4,5,6-pentafluorobenzyl pentafluorophenyl sulfide. However, good yields (65–84%, Table 1, entries 1–3) of the corresponding enantiopure (>98% ee) sulfoxides **1b**¹⁴–**3b** were obtained. Taking into account all the aryl 2,3,4,5,6-pentafluorobenzyl sulfides that were oxidised in the previous^{9,10,12} and in the present work, the only exception to the synthesis of an enantiopure sulfoxide remains the cited 2,3,4,5,6-pentafluorobenzyl pentafluorophenyl sulfide. A further exception, limited to the lowering of the yield, in a framework of generally high isolated yields (80–96%) can be considered the oxidation of 4-methoxyphenyl pentafluorobenzyl sulfide **3a** (Table 1, entry 3), in which the yield decreases to 65%.

A further series of oxidation was performed focusing on pentafluorophenyl sulfides **4a** and **5a** (Table 1, entries 4 and 5), in which the complete fluorination was reserved only to the aryl moiety, as occurs, for example, in the case of the very successful oxidation of simple benzyl pentafluorophenyl sulfide.¹⁰ Actually, in the oxidation of the 2,4-dichlorobenzyl pentafluorophenyl sulfide **4a**, we observed (Table 1, entry 4) only a slight decrease both of the isolated yield (72%) of sulfoxide **4b** and of the enantioselectivity of the process (88% ee value), in comparison with the very high ee values of the other reactions performed with fluorinated substrates. However, the crystallisation of sulfoxide **4b** allowed us to obtain it in an enantiopure form (>98% ee). At this point, we considered it of interest to test for the first time an iodinated sulfide as a reaction substrate. With this aim, 4-iodobenzyl pentafluorophenyl sulfide **5a** was chosen. In this case, we observed a good isolated yield (81%) of sulfoxide **5b**, but having only a 73% ee value. The crystallisation step was able to increase the ee value only to 85% (Table 1, entry 5).

The effect of the iodine atom of the benzyl phenyl group prompted us to consider other oxidation reactions of iodinated sulfides that had not been investigated previously. Therefore, we decided to test for the first time some iodinated non-fluorinated aryl benzyl sulfides. In a first run, we chose to react *p*-tolyl 4-iodobenzyl sulfide **6a**¹⁵ and 4-bromophenyl 4-iodobenzyl sulfide **7a**¹⁶ (Table 1, entries 6 and 7). Good isolated yields (84% and 95% respectively) of the corresponding sulfoxides **6b**¹⁵ and **7b**¹⁶ were obtained having the usual high enantiomeric enrichment value (95 and >98% ee respectively). Sulfoxide **6b** was also obtained in an enantiopure form after crystallisation (Table 1, entry 6). At this stage we considered it of interest to compare the results obtained for 4-bromophenyl 4-bromobenzyl sulfide **8a**¹⁶ (Table 1, entry 8). Only a slight decrease of the ee value was measured (93% ee) that was soon balanced by a crystallisation step that allowed us to obtain the enantiopure **8b**¹⁶ (Table 1, entry 8). For a better comparison, we also reported in Table 1 the oxidation of the unsubstituted benzyl phenyl sulfide **9a**,¹⁷ to give sulfoxide **9b**,¹⁸ that had not been previously oxidised with our protocol, and the oxidation of benzyl 4-bromophenyl sulfide **10a**,⁴ that was reported at the beginning of our investigation on this procedure. The inspection of the data reported in entries 6–10 of Table 1 can be considered homogeneous (84–95% isolated yields; 93–>98% ee values) upon varying the halogen atom in the *para*-position of both the aryl rings. Thus, the unusual decrease of the ee value observed for the oxidation of sulfide **5a** should be due only to a combined effect of both the iodine atom on the benzyl group and the pentafluorophenyl moiety.

Table 1

Enantioselective oxidation of aryl sulfides by TBHP in the presence of a titanium/(*S,S*)-hydrobenzoin complex

Entry	Sulfide	Ar ¹	Ar ²	Sulfoxide	Yield % ^a	ee (%) ^b
1	1a	4-Me-C ₆ H ₄	C ₆ F ₅	(<i>R</i>)- 1b	84	>98
2	2a	4-O ₂ N-C ₆ H ₄	C ₆ F ₅	(<i>R</i>)- 2b	80	>98
3	3a	4-MeO-C ₆ H ₄	C ₆ F ₅	(<i>R</i>)- 3b	65	>98
4	4a	C ₆ F ₅	2,4-Cl ₂ C ₆ H ₃	(<i>R</i>)- 4b	72	88 (>98) ^c
5	5a	C ₆ F ₅	4-I-C ₆ H ₄	(<i>R</i>)- 5b	81	73 (85) ^c
6	6a	4-MeC ₆ H ₄	4-I-C ₆ H ₄	(<i>R</i>)- 6b	84	95 (>98) ^c
7	7a	4-Br-C ₆ H ₄	4-I-C ₆ H ₄	(<i>R</i>)- 7b	95	>98
8	8a	4-Br-C ₆ H ₄	4-Br-C ₆ H ₄	(<i>R</i>)- 8b	80	93 (>98) ^c
9	9a	C ₆ H ₅	C ₆ H ₅	(<i>R</i>)- 9b	87	>98
10	10a	4-Br-C ₆ H ₄	C ₆ H ₅	(<i>R</i>)- 10b ^d	85 ^d	>98 ^d
11	11a	2-HOOC-C ₆ H ₄	C ₆ H ₅	(<i>R</i>)- 11b	—	—
12	12a	2-HOH ₂ C-C ₆ H ₄	C ₆ H ₅	(<i>R</i>)- 12b	74	29

^a Yields refer to pure isolated products.

^b Determined by HPLC.

^c After crystallisation.

^d Data already reported in Ref. 4.

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