Tetrahedron 74 (2018) 2041–2047

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A dichotomy in the enantioselective oxidation of aryl benzyl sulfides: A combined experimental and computational work

Maria Annunziata M. Capozzi [b], Andrea Bottoni [c, **], Matteo Calvaresi [c], Cosimo Cardellicchio [a, *]

[a] CNR ICCOM - Dipartimento di Chimica, Università di Bari, via Orabona 4, 70125 Bari, Italy
[b] Dipartimento di Chimica, Università di Bari, via Orabona 4, 70125 Bari Italy
[c] Dipartimento di Chimica "G. Ciamician", Alma Mater Studiorum, Università di Bologna, via F. Selmi 2, 40126 Bologna, Italy

ARTICLE INFO

Article history:
Received 1 February 2018
Received in revised form
28 February 2018
Accepted 4 March 2018
Available online 8 March 2018

Keywords:
Titanium
Sulfoxide
DFT computations
Hydrobenzoin
Oxidation mechanism

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.

1. 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 procedures[6,7] 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*)-omeprazole[11]). 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 papers[12–19] on the enantioselective oxidation of sulfides with *tert*-butyl hydroperoxide (TBHP) in the presence of a 1:2 complex between titanium *i*-propoxide and (*S*, *S*)- or (*R*, *R*)-hydrobenzoin (Chart 1, Ligand A), a cheap and commercially available ligand.[20]

* Corresponding author. CNR ICCOM - Dipartimento di Chimica, Università di Bari, via Orabona 4, 70125 Bari, Italy.
** Corresponding author.
E-mail address: cardellicchio@ba.iccom.cnr.it (C. Cardellicchio).

https://doi.org/10.1016/j.tet.2018.03.005
0040-4020/

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 before[22,23] or after[24,25] 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.

2. 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]

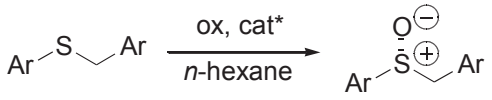
The oxidation process was preliminarily investigated with different procedures, such as the hydroperoxide oxidation in the presence of a titanium/tartrate complex,[11,26] but poor ee values were obtained. Poor enantioselectivity was obtained also by employing hydrogen peroxide in the presence of a chiral 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.

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$\cdots\pi$ interactions[28] 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)-1,2-dihydroxyethane (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 oxidised 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 us[19] 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.

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



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

Entry	Ar	Sulfide	Oxidant	Ligand[a]	Product	Yield (%)[b]	ee (%)[c]
1	C_6F_5	**1a**	TBHP	**A**	(*R*)-**1b**	19[d]	61[d]
2	C_6F_5	**1a**	TBHP	**A**	(*R*)-**1b**	26[e]	52[e]
3	C_6F_5	**1a**	TBHP	**B**	(*R*)-**1b**	29	20
4	C_6H_5	**2a**	CHP	**A**	(*R*)-**2b**	46	8
5	C_6H_5	**2a**	TBHP	**A**	(*R*)-**2b**	87[f]	>98[f]
6	C_6F_5	**1a**	CHP	**A**	(*R*)-**1b**	76	>98

[a] **A** = (*S*, *S*)-1,2-bis-diphenyl-1,2-di-hydroxyethane (hydrobenzoin). **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]