Applications of Catalytic Asymmetric Sulfide Oxidations to the Syntheses of Biologically Active Sulfoxides

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Received: June 30, 2004; Accepted: October 18, 2004

Abstract: Optically active sulfoxides are important compounds for medicinal and pharmaceutical chemistry. Driven by the increasing demand for efficient, selective and environmentally friendly industrial processes, several catalytic methodologies have been developed in recent years for the stereoselective oxidation of sulfides for the preparation of biologically active sulfoxides. Both small-scale approaches to the problem as well as some large-scale applications that are already in industrial use are described in this review.

Keywords: asymmetric catalysis; chiral sulfoxides; drugs; lansoprazole; omeprazole; oxidation

1 Introduction

The concept of stereochemistry has played a major role in academic organic chemistry for several decades. However, it is only since 1992 that it became of utmost relevance for the chemical industry, when the American Food and Drug Administration (FDA) issued a policy statement highlighting the importance of single enantiomer drugs.[1] Since then, the number of chiral compounds that have been marketed in enantiopure form has increased tremendously: in 2003, in six of the top ten drugs the active ingredients were single enantiomers.[2] The fact that one enantiomer (the eutomer) can have the desired biological activity, while the other is less effective, non-effective, or even has a negative or parallel effect, forces both of them to be separately tested before the corresponding drug can be commercialized, even as a racemate.

In this context, many sulfoxides are known to have high biological activity.[3] Prominent examples are the sulfinyl-substituted benzimidazoles which are proton pump inhibitors (PPIs), a powerful class of anti-ulcer agents.[4] Until recently the leading molecule of this family was omeprazole. Commercialized as Losec™ it was the world's highest selling drug in 1997.[1] Although the compound was sold as a racemate for a long time, the (*S*)-enantiomer of omeprazole (esomeprazole) was reported to have superior activity, and after a "chiral switch"[5] the latter is now available in enantiopure form under the name of Nexium™. In 2003, Nexium™ was the 7th most sold drug (with 3.8 billion $ sales).[2]

Generally, there are three ways to obtain organic compounds in enantiomerically pure form: (a) the use of substrates from the "chiral pool" and their stereospecific conversions, (b) resolutions of racemic mixtures, and (c) asymmetric synthesis. Within the latter strategy we can distinguish between the utilization of reagents or chiral auxiliaries in stoichiometric quantities and the application of asymmetric catalysis.[6] For the preparation of optically active sulfoxides[7] the first approach is not applicable at all, since there are no readily available chiral sulfoxides in the "chiral pool". With respect to the second route it is important to note that there are many industrial processes that apply resolutions of racemic mixtures (*via* crystallization, enzymatic resolution, etc.), but the inherent limit of 50% chemical yield constitutes a severe drawback. Although in recent years several new strategies (such as dynamic and parallel kinetic resolutions,[8,9] as well as de-racemizations[10]) have been developed to overcome these limitations, none of them has yet been applied to the preparation of sulfoxides. The third synthetic approach involves the use of chiral auxiliaries or reagents. In fact, one of the major approaches towards enantiomerically pure sulfoxides has been historically the stereospecific substitution of optically active sulfinates with Grignard reagents (Andersen's method).[11] Here, however, important drawbacks are the tedious procedure and, until recently, the

 DOI: 10.1002/adsc.200404206

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Juan R. Dehli was born in Seville (Spain) in 1974. He studied chemistry at the University of Oviedo, where he received his BSc and MSc degree in 1997 and 1999, respectively. He then stayed as a researcher in the group of Professor Furstoss at the CNRS in Marseille (France), where he applied epoxide hydrolases in asymmetric synthesis. Beginning 2000 he came back to Oviedo and carried out his PhD studies under the supervision of Professor Gotor on the biocatalyzed enantioselective reduction of ketones. After completing his doctoral studies with honours in 2002 he moved to the RWTH Aachen (Germany), where he was a Marie Curie postdoctoral fellow in the research group of Professor Bolm, focusing on the chemistry of oxidized sulfur compounds. Since 2005 he is Lab Head at the Department of Process Development at Boehringer Ingelheim GmbH.

Carsten Bolm was born in Braunschweig (Germany) in 1960. He studied chemistry at the TU Braunschweig (Germany) and at the University of Wisconsin, Madison (USA). In 1987 he obtained his doctorate with Professor Reetz in Marburg (Germany). After postdoctoral training with Professor Sharpless at MIT, Cambridge (USA), Carsten Bolm worked in Basel (Switzerland) with Professor Giese to obtain his habilitation. In 1993 he became Professor of Organic Chemistry at the University of Marburg (Germany), and since 1996 he has a chair of Organic Chemistry at the RWTH Aachen (Germany). His awards include the Heinz-Maier-Leibnitz prize, the ADUC-Jahrespreis for habilitands, the annual prize for Chemistry of the Akademie der Wissenschaften zu Göttingen, the Otto-Klung prize, the Otto-Bayer award, and a fellowship of the Japan Society for the Promotion of Science.

limited substrate scope.[7,12] Other attempts involve stoichiometric chiral oxidants, such as oxaziridines,[13] but their high cost, restricted availability and the low concentration required for their utilization make this approach less attractive. The only practical synthetic route towards chiral sulfoxides that has already found acceptance by industry during the last two decades is the catalytic enantioselective oxidation of prochiral sulfides. It is a general, powerful approach that also proved suitable for scale-up.[14] This review will present metal-[15] and enzyme-catalyzed[15c,16] processes to access biologically active sulfoxides and highlight related synthetic industrial applications. Chiral sulfoximines (iminated derivatives of sulfoxides), which also show biological activity, will not be considered, since they are commonly prepared from sulfoxides. Furthermore, their chemistry has very recently been reviewed.[17]

2 Metal-Catalyzed Processes

The use of chiral transition metal complexes, in combination with an oxidant, is a powerful method to generate optically active sulfoxides. Whereas catalysts involving titanium are the most prominent ones, efficient methods utilizing manganese, vanadium and iron have also been developed (Table 1).[15] It should be noted that they are mainly homogeneous catalysts.

After the pioneering work of Modena (entry 1)[18] and Kagan (entry 2),[19] who independently introduced modified Sharpless reagents for enantioselective sulfoxidations at almost the same time, a wide variety of other chiral titanium reagents based on C_2-symmetrical diols has been applied in this reaction.[15] Uemura extended the sulfoxidation chemistry and applied a combination of Ti(O-*i*-Pr)$_4$ and BINOL as catalyst (entry 3).[20] In 1992, Jacobsen, followed by Katsuki, reported the use of (salen)Mn(III) (**1**, Figure 1). H_2O_2 proved to be a suit-

Table 1. Main metal-promoted asymmetric sulfide oxidation methods.[a]

Entry	Catalyst (equivs.)	Oxidant	Solvent	Temp.
1	Ti(O-*i*-Pr)$_4$/DET (1:4)	TBHP	CH_2Cl_2	−20 °C
2[b]	Ti(O-*i*-Pr)$_4$/DET/H_2O (1:2:1)	TBHP or CHP	CH_2Cl_2	−20 °C
3	Ti(O-*i*-Pr)$_4$/BINOL (0.1:0.2)	TBHP	CCl_4	0 °C
4	Mn^{III}(salen) **1** (0.02)	aqueous H_2O_2 or PhIO	MeCN	RT
5	VO(acac)$_2$/**2a** (0.01:0.015)	aqueous H_2O_2	CH_2Cl_2	RT
6	Fe(acac)$_3$/**2b**/4-MeOC$_6$H$_4$CO$_2$X (0.02:0.04:0.01)	aqueous H_2O_2	CH_2Cl_2	RT

[a] Abbreviations: DET = diethyl tartrate: (*R*,*R*)-L-(+)-DET (natural) and (*S*,*S*)-D-(−)-DET (unnatural); BINOL = 1,1′-bi(2-naphthol): (*S*)-(−)-BINOL and (*R*)-(+)-BINOL; TBHP = *tert*-butyl hydroperoxide, CHP = cumyl hydroperoxide.
[b] Substoichiometric amounts of [Ti] and DET can also be used.

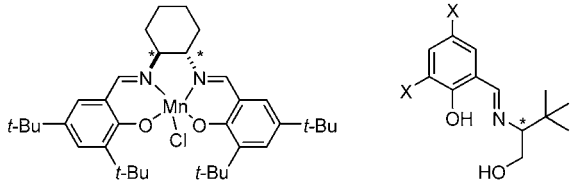

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Figure 1. A manganese complex and ligands used in metal-catalyzed asymmetric sulfide oxidations.

able oxidant, but higher enantioselectivities were achieved with PhIO (entry 4).[21] In the development of practical syntheses the simplicity of the process as well as the availability and toxicity of the reactants play a very significant role. In this line, Bolm reported a highly efficient vanadium catalysis, which utilizes Schiff bases of type **2** as chiral ligands (Figure 1) and which proceeds under very simple and mild reaction conditions. Thus, the oxidations are performed at room temperature under air, and aqueous H_2O_2 serves as terminal oxidant (entry 5).[22] Very recently, the same group developed a new catalytic asymmetric sulfide oxidation process that exhibits the same advantages but involves one of the most inexpensive and user-friendly metals: iron (entry 6).[23]

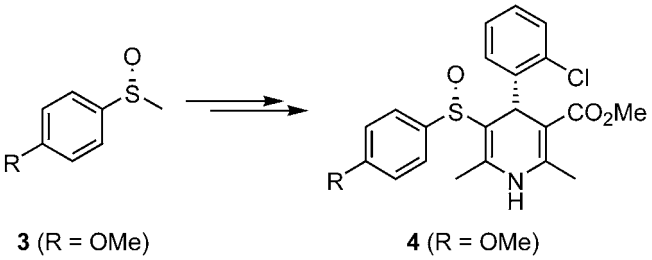
2.1 Enantioselective Oxidations

The efficiency of metal-catalyzed asymmetric sulfide oxidations is dependent on the structure of the starting material, and the reaction conditions that have been optimized for one substrate may not be suitable for another. Sulfides with two substituents of very different size are generally considered as the "easiest" substrates for enantioselective oxidations, and thioethers of the general structure Ar–S–Me constitute the ideal model for the first assessment of a new enantioselective process. For sulfides that are outside this general frame, modifications of the reaction conditions may be necessary to obtain high enantioselectivities.[15] In the case of biologically active compounds the situation is complicated by the fact that those substrates generally possess various functional groups. Two main strategies can then be adopted: 1) performing the sulfide oxidation on a simpler compound at an early stage of the synthesis of the target molecule, or 2) performing the key reaction as the last step, accepting that the result of the reaction is difficult to predict.

2.1.1 Enantioselective Oxidation at an Early Stage

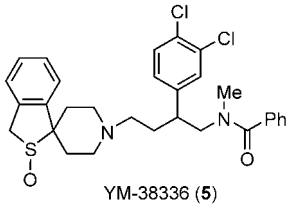
Already in 1988 Davis, Pfister and co-workers reported the catalytic asymmetric synthesis of a Hantzsch-type ester **4** bearing a chiral sulfinyl group. The key intermediate was enantiopure 4-methoxyphenyl methyl sulfoxide (**3**),[24] which can easily be prepared in good yields with an enantiomeric excess (ee) in the range of 85–92% using various metal-based procedures (Scheme 1).[19c,22d,23c] Whereas the authors used the sulfinyl moiety as chiral auxiliary for the subsequent introduction of the other stereogenic center in the β position, and then oxidized the sulfoxide to the corresponding sulfone, it was later shown that analogues of **4** (with R = Me) exhibit good activity as calcium channel antagonists.[25]

Spiro-substituted piperidines are efficient neurokinin receptor antagonists and, among 30 compounds, racemic sulfoxide YM-38336 (**5**) was the most potent molecule in an NK_2 receptor agonist-induced bronchoconstriction model when intravenously injected (Figure 2).[26]



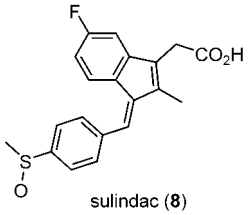
3 (R = OMe) 4 (R = OMe)

Scheme 1.



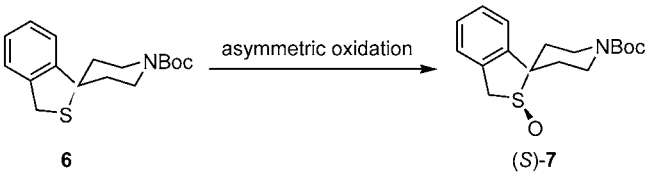
YM-38336 (**5**)

Figure 2. An efficient neurokinin receptor antagonist.



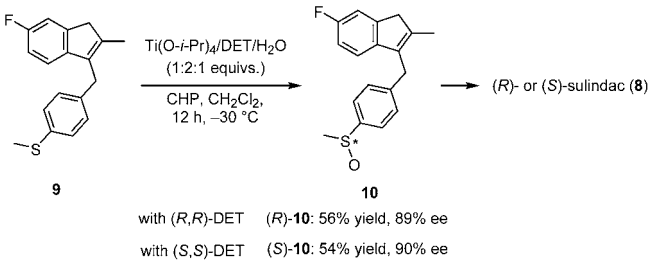
sulindac (**8**)

Figure 3. An efficient anti-inflammatory drug.



6 (*S*)-**7**

Scheme 2.



Scheme 3.

The synthesis of YM-38336 involves racemic sulfoxide **7** as key intermediate. In 1998 enantiomerically enriched (*S*)-**7** was prepared by asymmetric sulfide oxidation starting from **6** at Sankyo laboratories (Scheme 2).[27]

An assessment of the main methods known at that time revealed that all of them led to (*S*)-**7** with low to moderate ee (Table 2). The best result in terms of both yield and enantioselectivity has been achieved by applying Bolm's vanadium-catalyzed process, which gave (*S*)-**7** with 54% ee in 80% yield (entry 4).

Sulindac (**8**) is an efficient anti-inflammatory drug mainly used in the treatment of pain, rheumatoid arthritis, osteoarthritis and acute gouty arthritis (Figure 3). Over the last ten years, the application of sulindac for cancer treatment has become an area of great interest.[28]

To date, sulindac has only been administered therapeutically as a racemic mixture. The first asymmetric synthesis of enantiopure sulindac has been recently reported by Maguire and co-workers (Scheme 3).[29]

Key step of Maguire's sulindac synthesis is the enantioselective oxidation of sulfide **9** according to Kagan's procedure. Both enantiomers of **10** were obtained in moderate yields but with high enantioselectivities (89% and 90% ee). (*R*)- and (*S*)-sulindac (**8**) (with $>89\%$ ee) were then prepared from **10** in a single step without racemization.

Very recently, Bolm applied the iron-catalyzed asymmetric sulfoxidation methodology[23] for the preparation of optically active sulindac.[23d] Apart from the obvious advantages of using an environmentally friendly metal and the mild reaction conditions (room temperature and aerobic atmosphere), both enantiomers could be obtained in good yield (up to 79% starting from **9**) and with up to 92% ee.

2.1.2 Enantioselective Oxidation at the Last Step

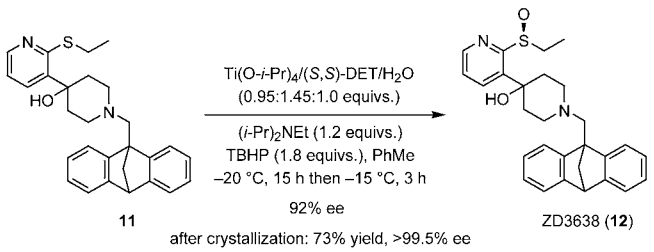
The candidate drug ZD3638 (**12**) is an enantiopure sulfoxide with *S* configuration which was in development from 1993 to 1997 as an atypical antipsychotic agent for the treatment of schizophrenia at AstraZeneca Pharmaceuticals.[30] ZD3638 was required in greater than 99% ee, as the minor enantiomer provided an unwanted central nervous system (CNS) profile. In 2002, the synthesis of ZD3638 using a modified Kagan procedure at the last step of the synthetic sequence was reported by the same laboratory (Scheme 4).[31]

The conditions used in the oxidation of prochiral sulfide **11** were the result of many investigations, which focused especially on the relative amounts of the metal (0.8–1.2 equivs.) and the ligand (0.95–2.35 equivs.). Depending on these quantities, enantioselectivities in the

Table 2. Metal-catalyzed asymmetric oxidation of **6** to give (*S*)-**7**.

Entry	Catalyst (equivs.)	Oxidant (equivs.)	Solvent	Temp. [°C]	Yield [%]	ee [%]
1	Ti(O-*i*-Pr)$_4$/(*S*,*S*)-DET (0.5 : 1.0)	TBHP (1.0)	CH_2Cl_2	−30	20	54
2	Ti(O-*i*-Pr)$_4$/(*S*)-BINOL (0.1 : 0.2)	TBHP (2.0)	CCl_4-H_2O	0	46	17
3	(*S*,*S*)-**1**	PhIO (1.0)	MeCN	25	70	10
4	$VO(acac)_2$/(*R*)-**2a** (0.1 : 0.15)	H_2O_2[a]	CH_2Cl_2	25	80	54

[a] Amount of H_2O_2 not given.



Scheme 4.

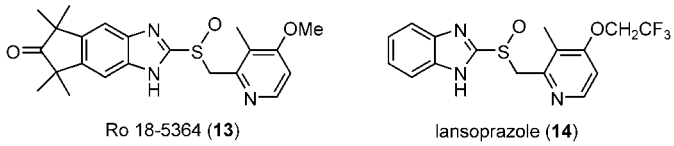
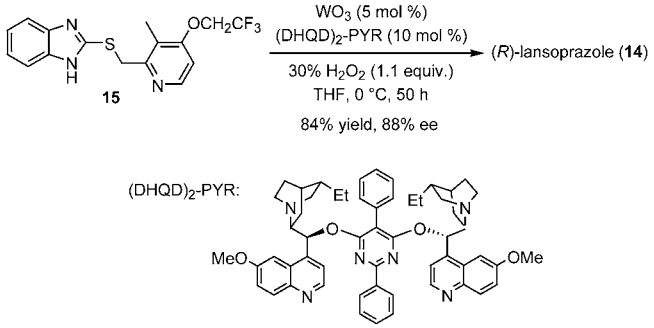


Figure 4. Efficient proton pump inhibitors.



Scheme 5.

range of 77 to 90% ee were observed in the formation of ZD3638 (**12**). Use of the Hünig's base [$(i\text{-Pr})_2$NEt] was inspired by previous studies by the same company (see Section 4) and led finally to sulfoxide **12** with 92% ee. After crystallization, the target compound was isolated with an ee > 99.5% in 73% yield.

Ro 18–5364 (**13**)[32] and lansoprazole (**14**, Prevacid™)[33] are sulfinyl-substituted benzimidazoles, and the latter compound is the current leading PPI and the 6th most sold drug in 2003 (Figure 4).[2] Both are clinically used as racemates, but attempts to prepare them in an enantioselective manner, have been reported.

The oxidation of prochiral sulfide (Ro 18-5362; not shown) according to Kagan's protocol led to the selective formation of the (*R*)- and (*S*)-enantiomers of Ro 18-5364 (**13**) (Ro 19-7860 and Ro 19-7861, respectively), but unfortunately the ee was low (30%).[32,34] In 2003, Thakur and Sudalai described a new heterogeneous catalytic system for the asymmetric oxidation of sulfide **15** leading to lansoprazole (**14**).[35] Using WO_3 as catalyst precursor, $(DHQD)_2$-PYR as ligand and aqueous hydrogen peroxide as terminal oxidant, the catalysis afforded (*R*)-lansoprazole (**14**) with 88% ee in 84% yield (Scheme 5).

Although there are no reports on different bioactivities of the enantiomers as anti-ulcer drugs yet, preliminary experiments revealed that the disposition of lansoprazole is influenced by an enantioselective protein binding and stereochemistry-depending metabolism.[36]

2.2 Diastereoselective Oxidations

In transformations of chiral compounds the existing stereogenic center can influence the formation of a new one. This asymmetric induction is distance-dependent, and high diastereoselectivities become likely when the reacting site of the molecule is close to its inducing part. If the distance is too large, external chiral reagents are required to prepare the product with the desired stereochemistry. As a consequence of interactions between the existing stereogenic center and the inducing chiral reagent, matched and mismatched effects can occur. The two metal-catalyzed asymmetric sulfide oxidations discussed below illustrate this scenario.

The ustiloxins are a family of cyclic peptides isolated from the fungus *Ustilaginoidea virens*.[37] Ustiloxin A (**16a**) and ustiloxin B (**16b**) are potent antimitotic agents, which inhibit the growth of several human cancer lines (Figure 5). Particular potency was found against human breast and lung cancer lines, and consequently ustiloxins A and B became important anti-cancer drug leads. Both ustiloxins contain a rather unusual derivative of 4-hydroxy-5-phenylsulfinylnorvaline, and for their total syntheses (2*S*,4*S*,6*R*)-**17** served as model compound.

Hutton and White reported the asymmetric synthesis of **17** by titanium-catalyzed oxidation of **18** (Scheme 6 and Table 3).[38]

With $Ti(O\text{-}i\text{-}Pr)_4$ as metal source and DET as ligand, the reaction proceeded well, but the stereoselectivity of the oxidation was low. Both enantiomers of DET afforded a slight excess of the (2*S*,4*S*,6*R*)-diastereomer of **19**, which paralleled the result obtained in a catalysis without the chiral ligand (Table 3, entries 1–3). In contrast, use of BINOL gave very good stereoselectivities. Both diastereomers of **19** became accessible by using one enantiomer of BINOL or the other, and a pronounced matched-mismatched effect occurred [88% de with (*S*)-BINOL, 96% de with (*R*)-BINOL]. The de-

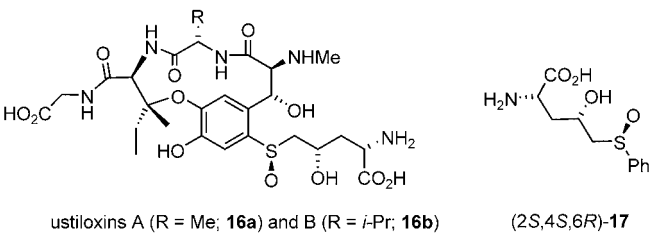
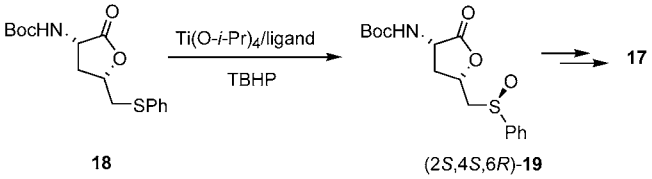


Figure 5. Potent antimitotic agents and a synthetically relevant model compound.

Table 3. Ti-catalyzed asymmetric oxidation of **18** to give **19**.

Entry	Ligand	Yield [%]	(2*S*,4*S*,6*R*)/(2*S*,4*S*,6*S*)-**19** (% de)
1	–	78	1.1:1 (5)
2	(*S*,*S*)-DET	87	1.1:1 (5)
3	(*R*,*R*)-DET	93	1.2:1 (9)
4	(*S*)-BINOL	68	1:16 (88)
5	(*R*)-BINOL	75	50:1 (96]



Scheme 6.

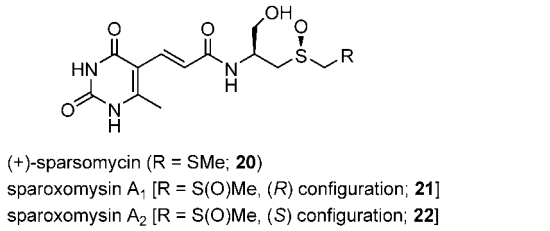
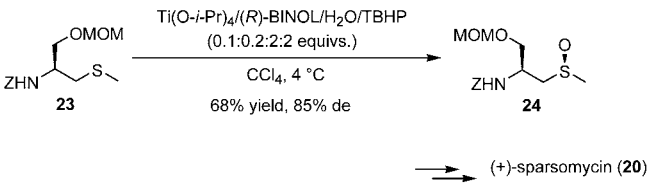


Figure 6. Sulfoxides with activity against several tumor systems, bacteria, fungi and viruses.



Scheme 7.

sired diastereomer (2*S*,4*S*,6*R*)-**19** was thereby obtained with 96% de in 75% yield.

(+)-Sparsomycin (**20**) is a metabolite of *Streptomyces sparsogenes* and *Streptomyces cuspidosporus*, which has been subject of a number of intensive biomedical investigations due to its activity against several tumor systems, bacteria, fungi and viruses (Figure 6).[39]

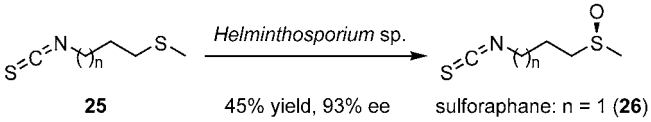
The synthesis of (+)-sparsomycin (**20**) was first reported by Helquist et al., who applied a non-stereoselective oxidation of **23** with $NaIO_4$. Thus, in order to isolate a useful synthetic precursor of (+)-sparsomycin, the diastereomers of **24** had to be separated.[39] Later, Nakajima and Ubukata reported the diastereoselective oxidation of **23**. Among all the methods assessed (Kagan, Jacobsen), Uemura's protocol gave the best results. Using (*R*)-BINOL as ligand, sulfoxide **24** was obtained with 85% de in 68% yield (Scheme 7).[40]

Noteworthy is the fact that sulfoxide **24** could also be used for the synthesis of other members of the pyrimidinylpropanamide antibiotic family, including sparoxomysins A_1 (**21**) and A_2 (**22**), which differ from sparsomycin in the oxidation level of the second sulfur atom.[40]

3 Biocatalytic Processes

For more than fifty years it has been known that enzymes are able to stereoselectively oxidize sulfides to the corresponding sulfoxides (and/or sulfones).[15c,16] The fact that the reactions are commonly carried out in water as solvent and the terminal oxidant is generally air, makes this approach environmentally friendly and most appealing for industrial applications. In fact, there are two major groups of enzymes that have been used for this biotransformation: peroxidases and monooxygenases. Although a few impressive results in terms of yield and stereoselectivity have been obtained with isolated enzymes, the necessity of special equipment and experience for the purification of the enzyme (most of them are not commercially available) as well as the requirement of tedious regenerating systems for the expensive cofactors (such as FAD or $NADP^+$) hamper this option (with a few exceptions) from being applied on a preparative scale. As most biocatalytic redox reactions, enzymatic sulfoxidations are therefore preferably carried out with whole cell systems. These are readily available in high quantities (*via* self-replication) and the metabolism of the microorganism takes care of the regeneration of the cofactor.

(*S*)-Sulforaphane (**26**) is a potent inducer of phase II detoxification enzymes in mammalian metabolism and is present in broccoli and related vegetables. Holland described its preparation by enantioselective oxidation of the corresponding sulfide **25** using the fungus *Helminthosporium* sp. NRRL 4671 giving (*S*)-sulforaphane with 93% ee in 45% yield (Scheme 8).[41]



Scheme 8.

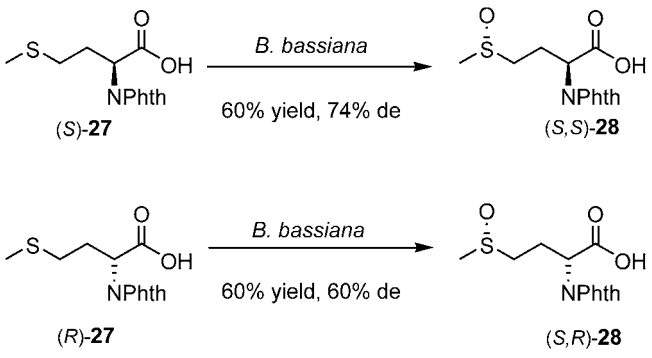
In this study, also some higher analogues, that had been isolated from various plant sources, as well as their precursors, were prepared (in up to 62% yield and with >95% ee). Interestingly, the fungus *Mortierella isabellina* ATCC 42613 produced the opposite enantiomer in most cases, albeit less stereoselectively and generally in lower yield (due to partial overoxidation to the corresponding sulfone).

The same group also reported the synthesis of all four stereoisomers of methionine sulfoxide (**28**). Oxidation and reduction of methionine are important since they have been implicated in the modulation of the potassium channel function and in the cellular response to oxidative stress. Diastereoselective sulfoxidation of both *N*-phthaloyl-(*S*)- and -(*R*)-methionine [(*S*)-**27** and (*R*)-**27**, respectively] with whole cells from the fungus *Beauveria bassiana* ATCC 7159 yielded mainly sulfoxides **28** with *S* configuration at the sulfur atom (with 74% and 60% de, respectively). Crystallization from methanol or silica gel chromatography led to the diastereomerically pure sulfoxides (*S,S*)-**28** and (*S,R*)-**28** (each in 60% overall yield), which could be quantitatively deprotected by treatment with hydrazine (Scheme 9).[42]

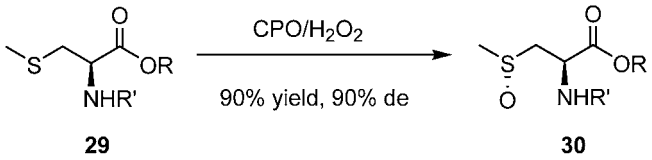
In a complementary manner, the preparation of the minor diastereomers (having the *R* configuration at the sulfur atom) could be achieved by oxidations of **27** with hydrogen peroxide. Although these sulfoxidations took place stereorandomly, both the *l* (homochiral) isomers of **28** [(*R,R*)- and (*S,S*)-**28**] and the *ul* (heterochiral) products [(*R,S*)- and (*S,R*)-**28**] could be isolated by crystallization and chromatography, respectively.

It was then demonstrated that the related fungus *Beauveria caledonica* ATCC 64970 was more efficient for these processes, giving up to 92% de. In a subsequent study both fungi were applied to the sulfoxidation of ethionine (not shown), whose carcinogenic properties have been linked to its *in vivo* oxidation.[43] The analogous *N*-phthaloyl-*S*-methyl-L-cysteine (**29** with R = H) was also tested as substrate, since derivatives of *S*-methyl-L-cysteine have been reported to be involved in a variety of biological processes, such as aroma and flavor components or antibacterial activities. Surprisingly, neither of the two fungi was able to catalyze this oxidation. Chloroperoxidase (CPO) from *Caldariomyces fumago*, in contrast, very efficiently oxidized esters of *S*-alkylcysteines (**29** with R = alkyl) with hydrogen peroxide giving the corresponding products **30** with 90% de in up to 90% yield (Scheme 10).[44]

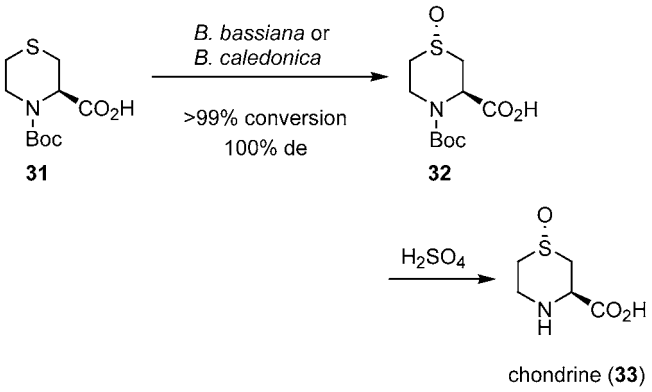
Interestingly, the biotransformation of *N-tert*-butoxycarbonyl-4-thiamorpholine-2-carboxylic acid (**31**), which is a cyclic *N*-alkylcysteine derivative, gave a quantitative conversion to the corresponding sulfoxide **32** with both *B. bassiana* and *B. caledonica*. The diastereoselection was complete. Removal of the Boc group yielded the natural product chondrine (**33**), which had been isolated from the algae *Chondria crassicaulis* and



Scheme 9.



Scheme 10.

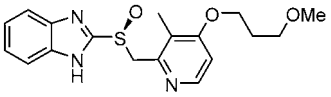


Scheme 11.

which is closely related to flavor precursors of onions (Scheme 11).

Nagasawa and co-workers carried out a microbial enantioselective sulfide oxidation with the fungus *Cunninghamella echinulata* MK40, which yielded the *S* enantiomer of the PPI rabeprazole (**34**, Figure 7). The reaction proceeded with excellent enantioselectivity, and the sulfoxide was obtained with >99% ee. Gratifyingly, the biotransformation gave no sulfone, and in order to obtain a higher productivity, glucose had to be added after 24 h reaction time. The microorganism proved to be highly substrate specific, since the analogous omeprazole sulfide was only slowly oxidized, and lansoprazole sulfide was not even accepted as substrate. Quite interesting, when the reaction was carried out with horseradish peroxidase, rabeprazole was obtained in racemic form.[45]

The non-steroidal anti-inflammatory drug sulindac (**8**) is administered clinically as a racemate. *In vivo* it is



(*S*)-rabeprazole (**34**)

Figure 7. The proton-pump inhibitor (*S*)-rabeprazole.

then reduced to the corresponding sulfide (Figure 3). This reversible process leads to an enrichment in the *R*-configured sulfoxide in the serum and the urine of the patients. In order to establish the origin for this enantioenrichment, Hall and co-workers studied the asymmetric oxidation of the sulindac sulfide with renal microsomes and flavin-monooxygenases. Although up to 97% ee was reached, the restricted availability of these biocatalytic systems makes it unlikely that they will find a direct application in preparative organic chemistry.[46]

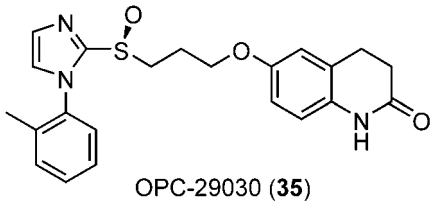
In fact, an enzymatic oxidation of sulindac sulfide had already been analyzed by Walsh and co-workers twenty years before using hog liver FAD-monooxygenase, which they assumed to be involved in the metabolism of the drug. This enzyme produced sulindac in virtually enantiopure form. In the same study, the authors used another enzyme (cyclohexanone monooxygenase from *Acinetobacter* NCIB9871) for the sulfoxidation of ethyl *p*-tolyl sulfide, and quite surprisingly they did not report on its application in the oxidation of sulindac sulfide.[47] In part this might be due to the fact that this latter microorganism is pathogenic and that the isolation of the enzyme therefore requires special expertise, making the overall process less "user-friendly" for synthetic purposes.

Recent developments in the laboratories of Kayser and Stewart in the field of genetic engineering will most likely open a new door for this enzyme, which was cloned and over-expressed in *E. coli* and baker's yeast. Although problems related to the competition of native enzymes from the host microorganisms were reported, this strategy undoubtedly represented a significant improvement in the options of biocatalytic sulfoxidations.[48]

4 Large Scale Applications

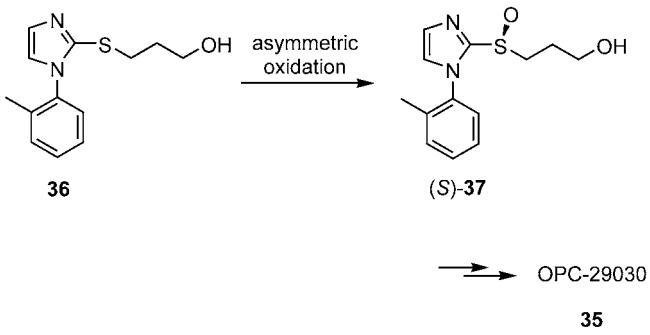
Despite the unrelenting progress in the research of catalytic asymmetric chemistry, relatively few catalytic processes are currently operating on a commercial scale.[2,49] However, there are some notable examples of metal-catalyzed asymmetric sulfide oxidations that have been performed on a multi-kilogram scale. All of them involve chiral titanium catalysts.

In 1995, researchers from Otsuka Pharmaceutical synthesized a sulfinyl derivative that exhibits potent inhibition of platelet adhesion by interfering with the release of 12(*S*)-hydroxyeicosatetraenoic acid (12-HETE).



OPC-29030 (**35**)

Figure 8. A platelet adhesion inhibitor.



36 (*S*)-**37** **35**

Scheme 12.

(Such platelets play a significant role in the early phase of arteriosclerosis.) Among the three forms of this compound (racemate, *R*- and *S*-enantiomer), the (*S*)-enantiomer, OPC-29030 (**35**, Figure 8), showed the best pharmacological profile during *in vivo* testing.[50]

The synthesis of OPC-29030 involves an asymmetric oxidation of sulfide **36**, which leads to sulfoxide (*S*)-**37** as key intermediate (Scheme 12 and Table 4).[51]

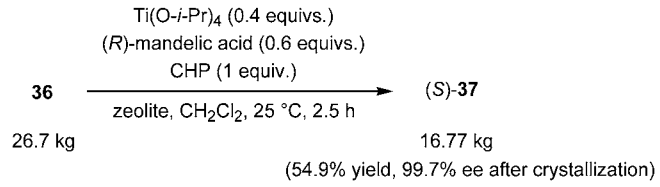
The application of the previously described methods (using the catalyst systems introduced by Kagan, Modena, Uemura and Jacobsen, entries 1–4) gave moderate or even poor enantioselectivities ($ee_{max} = 54\%$). Screening of several (potential) ligands in combination with $Ti(O\text{-}i\text{-}Pr)_4$ as metal source, and CHP as oxidant, revealed that (*R*)-mandelic acid afforded sulfoxide **37** in high yields (89%) and with good enantioselectivity (76% ee, entry 5). The use of the *p*-methoxy-substituted analogue of mandelic acid increased the enantioselectivity slightly (77% ee), but the yield significantly decreased (to 63%, entry 6). Moreover, it was found that performing the reaction without molecular sieves and adding water to the reaction medium (1 equiv.) did not affect the enantioselectivity.[51b] While the nature of the catalytic species remained unknown, parallel experiments demonstrated that the presence of the $(CH_2)_3OH$ chain was essential for the enantioselectivity and that this moiety played a key role in the active species. The asymmetric oxidation was performed with 26.7 kg of **36** in a pilot plant and, after crystallization, 16.77 kg (54.9% yield) of sulfoxide (*S*)-**37** with 99.7% ee were obtained (Scheme 13).

Several aspects make this oxidation particularly suitable for large-scale production: 1) the reaction proceeds

Table 4. Metal-catalyzed asymmetric oxidation of **36** to give (*S*)-**37**.

Entry	Catalyst (equivs.)	Oxidant (equivs.)	Solvent	Temp. [°C]	Yield [%][a]	ee [%]
1[b]	Ti(O-*i*-Pr)$_4$/(*R*,*R*)-DET/H_2O (0.5:1.0:0.5)	CHP (1.0)	$C_2H_4Cl_2$	−30	n.g.	4
2[b]	Ti(O-*i*-Pr)$_4$/(*R*,*R*)-DET (0.5:2)	CHP (1.0)	CH_2Cl_2	−20	78	54
3[b]	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL (0.5:1.0)	CHP (2.0)	CH_2Cl_2	25	n.g.	36
4	(−)-**1**	H_2O_2 in *t*-BuOH	MeCN	25	n.g.	14
5[b]	Ti(O-*i*-Pr)$_4$/(*R*)-mandelic acid (0.4:0.6)	CHP (1.0)	CH_2Cl_2	25	89	76
6[b]	Ti(O-*i*-Pr)$_4$/(*R*)-4-MeOC$_6$H$_4$CH(OH)CO$_2$H (0.4:0.6)	CHP (1.0)	CH_2Cl_2	25	63	77

[a] n.g.: not given.
[b] Reaction performed in presence of molecular sieves MS 4 Å.



Scheme 13.

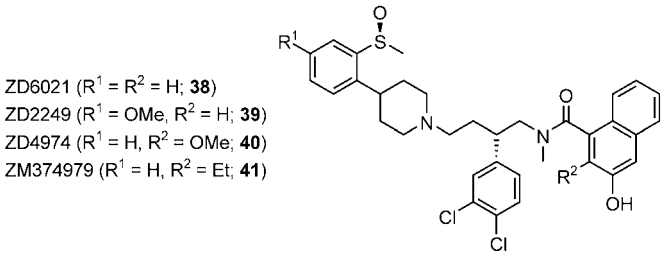
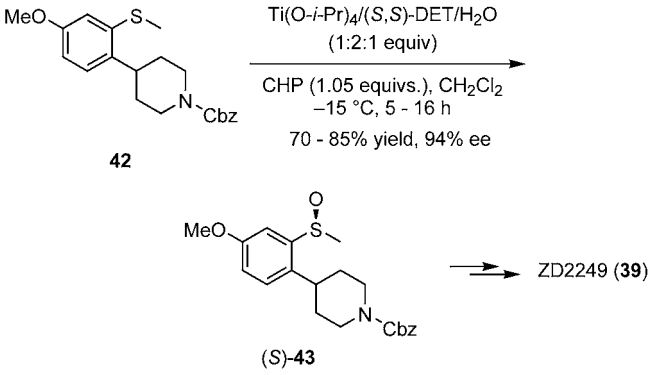


Figure 9. Neurokinin antagonists.



Scheme 14.

at room temperature without a negative influence of atmospheric moisture; 2) the amounts of the titanium reagent and the chiral ligand are at an acceptable level (40 mol % and 60 mol %, respectively); 3) mandelic acid is inexpensive and can be easily recovered by extraction with a weak base.

In the past few years, AstraZeneca has started an active research and development program investigating neurokinin antagonists for the treatment of asthma, depression and urinary incontinence. In this project a series of four structurally related compounds, ZD6021 (**38**), ZD2249 (**39**), ZD4974 (**40**) and ZM374979 (**41**) had to be evaluated in preliminary toxicity and clinical studies.[52]

This obliged the Process R&D Department to prepare approximately 1 kg of each compound as quickly as possible, and they were able to deliver the required quantity of each compound within 6–7 months from the start of lab work.[53] The processes, which involved an asymmetric oxidation of sulfide **42** according to Kagan's protocol, were scaled up to 100 L since process safety and robustness were not compromised (Scheme 14).[53d]

Various parameters had to be optimized. For example, the temperature was found to be critical. Thus, performing the oxidation at −5 °C gave (*S*)-**43** with an ee of 85%, and at −15 °C the ee was improved to up to 94%. Moreover, as the addition of CHP was exothermic, which eroded the enantioselectivity, the addition rate had to be adjusted so that the internal temperature could be kept at a suitable level. Under those conditions, a good conversion was achieved, and only a small amount of sulfone was detected (1.3%). An appropriate work-up completely eliminated cumene alcohol, titanium residues and DET (< 0.1%). Sulfoxide **43** was thus obtained with high ee in good yield (94 and 70–86%, respectively) having a purity that was sufficient for the following step.

Pitchen and co-workers, from Rhône-Poulenc Rorer, described the preparation of multi-kilogram batches of two enantiopure drugs: RP 52891 (**44**) and RP 73163 (**45**, Figure 10). The enantiomers of these compounds are inactive.[14]

RP 52891 (**44**) is a potassium channel opener which has possible clinical indications in the treatment of, for instance, hypertension, coronary artery and peripheral vascular disease and obstructive airway disease.[54] Starting with an oxidation of sulfide **46** (Figure 11) was obviously not the best strategy as four possible isomeric sulfoxides could be expected to result from the racemic mixture of **46**. Assessments with sulfide **47** led to unsatisfac-

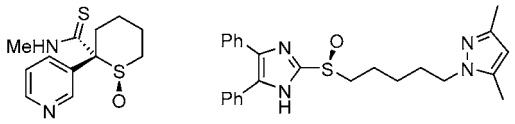


Figure 10. A potassium channel opener and a hypocholesterolemic agent.

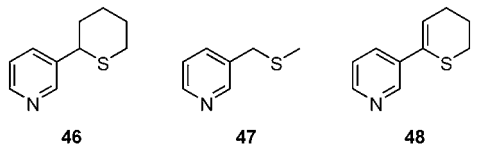
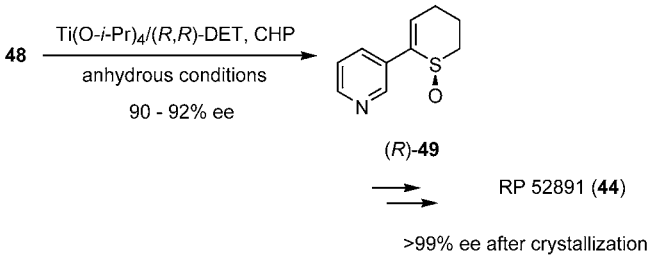
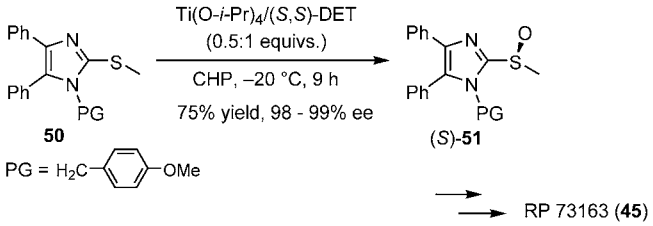


Figure 11. Potential substrates for the asymmetric preparation of RP 52891.



Scheme 15.



Scheme 16.

tory results (<20% ee), which were attributed to the facile rotation about the CH_2–S bond. Thus, oxidation of a more rigid substrate such as sulfide **48**, where the sp^3 nicotinic CH_2 group is replaced by an sp^2 center, appeared more promising (Figure 11).[14]

Indeed, the hypothesis was confirmed, and with Ti(O-*i*-Pr)$_4$, (*R*,*R*)-DET and CHP as oxidant under anhydrous conditions vinylic sulfide **48** was oxidized giving sulfoxide (*R*)-**49** with 90–92% ee (Scheme 15).[14] Subsequently, after two further steps, RP 52891 (**44**) was obtained having more than 99% ee after crystallization.

RP 73163 (**45**) is a hypocholesterolemic agent, which acts by inhibiting the enzyme ACAT. Probably due to the large size of both substituents at the sulfur atom, Kagan's titanium-catalyzed enantioselective oxidation of the corresponding sulfide afforded the desired sulfoxide in good yield but as racemic mixture.[55] The authors then decided to perform the asymmetric oxidation on substrate **50** bearing a methyl group instead of an alkylpyrazole chain. First assessments showed that the presence of a protecting group on the imidazole moiety greatly enhanced the enantioselectivity with *p*-methoxybenzyl groups proving optimal. Further optimizations were required, and with sub-stoichiometric amounts of the titanium reagent and under anhydrous conditions, sulfoxide (*S*)-**51** was obtained after acidic work-up as a crystalline material having an ee of 98–99% in 75% yield (Scheme 16).[14,55] Surprisingly, sulfoxide (*S*)-**51** was completely stable under acidic conditions. RP 73163 (**45**) with 99% ee (after recystallization) could then be obtained after three further steps.

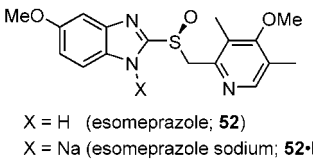
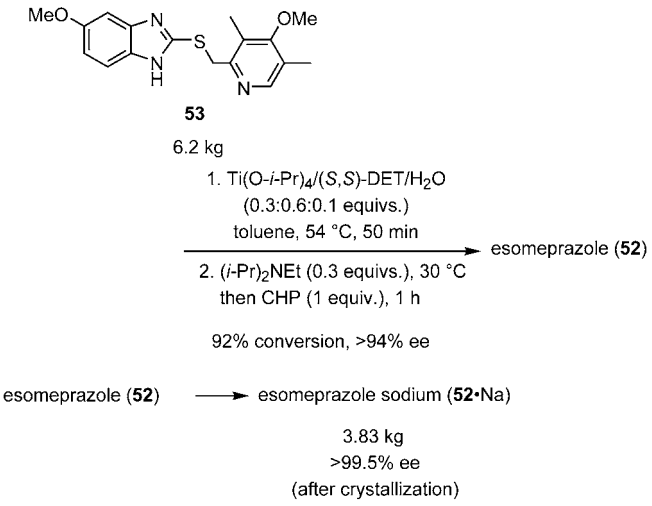


Figure 12. Esomeprazole and its sodium salt.

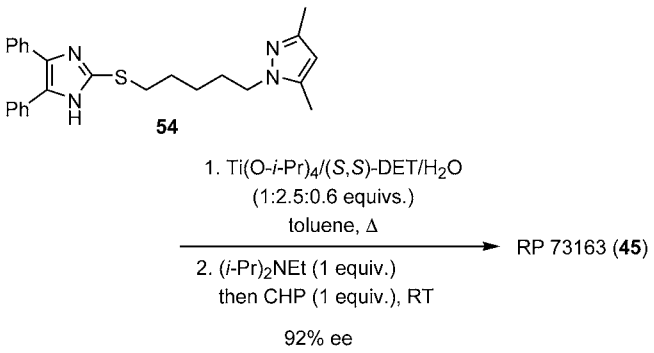


Scheme 17.

The most remarkable use of a metal-catalyzed sulfide oxidation is the synthesis of esomeprazole (**52**), the (*S*)-enantiomer of omeprazole (Figure 12).[56] Esomeprazole is commercialized as its magnesium salt (called perprazole), under the name of Nexium™.

While the patent of Astra is ten years old, the synthesis of the esomeprazole sodium (**52**·Na) has only been reported in 2000. Its synthesis involves the use of a modified Kagan reagent at the last step of the synthesis (Scheme 17).[57]

The process relies on very specific features and shows marked differences with respect to the usual conditions. Whereas Kagan's reagent is normally carefully preformed in chlorinated solvents and used at low temperatures, in the Astra process [Ti(O-*i*-Pr)$_4$], DET, water and the substrate are all mixed together in warm toluene



Scheme 18.

(54 °C) without particular precautions, under air. Moreover, the subsequent addition of a weak base, preferably $(i\text{-Pr})_2$NEt, before adding the oxidant is necessary for obtaining a high enantioselectivity. The role of the base is still unclear, but it can be assumed that it also helps to stabilize the rather acid-sensitive product. Under these conditions, 92% conversion of **53** into esomeprazole with excellent 94% ee can be achieved. After work-up and crystallization, the sodium salt of esomeprazole is obtained in almost enantiopure form (>99.5% ee). This reaction has been performed on a 6.2 kg scale, affording 3.83 kg of esomeprazole sodium (**52**·Na).

Related reaction conditions have also been applied for the asymmetric oxidation of sulfide **54** (Scheme 18), which is the direct precursor of RP73163 (**45**).[57b] Previous attempts to oxidize **54** directly had been unsuccessful (*vide supra*), but under conditions closely related to the ones used in the esomeprazole synthesis, RP73163 (**45**) was obtained with 92% ee. In this case, however, stoichiometric quantities of the titanium reagent were required to achieve such high enantioselectivity.[58]

In the field of biocatalysis very few sulfoxidation processes have been significantly scaled-up for the synthesis of biologically active compounds. Although several clear advantages have been already pointed out (*vide supra*), some key bottlenecks, such as inhibition of the enzyme activity by (high concentration of) both substrate and product, the low availability of catalyst and the downstream product recovery, due (in part) to the high dilution conditions have so far hampered the application of this methodology.[59] In spite of this, it should be mentioned that important research has been done in the laboratories of Astra for the preparation of esomeprazole and some related sulfoxides by microbial oxidation. Using whole cells from the fungus *Penicillium frequentans*, enantiopure sulfoxides could thereby be obtained.[60]

5 Conclusion

The importance of optically active sulfoxides in current medicinal chemistry is highlighted by the "billion dollar molecule" esomeprazole, a remarkable anti-ulcer agent. When it comes to synthesis, asymmetric catalysis applied on an industrial scale has already found its place in the sulfoxidation area. In this context, both metal complexes and enzymes have been shown to be highly efficient in the preparation of sulfinyl-containing compounds with biological activity. Both methodologies are complementary in many cases, and metal-catalyzed processes have already been applied on a multi-kilogram scale. New scientific and technological advances that overcome the limitations of current asymmetric sulfide oxidations, such as the possibility of using more environmentally friendly and economical metals or the cloning and over-expressing of enzymes[61] in easier-to-handle microorganisms, will lead this oxidation chemistry into a bright future.

Acknowledgements

We are grateful to the Fonds der Chemischen Industrie and to the Deutsche Forschungsgemeinschaft (DFG) within the SFB 380 "Asymmetric Synthesis by Chemical and Biological Methods" for financial support. We also thank the Alexander von Humboldt Foundation and the European Commission for postdoctoral fellowships (to J. L. and J. R. D. respectively).

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