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Catalytic Asymmetric Oxidation of Heteroaromatic Sulfides with *tert*-Butyl Hydroperoxide Catalyzed by a Titanium Complex with a New Chiral 1,2-Diphenylethane-1,2-diol Ligand

Biao Jiang,*[a] Xiao-Long Zhao,[a] Jia-Jia Dong,[a] and Wan-Jun Wang[a]

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Heteroaromatic sulfoxides, especially 1*H*-benzimidazolyl pyridinylmethyl sulfoxides, usually used as the blockbuster gastric proton pump inhibitors (PPIs), have been prepared highly enantioselectivily by catalytic asymmetric oxidation of sulfides attached to nitrogen-containing heterocyles with *tert*-butyl hydroperoxide in the presence of a chiral titanium complex, formed in situ from Ti(*i*PrO)$_4$, chiral 1,2-diphenylethane-1,2-diol **3c** and water. The chiral sufoxides were obtained in high yield (97 %) with excellent enantiomeric excess (up to 98 %).

Introduction

Catalytic asymmetric oxidation of sulfides to chiral sulfoxides is an important synthetic method.[1] The efficiency of metal-catalyzed asymmetric sulfide oxidation is dependent on the structure of the starting material, and the reaction conditions, which 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 sulfides of the general structure ArSMe (Aryl methyl sulfides) 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.[2] Highly enantioselective oxidations of sulfides bearing two large and similarly sized groups, especially heteroaromatic ones, have scarcely been reported, such as the blockbuster gastric proton pump inhibitor (PPI) esomeprazole, which is a chiral sulfoxide bearing two large groups: benzimidazolyl and pyridinylmethyl.[3,4] The chiral switch drug esomeprazole [(*S*) isomer of omeprazole], the first single-optical-isomer PPI, generally provides better acid control than current racemic PPIs and has a favourable pharmacokinetic profile relative to omeprazole.[5] Owing to the existence of pharmacological and toxicological differences between stereoisomers, chiral recognition has now become an integral part of drug research and development. Nevertheless, regulatory authorities demand experimental proof of enantiomeric ratio and bioequivalence for registration of new drugs. Subsequently, other PPI drugs, also substituted benzimidazoles (Figure 1) – namely lansoprazole, pantoprazole and rabeprazole – with similar modes of action, were developed. All of these PPIs are racemates. Drug firms continue to develop chiral drugs as single enantiomers, to carry out racemic switches, and to manage drug life cycles.

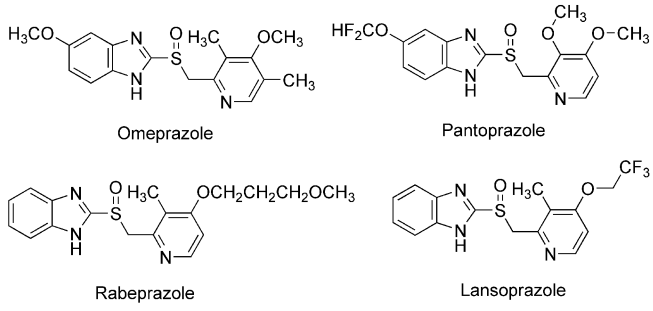

Figure 1. Clinically used PPIs.

The first process employed by von Unge et al.[3] involves asymmetric oxidation of 1*H*-benzimidazolyl pyridinylmethyl sulfide by using cumene hydroperoxide (CHP) together with Hünig's base (*i*Pr$_2$NEt, 0.3 equiv.) as a crucial component in the presence of catalytic amounts of Ti(*i*PrO)$_4$ (0.3 equiv.) and diethyl D-tartrate (0.6 equiv.) to afford esomeprazole, the active ingredient in AstraZeneca's antiulcer drug Nexium® with 94 % *ee*. *Application of Hünig's base and nearly stoichiometric amounts of chiral ligand are required for improvement of the enantioselectivity.* Later, Sudalai et al.[4] reported a heterogeneous catalytic system for the asymmetric oxidation of lansoprazole sulfide to lansoprazole by using WO_3 as catalyst precursor, (DHQD)$_2$-PYR as ligand and aqueous hydrogen peroxide as terminal oxidant;

[a] CAS Key Laboratory of Synthetic Chemistry of Natural Substance, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
354 Fenglin Road, Shanghai 200032, P. R. China
Fax: +86-21-64166128
E-mail: jiangb@mail.sioc.ac.cn
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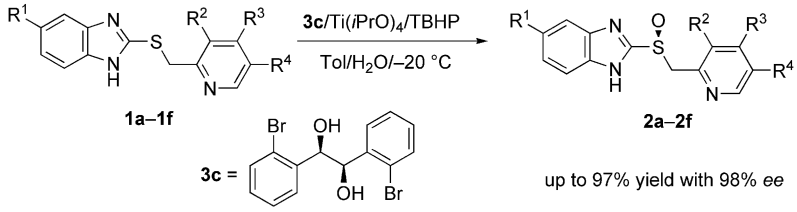


Scheme 1. Enantioselective oxidation of 1*H*-benzimidazolyl pyridinylmethyl sulfides.

the catalysis afforded (*R*)-lansoprazole with 88% *ee* in 84% yield. Therefore, it is highly desirable to search for an efficient asymmetric oxidation system of 1*H*-benzimidazolyl pyridinylmethyl sulfide. Herein, we disclose a simple and efficient catalytic asymmetric oxidation of 1*H*-benzimidazolyl pyridinylmethyl sulfides to 1*H*-benzimidazolyl pyridinylmethyl sulfoxides with *tert*-butyl hydroperoxide (TBHP) in the presence of a chiral titanium complex formed in situ from Ti(*i*PrO)$_4$, (1*R*,2*R*)-1,2-bis(2-bromophenyl)ethane-1,2-diol (**3c**) and water, without using Hünig's base (Scheme 1).

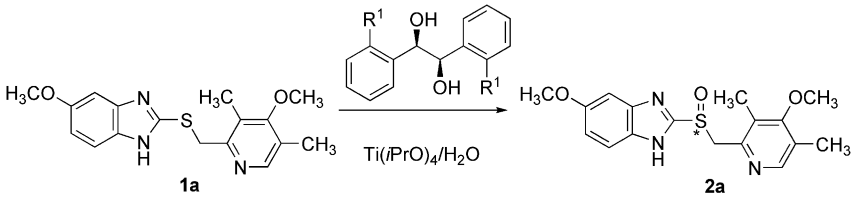
Results and Discussion

For studying the catalytic asymmetric oxidation of 1*H*-benzimidazolyl pyridinylmethyl sulfides, pyrmetazole (**1a**) was chosen as a model substrate. It is known that a catalytic procedure for the asymmetric oxidation of simple alkyl aryl and aryl benzyl sulfides to optically active sulfoxides by *tert*-butyl hydroperoxides was reported by Rosini.[6] This oxidation of sulfides is mediated by a chiral titanium complex formed in situ from Ti(*i*PrO)$_4$, (1*R*,2*R*)-1,2-diphenylethane-1,2-diol (**3a**), and water to afford optically active sulfoxides in good yields (60–75%) with good to high *ee* values. Initially, according to Rosini's standard asymmetric oxidation procedure, the reaction gave esomeprazole only with 43% *ee* in 80% yield at 0 °C by using 10 mol-% (1*R*,2*R*)-1,2-diphenylethane-1,2-diol (**3a**) as ligand in toluene (Entries 1 and 2, Table 1).

We envisioned that the stereo effect of the titanium complex influenced the enatioselectivity of the oxidation. The substitution effect of the benzyl ring was firstly considered to prove the enatioselectivity. Thus, a series of the (1*R*,2*R*)-1,2-bis(2-substituted-phenyl)ethane-1,2-diol derivatives synthesized from the diphenylethylene derivatives by Sharpless asymmetric oxidation, were tested, and the results are listed in Table 1. It was found that (1*R*,2*R*)-1,2-bis(2-substituted-phenyl)ethane-1,2-diol could improve the enantioselectivity. When the *ortho* position bears a halide atom, the enantioselectivity is improved significantly. The chloro compound **3b** (Entry 2, Table 1) and the iodo compound **3d** (Entry 4, Table 1) gave moderate yields and *ee* values. A similar result was obtained with the methyl compound **3e** (Entry 5, Table 1). We were very delighted to find that an excellent yield with a high enantioselectivity of 82% *ee* could be achieved by using diol **3c** (the *ortho* position bearing a bromine atom) as a ligand (Entry 3, Table 1). Surprisingly, when the substituent was a methoxy group, a drastic decrease in the chemical yield to 59% with an extremely low *ee* value (Entry 6, Table 1).

We next investigated the factors influencing the selectivity of the asymmetric oxidation of the sulfide, such as solvent, oxidant, amount of oxidant and temperature, by using ligand **3c**. The results are summarized in Table 2. With 10 mol-% of **3c** as the ligand at 0 °C, the asymmetric oxidation of **1a** was performed in several solvents such as CH_2Cl_2 (68% *ee*), CCl_4 (35% *ee*), CCl_4/CH_2Cl_2 [1:1 (v/v),

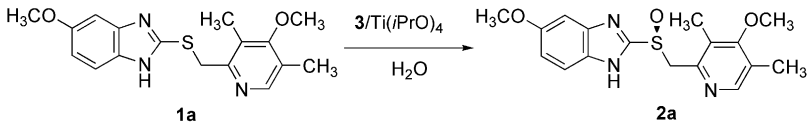
Table 1. Enantioselective oxidation of esomeprazole sulfide: effect of (1*R*,2*R*)-1,2-bis(2-substitued-phenyl)ethane-1,2-diol derivatives.[a]



Entry	Ligand	R^1	Yield (%)[b]	*ee* (%)[c]	Confuration[d]
1	**3a**	H	80	43	(*S*)
2	**3b**	Cl	84	54	(*S*)
3	**3c**	Br	91	82	(*S*)
4	**3d**	I	86	62	(*S*)
5	**3e**	Me	69	70	(*S*)
6	**3f**	MeO	59	8	(*S*)

[a] Reaction conditions: unless otherwise noted, all reactions were carried out with sulfide **1a**/ligand **3**/Ti(*i*PrO)$_4$/H_2O/TBHP (70% in water) = 1.0:0.1:0.05:1.0:2.0 in toluene at 0 °C under an inert gas, according to the sequence in the Experimental Section. [b] Isolated yields. [c] Enantiomeric excess was determined by HPLC analysis.[8] [d] Absolute configuration was assigned by comparison of optical rotation and retention time of HPLC analysis reported in the literature.[8]

Table 2. Enantioselective oxidation of esomeprazole sulfide: effect of different reaction conditions.[a]



1a 2a

Entry	Ligand	Solvent	Temperature [°C]	Oxidant (equiv.)	Yield (%)[b]	*ee* (%)[c]
1	**3c**	CH_2Cl_2	0	TBHP (2.0)	88	68
2	**3c**	CCl_4	0	TBHP (2.0)	72	35
3	**3c**	CCl_4/CH_2Cl_2	0	TBHP (2.0)	92	68[d]
4	**3c**	toluene	0	TBHP (2.0)	91	82
5	**3c**	toluene	0	TBHP (1.0)	61	80
6	**3c**	toluene	0	TBHP (3.0)	87	83
7	**3c**	toluene	0	CHP (2.0)	81	53[e]
8	**3c**	toluene	0	TBHP (2.0)	90	80[f]
9	**3c**	toluene	0	TBHP (2.0)	89	66[g]
10	**3c**	toluene	20	TBHP (2.0)	85	81
11	**3c**	toluene	–20	TBHP (2.0)	92	96
12	**3a**	toluene	–20	TBHP (2.0)	38	68
13	**3b**	toluene	–20	TBHP (2.0)	80	75
14	**3d**	toluene	–20	TBHP (2.0)	64	79
15	**3e**	Toluene	–20	TBHP (2.0)	82	83
16	**3f**	toluene	–20	TBHP (2.0)	57	3

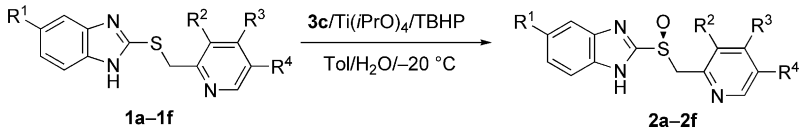
[a] Reaction conditions: unless otherwise noted, all reactions were carried out with sulfide **1a**/ligand **3**/Ti(*i*PrO)$_4$/H_2O/TBHP (70% in water) = 1.0:0.1:0.05:1.0:2.0 under an inert gas, according to the sequence in the Experimental Section. [b] Isolated yields. [c] Enantiomeric excess was determined by HPLC analysis.[8] [d] CCl_4/CH_2Cl_2 = 1:1 (v/v). [e] 80% cumene hydroperoxide (CHP) was used as oxidant. [f] 0.2 equiv. of **3c** was used. [g] Water added before the addition of Ti(*i*PrO)$_4$.

68% *ee*] and toluene (82% *ee*). Toluene was chosen as the optimal solvent since the reaction in toluene afforded an excellent yield with high enantioselectivity (Entry 4, Table 2). In the presence of 10 mol-% of **3c** as the ligand in toluene at 0 °C and a reduced amount of TBHP the chemical yield decreased from 91% to 61% (Entry 5, Table 2), whereas an increase of the amount of oxidant TBHP led to no obvious changes in the yield and the *ee* value (Entry 6, Table 2). Change of the oxidant from TBHP to cumene hydroperoxide (CHP) produced esomeprazole in only 81% yield with 53% *ee* (Entry 7, Table 2). With 20 mol-% of **3c**, the product formed with no distinct change of yield and *ee* value (Entry 8, Table 2). The sequence of the material addition is also important in the enantioselective oxidation: in the case of "water added before the Ti(*i*PrO)$_4$", the *ee* value decreased from 82% to 66% (Entry 9, Table 2). In general, the reaction temperature also has a significant impact upon the enantioselectivity. Interestingly, raising of the temperature from 0 °C to 20 °C has no effect on the yield and the enantioselectivity (Entry 10, Table 2), whereas decreasing of the temperature from 0 °C to –20 °C afforded a 92% yield with 96% *ee* (Entry 11, Table 2). Other ligands **3** were retested under the same reaction condions (–20 °C), although the enantioselectivities were improved significantly (Entries 12–16, Table 2), ligand **3c** was still the best choice for its outstanding catalytic efficiency.

With the optimized conditions established (2 equiv. of TBHP and 10 mol-% of **3c** in toluene at –20 °C), consequently there is a strong inherent interest to assess the synthetic scope of related selective oxidation reactions. The reaction is applicable to 1*H*-benzimidazolyl pyridinylmethyl sulfides **1a**–**1f**, which gave **2a**–**2f**, and the results are collected in Table 3. Pantoprazole (**2b**) (5-difluoromethoxy substitution of benzimidazole and 3,4-dimethoxyl substitution of pyridine derivative), was formed in 90% yield with 92% *ee* (Entry 3, Table 3). Similar results were also obtained with lansoprazole (**2d**) [3-methyl-4-(2,2,2-trifluoroethoxy) substituion of pyridine derivative] (Entry 5, Table 3) and **2e** [5-methoxy substituion of benzimidazole and 3-methyl-4-(2,2,2-trifluoroethoxy) substituion of pyridine derivative] (Entry 6, Table 3). Rabeprazole (**2c**) [with a long alkyloxy chain substituent, 4-(3-methoxypropoxy)-3-methyl substitution of pyridine derivative], was formed with only moderate enantioselectivity, 80% *ee* (Entry 4, Table 3). We were very delighted to find that **2f** (5-demethoxyomperazole) was produced in a high yield of 97% with excellent enantioselectivity of 98% *ee* (Entry 7, Table 3). The enantiomeric excess of the product could then be further enhanced by preparing a metal salt and subsequently crystallising from a suitable solvent. When the reaction was run on a 10-gram scale, **2a** was obtained in 70% yield with >99% *ee* as sodium salt by a simple recrystallization from an aqueous solution of sodium hydroxide, methyl isobutyl ketone and acetonitrile (Entry 2, Table 3).

The above results clearly show that the diol **3c**/titanium catalytic asymmetric oxidation system is efficient to produce chiral 1*H*-benzimidazolyl pyridinylmethyl sulfoxides. Although the mechanistic details of this reaction are not clear yet, we reasoned that the activity of the chiral titanium complex formed in situ by treating Ti(*i*PrO)$_4$ with the ligand was synergistically determined by the electronic and the steric effects. Moreover, the NH group and the nitrogen atom

Table 3. Enantioselective oxidation of 1*H*-benzimidazolyl pyridinylmethyl sulfides **1**.[a]



1a–1f **2a–2f**

1a $R^1 = OCH_3$; $R^2 = CH_3$; $R^3 = OCH_3$; $R^4 = CH_3$
1b $R^1 = OCF_2H$; $R^2 = R^3 = OCH_3$; $R^4 = H$
1c $R^1 = H$; $R^2 = CH_3$; $R^3 = OCH_2CH_2CH_2OCH_3$; $R^4 = H$
1d $R^1 = H$; $R^2 = CH_3$; $R^3 = OCH_2CF_3$; $R^4 = H$
1e $R^1 = OCH_3$; $R^2 = CH_3$; $R^3 = OCH_2CF_3$; $R^4 = H$
1f $R^1 = H$; $R^2 = CH_3$; $R^3 = OCH_3$; $R^4 = CH_3$

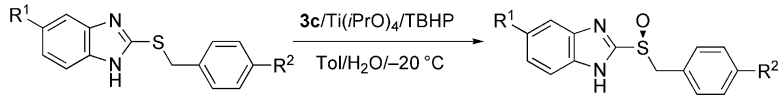
2a, Esomeprazole
2b, Pantoprazole
2c, Rabeprazole
2d, Lansoprazole
2e
2f

Entry	Substrate	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	**1a**	92	96	(*S*)
2	**1a**	70	>99[e]	(*S*)
3	**1b**	90	92	(*S*)
4	**1c**	81	80	(*S*)
5	**1d**	86	90	(*S*)
6	**1e**	87	92	(*S*)
7	**1f**	97	98	(*S*)

[a] Reaction conditions: unless otherwise noted, all reactions were carried out with sulfide **1**/ligand **3c**/Ti(*i*PrO)$_4$/H_2O/TBHP (70% in water) = 1.0:0.1:0.05:1.0:2.0 in toluene at –20 °C under an inert gas, according to the sequence in the Experimental Section. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis.[8] [d] Absolute configuration was assigned by comparison of optical rotation or retention time of HPLC analysis reported in the literature.[8] [e] The reaction was performed on a 10-gram scale, **2a** was obtained as sodium salt.

in the sulfide substrate are probably involved in further complexation with the active component of the catalyst complex. Recently, Szabo[7] reported a tartrate/Ti(*i*PrO)$_4$/CHP/*i*Pr$_2$NEt catalytic system used in the asymmetric oxidation of heterocyclic sulfides, including imidazole, benzimidazole, indole and pyrimidine derivatives. They found that an imidazole substituent in heterocyclic sulfides is more efficient in directing the enantioselection process than the isosteric phenyl group. However, in Szabo's catalytic system, the application of the base *i*Pr$_2$NEt is required for an improvement of the enantioselectivity, the modulation effect is probably exerted by association of *i*Pr$_2$NEt to the substrate or to the titanium complex. Therefore, we believe that the presence of a pyridine ring in the substrate is required for an efficiently catalyzed asymmetric oxidation of 1*H*-benzimidazolyl pyridinylmethyl sulfoxides in our catalytic system. In order to test our speculation, 1*H*-benzimidazolyl benzyl sulfides **4a**–**4c** were used in the diol **3c**/titanium catalytic asymmetric oxidation system. The results are summarized in Table 4. 1*H*-Benzimidazolyl benzyl sulfoxide (**5a**), was achieved in only 37% yield with 50% *ee* (Entry 1, Table 4). Benzyl 5-difluoromethoxy-1*H*-benzimidazolyl sulfoxide (**5b**) was obtained in a slightly higher yield (63%) with enantioselectivity (62% *ee*) (Entry 2, Table 4). 4-Chloro substitution of the benzyl group, and 5-difluoromethoxy substitution of the benzimidazole afforded sulfoxide **5c** in excellent yield (96%) with higher enantioselectivity (73% *ee*) (Entry 3, Table 4). All the 1*H*-benzimid-

Table 4. Enantioselective oxidation of benzyl 1*H*-benzimidazole sulfides **4**.[a]



4a–4c **5a–5c**

Entry	Substrate	R^1	R^2	Yield (%)[b]	*ee* (%)[c]
1	**4a**	H	H	37	50
2	**4b**	OCF_2H	H	63	62
3	**4c**	OCF_2H	Cl	96	73

[a] Reaction conditions: unless otherwise noted, all reactions were carried out with sulfides **4**/ligand **3c**/Ti(*i*PrO)$_4$/H_2O/TBHP (70% in water) = 1.0:0.1:0.05:1.0:2.0 in toluene at –20 °C under an inert gas, according to the sequence in the Experimental Section. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis.[8]

azolyl benzyl sulfides gave a significantly lower enantioselectivity than the 1*H*-benzimidazolyl pyridinylmethyl sulfides. The following interesting conclusions can be drawn: a pyridine ring in the substrate is indispensable for high enantioselectivities, and the substituents of the benzyl, pyridinylmethyl, or benzimidazolyl moiety have an important impact on the enantioselectivities.

Conclusions

We have developed a simple and efficient catalytic asymmetric oxidation of 1*H*-benzimidazolyl pyridinylmethyl sulfides to 1*H*-benzimidazolyl pyridinylmethyl sulfoxides with *tert*-butyl hydroperoxide in toluene in the presence of a chiral titanium complex formed in situ from Ti(*i*PrO)$_4$, chiral diol **3c** and water. The chiral sulfoxides were obtained in high chemical yields with excellent enantiomeric excesses. Investigations are underway to utilize this method for the asymmetric synthesis of other chiral sulfoxides exhibiting important biological activities.

Experimental Section

General Experimental Procedures: In a typical experiment, Ti(*i*PrO)$_4$ (4.5 mg, 0.016 mmol) was added to a solution of ligand **3c** (12 mg, 0.032 mmol) in toluene (2 mL) at 25°C. The solution was stirred for 10 min. Water (5.7 mg, 0.32 mmol) was added to the mixture, and the solution was stirred for another 10 min. Pyrmetazole sulfide (**1a**) (105 mg, 0.32 mmol) was then added to the solution, and the temperature was then adjusted to –20°C; subsequently, *tert*-butyl hydroperoxide (70%, 96 μL, 0.64 mmol) was slowly added. After 24 h at –20°C, the solution was extracted three times with aqueous ammonium hydroxide (12.5% of NH_3, 3 × 5 mL). Subsequently, isobutyl methyl ketone (5 mL) was added to the combined aqueous extracts. The aqueous phase was adjusted to pH = 7 with acetic acid, separated and extracted with an additional portion of isobutyl methyl ketone (5 mL). The combined organic solutions were dried with anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purfied by chromatography on silica gel to afford **2a** (101 mg, 92% yield, 96% *ee*).

Supporting Information (see footnote on the first page of this article): Experimental procedures and full spectroscopic data.

Acknowledgments

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[8] For details of the experimental procedures, see the Supporting Information.

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