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Sulfoxidations in the solid phase

Aina Colombo,[a] Fernando Albericio[a,b,*] and Pilar Forns[a,*]

[a]*Almirall Prodesfarma-Barcelona Science Park Unit, Josep Samitier 1-11, 08028 Barcelona, Spain*
[b]*Institute for Research in Biomedicine, Barcelona Science Park, Josep Samitier 1-11, 08028 Barcelona, Spain*

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Abstract—The asymmetric oxidation of a sulfide in the solid phase using two distinct scaffolds as models is described.

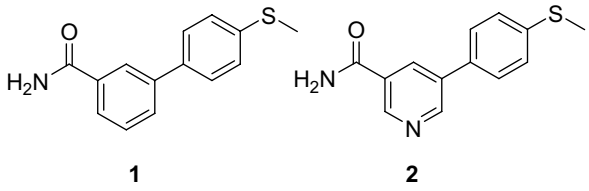
1. Introduction

Interest in sulfoxides as synthetic intermediates for obtaining biologically active compounds has fueled research into new methodologies for sulfoxide synthesis.[1] Many chiral sulfoxides show biological activity,[2] such as omeoprazole, a proton-pump inhibitor,[3] aprikalim, an activator of the potassium channel,[4] and oxisurane, an immunosuppressor.[5] Controlled oxidation of sulfides is the methodology most often used for obtaining sulfoxides.

Our group has developed combinatorial strategies for the generation of primary screening small libraries,[6] from which pharmaceutically attractive lead molecules are identified. Some of our research has been carried out using the solid-phase approach,[7,8] which is useful for the rapid and efficient preparation of small molecule libraries to feed high-throughput screening systems.

In this context, one of our studies focused on the development of a methodology to oxidize sulfides into sulfoxides. This type of oxidation can be carried out to obtain either the racemate or only one enantiomer. Two enantiomers can have distinct properties, such as taste or odor, and may show distinct behavior when used as drugs.[9] From a pharmaceutical point of view, the first screening can be carried out with the racemate in order to establish interaction or activity of the compound. It is, therefore of interest to have a good solid-phase chemistry methodology for obtaining the racemate for the first screening stage, and another to generate the two enantiomers separately for a second and more accurate biological evaluation. Herein we focus our study on the asymmetric oxidation.

Two sulfides were used for this study (Scheme 1). Compound **1** was chosen because the related *p*-tolyl methyl sulfide is the model compound most often used in studies of asymmetric oxidations.[10–13] In contrast, compound **2** was examined because pyridine is a common motif in many biologically active compounds. Furthermore, it is of interest to determine whether this methodology is also applicable to this type of π-deficient compounds.



1 **2**

Scheme 1. Sulfides used in the oxidation study.

Racemic sulfoxidations have been studied in solution and in the solid phase using several types of oxidizing reagents. For example, in solution, hydrogen peroxide is one of the most used,[14] but also classical oxygen transfer reagents, such as metachloroperbenzoic acid (MCPBA)[15] or ozone[16] have also been examined. In the solid phase, there are some references to sulfide oxidation using hydrogen peroxide with a catalytic amount of acetic acid[17] or $Sc(OTf)_3$,[18] MCPBA,[19] a peroxide agent, such as *tert*-butylhydroperoxide (TBHP) with *p*-toluenesulfonic acid (*p*-TsOH) as catalyst[20] or using the 4,8b-dihydro-3*H*-[1,2]oxazireno[3,2-*a*]isoquinoline[21] **3** (Scheme 2).

* Corresponding authors. Tel.: +34 934 034 705/706; fax: +34 934 037 109; e-mail addresses: albericio@pcb.ub.es; pforns@pcb.ub.es

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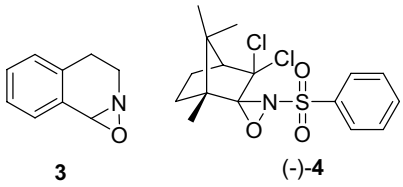
Several methods for the asymmetric oxidation of prochiral sulfides have been reported in solution. Thus Kagan et al.[11] and Modena et al.[12] have developed methods based on a modification of the Sharpless reagent for the asymmetric oxidation of allylic alcohols.[22] This method uses $Ti(O^iPr)_4$, (*R*,*R*)-diethyl tartrate (DET) and TBHP in a ratio of 1:1:2. The coordination between $Ti(O^iPr)_4$ and the L- or D-DET produces a not very well refined complex that allows asymmetric oxidation. Chiral oxidants, such as the oxaziridines developed by Davis et al.[13] (−)-**4** (Scheme 2), as well as a great variety of enzymes[23] and other transition metals have also been used. One example is the method developed by Bolm and Bienewald[24] using hydrogen peroxide, and a catalytic system of vanadium and a chiral Schiff base. In addition, some groups have come across the problem of performing the reaction in the presence of solid supported vanadium[25] and titanium[26] chiral Schiff base catalysts. However, there are no precedents for asymmetric oxidation of a sulfide supported in a solid phase.



3 (-)-**4**

Scheme 2. Oxaziridines used in sulfoxide formation.

2. Results and discussion

The variety of methodologies used, reflects considerable interest in this type of transformation. Moreover, it is evident that several approaches should be tested for each particular case, in order to identify the method, which provides better yields and, when applicable, improved enantiomeric excess (ee). Thus, using the two scaffolds previously mentioned as models, we examined a number of asymmetric sulfoxidation methods in the solid phase, which have not been reported previously.

Compounds **1** and **2** were built on the solid phase by incorporating 3-bromobenzoic and 5-bromonicotinic acids to a commercial Rink Amide resin using 1,3-diisopropylcarbodiimide (DIC), 1-hydroxybenzotriazole (HOBt), and *N*,*N*-dimethylaminopyridine (DMAP) in *N*,*N*-dimethylformamide (DMF). A Suzuki reaction under the same conditions as reported before[8] was then performed on resins **5** and **6**, respectively, to afford resins **7** and **8** with purities between 75–90% and a 85–95% yield, respectively (Scheme 3).[27]

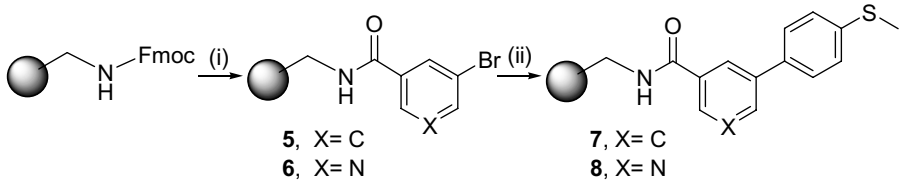
2.1. Asymmetric oxidations

As discussed above, a wide range of conditions have been reported for asymmetric sulfoxidations in solution. Table 1 shows the results of the asymmetric oxidation of resin **7** to obtain resin **9**[28] (Scheme 4) with the methods described by Kagan[11a] and Modena,[12a] who independently modified the Sharpless reagent, following the initial reports of Kagan and Modena, and with the chiral oxaziridine (−)-**4** developed by Davis.[13]

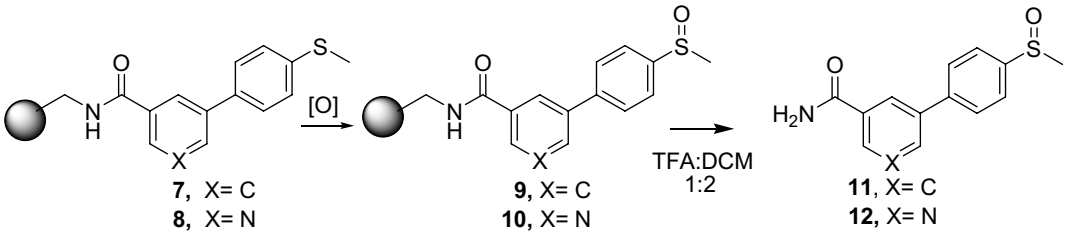
Kagan's conditions consist of forming a complex between the $Ti(O^iPr)_4$, L- or D-DET, H_2O and a peroxide as an oxidizing agent in a 1:2:1:2 ratio. The peroxides that have been mostly used in this method are TBHP[11a] and CHP.[11b] Replacing of TBHP by CHP sometimes resulted in an increased enantiomeric excess of sulfoxides,[11b] meaning the latter was used. As the reaction was performed on solid phase, 3 equiv of the peroxide, 3 equiv of $Ti(O^iPr)_4$, 6 equiv of L-DET, and 4 equiv of H_2O were used at −20 °C for 16 h, but an ee of only 49% was achieved (Table 1, entry 1).[29]

Modena's conditions, which differ from those of Kagan in the high content of DET and absence of H_2O, were then used with 3 equiv of $Ti(O^iPr)_4$, 12 equiv of L-DET and 6 equiv of CHP[12] at −20 °C for 16 h in anhydrous CH_2Cl_2, and the ee obtained was 70%.[30] Given that distinct chlorinated solvents affect the ee and reactivity of sulfoxidations,[10a] some of them were tested (# 2–6 Table 1). In this case, the ee and yield decreased in the following order CH_2Cl_2 (70% ee) > $CHCl_3$ (51%), CH_3CHCl_2 (50%) ≫ CCl_4.

Finally, the chiral oxaziridine (−)-**4**, developed by Davis,[13] was tested (# 7–14). The reaction was performed with 5 equiv of (−)-**4** for 24 h.[31] First of all, three temperatures were tested (# 7–9), and the best ee (70%, # 7) was obtained at room temperature. Several solvents were also tested (# 10–14) and in this case the reactivity and the ee using CH_2Cl_2 and $CHCl_3$ was similar and slightly superior to the results obtained with $CH_3CH_2Cl_2$. Comparison of the three methodologies showed that oxaziridine (−)-**4** was the best. Thus, and although it gave the same ee, the total conversion into the sulfoxide [yields from 70% to 99% (# 7–11) without purification compared with the 17–58% obtained using Modena conditions (# 1–5)] and the total absence of over-oxidation makes it the method of choice for this solid-phase transformation.



Scheme 3. Reagents and conditions: (i) 3-bromobenzoic acid or 5-bromonicotinic acid, DIC, HOBt, DMAP in DMF, (ii) 4-(methylthio)phenylboronic acid, $Pd(PPh_3)_4$, 2 N Na_2CO_3, 90 °C, 24 h.



Scheme 4. Oxidation of sulfides.

Table 1. Asymmetric oxidation conditions using resin **7**

Entry	Method[a]	Solvent	*T* (°C)	Time (h)	ee[d]	Yield[e]
1	Kagan[b]	CH_2Cl_2	−20	16	49	72
2	Modena[c]	CH_2Cl_2	−20	16	70	60
3	Modena[c]	CH_2Cl_2	−20	16	67	58
4	Modena[c]	$CHCl_3$	−20	16	51	31
5	Modena[c]	CH_3CHCl_2	−20	16	50	15
6	Modena[c]	CCl_4	−20	16	—	10
7	(−)-**4**	CH_2Cl_2	rt	24	70	99
8	(−)-**4**	CH_2Cl_2	4	24	66	91
9	(−)-**4**	CH_2Cl_2	−20	24	63	70
10	(−)-**4**	$CHCl_3$	rt	24	70	79
11	(−)-**4**	CH_3CHCl_2	rt	48	64	99
12	(−)-**4**	CCl_4	rt	24	—	3
13	(−)-**4**	CCl_4	rt	72	—	5
14	(−)-**4**	CCl_4	rt	120	64	48

[a] Experiments were carried out in duplicate to check reproducibility.
[b] Kagan reagents: Ti(O^iPr)$_4$/L-DET/H_2O/CHP (3:6:3:6).
[c] Modena reagents: Ti(O^iPr)$_4$/L-DET/CHP (3:12:6).
[d] Measured by ^1H NMR (400 Hz) using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.
[e] Corresponding to the target sulfoxide **11**.

To compare the ee obtained in solid phase with those obtained in solution, the two best methodologies from this study were tested in solution with compound **1**. In these two assays, the equivalents were reduced using Modena's conditions (Ti(O^iPr)$_4$/L-DET/CHP (1:2:1)) and CH_2Cl_2 as a solvent. An ee of 81% was obtained but with a yield of only 24% because the sulfide and the sulfone were also obtained. In the case of oxaziridine (−)-**4** (1 equiv), an ee of 62% and yield of 87% were achieved using CH_2Cl_2 as the solvent. Although there was no difference in the ee between solid and solution phase in the case of oxaziridine, when titanium complexes were used the performance in solid phase decreased. This decrease could be attributable to the heterogeneous character of the solid-phase reactions using polystyrene and/or the steric hindrance of the solid support itself.

Having identified the best conditions for resin **7**, we proceeded with the asymmetric oxidation with resin **8** to obtain resin **10**[32] (Table 2) using the same methodology as above. In this case, the best ee's were obtained using Modena's conditions (83%, entry 2) and oxaziridine (−)-**4** (84% ee, entry 3). However, the best yields were obtained with oxaziridine (−)-**4** (entries 3–5). The two methodologies were also performed in solution with compound **2**. In this case, the ee's for Modena and oxaziridine were worse in solution than in solid phase, 45% and 62%, respectively, compared with 83% and 80% in solid-phase mode.

Table 2. Asymmetric oxidation conditions using scaffold **8**

Entry	Method	Solvent	*T* (°C)	Time (h)	ee[c]	Yield[d]
1	Kagan[a]	CH_2Cl_2	−20	16	58	26
2	Modena[b]	CH_2Cl_2	−20	16	83	60
3	(−)-**4**	CH_2Cl_2	rt	24	84	90
4	(−)-**4**	$CHCl_3$	rt	24	80	87
5	(−)-**4**	$CH_2CH_2Cl_2$	rt	24	72	82

[a] Kagan reagents: Ti(O^iPr)$_4$/L-DET/H_2O/CHP (3:6:3:6).
[b] Modena reagents: Ti(O^iPr)$_4$/L-DET/CHP (3:12:6).
[c] Measured by ^1H NMR (400 Hz) using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.
[d] Corresponding to the target sulfoxide **12**.

As described in the literature, the absolute configuration of the sulfoxide obtained using Kagan and Modena methods can be predicted depending on the DET used.[10,11] In our case, L-DET was used predicting that the (*R*)-sulfoxides would be obtained. In the case of oxaziridine (−)-**4**, the absolute configuration can also be predicted, and in this case the (*S*)-sulfoxide will be obtained.[13] This is in agreement with our ^{1}H NMR results when (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol was used, where the major sulfoxide obtained was the same for the Modena and Kagan methods and differed when oxaziridine (−)-**4** was used.

3. Conclusions

We can conclude that in solid-phase synthesis, the optimal reagent for obtaining sulfoxides with some ee was oxaziridine **4**. Other asymmetric methodologies tested in the solid phase gave worse results than oxaziridine **4**, perhaps because of the intrinsic properties of the solid support. Furthermore, the Modena and Kagan conditions require fine tuning of the experimental procedures and the use of air sensitive reagents, which could make these methodologies less attractive for the production of libraries. Finally, it is important to point out that in some cases, the results obtained in the solid phase were better than those obtained in solution.

Acknowledgments

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27. Purity was measured by HPLC, after detaching the compound from the resin.
28. After cleavage with TFA/DCM 1:2 compound 3-4-(methylsulfinyl)phenyl benzamide **11** was obtained and characterized by NMR. ^{1}H NMR (400 MHz, DMSO) δ ppm 2.78 (s, 3H), 7.56 (t, $J = 7.5$ Hz, 1H, ArH), 7.75–7.79 (m, 6H, ArH), 8.1 (t, 1H, $J = 2$ Hz, ArH). ^{13}C (400 MHz, DMSO) δ ppm 43.65, 126.3, 126.9, 128.7, 129.8, 134.26, 139.53, 142.8, 144.6, 168.7.
29. General procedure for asymmetric sulfoxidations using the Kagan conditions in solid phase: 0.825 mmol of titanium tetraisopropoxide (3 equiv) was added rapidly to a solution of

1.65 mmol of L-DET (6 equiv) in 1 ml of the corresponding solvent (see Tables 1 and 2). After 2.5 min, 0.825 mmol of water was added and the resulting mixture was stirred for 20 min at room temperature. Then the complex was added to a solution of the corresponding resin (0.25 mmol, 1 equiv) in 0.5 ml of the corresponding solvent that was cooled at −20 °C. Finally 1.65 mmol of precooled cumene hydroperoxide (6 equiv) was added. After 16 h the resin was washed firstly with a solution of 5% citric acid (5 × 0.5 min), DCM (5 × 0.5 min), DMF (5 × 0.5 min), and MeOH (5 × 0.5 min). The resin was cleaved with TFA/DCM 1:2 and the crude analyzed by HPLC. Flash chromatography of the crude product yielded pure sulfoxide. The fractions of sulfoxide were mixed before ee measurement.

30. General procedure for asymmetric sulfoxidations using Modena conditions in solid phase: 0.825 mmol of titanium tetraisopropoxide (3 equiv) was added rapidly to a solution of 3.3 mmol of L-DET (12 equiv) in 1 ml of the corresponding solvent (see Tables 1 and 2) and the resulting mixture was stirred for 20 min at room temperature. Then the complex was added to a solution of the corresponding resin (0.25 mmol, 1 equiv) in 0.5 ml of the corresponding solvent that was cooled at −20 °C. Finally 1.65 mmol of precooled cumene hydroperoxide (6 equiv) was added. After 16 min the resin was washed with a solution of 5% citric acid (5 × 0.5 min), DCM (5 × 0.5 min), DMF (5 × 0.5 min), and MeOH (5 × 0.5 min). The resin was cleaved with TFA/DCM 1:2 and the crude analyzed by HPLC. Flash chromatography of the crude product yielded pure sulfoxide. The fractions of sulfoxide were mixed before ee measurement.
31. General procedure for asymmetric sulfoxidations using oxaziridines in solid phase: 0.1 mmol of the corresponding resins was swollen in the corresponding anhydrous solvent. Then 0.5 mmol of oxaziridine **4** (5 equiv) was added and the reaction was performed at room temperature for the desired time (see Tables 1 and 2). Afterwards the resin was washed as indicated above and cleaved. The crudes were analyzed by HPLC and no purification was done to determine the ee.
32. After cleavage with TFA/DCM 1:2, the compound 5-(4-(methylsulfinyl)phenyl)pyiridine-3-carboxamide (**12**) was obtained and characterized by NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.94 (s, 3H), 7.92 (d, $J = 2.8$ Hz, 4H, ArH), 9.13 (t, $J = 2$ Hz, 1H, PyrH), 9.20 (d, 1H, $J = 2$ Hz, PyrH), 9.55 (d, 1H, $J = 2$ Hz, PyrH). ^{13}C (400 MHz, $CDCl_3$) δ ppm 43.8, 124.2, 127. 9, 129.3, 129.8, 134.0, 134.9, 139.6, 145.8, 148.6, 150.3, 168.7.