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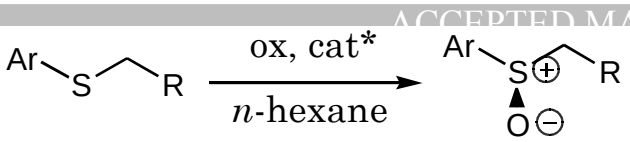

93 > 98% ee

cat* = 5% Ti(O-*i*-Pr)$_4$/(*S*, *S*)-hydrobenzoin

Ox= TBHP or CHP R= C_6F_5, $C_6H_5CH_2C(O)$

New insights into the titanium-mediated enantioselective oxidation of fluorinated aryl benzyl sulfides and aryl phenacyl sulfides.

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Keywords:

Catalysis; Sulfoxide; Circular Dichroism; Oxidation mechanism; Hydrobenzoin.

Abstract.

A fruitful switch from *tert*-butyl to cumene hydroperoxide was able to overcome a difficulty arose in the enantioselective oxidation of fluorinated aryl benzyl sulfide with hydroperoxides in the presence of a titanium/(*S*, *S*)-hydrobenzoin catalyst. New experiments show the complementarity of the old and the new protocols and indicate unequivocally the right choice leading to the corresponding highly enantioenriched sulfoxides. Moreover, in a totally unexpected way, the new protocol was able to overcome another difficulty arose in another field of research, that is the enantioselective oxidation of a fluorinated aryl phenacyl sulfide. Also in this case, the complementarity of behavior is acting. Finally, this investigation gives new support to the attribution of configuration of sulfoxides with ECD techniques, but only if the protocol outlined in our past research was followed thoroughly.

Introduction

The synthesis of enantiopure sulfoxides[1-3] is a milestone in asymmetric synthesis, because these molecules have been employed as starting materials in many synthetic strategies.[1-5] Moreover, some of them are bioactive[6] and two of them, (*S*)-omeprazole and (*R*)-modafinil, are currently sold in

large amounts as drugs.[6-9]

The progress in the asymmetric synthesis of sulfoxides[1-3] started at beginning of the '60's, when the Andersen-Mislow procedure, and all the methods deriving from it, provided for many years a secure source of some classes of enantiopure sulfoxides.[1-2] They were obtained by an enantiospecific displacement with organometallic reagents (*e.g.* a Grignard reagent) of suitable leaving groups on an *S*-resolved sulfinyl compound, thus achieving the formation of a new carbon-sulfur bond.

In a different approach, since the pioneering work of Modena and Kagan in 1984,[1-2] pro-chiral sulfides were asymmetrically oxidized to chiral sulfoxides by suitable oxidants in the presence of a chiral metal complex, in this case with the formation of a new sulfur-oxygen bond.[3]

These two strategies have represented the classical methods, until a third and different approach of forming a new carbon-sulfur bond has achieved only recently the stage of a mature technology.[10-13] In this strategy, sulfenate anions are asymmetrically arylated[10-11] in the presence of chiral metal complexes. Metal-free asymmetric arylations were also reported under phase transfer conditions[12] or in the presence of iodonium salts.[13]

Other strategies, based upon biocatalyzed transformation,[1-2] metal-free oxidation procedures[1-3] and carbanionic leaving groups displacements,[14] received less attention.

Notwithstanding this large variety of methods, the production on an industrial scale of the two most relevant enantiopure sulfoxides (the blockbuster (*S*)-omeprazole and (*R*)-modafinil)[7-9] is achieved by an enantioselective oxidation of the corresponding sulfide with hydroperoxides in the presence of the “classical” Kagan-Modena titanium/diethyl tartrate complex, according to the useful modifications introduced by the Astra-Zeneca company.[7-8]

After these modifications, this approach becomes well suited for an industrial production because: (i) titanium is a cheap and non-toxic metal; (ii) diethyl tartrate is a very cheap stereodefinite ligand; (iii) the crude reaction mixture can be treated without resorting to chromatography; (iv) non-toxic solvents can be used; (v) the reaction is performed at room temperature, or with only a moderate

heating.

On the other hand, nowadays it looks unlikely that methods that employ organometallic reagents (such as the Andersen procedure[1-2]) or expensive chiral ligands of precious metals (such as the enantioselective arylation of sulfenate anions[10-11]) can have a comparable success in industry.

Having in mind this framework, our research in the last years[15-28] has dealt with the enantioselective oxidation of sulfides with hydroperoxides in the presence of a catalytic amount of the 1:2 complex between titanium *i*-propoxide and (*S*, *S*)- or (*R*, *R*)-hydrobenzoin.[29] Hydrobenzoin is a cheap chiral ligand depicted in Figure 1.

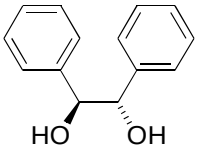


Figure 1. (*S*, *S*)-hydrobenzoin

This procedure was first reported some decades ago,[30] but systematically investigated in its many features only by our work.[15-28] Beyond the case of the asymmetric synthesis of Sulindac esters,[15] we were struck by the highly valuable results obtained studying the asymmetric synthesis of aryl phenacyl sulfoxides[16] and aryl benzyl sulfoxides with this protocol.[17-24]

The latter case is of particular relevance. Aryl benzyl sulfides were oxidized with high enantioselectivity by the oxidation system formed by *tert*-butyl hydroperoxide in the presence of a chiral titanium/hydrobenzoin complex catalyst.[17-24]

The reaction proceeds with good isolated yields (57-96%), because only traces of the corresponding sulfones were produced, if any.[17-22] This procedure faces satisfactory with the industrial oxidation based upon hydroperoxides in the presence of a titanium/diethyl tartrate protocol, because the only difference lies in the fact that enantiopure hydrobenzoin is a little more expensive than the very cheap diethyl tartrate. Similar to the titanium/diethyl tartrate procedure, our protocol also uses a cheap titanium compound as a metal catalyst; in the cases in which a large scale synthesis was investigated,[17, 22] our protocol was also optimized for a chromatography-free purification; our

protocol too does not use highly toxic solvents and is performed at room temperature; finally, our protocol has a simple work-up, just a mix-and-wait procedure.[17-23]

Tens of enantiopure (>98% ee) aryl benzyl sulfoxides were obtained by using our strategy, thus yielding a rich chemical library of chiral nonracemic molecules.[23] Some of them were also transformed into other different enantiopure sulfoxides.[17, 23] Some exceptions[21, 23] of a lower enantioselectivity were connected only to the presence on the starting sulfide of free hydroxy- or amino-groups, that should be able to alter the productive coordination of the sulfide to the titanium. However, it must be underlined that these few cases are easily predictable on the basis of our theoretical and mechanistic investigations.[17-23]

An unexpected and singular behavior of this oxidation system emerged when we tried to oxidize 2,3,4,5,6-pentafluorobenzyl 2,3,4,5,6-pentafluorophenyl sulfide, after having successfully oxidized many sulfides bearing only one pentafluorophenyl moiety.[20, 22-24] An “unusual” 61% ee (unusual, if compared with the many enantiopure products obtained during the years) was observed, together with a 19% isolated yield. This result remained a serious issue of our oxidation system, until we found that the counter-intuitive substitution of the *tert*-butyl hydroperoxide (TBHP) with cumene hydroperoxide (CHP), usually a less performing oxidant in this type of oxidation,[15, 24] yielded the enantiopure (>98% ee) pentafluorobenzyl pentafluorophenyl sulfoxide in good yields (76%) without resorting to a chromatographic separation.[24]

The whole reactivity framework was analyzed by DFT calculations.[18, 20, 24] A general mechanism, that follows the development of the experimental work-up, was designed. Five cases of different fluorinated and non-fluorinated aryl benzyl sulfides were chosen as representative items of successful and troublesome reactions, and the reaction mechanism was tested in all these situations.[18, 20, 24] DFT calculations were able to account for all the experimental results obtained so far. In the case of the successful oxidation with TBHP of non-fluorinated aryl benzyl sulfides,[18] the stereochemical pathway towards the preferred (*R*)-sulfoxide, when (*S, S*)-hydrobenzoin was used as

a chirality inducer, was due to an intermediate stabilized by CH···π interactions.[31] On the other hand, in the case of aryl benzyl sulfides bearing only one pentafluorophenyl moiety, our calculation showed[20] that, when the same chiral ligand was used, the stereochemical pathway towards the preferred (*R*)-sulfoxide was due to an intermediate stabilized by π–π interactions.[32] The case of the successful oxidation of the pentafluorobenzyl pentafluorophenyl sulfide with CHP was peculiar,[24] because our calculations proposed that the route to the (*R*)-sulfoxide was stabilized by the interactions involving the two π-systems of the pentafluorophenyl groups of the sulfide, the first interacting with one phenyl group of one hydrobenzoin, and the other with the phenyl group of the CHP. In Figure 2, the crucial oxygen transfer from CHP to the pentafluorobenzyl pentafluorophenyl sulfide with the formation of the (*R*)-sulfoxide is sketched.

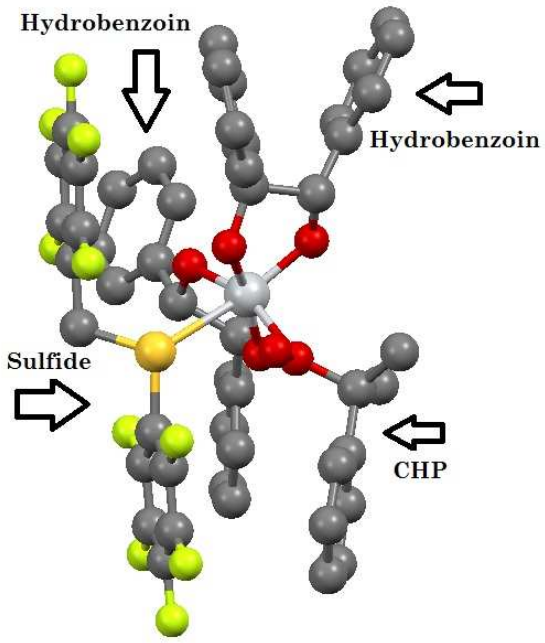


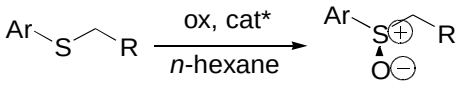
Figure 2. DFT calculated reaction pathway for the oxygen transfer around the chiral titanium complex from CHP to the pentafluorobenzyl pentafluorophenyl sulfide **1a** with the formation of sulfoxide **1b**.

At this point, with the support of our calculations for the reaction mechanism, we considered of interest to examine in more details the new CHP-based oxidation to evaluate new opportunities that this protocol can provide.

Results and Discussion

Having in mind the mechanism outlined in Figure 2, we organized the following experimental work on the enantioselective oxidation of aryl sulfides with hydroperoxides, in the presence of catalytic amounts (5%) of a complex between titanium and (*S*, *S*)-hydrobenzoin, as shown in Table 1.

Table 1. Enantioselective oxidation of aryl benzyl or phenacyl sulfides.



cat* = 5% $Ti(O\text{-}i\text{-}Pr)_4$/(*S*, *S*)-hydrobenzoin

Entry	Ar	R	Sulfide	Oxidant	Product	Yield (%)[a]	ee (%)[b]
1 [c]	C_6F_5	C_6F_5	**1a**	TBHP	(*R*)-**1b**	19	61
2 [c]	C_6F_5	C_6F_5	**1a**	CHP	(*R*)-**1b**	76 [d]	>98
3	4-H-C_6F_4	C_6F_5	**2a**	TBHP	(*R*)-**2b**	16	36
4	4-H-C_6F_4	C_6F_5	**2a**	CHP	(*R*)-**2b**	79	>98
5	C_6Cl_5	C_6F_5	**3a** [e]	TBHP	(*R*)-**3b**	-- [f]	
6	C_6Cl_5	C_6F_5	**3a** [e]	CHP	(*R*)-**3b**	51	93 (>98) [g]
7 [h]	2,4-$Cl_2C_6H_3$	C_6F_5	**4a**	TBHP	(*R*)-**4b**	91	>98
8	2,6-$Cl_2C_6H_3$	C_6F_5	**5a**	TBHP	(*R*)-**5b**	-- [f]	
9	2,6-$Cl_2C_6H_3$	C_6F_5	**5a**	CHP	(*R*)-**5b**	33	89
10 [i]	C_6F_5	C_6H_5-C(O)	**6a**	TBHP	(*R*)-**6b**	20	60
11	C_6F_5	C_6H_5-C(O)	**6a**	CHP	(*R*)-**6b**	58 [d]	>98
12 [i]	2-F-C_6H_4	C_6H_5-C(O)	**7a**	TBHP	(*R*)-**7b**	88	>98
13	2-F-C_6H_4	C_6H_5-C(O)	**7a**	CHP	(*R*)-**7b**	84	33
14	2,4-$Cl_2C_6H_3$	C_6H_5-C(O)	**8a**	TBHP	(*R*)-**8b**	80 [d]	>98
15	2,4-$Cl_2C_6H_3$	C_6H_5-C(O)	**8a**	CHP	(*R*)-**8b**	83 [d]	57

[a] Yields refer to pure isolated products. [b] Determined by HPLC (see text). [c] Data already reported in ref. 24. [d] Yield refer only to the precipitated product. Further batch of sulfoxide can be obtained by chromatography of the mother liquor. [e] 10% of carbon tetrachloride was added to the *n*-hexane to improve the solubility of the mixture. [f] Analysis of the crude reaction mixture revealed too low amounts of sulfoxide (<10%) to undertake a worthy separation. The reaction was not investigated further. [g] After crystallization. [h] Data already reported in ref. 22. [i] Data already reported in ref. 28.

For the sake of the clarity, in Table 1, some previous results were added to those obtained in the present work. The present research moved from the observation that the 2,3,4,5,6-pentafluorobenzyl 2,3,4,5,6-pentafluorophenyl sulfide **1a** was oxidized (Table 1, entry 1) by TBHP in the presence of

the complex between titanium and (*S*, *S*)-hydrobenzoin with lower yields (19%) and with lower ee values (61%) in comparison with other fluorinated aryl benzyl sulfoxides that were obtained in an enantiopure form.[20, 24] On the other hand, the fruitful switch to CHP as the oxidant agent with the same chiral complex in the same reaction conditions yielded the enantiopure (*R*)-**1b** in good isolated yields (76%, Table 1, entry 2).[24]

The DFT calculated mechanism of the successful CHP oxidation of sulfides in the presence of the titanium/hydrobenzoin complex requires the presence of two pentafluorophenyl groups on the sulfide to be oxidized.[24] Thus, we reasoned that the analogous 2,3,4,5,6-pentafluorobenzyl 2,3,5,6-tetrafluorophenyl sulfide **2a**, in which there is only a substitution of the fluorine in the *para*-position of the pentafluorophenyl group with one hydrogen atom, should behave in the same manner of sulfide **1a**. Actually, a low yield and a low ee value were obtained when sulfide **2a** was oxidized with TBHP (Table 1, entry 3) in the presence of the usual chiral catalyst. On the other hand (Table 1, entry 4), a decisive improvement was obtained by using CHP as the oxidant agent. A good yield (79%) and an enantiopure compound (>98% ee) were observed, in strict analogy with the results reported for sulfide **1a** (Table 1, entries 3 and 4).

At this point, we decided to investigate the oxidation of 2,3,4,5,6-pentafluorobenzyl 2,3,4,5,6-pentachlorophenyl sulfide **3a**, deriving from a substitution of the pentafluorophenyl with a pentachlorophenyl group (Table 1, entries 5 and 6). In principle, the nature of electron-poor aryl group was maintained after this substitution. However, in our calculated mechanism,[24] some fluorine atoms contribute to establish further weak stabilizing interactions, and their substitution, in principle, could not be innocent. From an experimental point of view, when sulfide **3a** was oxidized with TBHP in the presence of the titanium/hydrobenzoin complex (Table 1, entry 5), low amounts of sulfoxide **3b** were obtained (<10%), and thus we decided to avoid the purification of the reaction mixture, as an unworthy operation. On the other hand, the reaction with CHP (table 1, entry 6) yielded the corresponding sulfoxide **3b** in high enantiopurity (93% ee; >98 after the crystallization)

and in a 51% isolated yield. Even if satisfactory, this yield is lower than the values (76-79%) obtained for the fluorinated sulfoxide **1b** and **2b**. Attempts to improve this value by increasing the reaction time were not satisfactory. Actually, the substitution of the pentafluorophenyl with the pentachlorophenyl moiety causes a decrease in the performance of the oxidation system.

Along the lines of the investigation of the chlorinated sulfides, we recalled that the asymmetric catalyzed oxidation of 2,4-dichlorophenyl pentafluorobenzyl sulfide **4a** was successful with TBHP (Table 1, entry 7),[22] and thus new reaction conditions were not required. However, we decided to synthesize the 2,6-dichlorophenyl pentafluorobenzyl sulfide **5a** that has only two chlorine atoms, as sulfide **4a**, but both close to the sulfur atom to be oxidized, as in the case of the pentachlorophenyl sulfide **3a**.

Sulfide **5a** was oxidized first with TBHP in the presence of the usual titanium/hydrobenzoin catalyst (Table 1, entry 8). The behavior was similar to the case of the oxidation of sulfide **3a**, that is a very low yield of sulfoxide **5b** (that was not isolated). On the other hand, the switch of the oxidant from TBHP to CHP was successful also in this case (table 1, entry 9). The sulfoxide **5b** was obtained in high enantiomeric purity (89% ee), even if the isolated yield was not so high (33%), due to the large amounts of unreacted sulfide **5a** that were collected after the reaction.

In summary, the dichotomy of behavior (successful with an oxidant; unsuccessful with the other one) in the asymmetric oxidation in the presence of the titanium/hydrobenzoin complex was maintained also in the cases shown in Table 1, entries 1-9. CHP was a better oxidant in the prototype case of pentafluorobenzyl pentafluorophenyl sulfide **1a**, in the case of the analogous **2a** and, to a certain extent, also in the case of the chlorinated **3a**. When only two chlorine atoms are present, as in the case of sulfides **4a** and **5a**, only when these atoms are close to the sulfur atom, as in **5a**, CHP is a better oxidant. Otherwise, as it occurs in **4a**, the usual highly successful TBHP-oxidation must be recommended.

At this point, in the analysis of results that were not satisfactory when TBHP was used as the oxidant, we were struck by a special and recent case in the oxidation of a fluorinated aryl phenacyl sulfide.[28] In a previous work,[16] we reported that TBHP in the presence of a complex between titanium and (*S, S*)-hydrobenzoin is highly successful also in the asymmetric oxidation of aryl phenacyl sulfides (91->98% ee values). However, when pentafluophenyl phenacyl sulfide **6a** was oxidized, a 20% yield with "only" a 60% ee value was obtained for the sulfoxide **6b** (Table 1, entry 10).[28] These values are singularly similar with the results reported in Table 1, entry 1, for the TBHP-oxidation of the pentafluorobenzyl pentafluorophenyl sulfide **1a**.

This result looks to be a mere coincidence. Even if a mechanism for the enantioselective oxidation of aryl phenacyl sulfides with hydroperoxides in the presence of a titanium/hydrobenzoin catalyst has not been designed, it is reasonable to believe that the presence of the carbonyl oxygen atom in these substrates should arrange the acting molecules around the chiral titanium catalyst in a way that is different with respect to aryl benzyl sulfides, that lacks the coordinating carbonyl moiety.

However, we decided to test also the enantioselective oxidation of the pentafluorophenyl phenacyl sulfide **6a** with CHP in the presence of the usual titanium/hydrobenzoin catalyst (Table 1, entry 11). With our gratification, also this reaction provided the enantiopure phenacyl sulfoxide **6b** (>98% ee) in satisfactory yields (58%). Thus, in an unexpected way, we added another item to the list of sulfides for which it is possible to return to the usual trend of high enantioselectivity by switching from the most successful TBHP to the less usual CHP.

We investigated other aryl phenacyl sulfides to gain more insight into this oxidation. The enantioselective oxidation of 2-fluorophenyl phenacyl sulfide **7a** with TBHP in the presence of the titanium/hydrobenzoin complex (Table 1, entry 12) yielded the enantiopure sulfoxide **7b** in good isolated yields (88%), as reported previously.[28] At this stage, we decided to perform the same reaction using CHP as the oxidant agent. We observed a slight decrease of the yield (Table 1, entry 13), but a critical decrease of the ee value (33%). This system behaves as the large majority of the

aryl benzyl sulfides, for which TBHP was the high performing oxidant, and CHP was successful only in the cases underlined in this paper.

Along these lines, we decided to complete our investigation by analyzing the case of 2,4-diclorophenyl phenacyl sulfide **8a**, in analogy with the results reported in entry 7. The analogous sulfide, as shown in Table 1, is successfully oxidized with TBHP in the presence of the titanium/hydrobenzoin complex and the same holds true also in this case.[22] The enantiopure (>98% ee) 2,4-dichlorophenyl phenacyl sulfoxide **8b** was obtained with TBHP in good yields (Table 1, entry 14). It was interesting to compare the behavior of CHP as the oxidant agent in this type of reaction (Table 1, entry 15). The isolated yield of the sulfoxide **8b** was good (83%) and similar to the values obtained with TBHP, but the ee values were lower (57%, table 1, entry 15). The combined values of yield and enantioselectivity points towards a reaction that is not so negative, as it occurs in the CHP-reaction reported in entry 13.

Before proceeding with other reactions, a theoretical mechanism that takes into account the past and the present experimental data about the enantioselective oxidation of aryl phenacyl sulfides with hydroperoxides should be designed and calculated, in parallel with the satisfactory DFT calculations that we performed with the different cases of aryl benzyl sulfides.

Absolute Configuration of sulfoxides. CD study

The absolute configuration of sulfoxides **1b**,[20, 24] **4b**,[22] **6b**,[28] and **7b**[28] was already established. The configuration of sulfoxides **2b**, **3b**, **5b** and **8b** was expected to be (*R*) when (*S, S*)-hydrobenzoin was employed as chiral ligand, in analogy with all previous cases. The configuration was confirmed by means of electronic circular dichroism (ECD) spectra, according to the procedure reported in our past work.[25-28] The ECD spectra of these compounds, measured in acetonitrile, are shown in Figure 3. They all feature a positive band above 250 nm and one negative band with a shoulder, or two negative bands, below 250 nm. The former band can in principle be employed to assign the absolute

configuration using the so-called empirical Mislow's rule.[33-34] We have however previously discouraged the use of this rule for perfluoro-substituted aryl sulfoxides,[25, 27] for a twofold reason: 1) the nature of the diagnostic band can be very different from a sulfoxide-centered n-π* transition which is covered by the rule;[33-34] 2) the presence of polar substituents may strongly alter the conformational distribution of these compounds which, together with the fact that various conformers are associated with very different ECD spectra, makes the overall spectra very conformation-dependent. This latter aspect is entirely neglected in the application of empirical rules. As an efficient alternative to assign absolute configurations, we found that DFT-based calculations of the ECD spectra of fluorinated aryl sulfoxides can reproduce very accurately the experimental spectra, provided that a proper functional and a continuum solvent models are employed both in the geometry optimizations and in excited-state calculations.[25-28] Computational details are reported in the Computational Section. Briefly, after a conformational search with molecular mechanics, all conformers were optimized with DFT at ωB97X-D/6-311+G(d,p) including PCM solvent model for acetonitrile, then excited state calculations were run at the CAM-B3LYP/def2-TZVP/PCM level. Boltzmann averaging of conformer spectra was accomplished using internal energies computed at MP2/6-311+G(d,p)/PCM level, which led to more satisfying results with respect to ωB97X-D energies. In fact, the agreement between experimental and calculated spectra is excellent in all cases (Figure 3). A partial exception is compound **3b**, for which the splitting of the short-wavelength negative band was not reproduced by calculations; this is likely due to the underestimation of the population of one specific conformer. In all cases, the similarity factor (SF)[35-36] between the experimental spectrum and that calculated for the (*R*)-enantiomer was > 0.9, leaving no doubt on the absolute configuration. This latter is definitely established as (*R*) for all investigated compounds. It is interesting to notice that the quality of the calculated spectra is not hampered at all by molecular flexibility. Compound **2b** has only 3 possible conformers and its SF is 0.99; conversely, compound **8b** is much more flexible and had 12 initial conformers, but the SF for

the final calculated spectrum remains as high as 0.93. This finding confirms that DFT-based calculations are completely adequate to reproduce ECD spectra of perfluorinated aromatic sulfoxides, despite the presence of significant non-bonded interactions among the various polar groups and of charge-transfer type electronic transitions.[27]

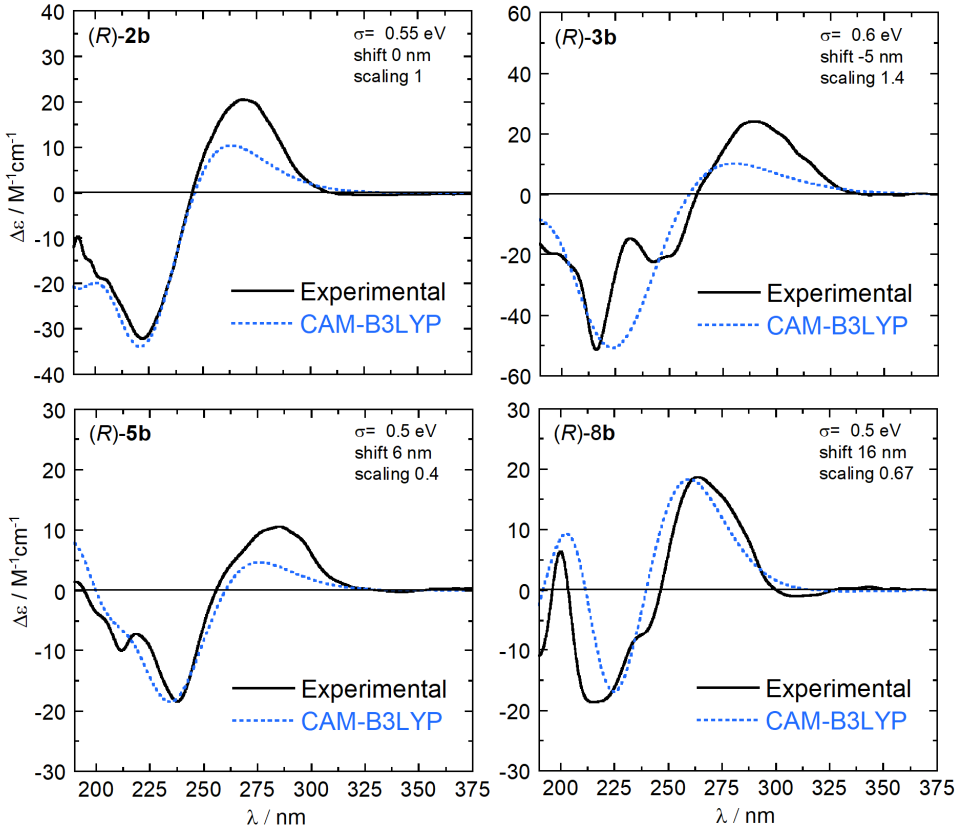


Figure 3. Comparison of experimental and calculated ECD spectra for (*R*)-sulfoxides **2b**, **3b**, **5b** and **8b**. Experimental spectra were recorded in acetonitrile solutions with concentrations ≈1-3 mM and quartz cells with 0.01 cm path length, and are not scaled for the enantiomeric excess. Calculated spectra were obtained at CAM-B3LYP/def2-TZVP/PCM//ωB97X-D/6-311+G(d,p)/ PCM level (PCM for acetonitrile), as Boltzmann averages at 300K of spectra calculated for the relevant conformers with populations estimated at MP2/6-311+G(d,p)/PCM level. Calculated spectra plotted as sums of Gaussians with exponential band-width σ, wavelength shift and scaling factor listed on each spectrum.

Conclusions

Notwithstanding the many different protocols that were reported in almost half a century for the synthesis of enantiopure sulfoxides, nowadays asymmetric oxidation of prochiral sulfides are still preferred in the industrial productions of bioactive molecules, and hardly new research based upon

expensive reagents will change this situation.

In this context, our oxidation protocol based upon hydroperoxides in the presence of a titanium/(*S*, *S*)-hydrobenzoin complex can become, in our opinion, an efficient and concrete alternative, because yields a large number of enantiopure sulfoxides with a simple procedure based upon inexpensive reagents.

As far as the present investigation is concerned, the mutually exclusive behavior of CHP and TBHP when employed as the oxidant agents of our asymmetric oxidation of sulfides, is confirmed. TBHP is almost always the successful choice, whereas CHP is usually a modest alternative. However, CHP can effectively substitute TBHP in those cases of a lower performance connected to the asymmetric oxidation of some perfluorinated sulfides, thus enlarging the already wide set of sulfoxides that can be obtained in high enantiomeric purity with this asymmetric oxidation.

The most intriguing aspect of the present investigation remains the analogy of behavior between fluorinated and not fluorinated aryl benzyl and aryl phenacyl sulfides, substrates that are clearly different, but share a common behavior when subjected to the hydroperoxide oxidation in the presence of the titanium/ hydrobenzoin catalyst.

Experimental Section

Chemicals were used as received. Elemental analyses were performed on a CHNS-O Elemental Analyzer. High resolution Mass Spectra were determined with a HPLC-QTOF spectrometer *via* direct infusion of the samples, using methanol as the elution solvent. NMR spectra were recorded on a ^{1}H-500 MHz, ^{13}C-125 MHz and ^{19}F-470 MHz spectrometer. Only absolute values of the coupling constants were reported. As far as the ^{19}F spectra are concerned, chemical shifts and coupling constant patterns were measured to be in accord with the reported values.[37] As for the ^{13}C-spectra of pentafluorophenyl bearing compounds are concerned, the $^{1}J_{CF}$ coupling constant is always reported to discriminate among overlapping signals. ECD spectra were recorded using a JASCO J-715 spectrometer in acetonitrile using a quartz cell with 0.01 cm path length.

Sulfides **1a-9a** were synthesized on a 6 mmol scale by adding the commercially available thiols to an ethanol solution of the corresponding benzyl or phenacyl bromides in the presence of potassium carbonate as the basic reagent.[28, 38] The mixture was reacted for 2 hours at room temperature. Usual work up gave a crude mixture that was purified by distillation. Usually, distilled sulfides solidify on standing.

Sulfides **1a**,[20] **4a**,[22] **6a**,[28] **7a**,[28] **8a**[39] were already reported.

2,3,4,5,6-Pentafluorobenzyl 2,3,5,6-tetrafluorophenyl sulfide (2a). Kugelrohr oven temp 90-95 °C, *p*=0.1 torr. Mp 69-70 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) 7.13 (tt, J= 9.5 Hz, J= 7.3 Hz, 1 H), 4.12 (t, J= 1.2 Hz, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$) 147.2 (dddd, $^{1}J_{CF}$ = 247 Hz, J= 13.1 Hz, J= 4.2 Hz, J= 2.1 Hz), 145.8 (dddd, $^{1}J_{CF}$ = 251 Hz, J= 15.3 Hz, J= 10.4 Hz, J= 4.8 Hz), 144.9 (dddm, $^{1}J_{CF}$ = 249 Hz, J= 15.3 Hz, J= 7.6 Hz), 140.9 (dm, $^{1}J_{CF}$ = 255 Hz), 137.4 (dm, $^{1}J_{CF}$ = 253 Hz), 112.9 (tm, J= 20.4 Hz), 111.5 (tm, J= 17.3 Hz), 107.7 (tm, J= 22.9 Hz), 25.9. ^{19}F-NMR (470 MHz, $CDCl_3$) -132.9 _-133.0 (m, 2 F), -137.3 _-137.4 (m, 2 F), -143.2 _-143.3 (m, 2 F), -153.8 (t, J= 21.6 Hz, 2 F), -161.2 _-161.4 (m, 2 F). Anal. Calcd for $C_{13}H_3F_9S$: C 43.11; H 0.83. Found C 43.15; H 0.68.

2,3,4,5,6-Pentachlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfide (**3a).** Kugelrohr oven temp 162-168 °C, *p*=0.1 torr. Mp 143-144 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) 4.15 (t, J= 1.4 Hz, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$) 145.0 (dm, $^{1}J_{CF}$ = 246 Hz), 139.3, 140.8 (dm, $^{1}J_{CF}$ = 255 Hz), 137.4 (dm, $^{1}J_{CF}$ = 252 Hz), 135.6, 132.4, 132.3, 111.5-111.1 (m), 26.1. ^{19}F-NMR (470 MHz, $CDCl_3$) -143.1 (dd, J=21.6 Hz, J=8.3 Hz, 2 F), -154.0 (dd, J=21.6 Hz, J=19.9 Hz, 1 F), 161.4 (ddd, J=21.6 Hz, J=19.9 Hz, J=8.3 Hz, 2 F). Anal. Calcd for $C_{13}H_2Cl_5F_5S$: C 33.76; H 0.44. Found C 33.78; H 0.59.

2,6-Dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfide (5a). Kugelröhr oven temp 130-135 °C, *p*=0.1 mbar. ^{1}H-NMR (500 MHz, $CDCl_3$) 7.37 (d, J= 7.8 Hz, 2 H), 7.22 (t, J= 7.8 Hz, 1 H), 4.11 (t, J= 1.2 Hz, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$) 145.0 (dm, $^{1}J_{CF}$ = 249 Hz), 142.2, 140.5 (dm, $^{1}J_{CF}$ = 254 Hz), 137.2 (dm, $^{1}J_{CF}$ = 250 Hz), 131.0, 130.4, 128.6, 112.1-111.7 (m), 25.7. ^{19}F-NMR (470 MHz, $CDCl_3$) -143.4 (dd, J=21.6 Hz, J=8.3 Hz, 2 F), -155.3 (dd, J=21.6 Hz, J=19.9 Hz, 1 F), 162.4

(ddd, J=21.6 Hz, J=19.9 Hz, J=8.3 Hz, 2 F) Anal. Calcd for $C_{13}H_5Cl_2F_5S$: C 43.48; H 1.40. Found C 43.32; H 1.37.

Racemic sulfoxides **1b-8b** were synthesized by standard mCPBA oxidation of the corresponding sulfides and were used as standard in the HPLC separation of enantiomers.

Enantioselective oxidation of sulfide (1a)-(8a) with hydroperoxides in the presence of a titanium/(*S, S*)-hydrobenzoin catalyst.

The enantioselective oxidation reactions in which TBHP was used as the oxidant follow the procedure already reported. When CHP was used as the oxidant, the following procedure is representative. A solution of Ti(O-*i*-Pr)$_4$ 99.999% (14 mg, 0.05 mmol) in 4 mL of *n*-hexane was added to a solution of (*S, S*)-hydrobenzoin (21 mg, 0.1 mmol) in 8 mL of *n*-hexane under a nitrogen atmosphere. The mixture was stirred for 1 hour at room temperature. A solution of the corresponding sulfide (1 mmol) in 8 mL of *n*-hexane was then added and the mixture was stirred for 30 minutes. After this time, 0.2 mL of a commercial solution of cumene hydroperoxide 80% was added and the stirring was continued for one day. During this time, the desired sulfoxide precipitated as a white solid. Further batch of sulfoxide could be obtained by purifying the mother liquor with chromatography. For sulfoxides **1b** and **3b**, the separation is facilitated if the residual cumyl alcohol was first distilled with a low-pressure kugelrohr apparatus.

Sulfoxides **1b**,[20, 24] **4b**,[22] **6b**[28] and **7b**[28] were already reported.

2,3,4,5,6-Pentafluorobenzyl 2,3,5,6-tetrafluorophenyl sulfoxide (2b). Mp 112-114 °C (ethanol). $[\alpha]_D^{25}$ = + 41.3 (c= 0.9, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) 7.33-7.26 (m, 1 H), 4.72-4.65 (m, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$) 145.9 (dm, $^1J_{CF}$ = 254 Hz), 145.7 (dm, $^1J_{CF}$ = 252 Hz), 144.7 (dm, $^1J_{CF}$ = 256 Hz), 141.8 (dm, $^1J_{CF}$ = 252 Hz), 137.7 (dm, $^1J_{CF}$ = 255 Hz), 122.0 (tm, J= 16.0 Hz), 110.6 (tm, J= 22.2 Hz), 103.6 (tm, J= 17.8 Hz), 47.2. ^{19}F-NMR (470 MHz, $CDCl_3$) -135.0 _-135.2 (m, 2 F), -139.6 _-139.7 (m, 2 F), -140.4 _-140.6 (m, 2 F), -150.2 (dd, J= 21.6 Hz, J= 19.9 Hz, 1 F), -159.8 _-160.0 (m, 2 F). LCMS-QTOF m/z: $[M+H]^+$ calculated for $C_{13}H_4F_9OS$ 378.9834; found

378.9822. The ee value was measured by HPLC (Column: Chiralcel OD-H. Eluent: *n*-hexane/*i*-propanol 7:3; flow rate 0.5 ml/min; t_R=16.7; t_S = 20.6; separation factor α =1.38).

2,3,4,5,6-Pentachlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (**3b).** mp 172-174 °C (*n*-hexane/acetone 4:1). $[\alpha]_D^{25}$ = +109.5 (c= 0.5, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) 4.74 (dm, J= 12.9 Hz, 1 H), 4.60 (dm, J= 12.9 Hz, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) 146.0 (dm, $^1J_{CF}$ = 247 Hz), 141.8 (dm, $^1J_{CF}$ = 257 Hz), 137.7 (dm, $^1J_{CF}$ = 254 Hz), 137.5, 137.1, 134.0, 132.7, 104.4-104.1 (m), 44.8. ^{19}F-NMR (470 MHz, $CDCl_3$) -140.3 (dd, J=21.6 Hz, J=6.6 Hz, 2 F), -150.8 (dd, J= 21.6 Hz, J= 19.9 Hz, 1 F), -160.1 _-160.3 (m, 2 F). LCMS-QTOF m/z: $[M+Na]^+$ calculated for $C_{13}H_2Cl_5F_5OS$-Na 498.8087; found 498.8070 (multiplet due to the Cl(37) atom at 500.8047, 502.8013 and 504.7985). The ee value was measured by HPLC (Column: Chiralcel OD-H. Eluent: hexane/*i*-propanol 7:3; flow rate 0.5 ml/min; t_R=15.5; t_S = 20.7; separation factor α =1.55).

(*R*)-2,6-Dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (5b). mp 160-162 °C (*tert*-BuOMe/MeCN 1:1. $[\alpha]_D^{25}$ = + 38.8 (*c*=0.3, $CHCl_3$) for a sulfoxide having a 89% ee value. ^{1}H-NMR (500 MHz, $CDCl_3$) 7.38-7.34 (m, 3 H), 4.75 (d, *J*= 12.7 Hz, 1 H), 4.64 (d, *J*= 12.7 Hz, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) 145.8 (dm, $^1J_{CF}$ = 250 Hz), 141.5 (dm, $^1J_{CF}$ = 256 Hz), 137.4 (dm, $^1J_{CF}$ = 250 Hz), 135.9, 135.3, 133.1, 130.3, 104.7-104.3 (m), 44.6. ^{19}F-NMR (470 MHz, $CDCl_3$) -140.6 (dd, J=21.6 Hz, J=8.3 Hz, 2 F), -151.7_-151.9 (m, 1 F), -160.8 _-161.0 (m, 2 F). Anal. Calcd for $C_{13}H_5Cl_2F_5OS$: C 41.62; H 1.34. Found C 41.83; H 1.32. The ee value was measured by HPLC (Column: Chiralcel OD-H. Eluent: hexane/*i*-propanol 7:3; flow rate 0.5 ml/min;t_R=11.5; t_S = 14.7; separation factor α =1.57).

2,4-Dichlorophenyl phenacyl sulfoxide (8b). Mp 135-137 °C (*i*-Pr_2O/MeCN 4:1). $[\alpha]_D^{25}$ = + 400.5 (c= 1.1, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) 7.93-7.89 (m, 2 H), 7.78 (d, J= 8.3 Hz, 1 H), 7.63-7.59 (m, 1 H), 7.49-7.45 (m, 3 H), 7.43 (d, J= 1.5 Hz, 1 H), 4.60 (d, J=14.2 Hz, 1 H), 4.31 (d, J=14.2 Hz, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$) 190.6, 139.6, 138.2, 136.2, 134.2, 130.7, 129.7, 128.9, 128.5, 127.5, 61.9. Anal. Calcd for $C_{14}H_{10}Cl_2O_2S$: C 53.69; H 3.22. Found C 53.56; H 3.21.

The ee value was measured by HPLC (Column: Chiralpak IA. Eluent: hexane/*i*-propanol 7:3; flow rate 0.5 ml/min; t_S=20.0; t_R = 24.5; separation factor α =1.32).

Computational Section

Molecular mechanics and preliminary DFT calculations were run with Spartan'16 (Wavefunction, Irvine CA), with standard parameters and convergence criteria. DFT and TDDFT calculations were run with Gaussian16,[40] with default grids and convergence criteria.

Conformational searches were run with the Monte Carlo algorithm implemented in Spartan'16 using the Merck Molecular Force Field (MMFF). Preliminary DFT calculations were run first at the ωB97X-D/6-31G(d) level, and then at the ωB97X-D/6-311+G(d,p) level in vacuo. All selected structures were then re-optimized at the ωB97X-D/6-311+G(d,p) level with PCM solvent model for CH_3CN. Single-point calculations were then run at the MP2/6-311+G(d,p) level with PCM solvent model for CH_3CN to estimate internal energies.

ECD calculations were run at TDDFT level with the CAM-B3LYP functional and the def2-TZVP basis set including the PCM model for CH_3CN. Average ECD spectra were computed by weighting the spectra of individual conformers using Boltzmann factors at 300 K estimated from MP2 internal energies. All conformers having population $\geqslant$0.1% at 298K were taken into consideration. The final spectra were generated using the program SpecDis ver. 1.70. The plotting parameters were decided on a best-fitting basis and are reported in each Figure. Similarity factors (SF) were also estimated using SpecDis.

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References

1. Han J, Soloshonok VA, Klika KD, Drabowicz J, Wzorek A, *Chem. Soc. Rev.* 2018; 47: 1307.
2. Wojaczyńska E, Wojaczyński J, *Chem. Rev.* 2010; 110: 4303.
3. O' Mahony GE, Ford A, Maguire AR, *J. Sulfur Chem.* 2013; 34: 301.
4. Otocka S, Kwiatkowska M, Madalińska L, Kiełbasiński P, *Chem Rev*. 2017; 117: 4147. Pellissier, H, *Tetrahedron* 2006; 62: 5559.
5. Trost BM, Rao, M, *Angew. Chem. Int. Ed. Engl.* 2015; 54: 5026.
6. Bentley R, *Chem. Soc. Rev*. 2005; 34: 609.
7. Cotton H, Elebring T, Larsson M, Li L, Sorensen H, von Unge S, *Tetrahedron: Asymmetry* 2000; 11: 3819.
8. Seenivasaperumal M, Federsel HJ, Szabó KJ, *Adv. Synth. Catal.* 2009; 351: 903.
9. Courvoisier, L.; Duret, G.; Graf, S.; Prat-Lacondemine, L; Rebiere, F.; Sabourault, N. Process for Enantioselective Synthesis of Single Enantiomers of Modafinil by Asymmetric Oxidation, US Patent US2013066111 – 2013-03-14.
10. Jia T, Zhang M, McCollom SP, Bellomo A, Montel S, Mao J, Dreher SD, Welch CJ, Regalado EL, Williamson RT, Manor BC, Tomson NC, Walsh PJ, *J. Amer. Chem. Soc.* 2017; 139: 8337.
11. Wang L, Chen M, Zhang P, Li W, Zang J, *J. Amer. Chem. Soc.* 2018; 140: 3467. Wu C, Berritt S, Liang X, Walsh PJ, *Org. Lett.* 2019; 21: 960.
12. Zong L, Tan CH, *Acc. Chem. Res.* 2017; 50: 842. Gelat F, Jayashankaran J, Lohier JF, Gaumont AC, Perrio S, *Org. Lett.* 2011; 13: 3170.
13. Yu H, Li Z, Bolm C, *Org. Lett.* 2018; 20: 7104. Wang L, Chen M, Zhang J, *Org. Chem. Front.* 2019; 6: 32.
14. Capozzi MAM, Cardellicchio C, Naso F, *Eur. J. Org. Chem.* 2004: 1855.

15. Naso F, Cardellicchio C, Affortunato F, Capozzi MAM, *Tetrahedron: Asymmetry* 2006; 17: 3226.
16. Cardellicchio C, Hassan Omar O, Naso F, Capozzi MAM, Capitelli F, Bertolasi V, *Tetrahedron: Asymmetry* 2006; 17: 223.
17. Capozzi MAM, Cardellicchio C, Naso F, Rosito V, *J. Org. Chem.* 2002; 67: 7289.
18. Naso F, Capozzi MAM, Bottoni A, Calvaresi M, Bertolasi V, Capitelli F, Cardellicchio C, *Chem. Eur. J.* 2009; 15: 13417.
19. Capozzi MAM, Centrone C, Fracchiolla G, Naso F, Cardellicchio C, *Eur. J. Org. Chem.* 2011: 4327.
20. Capozzi MAM, Capitelli F, Bottoni A, Calvaresi M, Cardellicchio C, *ChemCatChem* 2013; 5: 210.
21. Capozzi MAM, Fracchiolla G, Cardellicchio C, *J. Sulfur Chem.* 2013; 34: 646.
22. Capozzi MAM, Capitelli F, Cardellicchio C, *Cryst. Growth Des.* 2014; 14: 5442.
23. Capozzi MAM, Terraneo G, Cavallo G, Cardellicchio C, *Tetrahedron* 2015; 71: 4810.
24. Capozzi MAM, Bottoni A, Calvaresi M, Cardellicchio C, *Tetrahedron* 2018; 74: 2041.
25. Pescitelli G, Di Pietro S, Cardellicchio C, Capozzi MAM, Di Bari L, *J. Org. Chem.* 2010; *75:* 1143.
26. Padula D, Di Pietro S, Capozzi MAM, Cardellicchio C, Pescitelli G, *Chirality* 2014; 26: 462.
27. Berardozzi R, Guido CA, Capozzi MAM, Cardellicchio C, Di Bari L, Pescitelli G, *Eur. J. Org. Chem.* 2015; 5554.
28. Górecki M, Capozzi MAM, Albano G, Cardellicchio C, Di Bari L, Pescitelli G, *Chirality*, 2018; 30: 29.
29. Okano K, *Tetrahedron* 2011; 67, 2483.

30. Yamamoto K, Ando H, Shuetake T, Chikamatsu H, *J. Chem. Soc. Chem. Commun*, 1989: 754. Donnoli MI, Superchi S, Rosini C, *J. Org. Chem.* 1998; 63*:* 9392.
31. Desiraju GR, Vittal JJ, Ramanan A, *Crystal Engineering. A Textbook.* World Scientific: Singapore, 2011. Nishio M, Umezawa Y, Fantini J, Weiss MS, Chakrabarti P, *Phys. Chem. Chem. Phys.* 2014; 16: 12648. Nishio M, *Phys. Chem. Chem. Phys.* 2011; 13: 13873. Cardellicchio C, Capozzi MAM, Alvarez-Larena A, Piniella JF, Capitelli F, *CrystEngComm*, 2012; 14: 3972.
32. Salonen LM; Ellermann M, Diederich F, *Angew Chem. Int. Ed. Engl.* 2011; 50:4808.
33. Mislow K, Green MM, Laur P, Melillo JT, Simmons T, Ternay Jr AL, *J. Am. Chem. Soc.* 1965, 87, 1958.
34. Mislow K, Ternay Jr A L, Melillo JT, *J. Am. Chem. Soc.* 1963, 85, 2329.
35. Bruhn, T.; Schaumlöffel, A.; Hemberger, Y.; Bringmann, G. *Chirality* 2013, 25, 243.
36. Bruhn, T.; Schaumlöffel, A.; Hemberger, Y.; Pescitelli, G.: Berlin, Germany, 2017, https://specdis-software.jimdo.com/.
37. Hogben MG, Graham WAG, *J. Amer. Chem. Soc.* 1969; 91: 283.
38. Seahadri R, Pegg WJ, Israel M, *J. Org. Chem.* 1981; 46: 2596.
39. Menon NK, Nargund KS, *Indian J. Chem.* 1967; 5: 478.
40. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Petersson GA, Nakatsuji H, Li X, Caricato M, Marenich AV, Bloino J, Janesko BG, Gomperts R, Mennucci B, Hratchian HP, Ortiz JV, Izmaylov AF, Sonnemberg JL, Williams-Young D, Ding F, Lipparini F, Egidi F, Goings J, Peng B, Petrone, A, Henderson T, Ranasinghe D, Zakrzewski VG, Gao J, Rega N, Zheng G, Liang W, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Throssell K, Montgomery Jr JA, Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Keith TA, Kobayashi R, Normand J, Raghavachari

K, Rendell AP, Burant JC, Iyengar SS, Tomasi J, Cossi M, Millam JM, Klene M, Adamo C, Cammi R, Ochterski JW, Martin RL, Morokuma K, Farkas O, Foresman JB, Fox DJ, Gaussian, Inc.: Wallingford CT, 2016.