CATALYTIC ASYMMETRIC SYNTHESIS OF ESOMEPRAZOLE BY A TITANIUM COMPLEX WITH A HEXA-AZA-TRIPHENOLIC MACROCYCLE LIGAND

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GRAPHICAL ABSTRACT

Abstract An efficient synthesis of esomeprazole via catalytic asymmetric oxidation of 1H-benzimidazolyl pyridinylmethyl sulfide by a titanium complex with a hexa-aza-triphenolic macrocycle ligand is described. Esomeprazole was prepared with 99.6% ee, which meets the high requirement of the European Pharmacopeia on enantiomeric purity.

Keywords Asymmetric catalysis; chiral macrocycles; enantioselective sulfoxidation; esomeprazole

INTRODUCTION

Peptic ulcer is one of the most common diseases in modern society. Blocking the hydrogen/potassium adenosine triphosphatase enzyme system of gastric parietal cells, proton pump inhibitors (PPIs) are the most important group of drugs for peptic ulcer. Omeprazole, a racemic mixture, was marketed as the first PPI drug in 1987 and has been the best-selling drug on the market from 1999 to 2001.[1] Esomeprazole, the (S)-enantiomer of omeprazole, provides better acid control than current racemic PPIs and has a favorable pharmacokinetic profile relative to omeprazole.[2] It

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became commercially available as the first single-optical-isomer PPI in 2001. Sales of esomeprazole reached 3.87 billion US dollars in 2013, and it is one of the top 25 best-selling drugs. Thus, the preparation of esomeprazole has received much attention in both academia and industry.

Esomeprazole contains a chiral sulfoxide center, which bears the two large groups benzimidazolyl and pyridinylmethyl. Catalytic asymmetric oxidation of the corresponding sulfide is the most attractive approach to esomeprazole. Since the pioneering work of Kagan and Modena, considerable progress has been made toward the development of enantioselective sulfoxidation methods. However, bearing two large and similarly sized groups, highly enantioselective oxidation of esomeprazole sulfide is a challenging task. Among numerous catalysts for enantioselective oxidation of sulfide, those applied in the preparation of esomeprazole include titanium=diethyltartrate, titanium=tartramide, titanium/chiral diol, Salen–Mn complexes, porphyrin-inspired manganese complex, and biocatalysis. Titanium=diethyltartrate is the most important one for successful application in industry. Although many achievements have been made, few of them meet the requirement of the European pharmacopeia on enantiomeric purity (no less than 99.6% ee). Thus, the catalyst for the synthesis of esomeprazole with high enantioselectivity is still desirable.

Chiral hexa-aza-triphenolic 27-membered macrocycles derived from 3 + 3 condensation of 2,6-diformylphenols and chiral diamines are important chiral macrocyclic ligands. As chiral host molecules having the potential to bind three metal ions through oxo-bridges, these macrocyclic ligands have received considerable attention. While most studies focused on the synthesis, structure, or magnetic property of their metal complexes, countable reports also documented the outstanding catalytic performance of their zinc(II) complex on hydrolytic cleavage of DNA and enantioselective direct aldol and Henry reaction. In addition, these macrocyclic amines have been shown to be efficient chiral shift reagents for carboxylic acids. Herein, we report the application of one of the macrocyclic ligands (L1) derived from 2,6-diformyl-4-methylphenol and (S,S)-1,2-diphenylethylenediamine ((S,S)-DPEN) in catalytic asymmetric oxidation of sulfide for the preparation of esomeprazole.

RESULTS AND DISCUSSION

The macrocyclic ligand L1 was synthesized from 2,6-diformyl-4-methylphenol and (S,S)-1,2-diphenylethylenediamine ((S,S)-DPEN) following the reported method. The catalyst was prepared in situ by treatment of titanium tetraisopropoxide with L1, and its catalytic performance for 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-thio]-1H-benimidazol (pyrmetazol, 1) with cumene hydroperoxide (80% in cumene, CHP) was explored (Scheme 1).

Because L1 has the potential to bind three titanium ions through oxo-bridges, the effects of different ratios of titanium tetraisopropoxide to L1 were explored first [caution: it is well known that chiral sulfoxides are prone to self-disproportionation of enantiomer (SDE) on achiral silica gel, so all fractions should be combined for determination of the enantiomeric purity during the purification of products by chromatography]. It is not surprising that L1 itself has no catalytic activity
Increasing the ratio of titanium tetraisopropoxide with \( \text{L1} \) from 1 to 3 resulted in an increased conversion and \( \text{ee} \) (entries 2–4). The best results were obtained with a slight excess of titanium tetraisopropoxide (entry 5), and further increasing the ratio of titanium tetraisopropoxide with \( \text{L1} \) to 65/13 gave almost the same results (entry 6). These results indicated an intramolecular cooperative effect of the three titanium atoms. In addition, lower catalyst loading resulted in an obvious decrease of conversion and \( \text{ee} \) (entry 8).

The fact that the addition of water has a positive impact on the enantioselectivity of asymmetric oxidation of sulfides has been confirmed by previous reports.\(^4,6,7\) Consequently, the effect of water was investigated. The reagents were dried and a residual amount of water was listed in Table 2. In the optimized condition, the total amount of water in the reagents amounts to 0.47 mg (0.026 mmol), in ratio of 0.4/1 (mol/mol) to \( \text{L1} \). The effect of water was determined by carrying out the reaction with addition of water (Table 3). When no additional water was added (entry 1), the reaction was very slow, and the percentage of the product was 20% in high-performance liquid chromatography (HPLC) with 19% \( \text{ee} \) for 1 h. Both the conversion and \( \text{ee} \) were increased when the molar ratio of water to \( \text{L1} \) was varied from

### Table 1. Effects of the content and loading of the catalyst on the reaction\(^a\)

| Entry | \( \text{Ti} \text{(OPr-i)}_4 / \text{L1} \) (mol%/mol%) | Time (h) | Ratio (HPLC, %)\(^b\) | \( \text{ee} \) (%)\(^c\) |
|-------|----------------------------------|---------|-----------------|-----------------|
| 1     | 0/13                             | 1       | 1               | nr              |
| 2     | 13/13                            | 0.5     | 60              | 30              | 10             | 21.0          |
| 3     | 26/13                            | 0.5     | 35              | 55              | 10             | 75.1          |
| 4     | 39/13                            | 0.5     | 10              | 85              | 5              | 90.0          |
| 5     | 47/13                            | 0.5     | 6               | 90              | 4              | 99.6          |
| 6     | 65/13                            | 0.5     | 6               | 90              | 4              | 99.0          |
| 7     | 36/10                            | 0.5     | 15              | 80              | 5              | 90.0          |
| 8     | 15/5                             | 1       | 45              | 50              | 5              | 6.4           |

\(^a\)Reaction conditions: \( \text{I} \) (165 mg, 0.5 mmol), \( \text{H}_2\text{O} / \text{L1} = 2 / 1 \) (mol/mol), \( \text{NEt(Pr-i)}_2 / \text{L1} = 2 / 1 \) (mol/mol), \( \text{CHP} \) (80%, 110.5 mg, 0.65 mmol, 1.3 eq.), toluene (20 mL), rt.

\(^b\)Measured by HPLC on Diamosil C18 column, acetonitrile/\( \text{buffer solution (pH 7.5)} = 27 / 73 \), 1.0 mL/min, 280 nm.

\(^c\)Measured by HPLC on CHIRAL-AGP column, acetonitrile/\( \text{buffer solution (pH 6.0)} = 64 / 36 \), 0.6 mL/min, 302 nm.
0.4 to 2 (entries 1–3). The best results were given when the ratio of water to \( \text{L1} \) was \( 2 = 1 \) (entry 3). Further increasing of the amount of water resulted in the decrease of the conversion and \( ee \) (entries 4 and 5).

Similar to the titanium/diethyltartrate system, introduction of amine to our catalytic system also has positive effect on the reaction (Table 4). If no base was used, the reaction gave poor results (entry 1). Meanwhile, the conversion and \( ee \) were increased sharply when \( \text{NEt}_3 \) or \( \text{NEt} \) \((\text{Pr-i})_2 \) were used (entries 2 and 9). Using of \( \text{PhNMe}_2 \) and \( \text{HNEt}_2 \) also had obviously positive effect (entries 3 and 5), but pyridine, \( \text{HN(Bu-n)}_2 \), or some inorganic bases gave low \( ee \) (entries 4, 6, and 11–13). In addition, the effect of the amount of \( \text{NEt} \) \((\text{Pr-i})_2 \) was also explored (entries 7–10). The enantioselectivity of the product was increased while the ratio of \( \text{NEt} \) \((\text{Pr-i})_2 \) to \( \text{L1} \) was increased from 0.5 to 2 (entries 7–9), and the best result (99.6\% \( ee \)) was obtained when the ratio of \( \text{NEt} \) \((\text{Pr-i})_2 \) to \( \text{L1} \) was 2 to 1 (entry 9). Further increasing the ratio of \( \text{NEt} \) \((\text{Pr-i})_2 \) to \( \text{L1} \) to 3 gave similar results (entry 10). These results indicated that \( \text{NEt} \) \((\text{Pr-i})_2 \) may participate in the chiral titanium complex instead of simple deprotonation.

Furthermore, the effect of solvents and oxidants were explored (Table 5). Most of the solvents were not suited for the reaction except toluene (entries 1–6, 9). The other two common oxidants, \( t \)-BuOOH and \( \text{H}_2\text{O}_2 \), were not efficient for the reaction (entries 11 and 12). The amount of CHP showed obvious effects on conversion

### Table 2. Amount of water in the reagents

| Reagent         | Amount (mg) | Water (wt%) | Water (mg) |
|-----------------|-------------|-------------|------------|
| \( \text{Ti(OPr-i)}_4 \) | 66.7        | 0           | 0          |
| \( \text{L1} \)    | 67.1        | 0.10%       | 0.067      |
| CHP             | 110.5       | 0.30%       | 0.33       |
| \( \text{NEt(Pr-i)}_2 \) | 16.8       | 0.05%       | 0.008      |
| Pyrmetazol     | 165         | 0.04%       | 0.066      |
| Toluene        | 20 mL       | 0           | 0          |

### Table 3. Effect of the amount of water on the reaction

| Entry | \( \text{H}_2\text{O}/\text{L1} \) (mol/mol) | Time (h) | Ratio (HPLC, %) | \( ee \) (%) |
|-------|---------------------------------------------|----------|-----------------|-------------|
|       |                                             |          | 1               | 2           | 3           |             |
| 1     | 0.4/1 <sup>d</sup>                        | 1        | 72              | 20          | 8           | 19          |
| 2     | 1/1                                         | 0.5      | 55              | 40          | 5           | 78          |
| 3     | 2/1                                         | 0.5      | 6               | 90          | 4           | 99.6        |
| 4     | 3/1                                         | 0.5      | 10              | 85          | 5           | 90.0        |
| 5     | 4/1                                         | 1        | 5               | 80          | 10          | 63.0        |

<sup>a</sup>Reaction conditions: \( \text{I} \) (165 mg, 0.5 mmol), \( \text{Ti(OPr-i)}_4 \) (66.7 mg, 0.235 mmol), \( \text{L1} \) (67.1 mg, 0.065 mmol, 13 mol\%), \( \text{NEt(Pr-i)}_2 \) (16.8 mg, 0.13 mmol), CHP (80\%, 110.5 mg, 0.65 mmol, 1.3 eq.), toluene (20 mL), rt.

<sup>b</sup>Measured by HPLC on Diamosil C18 column, acetonitrile/buffer solution (pH 7.5) = 27/73, 1.0 mL/min, 280 nm.

<sup>c</sup>Measured by HPLC on CHIRAL-AGP column, acetonitrile/buffer solution (pH 6.0) = 64/36, 0.6 mL/min, 302 nm.

<sup>d</sup>No additional water was added.
and chemical selectivity but very slight effects on enantioselectivity (entries 7–10). When 1 equivalent of CHP was used, the conversion of 1 was a little low (entry 7). The conversion of 1 increased with the increased amount of CHP (entries

| Entry | Base         | Base/L1 (mol/mol) | Time (h) | 1 | 2 | 3 | ee (%) |
|-------|--------------|-------------------|----------|---|---|---|--------|
| 1     | —            | 0                 | 0.5      | 10| 85| 5 | 0      |
| 2     | NEt₃        | 2/1               | 0.5      | 10| 85| 5 | 94.1   |
| 3     | PhNMe₂       | 2/1               | 0.5      | 10| 85| 5 | 42.0   |
| 4     | Pyridine     | 2/1               | 0.5      | 20| 70| 10| 1.9    |
| 5     | HNEt₂        | 2/1               | 0.5      | 15| 80| 5 | 74.0   |
| 6     | HN(Bu-n)₂    | 2/1               | 1        | 77| 20| 3 | 3.0    |
| 7     | NEt(Pr-i)₂   | 0.5/1             | 0.5      | 15| 80| 5 | 4.0    |
| 8     | NEt(Pr-i)₂   | 1/1               | 0.5      | 11| 85| 4 | 87.0   |
| 9     | NEt(Pr-i)₂   | 2/1               | 0.5      | 6 | 90| 4 | 99.6   |
| 10    | NEt(Pr-i)₂   | 3/1               | 0.5      | 6 | 90| 4 | 99.0   |
| 11    | Na₂CO₃       | 2/1               | 0.5      | 10| 85| 5 | 7.5    |
| 12    | NaHCO₃       | 2/1               | 0.5      | 15| 80| 5 | 5.6    |
| 13    | NaOH         | 2/1               | 1        | 80| 18| 2 | 0      |

*Reaction conditions: 1 (165 mg, 0.5 mmol), Ti(OPr-i)₄ (66.7 mg, 0.235 mmol), L₁ (67.1 mg, 0.065 mmol, 13 mol%), H₂O/L₁ = 2/1 (mol/mol), CHP (80%), 110.5 mg, 0.65 mmol, 1.3 eq.), toluene (20 mL), rt.

When 1 equivalent of CHP was used, the conversion of 1 was a little low (entry 7). The conversion of 1 increased with the increased amount of CHP (entries

| Entry | Solvent | Oxidant (amount) | Time (h) | 1 | 2 | 3 | ee (%) |
|-------|---------|------------------|----------|---|---|---|--------|
| 1     | CH₂Cl₂  | CHP (1.3 eq)     | 1        | 65| 25| 10| 0      |
| 2     | THF     | CHP (1.3 eq)     | 1        | 97| 3 | 0 | 1.4    |
| 3     | AcOEt   | CHP (1.3 eq)     | 0.5      | 15| 85| 5 | 0      |
| 4     | MeCN    | CHP (1.3 eq)     | 1        |   |   |   |        |
| 5     | i-PrOH  | CHP (1.3 eq)     | 1        | 99| 1 | 0 | 11.4   |
| 6     | Acetone | CHP (1.3 eq)     | 1        |   |   |   |        |
| 7     | Toluene | CHP (1.0 eq)     | 0.5      | 16| 80| 4 | 99.1   |
| 8     | Toluene | CHP (1.1 eq)     | 0.5      | 10| 85| 5 | 99.7   |
| 9     | Toluene | CHP (1.3 eq)     | 0.5      | 6 | 90| 4 | 99.6   |
| 10    | Toluene | CHP (1.5 eq)     | 0.5      | 2 | 90| 8 | 99.2   |
| 11    | Toluene | t-BuO₂O (1.3 eq)| 1        |   |   |   |        |
| 12    | Toluene | H₂O₂ (1.3 eq)    | 1        |   |   |   |        |

*Reaction conditions: 1 (165 mg, 0.5 mmol), Ti(OPr-i)₄ (66.7 mg, 0.235 mmol), L₁ (67.1 mg, 0.065 mmol, 13 mol%), H₂O/L₁ = 2/1 (mol/mol), NEt(Pr-i)₂ (16.8 mg, 0.13 mol), solvent (20 mL), rt.

and chemical selectivity but very slight effects on enantioselectivity (entries 7–10). When 1 equivalent of CHP was used, the conversion of 1 was a little low (entry 7). The conversion of 1 increased with the increased amount of CHP (entries
8–10). However, a little more overoxidized by-product, sulfone, was found by HPLC (entry 10). With overall consideration of yield and enantioselectivity, 1.3 equivalent of CHP was the best choice.

Finally, the reaction was carried out on a gram scale. After the reaction, a solution of potassium hydroxide in methanol was added, and thus the potassium salt of esomeprazole was isolated, which was transferred to sodium salt[18] in 72% total yield with 99.6% ee, HPLC purity 99.4% (Scheme 2).

CONCLUSION

In summary, the macrocyclic ligand (L1) derived from 2,6-diformyl-4-methylphenol and (S,S)-DPEN was successfully applied in the catalytic asymmetric oxidation of pyrmetazol for the preparation of esomeprazole. Under the optimized conditions, esomeprazole was prepared with 99.6% ee, which meets the high requirement of pharmacopeia on enantiomeric purity.

EXPERIMENTAL

All reactions were performed under a nitrogen atmosphere in oven-dried glassware with magnetic stirring. Anhydrous solvents were freshly distilled from sodium and benzophenone. Column chromatography was performed on silica gel (100–200 mesh) using CH2Cl2/MeOH (25/1) as an eluant. NMR spectra were recorded in dimethylsulfoxide (d6-DMSO) at 300 MHz (1H) and 75 MHz (13C) on a spectrometer. Chemical shift (δ) were reported in parts per million (ppm) relative to the residual solvent signal. Mass spectra were performed in electrospray ionization (ESI) mode. L1 was prepared from 2,6-diformyl-4-methylphenol and (S,S)-DPEN following the reported method.[15] Other reagents were purchased from commercial sources.

Titanium tetraisopropoxide (66.7 mg, 0.235 mmol) and water (8.0 mg, the total amount of water is 8.47 mg, 0.47 mmol) were added to a solution of L1 (67.1 mg, 0.065 mmol) in toluene (20 mL) at 25°C. After stirring at that temperature for 1 h, pyrmetazol (165.0 mg, 0.5 mmol) was added. Then, the mixture was heated to 50°C and maintained for 1 h. After the mixture was cooled to 25°C, N,N-diisopropylethylamine (16.8 mg, 0.13 mol) and cumene hydroperoxide (80% in cumene, 110.5 mg, 0.65 mmol) were added subsequently. After stirring at 25°C for 1 h, a small sample of reaction mixture was taken for HPLC analysis for conversion and selectivity, and
the product was isolated by preparative thin-layer chromatography (TLC; eluent: CH₂Cl₂/MeOH = 25/1) for determination of the enantiomeric purity. Analytical data for esomeprazole sodium [6a]: [α]D²⁰ = +30 (c 1.0, H₂O). ¹H NMR (300 MHz, d⁶-DMSO) δ = 2.16 (s, 3H), 2.21 (s, 3H), 3.68 (s, 3H), 3.72 (s, 3H), 4.41 (d, J = 12.9 Hz, 1 H), 4.60 (d, J = 12.9 Hz, 1 H), 6.57 (dd, J = 8.4, 2.7 Hz, 1H), 7.00 (d, J = 2.7 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 8.24 (s, 1H). ¹³C NMR (75 MHz, d⁶-DMSO) δ = 11.2, 12.8, 55.1, 59.6, 60.4, 99.3, 108.9, 117.3, 124.9, 126.3, 141.3, 146.7, 148.9, 151.6, 153.5, 161.1, 163.3. MS (ESI, negative) m/z: 344 ([M – Na]⁻).

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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18. The sodium salt of esomeprazole is easier to dry and more stable than potassium salt, but potassium salt is easier to be separated out from the reaction mixture.