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Enantioselective Organocatalytic Oxidation of Functionalized Sterically Hindered Disulfides

Noureddine Khiar,*,† Siham Mallouk,§ Victoria Valdivia,† Khalid Bougrin,§ Mohammed Soufiaoui,§ and Inmaculada Fernández*,‡

Instituto de Investigaciones Químicas, C.S.I.C-Universidad de Sevilla, c/. Américo Vespucio, 49, Isla de la Cartuja, 41092 Sevilla, Spain, Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, 41012 Sevilla, Spain, and Laboratoire de Chimie des Plantes et de Synthèse Organique et Bio-organique, Université Mohammed V-Agdal, Faculté des Sciences, B.P. 1014 R.P. Rabat, Morrocco

khiar@iiq.csic.es; inmaff@us.es

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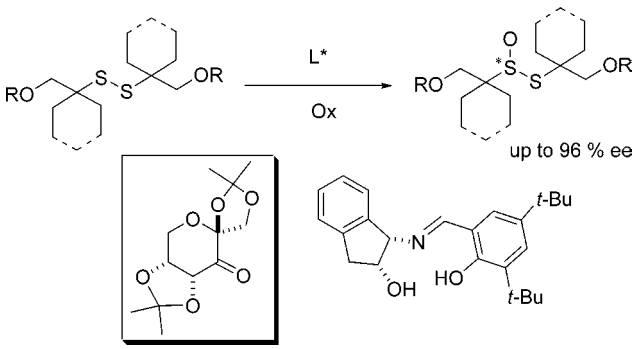
ABSTRACT



The first study on enantioselective oxidation of functionalized sterically hindered disulfides is reported. This study shows that the Shi organocatalytic system using carbohydrate-derived ketone with oxone is superior to the Ellman–Bolm vanadium catalyst in terms of chemical yield and enantioselectivity. Whereas the latter system afforded mostly racemic thiosulfinates in low to moderate yields, the former one afforded thiosulfinates with up to 96% ee.

The preparation of chiral sulfinyl derivatives has been a standing area of interest over the past 3 decades.[1] This interest was mainly directed toward the preparation of chiral sulfoxides as a consequence initially of their high efficiency as chiral controllers in asymmetric carbon−carbon and carbon−heteroatom bond formation[2] and also because of the pharmacological significance of some synthetically and naturally occurring sulfoxides.[1] Nevertheless, the advances made in the preparation of chiral sulfinyl derivatives at the beginning of the 1990s have widened their applicability to all branches of asymmetric synthesis.[3] Among the recent applications of chiral sulfoxides is their utilization as chiral ligands or ligand precursors in metal-catalyzed asymmetric reactions,[1] in coordination chemistry[1,4] and as Lewis base in organocatalysis.[5] Additionally, one of the most significant break-

† C.S.I.C-Universidad de Sevilla.
‡ Facultad de Farmacia, Universidad de Sevilla.
§ Université Mohammed V-Agdal.

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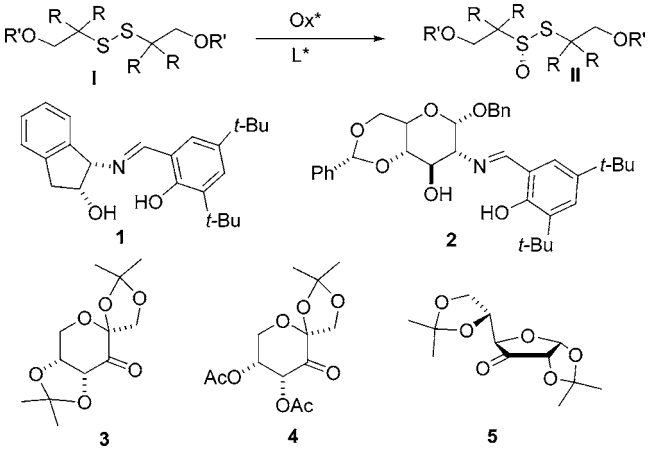
throughs in the chemistry of sulfinyl derivatives is the development of efficient approximations for the synthesis of sulfinamides[6,7] and the corresponding sulfinylimines. Accordingly, the exceptional behavior of the chiral sulfinyl group in sulfinylimines as activator, chiral controller, and finally as useful protective group makes the sulfinamides an extremely versatile chiral ammonia equivalent.[8,9] On the other hand, recent studies have demonstrated that hindered alkyl substituents on the sulfur confer better stereochemical control in different processes compared to their aryl counterparts.[10−13] These results promoted an active search of new and more hindered sulfinylating agents, of which there are a number in the literature.[14] Surprisingly, the synthesis of functionalized sterically demanding sulfinating agents did not attract much interest. Significantly, the high interest in the synthesis of complex molecules on solid support and the recent use of chiral sulfoxides as Lewis bases in organocatalysis make the synthesis of conveniently functionalized sterically hindered sulfinylating agents an attractive research goal. With these premises in mind, we started a research program for development of an efficient route for the synthesis of enantiomerically pure functionalized sterically demanding thiosulfinates.[15] In the present work we report our preliminary results on the catalytic enantioselective oxidation of sterically hindered disulfide diols and the corresponding diesters and diethers **I** using two different catalytic systems. The first system employs an oxovanadium complex derived from indanol Schiff base **1**, which represents the actual state of the art in the oxidation of sterically hindered alkyl disulfides,[16] and the carbohydrate Schiff base **2**[17] (Scheme 1). The second system is based on the Shi organo-

Scheme 1

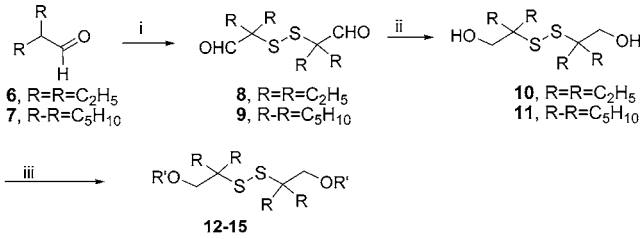


catalytic process and utilizes chiral diooxiranes derived from D-fructose (**3** and **4**)[18−20] and D-glucose (**5**) (Scheme 1).

The synthesis of the starting disulfides was achieved using an approximation developed more than 3 decades ago, which surprisingly has never been used in the synthesis of chiral sulfinyl derivatives.[21] Aliphatic aldehydes **6** and **7**, with an enolizable proton, react with sulfur monochloride (S_2Cl_2) to give 2,2,5,5-tetraalkyl (ethyl or cyclohexyl)-3,4-dithiahexane-1,6-dial **8** and **9** in excellent yields. A chemoselective reduction of the dialdehydes with sodium borohydride afforded the corresponding diols. Acylation or etherification of these diols affords the fully protected disulfides **12**−**15** as white crystalline compounds in general.

It is worth mentioning that following the modular strategy described in Scheme 2 various sterically hindered disulfides

Scheme 2



(i) S_2Cl_2, CCl_4; (ii) $NaBH_4$, EtOH; (iii) R'COCl, or R'-X

with different protective groups can be obtained. The possibility of changing the protective group enhances the probability of tuning the structure of the disulfide for a high

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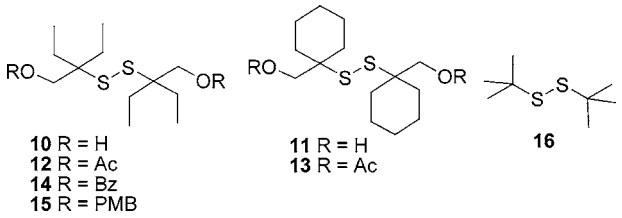


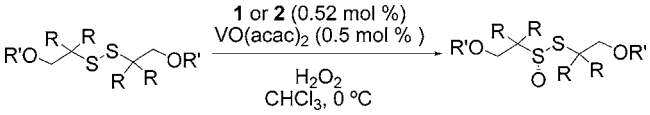
Figure 1. Structures of disulfides used in the synthesis of chiral thiosulfinates.

enantioselectivity. The disulfides used in the present study, **10**−**15**, are shown in Figure 1 and were chosen mainly to determine the influence of the electronic nature of the protective group on the enantioselective process. In order to determine the role of the hydroxylic function on the enantioselectivity, the oxidation of *tert*-butyl disulfide **16** was also carried out with both approximations.

Our first approach for the synthesis of our enantiomerically pure thiosulfinates was by the Ellman−Bolm process as it constitutes the actual state of the art for the oxidation of disulfide **16**. Additionally, taking into account the presence of a hydroxylic function in the substrate, which may permit a well-defined transition state, we were confident on the enantioselectivity of the process.

Surprisingly, employing the best conditions in terms of catalyst loading, temperature, and solvent described in the literature for ligand **1**, the final thiosulfinate esters **17**−**22** have been obtained in very low ee's in general and in low to modest yields at best (Table 1, entries 1−6). With the

Table 1. Enantioselective Oxidation of Disulfides **10**−**15** and **16** with Schiff Base−Vanadium Complexes[3]



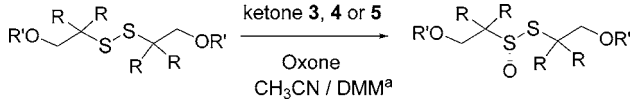
entry[a]	disulfide	R	R′	ligand	thiosulfinate	yield (%)[b]	ee (%)[c]
1	**10**	Et	H	**1**	**17**	61	29
2	**11**	C_5H_{10}	H	**1**	**18**	71	0
3	**12**	Et	Ac	**1**	**19**	8	0
4	**13**	C_5H_{10}	Ac	**1**	**20**	20	17
5	**14**	Et	Bz	**1**	**21**	15	0
6	**15**	Et	PMB	**1**	**22**	15	0
7	**10**	Et	H	**2**	**17**	47	0
8	**12**	Et	Ac	**2**	**19**	7	28
9	**16**			**1**	**23**	90	85
10	**16**			**2**	**23**	20	58

[a] Reactions were conducted in $CHCl_3$ using 0.5 mol % of the ligand and 1.1 mol equiv of H_2O_2. [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC analysis.

free hydroxyl groups, the reaction takes place with modest yield (up to 71%, Table 1, entry 2) and very low ee (0% and 29%). The protection of the hydroxyl groups has a dramatic effect on the reaction, as the final thiosulfinate esters **19**−**21** (Table 1, entries 3−5) and the thiosulfinate ether **22** (Table 1, entry 6) were always obtained in very low yields and in most cases in racemic form (Table 1, entries 3−6). As part of a research program directed toward the utilization of carbohydrates as cheap ligands in asymmetric catalysis,[22] we were also interested on the behavior of the glucosamine-derived Schiff base **2** in the same process. As can be seen (Table 1, entries 7 and 8), ligand **2** behaves as **1** with regard to the oxidation of functionalized sterically hindered thiosulfinates. Interestingly, an appealing 58% ee (Table 1, entry 10) was obtained in the oxidation of **16** albeit in low yield.

In keeping with our interest in using carbohydrates as ligands, our second approximation was the organocatalytic oxidation of the sought disulfides using chiral dioxiranes derived from carbohydrates. Three ketones, **3**−**5**, were used in this study, employing the optimal Shi conditions described for the oxidation of alkenes, and the results are given in Table 2. Screening the three ketones in the oxidation of disulfide

Table 2. Enantioselective Oxidation of Disulfides **10**−**16** with Oxone and Carbohydrate-Derived Ketones **3**−**5**



entry[b]	disulfide	R	R′	ligand	thiosulfinate	yield (%)[c]	ee (%)[d]
1	**10**	Et	H	**3**	**17**	80	72
2	**10**	Et	H	**4**	**17**	76	60
3	**10**	Et	H	**5**	**17**	70	0
4	**11**	C_5H_{10}	H	**3**	**18**	82	70
5	**12**	Et	Ac	**3**	**19**	89	89
6	**13**	C_5H_{10}	Ac	**3**	**20**	57	96
7	**14**	Et	Bz	**3**	**21**	89	93
8	**15**	Et	PMB	**3**	**22**	20	90
9	**16**			**3**	**23**	97	84

[a] DMM: dimethoxymethane. [b] Reactions were conducted in CH_3CN/DMM (1:2) using 30 mol % of the ketone and 1.4 molar equiv of oxone. [c] Isolated yield. [d] Enantiomeric excesses were determined by chiral HPLC analysis.

diol **6** shows that ketone **5** is not suitable for this transformation (Table 2, entry 3), while ketone **3** behaves better than ketone **4** and gives the best results both in terms of reactivity and enantioselectivity (Table 2, entry 1). The oxidation of the other disulfides has thus been conducted with ketone **3**, which affords in all cases the final thiosulfinates in very good yields and in good to excellent enatioselectivities. Interestingly, the acylation of the starting disulfides has a beneficial effect both on their reactivities and on the enantioselectivities

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of the processes, in contrast to the results obtained with the Schiff base/$VO(acac)_2$ system.

The acetylated thiosulfinates (**19**, **20**) and the benzoylated thiosulfinate **21** were obtained in very good yields and excellent enantioselectivities (up to 96%, Table 2, entries 6 and 7). The oxidation of the electronically rich disulfide **15** gave the corresponding thiosulfinate **22**, in a good 90% ee but in low yield (Table 2, entry 19). These results show that the structure of the starting disulfide is crucial for a good result with the oxone/chiral ketone system. Electron-poor protective groups afford better results than electron-rich protective groups both in terms of chemical yields and enantioselectivities. In conclusion, we have shown for the first time that it is possible to have excellent enantioselectivities and reactivities in the oxidation of functionalyzed sterically demanding disulfides. These disulfides are actually being used in the synthesis of polymer-supported sulfinamides and sulfoxides in order to develop recyclable sulfur-based ligands for asymmetric catalysis.

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Supporting Information Available: Representative experimental procedures for the synthesis of compounds **10**−**15** and the corresponding thiosulfinates **17**−**22**, and ^1H and ^{13}C NMR and HPLC data for the determination of enantiomeric excesses of thiosulfinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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