Factors influencing the selectivity in asymmetric oxidation of sulfides attached to nitrogen containing heterocycles†

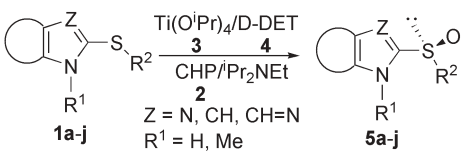
Muthu Seenivasaperumal,[a] Hans-Jürgen Federsel,[b] Anne Ertan[c] and Kálmán J. Szabó*[a]

Received (in Cambridge, UK) 18th January 2007, Accepted 12th February 2007
First published as an Advance Article on the web 2nd March 2007
DOI: 10.1039/b700860k

Asymmetric oxidation of heterocyclic sulfides, including imidazole, benzimidazole, indole and pyrimidine derivatives, were studied using a tartrate/Ti(^{i}OPr)$_4$ catalyst system.

The esomeprazole process of AstraZeneca is one of the less than two dozens of cases when asymmetric catalysis has been used for manufacturing of pharmaceuticals or other important chemicals.[1a–c] Consequently there is a strong inherent interest for understanding the basic principles of this chemistry and to assess the synthetic scope of related selective oxidation reactions.[2] The original process involves asymmetric oxidation (Scheme 1) of pyrmetazole (**1a**) using cumene hydroperoxide (**2**) together with Hünig's base (^{i}Pr$_2$NEt) as a crucial component in the presence of catalytic amounts of Ti(^{i}OPr)$_4$ (**3**) and diethyl D-tartrate (**4**) affording esomeprazole (**5a**), the active ingredient in AstraZeneca's antiulcer drug Nexium® (Table 1, entry 1) at >90% ee.[1d,e] Although, a number of excellent asymmetric sulfoxidation systems have been developed in recent years[3a,4,5] the highly efficient and operationally simple Ti(^{i}OPr)$_4$ (**3**)/tartrate (**4**) system employed in the esomerazole process still has a number of unexplored attractive features. For example, the asymmetric sulfoxidation of **1a** can be achieved with a high enantiomeric excess, in spite of the fact that the substituents of the sulfur atom are of similar size.[1e]

We have now found that the high enantioselectivity of the esomeprazole process arises from the electronic effects of the imidazole motif in **1a**, and that the beneficial features of the oxidation reaction can be extended to a large variety of imidazole derivatives obeying a certain substituent pattern. These recent findings are based on catalytic oxidation of a wide range of heteroaromatic/aromatic sulfides **1a–k** using the reaction conditions of the esomeprazole process. In addition, we were able to asses some previous hints concerning the reactivity and selectivity



Scheme 1 Asymmetric sulfoxidation of nitrogen containing heterocycles.

[a]*Stockholm University, Arrhenius Laboratory, Department of Organic Chemistry, Sweden. E-mail: kalman@organ.su.se.*
[b]*Global Process R&D, AstraZeneca, SE-151 85, Södertälje, Sweden*
[c]*Early Development, Pharmaceutical and Analytical R&D, AstraZeneca, SE-151 85, Södertälje, Sweden*

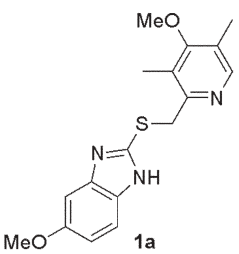
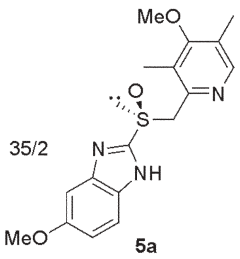
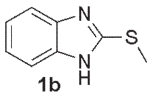
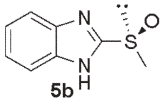
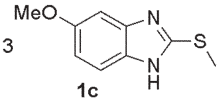
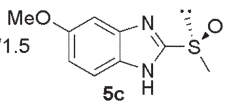
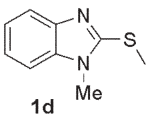
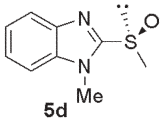
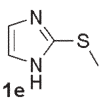
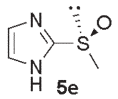
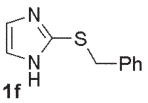
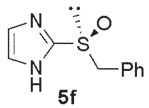
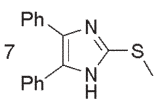
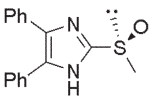
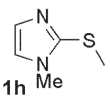
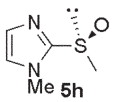
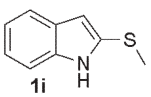
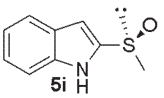
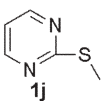
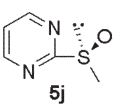
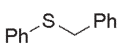
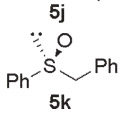
† Electronic supplementary information (ESI) available: Experimental procedures, NMR data as well as ^{1}H and ^{13}C NMR spectra of products **5a–g** and **5i–k** and the X-ray structure of **5e**. See DOI: 10.1039/b700860k

of the sulfoxidation of heterocyclic substrates that were published in connection with the asymmetric synthesis of esomeprazole.[1e] In a typical sulfoxidation reaction we have employed[1d,e] a modified Orsay procedure.[3] Accordingly, the corresponding sulfide **1**, catalytic amounts of **4** and water (1.0/0.6/0.2 equiv.) were heated to 50 °C for 15 min followed by addition of **3** (0.3 equiv.) and this mixture was kept at 50 °C for 45 min. Subsequently, ^{i}Pr$_2$NEt and cumene hydroperoxide (CHP) **2** (0.3/1.0 equiv.) were added, and the obtained reaction mixture was stirred at the allotted temperatures and times (Table 1).

The reactivity of the various sulfides is highly dependent on the heterocyclic motifs. Oxidation of the benzimidazole containing substrates **1a–b** and **1d** (entries 1, 2, 4) required higher reaction temperature for completion than the imidazole derivatives **1e**, **1f** and **1g** (entries 5–7). In fact, competitive experiments involving imidazole derivative **1e** and benzimidazole derivative **1b** shows that under the same reaction conditions **1e** can be completely converted to **5e**, while **1b** could be recovered unchanged (Scheme 2(a)). Methoxy substitution of **1b** (**1c**) leads to increased reactivity (*cf.* entries 2 and 3), which is in line with Kagan's observation[3c] that the oxidation reaction involves an electrophilic process. Interestingly, oxidation of indole derivative **1i** can also be carried out at lower temperature (entry 9) than oxidation of benzimidazole **1b** (entry 2). Similarly to **1e** indole derivative **1i** can be oxidized to **5i** without affecting **1b** (Scheme 2(b)).

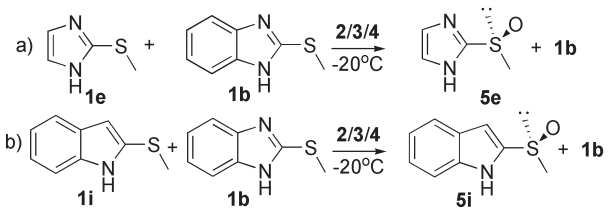
The sulfoxidation reactions proceed with very high enantioselectivity for benzimidazole derivatives **1a–c** (entries 1–3). The other functionality on the sulfur atom (*cf.* entries 1 and 2) or substitution of the fused phenyl ring (*cf.* entries 2 and 3) do not or only marginally affect the chiral induction. On the other hand, methyl substitution of one of the nitrogens of benzimidazole derivative **1b** (**1d**) leads to formation of a racemic product (entry 4). Our studies clearly demonstrate that the fused phenyl ring or other substituents are not necessary for the high level of enantioselection. Thus, imidazole derivative **1e** (entry 5) reacts with as high an enantioselectivity as **1b** (entry 2). Furthermore, according to X-ray structure determination (see ESI†)‡ the absolute configuration of the sulfur atom in product **5e** (Fig. 1) and in esomeprazole **5a** is identical (*i.e. S*-configuration). Thus, the bulky pyridyl moiety in **1a** and/or the fused phenyl ring in **1b–c** does not affect significantly the enantioselection process using the Ti(^{i}OPr)$_4$ (**3**)/diethyl D-tartrate (**4**) catalytic system. Surprisingly, the high enantioselectivity of the reaction is maintained, even if the methyl group of **1e** is replaced by a benzyl substituent (**1f**). Accordingly, oxidation of **1f** can be accomplished with a high enantioselectivity (95% ee), despite of the fact that the benzyl substituent on the sulfur atom is sterically more demanding than the heterocyclic imidazole ring

Table 1 Asymmetric oxidation of imidazole derived sulfides into corresponding sulfoxides[a]

entry	sulfide	Conditions[b]	Product	Yield[c]	ee[d]
1	 **1a**	35/2	 **5a**	78	97
2	 **1b**	35/2	 **5b**	65	98
3	 **1c**	-20/1.5	 **5c**	63	94
4	 **1d**	35/1	 **5d**	48	<2
5	 **1e**	-20/1.5	 **5e**	62	97
6	 **1f**	-20/1.5	 **5f**	61	95
7	 **1g**	-20/2	 **5g**	50	80
8	 **1h**	35/2	 **5h**	33[e]	<2
9	 **1i**	-20/0.5	 **5i**	55	69
10	 **1j**	35/2	 **5j**	35	40
11	 **1k**	-20/1	 **5k**	64	10

[a] The reactions were conducted in toluene using **2** as oxidizing reagent in the presence of 30 mol% of **3** and 60 mol% of **4** as catalyst. [b] Reaction conditions [°C/h]. [c] Unless stated otherwise isolated yield [%]. [d] Enantiomeric excess [%] determined by HPLC. For **5h** and **5j** the ee values were determined by using shift reagent. [e] The yield determined by ^{1}H NMR.

(entry 6). Thus, for the first time we could demonstrate that the high selectivity in the presence of two similarly large substituents (observed in the esomeprazole process[1e]) is not restricted to oxidation of **1a** but it is an inherent property of the oxidation of imidazole sulfide derivatives, such as **1f**.



Scheme 2 Competitive sulfoxidation of benzimidazole derivative **1b** with imidazole (**1e**) and indole (**1i**) based substrates.

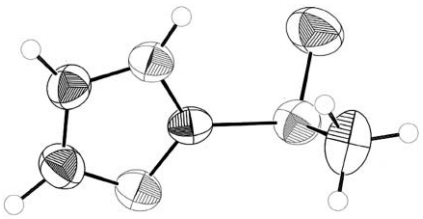
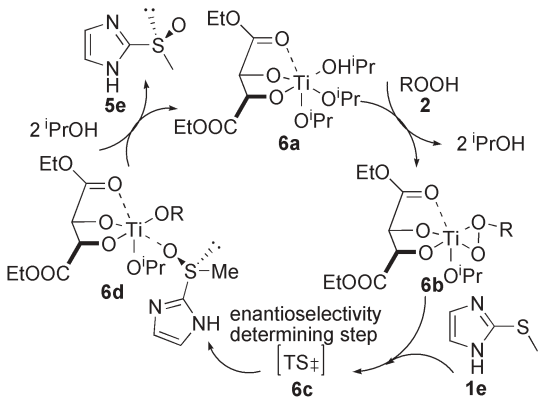


Fig. 1 X-Ray structure of **5e** displaying *S*-configuration for the sulfur atom, which is the same absolute configuration as in esomeprazole **5a**. Displacement ellipsoids are drawn at the 50% probability level.

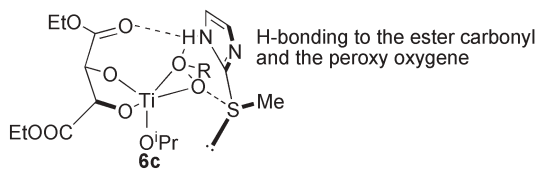
Furthermore, the high level of enantioselectivity in oxidation of **1f** is in sharp contrast to the selectivity in the corresponding process for the closely isosteric phenyl benzyl sulfide (**1k**). Thus, replacement of the imidazole moiety of **1f** with the isosteric phenyl group (**1k**) leads to drop of the enantiomeric excess from 97% to 10% (entries 6 and 11). Phenyl substitution (**1g**) of the carbon atoms of the imidazole ring (entry 7) leads to a slight decrease of the enantioselectivity (80% ee). Similarly to the benzimidazole substrate (**1d**) methylation of the imidazole ring nitrogen (**1h**) leads to a complete loss of the enantioselectivity affording racemic product **5h** (entry 8).

The fact that both (unsubstituted) nitrogen atoms are required for the high level of enantioselection can be illustrated by oxidation of indole derivative **1i**. This sulfoxidation (entry 9) proceeds with a significantly lower enantiomeric excess (69% ee) than the corresponding process (entry 2) with **1b** (98% ee). The relevance of the five membered ring imidazole architecture for the enantioselection can be illuminated by comparison of the efficiency of the oxidation of pyrimidine derivative **1j** with **1e** (entries 5 and 10). While **1e** is oxidized with an excellent enantioselectivity, sulfoxidation of **1j** proceeds with only moderate (40%) ee. Application of base (^{i}Pr$_2$NEt) is necessary to obtain a high selectivity in oxidation of imidazole derivative **1e**, as the ee was decreased from 97 to 77%, when the base was omitted. On the contrary, the enantioselectivity is practically invariant with respect to application of base for other substrates, such as indole derivative **1i** (69 → 61%) or phenyl sulfide **5k** (10 → 7%).[3c]

The above results clearly show that the smallest subunit required for an efficient **3/4** catalyzed asymmetric sulfoxidation of pyrmetazole **1a** and related heterocyclic systems **1b–1h** is the presence of an imidazole ring with unsubstituted nitrogen atoms. Although, the exact role of the heterocyclic systems is not completely known in the presented reactions (Scheme 1), it can be concluded that the imidazole ring is more efficient in directing the enantioselection process than the isosteric phenyl group. Previous reports[3a,b,4] indicate that by using the Orsay reagent the sulfoxidation process involves a monomeric titanium complex and in the transition state structure of the enantioselectivity determining step the sulfur atom



Scheme 3 Plausible catalytic cycle.



Scheme 4 Possible ligand substrate interactions in the assumed TS of the oxidation.

is not coordinated to titanium. Based on these assumptions[3a,b,4] a plausible catalytic cycle was constructed (Scheme 3). Accordingly, the catalytic cycle is supposed to start with complex **6a**, in which the tartrate is coordinated to titanium in a bidentate fashion. The empty coordination site of the metal atom probably interacts with the carbonyl group of the tartrate.[3b,4] The next step of the catalytic cycle is formation of complex **6b** from **6a** by an η^2-coordination of peroxide **2**.[6] Subsequently, complex **6b** oxidizes the corresponding sulfide, such as **1e**, to give **6d**, in which the sulfoxide product is probably coordinated[5e] to titanium. Kagan's assumption that the substrate is not coordinated to titanium is based on the conclusion that the oxidation of sulfur is an electrophilic process.[3c] As we came to the same conclusion comparing the reactivity of **1b** and **1c** (*vide supra*), the imidazole based substrate probably does not coordinate to titanium either under the oxidation process. Considering the electrophilic nature of the oxidation the increased reactivity of the indole derivative **1i** compared to the isosteric benzimidazole derivative **1b** (Scheme 2(b)) can easily be rationalized, as the indole moiety (comprising one nitrogen) is a better electron donor than benzimidazole (with two nitrogens). Furthermore, the steric effects are also expected to influence the reactivity. Thus the bulkier benzimidazole sulfide **1b** is oxidized much more slowly than **1e** (Scheme 2(a)). The final step of the catalytic cycle is decomplexation of the product (*e.g.* **5e**), which also leads to regeneration of the catalyst (**6a**).

The most important step of the catalytic cycle is oxidation of **1e** (**6b** → **6d**) *via* TS structure **6c**, which determines the enantioselectivity of the reaction. The high levels of enantioselectivity obtained for functionalized imidazole sulfides **1a–c** and **1e–1f** can be explained by stabilizing electronic interactions between the substrate and ligand in **6c**. For example, the protonated nitrogen of the imidazole ring may be involved in hydrogen bonding with the carbonyl group of the tartrate and/or one of the oxygens of the peroxy ligand (Scheme 4). However, methyl substitution of the imidazole nitrogen (*e.g.* **1d** and **1h**) results in weakening of the interactions between the chiral complex and the heterocyclic substrate, which leads to a decrease in enantioselectivity. Application of base is required for improvement of the enantioselectivity by about 20–25%. This modulation effect is probably exerted by association of $^{i}Pr_2NEt$ to the substrate or to the titanium complex.

In summary, we have shown that imidazole substituents in heterocyclic sulfides exert important effects on the enantioselection of the oxidation reaction, when titanium tartrate complexes are employed as catalysts. Substitution of the carbon atoms of the imidazole ring and application of sterically similar substituents on sulfur does not influence the high enantioselectivity of the sulfoxidation.

The authors want to express their gratitude to Dr Hans Adolfsson, Stockholm University and Dr Sverker von Unge and Dr Magnus Larsson, AstraZeneca R&D for the fruitful discussions. This work was supported by AstraZeneca and the Swedish Research Council (VR). The authors also acknowledge the Knut and Alice Wallenberg Foundation for funding the purchase of a UPLC instrument.

Notes and references

‡ CCDC 634379. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b700860k

1 (*a*) *Asymmetric Catalysis on Industrial Scale*, ed. H.-U. Blaser and E. Schmidt, Wiley-VCH, Weinheim, 2004; (*b*) H.-U. Blaser, B. Pugin and F. Spindler, *J. Mol. Catal. A: Chem.*, 2005, **231**, 1; (*c*) H.-J. Federsel, Stereoselective Synthesis of Drugs – An Industrial Perspective, in *Chirality in Drug Research*, ed. E. Francotte and W. Lindner, Wiley-VCH, Weinheim, 2006, vol. 33, p. 29; (*d*) H.-J. Federsel and M. Larsson, An Innovative Asymmetric Sulfide Oxidation: The Process Development History Behind the New Antiulcer Agent Esomeprazole, in ref. 1*a*, ch. IV:7, p. 413; (*e*) H. Cotton, T. Elebring, M. Larsson, L. Li, H. Sörensen and S. von Unge, *Tetrahedron: Asymmetry*, 2000, **11**, 3819.

2 H.-J. Federsel, *Nat. Rev. Drug Discovery*, 2005, **4**, 685.

3 (*a*) H. B. Kagan and T. O. Luukas, Catalytic Asymmetric Sulfide Oxidations, in *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 2004, vol. 2, p. 479; (*b*) H. B. Kagan, Asymmetric Oxidation of Sulfides, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, Weinheim, 2000, p. 327; (*c*) P. Pitchen, E. Duñach, M. N. Deshmukh and H. B. Kagan, *J. Am. Chem. Soc.*, 1984, **106**, 8188; (*d*) J.-M. Brunel, P. Diter, M. Deutsch and H. B. Kagan, *J. Org. Chem.*, 1995, **60**, 8086; (*e*) S. H. Zhao, O. Samuel and H. B. Kagan, *Tetrahedron*, 1987, **43**, 5135.

4 (*a*) I. Fernández and N. Khiar, *Chem. Rev.*, 2003, **103**, 3651; (*b*) C. Bolm, K. Muñiz and J. P. Hildebrand, Oxidation of Sulfides, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Berlin, 1999, vol. 2, p. 697; (*c*) L. Legros, J. R. Dehli and C. Bolm, *Adv. Synth. Catal.*, 2005, **347**, 19.

5 (*a*) N. Komatsu, M. Hashizume, T. Sugita and S. Uemura, *J. Org. Chem.*, 1993, **58**, 4529; (*b*) N. Komatsu, M. Hashizume, T. Sugita and S. Uemura, *J. Org. Chem.*, 1993, **58**, 7624; (*c*) M. T. Reetz, C. Merk, G. Naberfeld, J. Rudolph, N. Griebenow and R. Goddard, *Tetrahedron Lett.*, 1997, **38**, 5273; (*d*) C. Bolm and O. A. G. Dabard, *Synlett*, 1999, 360; (*e*) F. Di Furia, G. Licini, G. Modena, R. Motterle and W. A. Nugent, *J. Org. Chem.*, 1996, **61**, 5175; (*f*) M. Bonchio, S. Calloni, F. D. Furia, G. Licini, G. Modena, S. Moro and W. A. Nugent, *J. Am. Chem. Soc.*, 1997, **119**, 6935; (*g*) S. Colonna, A. Manfredi, M. Spadoni, L. Casella and M. Gulotti, *J. Chem. Soc., Perkin Trans. 1*, 1987, 71; (*h*) C. Bolm and F. Bienewald, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2640; (*i*) J. Legros and C. Bolm, *Chem. Eur. J.*, 2005, **11**, 1086; (*j*) M. Palucki, P. Hanson and E. N. Jacobsen, *Tetrahedron Lett.*, 1992, **33**, 7111; (*k*) K. Noda, N. Hosoya, K. Yanai, R. Irie and T. Katsuki, *Tetrahedron Lett.*, 1994, **35**, 1887; (*l*) K. Imagawa, T. Nagata, T. Yamada and T. Mukiyama, *Chem. Lett.*, 1995, 335.

6 G. Boche, K. Möbus, K. Harms and M. Marsch, *J. Am. Chem. Soc.*, 1996, **118**, 2770.