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A new titanate/(+)-(1*R*,2*S*)-*cis*-1-amino-2-indanol system for the asymmetric synthesis of (*S*)-tenatoprazole

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ABSTRACT

Tenatoprazole, a substituted imidazopyridinyl derivative, is an irreversible proton pump inhibitor (PPI), which is used for the prevention and treatment of gastric acid-related diseases. A new highly efficient asymmetric oxidation using cumene hydroperoxide (CHP) as the oxidant in the presence of titanium tetraisopropoxide ($Ti(OiPr)_4$) and (+)-(1*R*,2*S*)-*cis*-1-amino-2-indanol, in a polar aprotic solvent at 0–20 °C, has been developed to prepare tenatoprazole with an enantiomeric excess of >99%, a chemoselectivity of >90% and a chemical yield of >90% from the corresponding sulfide. This procedure was successfully implemented on scales ranging from 100 mg to multiple kilograms. Detailed studies of the parameters controlling purity and yield for this reaction are presented.

As part of our studies toward the synthesis of (*S*)-tenatoprazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]imidazo[4,5-b]pyridine **1**, a pharmaceutically active compound having anti-ulcer activity,[1] we were interested in the synthesis of chiral sulfoxides, particularly using asymmetric oxidations of sulfides. Asymmetric sulfoxides are both important intermediates and active ingredients in pharmaceutical industry and their synthesis has been studied extensively.[2]

In initial studies, (*S*)-tenatoprazole **1** (Fig. 1) was prepared applying Bolm's vanadium-catalyzed asymmetric sulfoxidation method[3] mediated by vanadyl acetylacetonate ($VO(acac)_2$) and a chiral Schiff's base derivative.[4] However, the enantiomeric excess obtained using this procedure was only 80% and two subsequent recrystallizations were required to reach 99% ee. As a consequence, this process could provide only small quantities of (*S*)-tenatoprazole (ee >99%), which were inadequate to satisfy the demands for early toxicological studies. We were, therefore, particularly interested in finding an efficient and robust synthesis of (*S*)-tenatoprazole.

A variety of systems for the enantioselective oxidation of thio-substituted benzimidazoles belonging to the family of Proton Pump Inhibitor (PPI) have been described. Esomeprazole **2** was efficiently synthesized via an oxidation catalyzed by titanium tetraisopropoxide ($Ti(OiPr)_4$), diethyl tartrate ((*R*,*R*)-DET), and ethyldiisopropylamine (iPr_2NEt)[5] using a modification of Kagan's system;[6] the precursor of lansoprazole **3** was oxidized effectively in the presence of a tungsten (VI) oxide (WO_3)-cinchona alkaloid system[7] and more recently, the oxidation of TU-501 **5** was described mediated by the Uemura system.[8] Using a combination of *tert*-butyl hydroperoxide (TBHP), $Ti(OiPr)_4$, (*R*)-(+)-binaphthol, and water, (+)-(*R*)-TU-199 was prepared with 80% ee.[9]

Studies toward improving the enantioselectivity obtained for the oxidation of TU-501 **5** to TU-199 **1** started with an evaluation of previously reported conditions applied to oxidize the sulfur atom of the thio-substituted benzimidazoles **2** and **3** (Table 1). The modified Kagan's system[5] gave (*S*)-TU-199 **1** with an ee of 60%. Relatively poor chemoselectivity was observed and significant quantities of the corresponding sulfone **6** were also obtained (entry 1). Results for other catalytic systems (entries 2 and 3) also showed modest enantioselectivity and significant overoxidation to sulfone **6** occurring.

Following these initial results, a range of conditions, varying catalysts, ligands, oxidants, and solvents were screened to identify a more optimal procedure for the enantioselective preparation of **1** from **5**.

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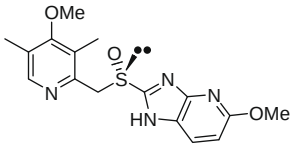
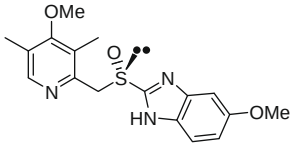
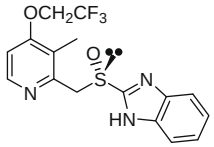


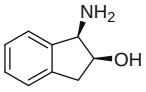
1 (*S*)-Tenatoprazole



2 (*S*)-Esomeprazole



3 (*S*)-Lansoprazole



4 (+)-cis-1-amino-2-indanol

Figure 1. Structures of prazoles'compounds and chiral auxiliary.

Detailed studies revealed that the oxidation of TU-501 **5** could successfully be carried out in the presence of 0.5 equiv of Ti(O*i*Pr)$_4$, 1.0 equiv of (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol,[10] and 2.32 equiv of cumene hydroperoxide (CHP) in 1-methyl-2-pyrrolidine (NMP) at 0 °C to give **1** in 90% yield with an enantiomeric excess of >99% (Fig. 2).[11]

The use of polar aprotic solvents such as NMP, pyridine, *N*,*N*-dimethylacetamide (DMA), and *N*,*N*-dimethylformamide (DMF) was investigated as they were found to be good solvents of TU-501 **5** with solubilities ranging from 75 to 200 g/L observed. When the oxidation of TU-501 **5** was performed in these solvents enantioselectivities of >90% were obtained. This is notable as previously it has been reported that the use of these solvents is detrimental to the enantiomeric excess obtained for sulfoxidation reactions.[2]

A range of temperature conditions were studied and for the examined temperature range, between 0 °C and 20 °C, little variation in chemo- and enantioselectivity was observed.

A range of oxidants was screened including alkyl hydroperoxides (CHP or TBHP), hydrogen peroxide (H_2O_2), hydrogen peroxide-urea adduct (UHP), and *meta*-chloroperbenzoic acid (*m*CPBA). Racemic TU-199 was obtained in the presence of *m*CPBA. The use of hydrogen peroxide or its complex with urea resulted in low enantio- and chemoselectivities. Alkyl hydroperoxides were found to give superior enantiomeric excesses, with TBHP and CHP giving 65% ee and 99% ee, respectively. This observation is in accordance with previous reports, where it has been hypothesized that alkyl peroxotitanate species are involved in the catalytic cycle.[2]

Using CHP as the oxidant of choice, it was demonstrated that fast addition of the oxidant to the mixture of the prochiral sulfide and the catalytic system in NMP was beneficial.

Our attention was also focused on the presence of water in the reaction media. A crucial role of water in asymmetric sulfoxidation reactions was shown in Kagan's early investigations.[2] This positive influence of water was not, however, corroborated with our system in NMP. Moreover, addition of 0.25–0.5 equiv of water resulted in a decrease in both conversion and enantioselectivity. The influence of other additives was also tested. When the oxidation was performed with a 1.0 equiv of CHP, 0.25 equiv of Ti(O*i*Pr)$_4$, 0.5 equiv of (+)-*cis*-1-amino-2-indanol, and 0.25 equiv of *i*PrOH, in accordance with the conditions elaborated in Modena's group[12] the conversion of the substrate decreased by 10%, whereas no effects on the enantio- and chemoselectivities were observed. The addition of 0.25 equiv of Hünigs base had no effect on the outcome of the reaction performed in a polar aprotic solvent at 20 °C.

Amongst the various β-amino alcohols tested, (+)-*cis*-1-amino-2-indanol afforded the best results in terms of enantio- and chemoselectivities. The oxidation proceeded equally well in the presence of (−)-*cis*-1-amino-2-indanol and (+)-*cis*-1-amino-2-indanol **4**. However, in the presence of (+)-*trans*-1-amino-2-indanol, the enantiomeric excess decreased to 10% and the conversion of TU-501 **5** to **1** dropped by 20%. Thus, the cis-configuration of the 1-amino-2-indanol is crucial in ensuring good selectivities in the reaction.[13] Substituted derivatives of (+)-*cis*-1-amino-2-indanol were prepared and tested in an attempt to modulate the activity of the catalyst. Reactions carried out using derivatives with substitution at either the amino or the hydroxyl groups gave significantly decreased levels of enantioselectivity. For all analogs investigated, compound **1** was prepared with less than 20% ee. It was concluded that the presence of both the primary amine and hydroxyl groups are important to obtain good enantioselectivity.

Analysis of these preliminary results confirmed our interest in Ti(O*i*Pr)$_4$ and (+)-*cis*-1-amino-2-indanol as an efficient system for the asymmetric oxidation of TU-501 **5** to (*S*)-TU-199 **1** by CHP. It was noted that:

- The choice of a polar aprotic solvent has positive effects on reactivity and stereoselectivity.
- Aging of the catalytic system is not favorable.
- The presence of water proved to be detrimental to selectivity.
- The ratio of Ti(O*i*Pr)4 to (+)-*cis*-1-amino-2-indanol **4** should be <1/2.

In conclusion, a new highly efficient enantioselective system for the preparation of (*S*)-tenatoprazole has been developed. Upon titanium-mediated asymmetric oxidation of the corresponding prochiral sulfide, sulfoxide **1** was obtained with more than 99%

Table 1
Results for the oxidation of TU-501 **5** under the literature conditions

Entry	Conditions (reference)	Monitored results [a](%)			
		ee (configuration)	TU-501 **5** conversion	TU-199 **1**	Sulfone **6**
1	0.25 equiv Ti(O*i*Pr)$_4$/(*R*,*R*)-DET (1:2), 0.25 equiv DIPEA, [b] toluene (Ref. 5)	60 (*S*)	90	73	17
2	WO_3/$(DHQ)_2$-PYR (5 mol %), 0 °C, H_2O_2 (30%), $CHCl_3$ (Ref. 6)	41 (*R*)	64	45	15
3	VO(acac)$_2$/chiral salen; [c] CH_2Cl_2, 20 °C, H_2O_2 (30%) (Ref. 4)	80 (*S*)	>98	75	23

[a] Determined by HPLC using Daicel Chiralpack AS column.
[b] Ethyldiisopropylamine.
[c] 2,4-Di-*tert*-butyl-6-[1-*S*-hydroxymethyl-2-methylpropylimino)-methyl]phenol.

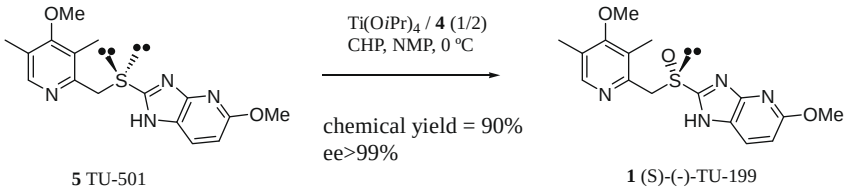


Figure 2. Asymmetric oxidation of TU-501 **5**.

enantiomeric excess. Main innovative features comprise a new highly efficient catalytic oxidation system and the use of polar aprotic solvents to perform the oxidation. Work is in progress to decrease the amount of titanium catalyst used for the reaction and to extend this original system to other prochiral sulfides. Further results will be reported in due course.

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References and notes

1. Matsuishi N.; Takeda H.; Iizumi K.; Murakami K.; Hisamitsu A., EP Patent 254,588, 1987.
2. Kagan, H. B.; Luukas, T., 2nd ed.. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 479–495; Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651–3705; *Asymmetric Oxidation Reactions*; Katsuki, T., Ed.; Oxford Press, 2001; Legros, J.; Delhi, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19–31; Kagan, H. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New-York, 2000; pp 327–356; Kagan, H. B. *Pure Appl. Chem.* **1985**, *57*, 1911–1916.
3. Bolm, C.; Bienewald, F.. *Angew. Chem.* **1995**, *107*, 2883–2885; . *Angew. Chem., Int. Ed.* **1996**, *34*, 2640–2642.
4. Schutze, F.; Chabit, S.; Cohen, A.; Martinet, F. FR patent 2852,956, 2003.
5. Federsel, H. J.; Larsson, M. In *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH, 2004; pp 413–436; Cotton, H.; Elebring, T.; Li, L.; Larsson, M.; Sörensen, H.; Von Unge, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3819–3825; Larsson, E. M.; Stenhede, U. J.; Sörensen, H.; Von Unge, P. O. S.; Cotton, H. K. WO9602535 A1, 1996.
6. Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193.
7. Thakur, V. V.; Sudalai, A. *Tetrahedron: Asymmetry* **2003**, *14*, 407–410.
8. Komatsu, N.; Hashizume, M.; Sugita, T.; Uemera, S. *J. Org. Chem.* **1993**, *58*, 4529–4533.
9. Yamashita, S.; Ebina, K. JP Patent WO2004074285 A1, 2004.
10. Gallou, I.; Senanayake, C. H. *Chem. Rev.* **2006**, *106*, 2843–2874.
11. *The general procedure used for the sulfoxidation reaction is as follows*: To a homogeneous solution of TU-501 **5** (0.4 g, 1.0 mol equiv), (+)-*cis*-1-amino-2-indanol **4** (0.136 g, 0.50 mol equiv), and $Ti(OiPr)_4$ (0.091 mL, 0.25 mol equiv) in 2 mL of anhydrous NMP at 0 °C was added cumylhydroperoxide as a 80% solution in cumene (0.26 mL, 1.16 mol equiv). The solution was stirred for 6 h and (+)-*cis*-1-amino-2-indanol (0.136 g, 0.50 mol equiv), $Ti(OiPr)_4$ (0.091 mL, 0.25 mol equiv), and cumylhydroperoxide as a 80% solution in cumene (0.26 mL, 1.16 mol equiv) were added successively each and in one portion. The reaction mixture was stirred for a further 10 h at 0 °C to give the crude product that was composed of 0.5% of TU-501 **5**, 7% of the sulfone TU-502 **6**, and 90% of sulfoxide **1** with an enantiomeric excess >99%.
12. Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325–326.
13. Rodriguez-Escrich, S.; Sola, L.; Jimeno, C.; Rodriguez-Escrich, C.; Pericas, M. A. *Adv. Synth. Catal.* **2008**, *350*, 2250–2260.