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A dichotomy in the enantioselective oxidation of aryl benzyl sulfides: a

combined experimental and computational work

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Abstract. Pentafluorobenzyl pentafluorophenyl sulfide is oxidised with moderate e.e. value and a low yield by the usually highly successful oxidation protocol based upon *tert*-butyl hydroperoxide (TBHP) in the presence of a titanium/hydrobenzoin complex. This disappointing result resisted until the present work, in which the switch of the oxidation agent (from TBHP to cumene hydroperoxide), suggested by our previous computations, yielded the enantiopure sulfoxide. This valuable chiral compound was obtained in good yields (76%) without resorting to a chromatographic separation. DFT computations uncovered that this favourable reactivity was originated by a stabilizing π - π -stacking between the phenyl group of the oxidant and the pentafluorophenyl moiety of the substrate.

Keywords: titanium; sulfoxide; DFT computations; hydrobenzoin; oxidation mechanism

Introduction

The synthesis of enantiopure sulfinyl compounds is a classic topic in asymmetric synthesis,¹ since a whole class of chiral sulfoxides were obtained for the first time at the beginning of the '60's by using the Andersen-Mislow synthesis.² In the following years, the easy availability of these

compounds favoured their employment as chirality inducer in the asymmetric synthesis of many bioactive compounds,³ or as ligands in asymmetric synthesis.^{1b, 4}

Many other procedures were proposed in this last half century to overcome the limitations of the original Andersen-Mislow synthesis.¹ These procedures are usually divided into two main groups, the first one being connected with the formation of a carbon-sulphur bond, whereas the second deals with the formation of a carbon-oxygen bond.

The organometallic procedures, in which chiral sulfinyl compounds are transformed into the target sulfoxides with the aid of an organometallic reagent, belong to the first group.¹⁻² The enantioselective arylation of sulfenate anions, that stimulated a recent interest,⁵ can be collected also in this group. On the other hand, the enantioselective oxidation reactions of prochiral sulfides,¹ either with the aid of metal catalysed procedures⁶⁻⁷ or in the absence of metal catalysis,⁸ are clear examples of the second group. Moreover, also combined approach were reported, such as the displacement reaction of carbanionic leaving groups on enantiopure sulfinyl intermediates, obtained via an enantioselective oxidation.⁹

The asymmetric catalysis methods, that are preferably selected by the pharmaceutical industry because of the tolerance towards the functional groups of the target chiral bioactive sulfoxides,¹⁰ have been prevailing over the years (see, for instance, the case of the blockbuster anti-ulcer drug (S)-omeprazole¹¹). However, up to now, it has not been found a general method for the enantioselective oxidation of any sulfide, the best result being the oxidation of a specific class of similar sulfides.^{1,6-7}

During the last years, we contributed to this research with a series of papers¹²⁻¹⁹ on the enantioselective oxidation of sulfides with *tert*-butyl hydroperoxide (TBHP) in the presence of a 1:2 complex between titanium *i*-proposide and (*S*, *S*)- or (*R*, *R*)-hydrobenzoin (Chart 1, Ligand A), a cheap and commercially available ligand.²⁰





(S, S)-Hydrobenzoin (Ligand A) (Ligand B) Chart 1. Chiral ligands employed in the asymmetric oxidation of sulfides.

When applied to aryl benzyl sulfides,^{12, 15-19} this oxidation protocol was demonstrated to be very convenient. First of all, it provides the desired sulfoxides in good yields with high enantiomeric purity. The procedure is easy to perform (just a "mix and wait" at room temperature), uses cheap and easily available reactants and yields the target sulfoxide without the formation of large amounts of the corresponding sulfones (a drawback of many oxidation protocols^{1, 6}). Moreover, when the e.e. values are beyond the threshold of 81-85%, the enantiopure intermediate is easily obtained by crystallization. Due to these favourable features, we have been able to build up a chemical library of more than 40 enantiopure aryl benzyl sulfoxides,¹⁹ and to investigate their crystal structures^{15, 17-19} and the circular dichroism patterns.²¹

Moreover, we contributed to the comprehension of this oxidation process with mechanistic investigations^{16, 19} and with DFT computations.^{15, 17} Our computations highlighted the importance of the weak non-covalent interactions involving aryl groups in the highly enantioselective oxygen transfer step.^{15, 17} For the sake of completeness, we must mention that other research groups, either before²²⁻²³ or after²⁴⁻²⁵ our work, employed in some instances this oxidation system, often proposing different experimental procedures.

In this very successful framework of reactivity and high enantioselectivity, the oxidation of pentafluorobenzyl pentafluorophenyl sulfide emerges as a stumbling block.¹⁷ While the oxidation of not fluorinated aryl benzyl sulfides are almost always successfully with our procedure,^{15-16, 19} and the oxidation of aryl benzyl sulfide with only one of the phenyl groups fully fluorinated provides even larger yields and ee values in comparison with the not fluorinated compounds,¹⁶⁻¹⁹ the same oxidation protocol produces a pentafluorobenzyl pentafluorophenyl sulfoxide having a 61% e.e.

value, but a yield of only 19%.¹⁷ Our theoretical model based on DFT computations provided also a rationale for this disappointing result,¹⁷ which, however, pointed out the need for a different oxidation procedure for this sulfide.

Results and discussions.

The purpose of our investigation was to find a new oxidation protocol to improve the quite unsatisfactory results (Table 1, entry 1) previously obtained in the oxidation of pentafluorobenzyl pentafluorophenyl sulfide **1a** to pentafluorobenzyl pentafluorophenyl sulfoxide **1b**.¹⁷

The oxidation process was preliminarily investigated with different procedures, such as the hydroperoxide oxidation in the presence of a titanium/tartrate complex,^{11, 26} but poor ee values were obtained. Poor enantioselectivity was obtained also by employing hydrogen peroxide in the presence of a chiral vanadium catalyst.²⁷ At this stage, we reasoned that it should be more fruitful to return to our protocol, and to change it according to hints coming from our theoretical model, that showed to be robust and reliable.

 Table 1. Enantioselective oxidation of aryl benzyl sulfide with the titanium/(S, S)

 hydrobenzoin complex.

Ar
$$\xrightarrow{S}$$
 Ar $\xrightarrow{ox, cat^*}$ $\xrightarrow{O^{\bigcirc}}$ Ar \xrightarrow{Ar} $\xrightarrow{S^{\oplus}}$ Ar

Entry	Ar	Sulfide	Oxidant	Ligand ^a	Product	Yield (%) ^b	ee (%) ^c
1	C ₆ F ₅	1a	ТВНР	Α	(<i>R</i>)-1b	19 ^d	61 ^d
2	C ₆ F ₅	1 a	TBHP	Α	(<i>R</i>)-1b	26 ^e	52 ^e
3	C ₆ F ₅	1 a	TBHP	В	(<i>R</i>)-1b	29	20
4	C ₆ H ₅	2a	СНР	Α	(<i>R</i>)-2b	46	8
5	C ₆ H ₅	2a	TBHP	Α	(<i>R</i>)- 2b	87 ^f	>98 ^f
6	C_6F_5	1 a	CHP	Α	(<i>R</i>)-1b	76	>98

cat* = 5% Ti(O-i-Pr)₄/(S, S)-hydrobenzoin

(a) $\mathbf{A} = (S, S)$ -1,2-bis-diphenyl-1,2-di-hydroxyethane (hydrobenzoin). $\mathbf{B} = (S, S)$ -1,2-bis-di-(2'-methoxyphenyl)-1,2-dihydroxyethane (see Chart 1). (b) yields refer to pure isolated products (c) Determined by chiral HPLC (see Experimental Section). (d) See ref. 17. (e) Inverse addition (see text). (f) See ref. 19.

In a first trial, we used a modification of the work-up procedure in which, after having obtained the in situ titanium/hydrobenzoin complex, the oxidant was added before the sulfide (inverse addition). In our previous work,¹⁶ we observed that this altered sequence of addition of the reactants provides better yields, but a lower enantioselectivity. This fact was confirmed also in this reaction, in which we observed (entry 2), a better yield (26%), but a lower enantioselectivity (52% ee). However, these values remain unsatisfactory. We observed that in a work on the synthesis of omeprazole-like molecule (that are indeed aryl benzyl sulfides), modified hydrobenzoin ligands were employed.²⁴ Since in our theoretical model, the CH $\cdots\pi$ interactions²⁸ play a crucial role, an increase of the electronic density of the phenyl groups of the hydrobenzoin, due for example to a methoxy group, should be beneficial. Thus, we synthesized the (S, S)-1,2-bis-di-(2'-methoxyphenyl)-1,2dihydroxyethane (Chart 1, ligand B) with an asymmetric dihydroxylation,²⁹ and we used it as a ligand of the titanium in the asymmetric oxidation of 1a (entry 3) with TBHP. We observed a modest increase of the yield (29%, Table 1), but a drop of the enantioselectivity (20% ee, entry 3). Probably, the presence of the methoxy group in the *ortho*-position of the phenyl groups of the hydrobenzoin is able to interfere with the coordination modes of the ligand.¹⁹ Another opportunity that we decided to evaluate was the variation of the oxidizing species. *tert*-Butyl hydroperoxide is a cheap and easily available oxidant, and has the special merit of leaving only *tert*-butanol, after the oxygen transfer. Other hydroperoxides were employed in the oxidation of sulfides, such as the furyl hydroperoxide,³⁰ or chiral hydroperoxides.³¹ However, these oxidants are not commercially available. Our attention was turned towards cumene hydroperoxide (CHP), a cheap and available oxidant, that had been sometimes used in previous works on sulfide oxidation in the presence of titanium complexes.²⁶ Generally speaking, CHP was considered a less performing oxidation agent in comparison with TBHP. For example, a lower enantioselectivity was obtained by us, by using our protocol, when CHP was used as the oxidant in the enantioselective oxidation of Sulindac sulfide methyl ester.¹⁴ On the other hand, a sporadic case of a better enantioselectivity was observed by Kagan *et al.* in the switch from TBHP to CHP, when some aryl methyl sulfide were asymmetrically oxidized in the presence of a complex between titanium and diethyl tartrate.²⁶

As a first test, we used CHP with a titanium/hydrobenzoin complex to oxidise benzyl phenyl sulfide **2a**, that is the simplest form of any aryl benzyl sulfide. The results were disappointing (entry 4), because we obtained a 46% yield of the sulfoxide **2b**, having a poor ee value (8%). This result is analogous to the oxidation experiment of methyl *p*-tolyl sulfide reported by other authors with the same oxidation reagents, but with a different experimental procedure.²³ This result is particularly disappointing, if it is compared with the identical oxidation performed by us¹⁹ with TBHP as the oxidant (entry 5). The enantiopure sulfoxide **2b** (>98%) was obtained with a good yield (87%), as occurred for many other aryl benzyl sulfoxides.

However, we reasoned that CHP differs from TBHP in the substitution of a methyl with a phenyl group. Since we found that the aryl groups play a crucial role in the mechanism that we proposed,^{15, 17} we decided that it was worthy to perform the oxidation of **1a** with our catalytic system, and CHP as the oxidant (entry 6). This result, even if counter-intuitive, was the turning point of this research, because we obtained (*R*)-pentafluorobenzyl pentafluorophenyl sulfoxide **1b**¹⁷ in an enantiopure form (>98% ee), but also in good yields (76%, entry 4), limiting this number only to the crystals that precipitated from *n*-hexane, as in our previous work,¹² without resorting to a chromatographic separation (see Experimental Section).

At this stage, the complementarity between the employment of CHP and TBHP in the oxidation reaction of aryl benzyl sulfide in the presence of a complex between titanium and hydrobenzoin emerges. The TBHP-protocol yielded enantiopure sulfoxides with almost every not fluorinated, or partially fluorinated, aryl benzyl sulfide. In the singular case of pentafluorobenzyl pentafluorophenyl sulfide **1a**, only the CHP-protocol, that usually gave inferior results in the previous cases, yielded the enantiopure sulfoxide **1b** in good yields.

At this stage, as in our previous work,¹⁷ we performed a DFT computational investigation which

can provide a rationale to the above discussed experimental data.

Computational Mechanistic Study. In our previous work,^{15, 17} we demonstrated that the enantioselectivity is governed by the relative energies of the two diastereomeric octahedral complexes that form when the oxidant (TBHP) is added to the initial adduct between the substrate and the $[(S,S)-hydrobenzoin]_2Ti$, before the oxygen transfer. They differ in the orientation of the substrate with respect to the metal and the oxidant and originate two distinct diastereomeric paths leading to the two sulfoxides characterized by opposite configuration of the newly formed sulphur chiral centre. The energy difference between the two complexes (simply denoted here as M and M') was rather large $(5.1 \text{ kcal mol}^{-1})$ in the presence of benzyl phenyl sulfide as substrate. The more stable and, thus, more populated species, was that (M') corresponding to the sulfide approaching orientation leading to configuration (R), *i.e.* the configuration experimentally observed. The larger stabilization of this adduct was due to the presence of stabilizing T-shaped structures³²⁻³⁴ involving the aromatic rings of the substrate and the [hydrobenzoin]₂Ti species. The two complexes became almost degenerate (the difference was only 0.4 kcal mol⁻¹) when pentafluorobenzyl pentafluorophenyl sulfide was used as a substrate and also the corresponding oxidation transition states were very close in energy.¹⁷ Thus, the two complexes were similarly populated and, since the activation barriers were very similar, the probability to follow the two diastereomeric reaction channels became comparable leading to the lower e.e. values experimentally observed.

Since the energy difference between the adducts, that anticipate the oxygen transfer transition states, was proved to be the key-factor governing the high or moderate observed enantioselectivity, we replaced in our original model-system the oxidant TBHP with CHP and we computed the structure and energy of the resulting **M** and **M'** complexes, considering as substrate either pentafluorobenzyl pentafluorophenyl sulfide or benzyl phenyl sulfide. We found that the trend of the **M/M'** energy difference in the two cases provides at least a qualitative explanation for the observed enantioselectivity.

In the case of pentafluorobenzyl pentafluorophenyl sulfide the nature of non-covalent interactions involving the aromatic rings of the adducts (π -stacking interactions) change significantly when we compare **M** to **M**'. The two complexes are schematically represented in Figure 1.



Figure 1. A schematic representation of **M'** (top-side) and **M** (bottom side) complexes involving pentafluorobenzyl pentafluorophenyl sulfide as substrate. Two different perspectives are given for **M** to show all important non-covalent interactions. Bond lengths are in ångstroms.

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In **M'** the two phenyl rings belonging to the substrate (ring **A**) and the oxidant CHP (ring **B**) lie in approximately parallel planes resulting in a typical "sandwich structure".³²⁻³⁵ Typical distances between the most effectively interacting carbon atoms of the two rings are in the range 3.51-3.75 Å, as evidenced in Figure 1, in agreement with the values computed in previous works.^{15, 17} Also, the substrate ring **A'** interacts with ring **D** of one hydrobenzoin moiety. However, in this case the two phenyl planes are displaced to give a structural arrangement that was demonstrated to provide more effective π - π stabilization.³²⁻³⁵ Furthermore, one fluorine atom of the substrate phenyl ring A' interacts with a hydrogen of the hydrobenzoin bridge (F^{...}HC distance = 2.79 Å) and the same fluorine atoms is involved in non-covalent interactions with the hydrobenzoin phenyl ring C.

In **M**, where the orientation of the substrate is reversed with respect to **M'**, the substrate is arranged in a folded conformation and the two rings A and B are too far away to give a significant stabilizing interaction (the shortest distances between fluorine atoms of ring A and the carbon atoms of ring B are 5.74 and 5.78 Å). This is the most important structural difference between the two adducts: the other interactions involving rings A', C and D do not change significantly and it is reasonable to believe that they provide in the average a similar stabilizing effect in **M** an **M'**. The overall effect of all above interactions is to make complex **M'** significantly more stable (and more populated) than **M**, and the computed energy difference (2.8 kcal mol⁻¹) significantly increases with respect to the reaction involving TBHP (only 0.4 kcal mol⁻¹). Since the two oxidation transition states, **TS** and **TS'**, are almost degenerate (the energy difference is only 0.3 kcal mol⁻¹), the probability to follow one or the other diastereomeric reaction channel is higher for the more populated intermediate **M'**. Thus, it is the equilibrium distribution of **M** and **M'** which determines the e.e. experimentally observed. A schematic energy diagram for the two diastereomeric reaction pathways (simply denoted as pro-(*R*) and pro-(*S*) reaction paths) is given in Figure 2.



Figure 2. A schematic energy diagram showing the diastereomeric reaction pathways that originate from the two complexes M and M'.

A different trend of non-covalent stabilizing interactions in the comparison between **M** and **M'** was observed for the non-fluorinated substrate (benzyl phenyl sulfide). In both **M** and **M'** the two phenyl rings A(substrate) and B(CHP) are involved in π -stacking and T-shaped interactions: typical values of carbon(A)-carbon(B) distances and hydrogen(A)-carbon(B) distances are reported in Figure 3. Similarly, interactions between phenyl ring A' and ring C can be recognized in both adducts. Even if, in general, T-shaped interactions are more stabilizing than π -stacking interactions,³²⁻³⁴ the presence of similar A-B and A'-C interactions in both **M** and **M'** reduces the energy difference between the two adducts, which becomes 1.9 kcal mol⁻¹ (it was 5.1 kcal mol⁻¹ when TBHP was used as oxidant). The two corresponding transition states (see Figure S2 in the SI file) are again almost degenerate (energy difference is 0.7 kcal mol⁻¹). Thus, the difference in the population of the two complexes decreases for the non-fluorinated substrate, with a consequent decrease of the enantiomeric excess, even if, in this particular case, it remains only on qualitative



Figure 3. A schematic representation of M' (top-side) and M (bottom side) complexes involving benzyl phenyl sulfide as substrate. Bond lengths are in ångstroms.

In summary, these computations show that the different nature of the oxidant CHP (compared to TBHP) is responsible for the increased e.e. observed with pentafluorobenzyl pentafluorophenyl sulfide. The CHP phenyl ring activates specific stabilizing π -stacking interactions with the pentafluorophenyl group only in **M'** where the two aromatic rings are arranged in a suitable relative position. This is not possible in **M** where the pentafluorobenzyl group is more distant from the CHP phenyl ring because of the methylene unit positioned between sulphur and the aromatic ring. In this case, the substrate adopts a more convenient folded conformation. Furthermore, with benzyl phenyl sulfide the presence of the CHP phenyl ring activates similar interactions in **M** and **M'** and the difference between the two intermediates becomes less pronounced.

Conclusions

The stumbling block, represented by the enantioselective oxidation of pentafluorobenzyl pentafluorophenyl sulfide in the presence of a titanium hydrobenzoin complex, was overcome. The counter-intuitive choice of a different, usually less performing oxidant (CHP) resolves the synthetic problems. The previously reported protocol, based on TBHP as oxidant, and the new one, in which TBHP was replaced by CHP, are complementary and should be used according to the sulfide that should be oxidised.

A theoretical model based on DFT computations can explain the trend of the the improvement of e.e. when TBHP is replaced by CHP as oxidant. As demonstrated in our previous work¹⁷ the enantioselectivity is dictated by the energy difference between the two diastereomeric octahedral complexes (**M** and **M'**) that form when the oxidant (CHP in the present case, TBHP in the previous work) is added to the initial adduct between the substrate and the $[(S, S)-hydrobenzoin]_2$ Ti, before the oxygen transfer.

The M/M' energy difference is in turn determined by non-covalent interactions, whose importance depends on the structural features of substrate and oxidant. In the present case, the phenyl ring of CHP is responsible for important stabilizing π -stacking interactions, which can be activated only

when the substrate pentafluorophenyl group can face the CHP phenyl ring: this occurs in complex **M'** leading to the observed configuration *R* of the sulfoxide product. When the position of the substrate is reversed (from up to down) as in complex **M** (leading to configuration (*S*)), these stabilizing π -stacking interactions disappear. The resulting energy difference computed with CHP is 2.8 kcal mol⁻¹, which is much larger than the value of 0.4 kcal mol⁻¹ computed in the presence of TBHP as oxidant.

Experimental section

Sulfides **1a** and **2a**, and sulfoxides **1b** and **2b** had been previously reported^{17,19} and fully characterised. Enantioselective oxidation of sulfides were performed according to our previous publications.¹³⁻¹⁹ The innovative CHP-oxidation is reported beneath.

Enantioselective oxidation of pentafluorobenzyl pentafluorophenyl sulfide (1a) with cumene hydroperoxide in the presence of a titanium/(*S*, *S*)-hydrobenzoin catalyst. A solution of Ti(O-*i*-Pr)₄ 99.999% (28 mg, 0.1 mmol) in 5 mL of *n*-hexane was added to a solution of finally grounded (*S*, *S*)-hydrobenzoin (43 mg, 0.2 mmol) in 10 mL of *n*-hexane under a nitrogen atmosphere. The mixture was stirred for 1 hour at room temperature. A solution of pentafluorobenzyl pentafluorophenyl sulfide¹⁷ **1a** (0.76 g, 2 mmol) in 10 mL of *n*-hexane was then added and the mixture was stirred for 30 minutes. After this time, 0.41 mL of a commercial solution of cumene hydroperoxide 80% was added and the stirring was continued for 21 hours. During this time, a white solid precipitated. 0.6 g of this solid, constituted by enantiopure sulfoxide **1b**, was filtered (76% yield). Further batch of **1b** could be obtained starting from the remaining solution, provided that the residual cumyl alcohol was preliminarily distilled with a low-pressure kugelrohr apparatus. (*R*)-Pentafluorobenzyl pentafluorophenyl sulfoxide¹⁷ **1b** (*n*-hexane/ethanol 9:1). $[\alpha]_D^{25} = + 36.9$ (*c*= 0.85, CHCl₃). The enantiopurity was checked with HPLC (Chiralcel OD-H column; *n*-hexane/*i*-propanol 7:3; 0.5 mL/min flow rate. $t_{(R)} = 23.1$ min.; $t_{(S)} = 28.0$ min; $\alpha = 1.29$). The absolute configuration had been previously attributed by CD spectra,^{17, 21c} and it follows our empirical rule,

according to which (R)-sulfoxides are obtained by our oxidation protocol, when (S, S)-hydrobenzoin was employed as a ligand of the titanium.

Computational methods. All DFT computations reported in the present paper, were carried out with the Gaussian 09 series of programs.³⁶ Since the investigated model-system involves aryl groups in the substrate and ligands, it is reasonable to believe that a reliable estimate of non-covalent interactions involving π systems (π - π stacking interactions, T-shaped interactions, H-contacts) is essential in the computation of the potential surface. Recently various new hybrid functional have been proposed for a reliable description of non-covalent interactions. In the interests of consistency with previous work we used the hybrid functional MPWB1K,³⁷ which was demonstrated to be capable of treating non-covalent interactions and medium-range correlation effects.³⁸⁻³⁹ The model-system was described with the DZVP basis,⁴⁰ which is a Local Spin Density (LSD)-optimised basis set of double-zeta quality that includes polarisation functions and is suitable to describe weak hydrogen and π interactions such as those occurring in the system investigated here. The transition vector of the various transition states was analysed by means of frequency computations.

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Supplementary data. Representation of the calculated transition states; Cartesian coordinates of the calculated intermediates.

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