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(54) **INTRAMOLECULAR AMIDATION OF
SULFAMATES CATALYZED BY
METALLOPORPHYRINS**

Related U.S. Application Data

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(57) **ABSTRACT**

An intramolecular amidation processes for substrates such as sulfamates using chiral and non-chiral metalloporphyrin complexes which can maximize catalytic activity, enhance efficiency, stereoselectivity and speed of amidation reactions is described. The chiral metalloporphyrin catalyzed amidation of sulfamates exhibits excellent cis-selectivity, affording cyclic sulfamidates with high enantiomeric excess values.

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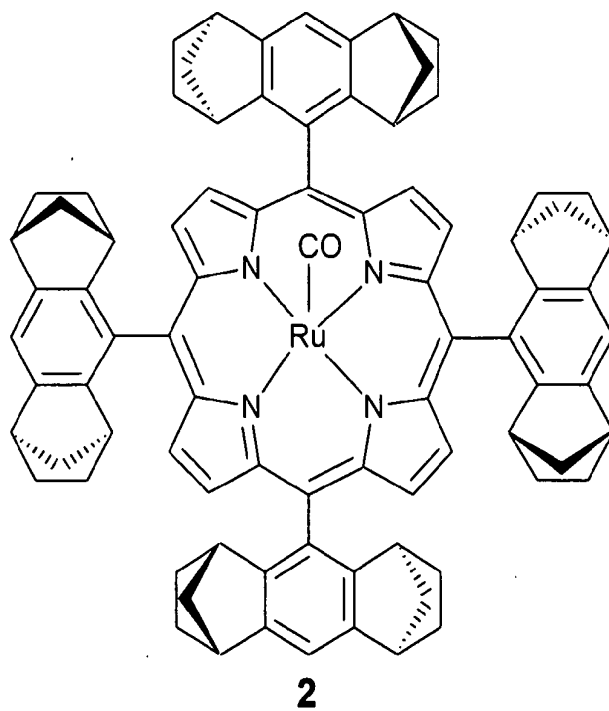
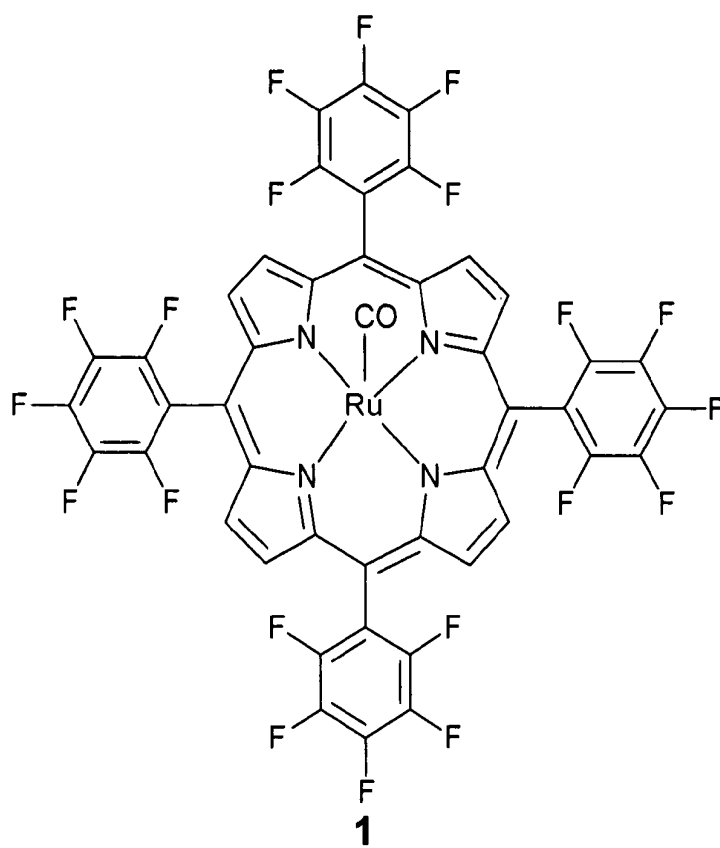
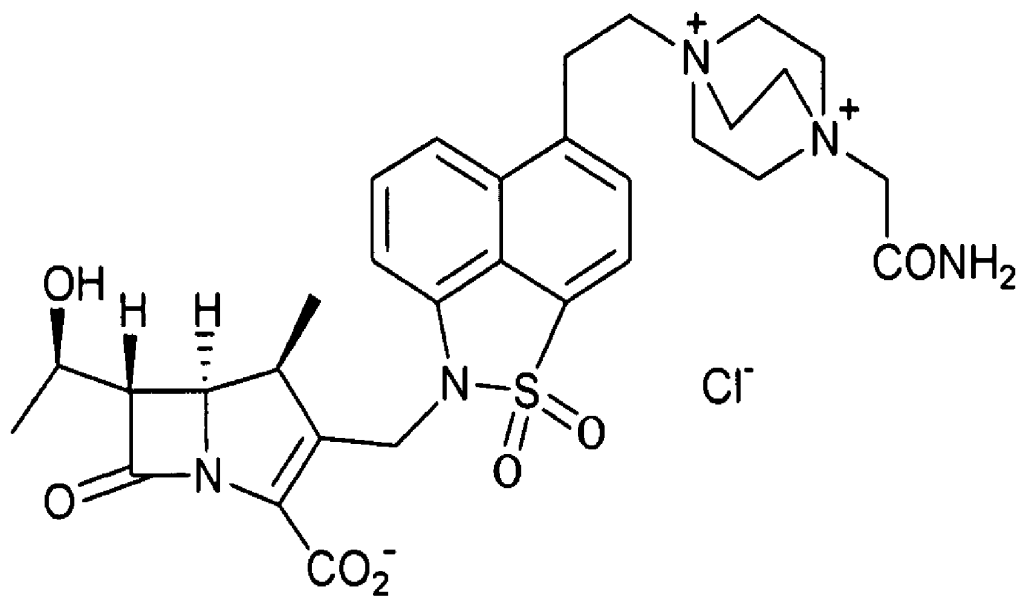
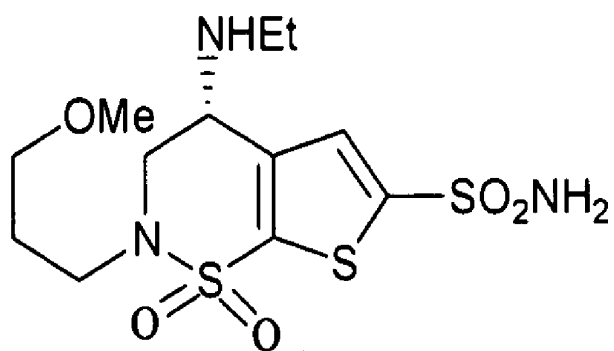


FIG. 1



L-786,392 **3**



Brinzolamide **4**

FIG. 2

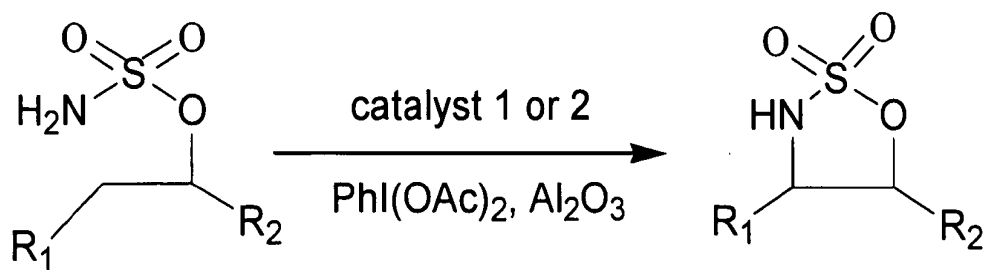
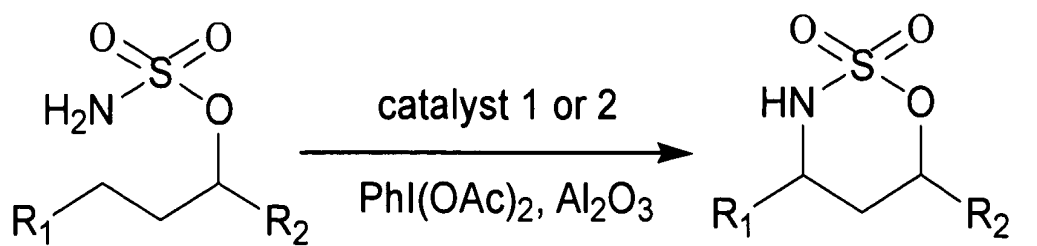
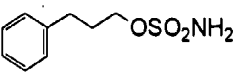
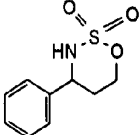
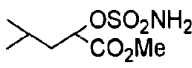
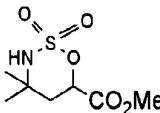
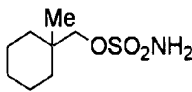
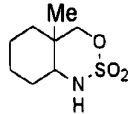
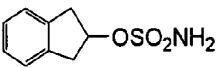
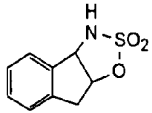
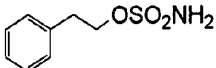
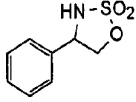
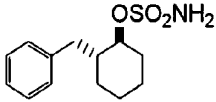
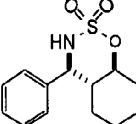


FIG. 3

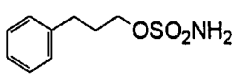
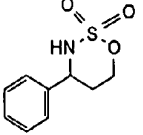
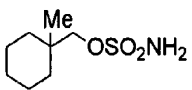
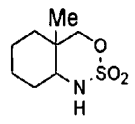
Intramolecular amidation catalyzed by $[\text{Ru}^{\text{II}}(\text{TPFPP})(\text{CO})]$ (1)^a

Entry	Substrates	Products	Yield (%)
1	 5	 11	77
2	 6	 12	76
3	 7	 (cis)-13	88
4	 8	 (cis)-14	61
5	 9	 15	56
6	 10	 16	88

^aReaction conditions: catalyst: substrate: $\text{PhI}(\text{OAc})_2 = 0.015: 1: 2$; CH_2Cl_2 , 40°C , 2 h.

FIG. 4

High turnover intramolecular amidation catalyzed by [Ru^{II}(TPFPP)(CO)] (1)

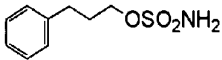
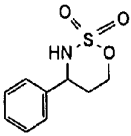
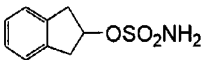
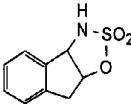
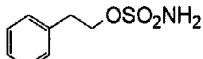
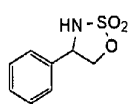
Entry	Substrate	Product	Yield (%)	Turnover
1 ^a	 5	 11	29	290
2 ^b	 7	 (cis)-13	38	301

^aReaction conditions: catalyst: substrate: PhI(OAc)₂ = 1: 1000: 2000; CH₂Cl₂, 40°C, 20 h.

^bReaction conditions: catalyst: substrate: PhI(OAc)₂ = 1: 800: 1600; CH₂Cl₂, 40°C, 20 h.

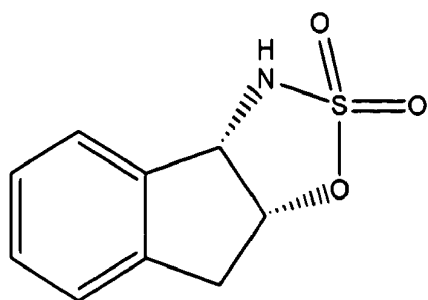
FIG. 5

Asymmetric intramolecular amidation catalyzed by $[\text{Ru}^{\text{II}}(\text{D}_4\text{-Por}^*)(\text{CO})]^\text{a}$

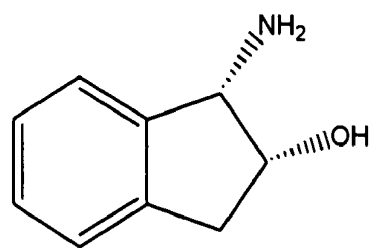
Entry	Substrate	Product	Solvent	Yield (%)	Ee (%) ^b
1			CH_2Cl_2	77	46
2	5	11	C_6H_6	63	79
3			C_6H_6	48	84 ^c
4			CH_2Cl_2	57	71
5			C_6H_6	53	81
6	8	14	C_6H_6	39	82 ^c
7			PhMe	39	77 ^d
8			CH_2Cl_2	53	69
9			C_6H_6	43	82
	9	15			
10			C_6H_6	35	87 ^c

^aReaction conditions: catalyst: substrate: $\text{PhI}(\text{OAc})_2 = 1: 10: 14$; 40°C for 2 h. ^bEe was determined by HPLC using chiral OD column. ^cReaction at 4°C and 8 h. ^dReaction at 0°C and 8 h.

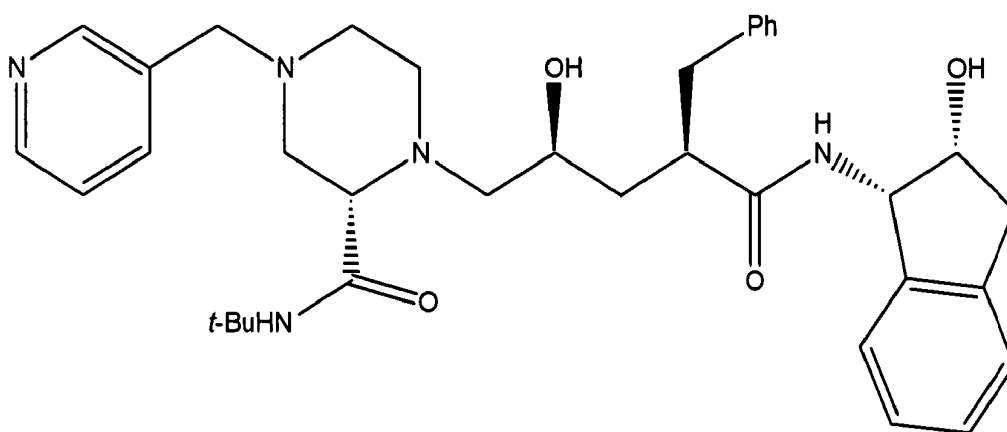
FIG. 6



(1S,2R)-14



17



18

FIG. 7

INTRAMOLECULAR AMIDATION OF SULFAMATES CATALYZED BY METALLOPORPHYRINS

[0001] This is a continuation-in-part of application Ser. No. 10/202,581, filed Jul. 23, 2002.

FIELD OF THE INVENTION

[0002] The invention relates to methods for direct intramolecular amidation of sulfamates affording cyclic sulfamidates. The method represents an example of asymmetric intramolecular amidation of sulfamate esters with high ee (enantiomeric excess) values, (typically 46-87% ee).

BACKGROUND OF THE INVENTION

[0003] Cyclic sulfamidates and sulfonamides are useful building blocks for organic synthesis and drug discovery. Major recent pharmaceutical applications include the carbapenem antibiotic L-786,392 3 and brinzolamide 4 for the treatment of glaucoma (Rosen et al. *Science* (1999), 283, 703; Dauban et al. *Org. Lett.* (2000), 2, 2327; Dauban et al. *Tetrahedron Lett.* (2001), 42, 1037; FIG. 2). Cyclic sulfamidates have also been utilized in the preparation of amino acids (Baldwin et al. *Tetrahedron: Asymmetry* (1990), 1, 881; Boulton et al. *J. Chem. Soc., Perkin Trans. 1* (1999), 1421; Halcomb et al. *J. Am. Chem. Soc.* (2002), 124, 2534) and have been shown to serve as useful chiral auxiliaries for organic synthesis (Oppolzer et al. *Tetrahedron Lett.* (1994), 35, 3509; Ahn et al. *Tetrahedron Lett.* (1998), 39, 6321; Lin et al. *Tetrahedron* (1999), 55, 13983).

[0004] Pioneering work by Breslow and co-workers in 1983 demonstrated catalytic intramolecular amidation of sulfonamides with either transition metal porphyrin complexes or rhodium acetate as catalysts gave cyclic sulfonamides in good yields (Breslow et al. *J. Am. Chem. Soc.* (1983), 105, 6728). Recent studies by Du Bois and co-workers reported rhodium acetate to be an efficient catalyst for intramolecular amidation of sulfamate esters, affording the corresponding cyclic sulfamidates in good to high yields (Du Bois et al. *J. Am. Chem. Soc.* (2001), 123, 6935). However, the challenge still remains to seek more stereoselective catalysts for the synthesis of optically active cyclic sulfamidates. To our knowledge, the asymmetric intramolecular amidation of such substrates using chiral catalysts is not known.

[0005] Metalloporphyrin catalyzed intermolecular nitrogen-atom transfer has attracted considerable attention because of their unique relationship to heme-containing enzymes, high stereoselectivity and catalytic turnover (Che et al. *Org. Lett.* (2000), 2, 2233). Moderate ee values have been obtained for asymmetric aziridination of alkenes and amidation of saturated C—H bonds (Che et al. *Chem. Commun.* (1997), 2373; Che et al. *Chem. Commun.* (1999), 2377; Marchon et al. *Chem. Commun.* (1999), 989; Che et al. *Chem. Eur. J.* (2002), 1563). The successful isolation of bis(tosylimido)ruthenium(VI) porphyrins have provided useful insights into the mechanism of ruthenium porphyrin catalyzed intramolecular nitrogen-atom transfer reactions (Che et al. *J. Am. Chem. Soc.* (1999), 121, 9120; Che et al. *Chem. Eur. J.* (2002), 1563).

[0006] The present invention describes the first intramolecular amidation of sulfamates catalyzed by a metallopor-

phyrin and asymmetric intramolecular amidation of sulfamidates catalyzed by a transition metal complex supported by a porphyrin macrocycle. The target cyclic sulfamidates can be easily converted to α - or β -amino alcohols (Du Bois et al. *J. Am. Chem. Soc.* (2001), 123, 6935), which are important precursors for drug synthesis and for the synthesis of chiral ligands for asymmetric catalysis (Kajiro et al. *Synlett* (1998), 51; Davies et al. *Tetrahedron Lett.* (1996), 37, 813; Ghosh et al. *J. Am. Chem. Soc.* (1996), 118, 2527).

BRIEF DESCRIPTION OF THE FIGURES

[0007] FIG. 1 provides representative examples of metalloporphyrin catalysts capable of catalyzing intramolecular amidation of sulfamates with high efficiency and high diastereo- and enantio-selectivity.

[0008] FIG. 2 provides representative examples of drugs containing the cyclic sulfonamide unit.

[0009] FIG. 3 illustrates the described method which involves the direct intramolecular amidation of sulfamates using metalloporphyrins as general and efficient catalysts.

[0010] FIG. 4 provides representative examples of intramolecular amidation of sulfamates catalyzed by an electron-deficient ruthenium porphyrin to give the corresponding cyclic sulfamidates in good to excellent yields and excellent diastereoselectivity.

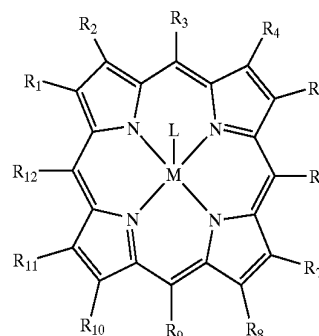
[0011] FIG. 5 provides representative examples of intramolecular amidation of sulfamates catalyzed by an electron-deficient ruthenium porphyrin with high turnover numbers.

[0012] FIG. 6 provides representative examples of asymmetric intramolecular amidation of sulfamates catalyzed by a chiral ruthenium porphyrin with high enantioselectivity.

[0013] FIG. 7 provides representative examples of pharmaceutical applications of α -amino alcohols.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The present invention provides an intramolecular amidation process using a non-chiral metalloporphyrin catalyst and a chiral metalloporphyrin catalyst represented by structural formula:



[0015] wherein

[0016] each R₁-R₁₂ is independently H, optionally substituted hydroxyl, optionally substituted amino, halogen, —CN, —NO₂, optionally substituted C₁₋₂₀ alkyl, optionally substituted phenyl; optionally substituted naphthyl; optionally substituted anthracenyl, —SR¹³, —SO₂R³, —CO₂R¹³, and optionally substituted heteroatom-containing aromatic ring, in which the optional substituents are independently selected from the foregoing alkyl, phenyl, naphthyl, anthracenyl and heteroatom-containing aromatic groups; R¹³ is independently selected from the same groups as R¹ other than —SR¹³ and —SO₂R¹³; and L is CO or R¹. The various R groups may be optically pure or can be stereo- and regioisomers.

[0017] In an embodiment of this invention, the metal-porphyrin is a transition metal porphyrin, such as ruthenium, manganese, iron, osmium, copper or cobalt porphyrin. In an embodiment of this invention, the porphyrin ligand is a tetraphenylporphyrin and the phenyl rings are attached at the meso-positions of the porphyrin. In an embodiment of the present invention, the catalysts are capable of exhibiting both regio- and stereo-selectivity. Two of the preferred catalysts are shown in **FIG. 1**. In an embodiment of the present invention, the catalyst is capable of selectively catalyzing intramolecular amidation of saturated C—H bonds. In an embodiment of the present invention, the catalyst is capable of catalyzing asymmetric intramolecular amidation of saturated C—H bonds. In an embodiment of this invention, the stereoselectivity is the formation of only cis-configuration cyclic sulfamidates.

[0018] Additionally, the present invention provides a method for the preparation of cyclic sulfamidates with the catalysts from sulfamates as starting materials. Further, the present invention provides a method for producing cis-cyclic sulfamidates with the catalyst. The present invention also provides a method for producing optically active cyclic sulfamidates with the catalyst. Preferably, the method involves the use of an oxidant which selectively alters the oxidation state of the substrate, preferably in the presence of a solvent and preferably in the presence of a base. The solvent can be MeOH, MeCN, DMF, C₄H₄Cl₂, CH₂Cl₂, and benzene. Typical oxidants include PhI(OAc)₂, PhIO and NBS (N-bromosuccinimide). Bases, which scavenge by-products, include Al₂O₃, MgO, ZnO, K₂CO₃ and NaOH. In an embodiment of this invention, the substrate is a sulfamate, a sulfamate derivative, or a hydrocarbon containing a sulfonamide functional group. As shown in the figures, carbon to which the sulfonamide moiety is attached can be a part of a cyclic or non-cyclic moiety, which in turn can be substituted with a functional group such as —CO₂Me or by an aromatic or cycloaliphatic group.

[0019] As used herein, the term, “stereoselective” refers to selection of an optical isomer. “Enantioselectivity” represents the maximal asymmetric induction and minimal racemization of the optically active products. The term “turn-over” refers to the relative number of molecules of products per number of molecules of catalyst prior to the exhaustion of a given reaction.

EXAMPLES

EXAMPLE 1

[0020] Intramolecular Amidation of Sulfamate Esters Catalyzed by Electron-Deficient Ruthenium Porphyrin 1

[0021] The invention relates to a direct method for the synthesis of cyclic sulfamidates using ruthenium porphyrin 1 (prepared according to: Murahashi et al. *Tetrahedron Lett.* (1995), 36, 8059; Groves et al. *J. Am. Chem. Soc.* (1996), 118, 8961) as a general and effective catalyst for the direct intramolecular amidation of sulfamates.

[0022] Typical conditions employ 1.5 mol % of 1, 1 equiv. of sulfamate ester, 2 equiv. of PhI(OAc)₂, 2.5 equiv. of anhydrous Al₂O₃ (pH=7-7.4) in CH₂Cl₂ (distilled from CaH₂ prior to use) under argon at 40° C. for 2 h. Commercially available Al₂O₃ was dried to a constant weight at 250° C. for 12 h. The reaction mixture was cooled to 25° C., diluted with 5 mL of CH₂Cl₂, and filtered through a pad of Celite®. The filter cake was rinsed with 2x5 mL of CH₂Cl₂ and the combined filtrates were evaporated under reduced pressure. The residue was purified by silica gel chromatography (Merck, 230-400 mesh) to afford the corresponding cyclic sulfamidates. AcOH generated as a by-product from PhI(OAc)₂ was scavenged from the reaction mixture by addition of base. Following a series of control experiments, Al₂O₃ proved to be the best among MgO, ZnO, K₂CO₃, Al₂O₃ and NaOH, in that it gave the highest product yields.

[0023] With only 1.5 mol % catalyst loading, sulfamates 5-10 were converted to the corresponding cyclic sulfamidates 11-16 in good to high yields (see **FIG. 4**). The highest yield (88%) was achieved for the intramolecular amidations of 7 and 10. Catalyst 1 shows high catalytic efficiency and excellent cis-selectivity. For substrates 7, 8 and 10, only cis-cyclic sulfamidates 12, 13 and 16 were obtained, respectively. The trans-cyclic sulfamidates were undetected. This shows that ruthenium porphyrin 1 has better stereoselectivity than rhodium acetate (a 8:1 mixture of cis and trans isomers was obtained for the reaction of 8 catalyzed by rhodium acetate. See: Du Bois et al. *J. Am. Chem. Soc.* (2001), 123, 6935). The oxidant used in the catalytic reaction is PhI(OAc)₂, which is commercially available. For substrates 5-7, and 10, six- rather than five-membered ring heterocycles 11-13 and 16 were formed in high yields (76-88%). For substrates 8 and 9, five-membered ring formation gave cycloadducts 14 and 15 in moderate yields of 61 and 56%, respectively.

[0024] All the target cyclic sulfamidates were characterized by ¹H, ¹³C and NOESY NMR spectroscopy and HRMS spectrometry. The spectral data of 11-14 are identical with those reported in the literature (see: Du Bois et al. *J. Am. Chem. Soc.* (2001), 123, 6935). 9: ¹H NMR (CDCl₃, 400 MHz): δ=7.29 (m, 5H), 4.82 (s, 2H), 4.37 (t, J=9.3 Hz, 2H), 3.03 (t, J=9.2 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ=136.4, 128.9, 128.7, 127.0, 71.4, 35.2; HRMS (EI) calcd. for C₈H₁₁NO₃S: 201.0460, found: 201.0456. 10: ¹H NMR (CDCl₃, 400 MHz) 7.23 (m, 5H), 4.66 (s, 2H), 4.34 (m, 1H), 3.15 (dd, 1H, J=13.6 Hz), 2.32 (m, 2H), 1.10-1.86 (m, 8H); ¹³C NMR (CDCl₃, 100 MHz) 140.0, 129.2, 128.3, 126.0, 87.2, 44.0, 38.9, 32.4, 30.0, 24.5, 24.4; HRMS (EI) calcd. for C₁₃H₁₉NO₃S: 269.1087, found: 269.1090. 15: ¹H NMR (CDCl₃, 400 MHz) 7.43 (m, 5H), 5.07 (m, 1H), 4.84 (m, 2H), 4.45 (t, J=6.5 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz)

135.3, 129.5, 129.4, 126.7, 75.0, 59.6; HRMS (EI) calcd. for $C_8H_9NSO_3$: 199.0303, found: 199.0297. 16: 1H NMR ($CDCl_3$, 400 MHz) 7.37 (m, 5H), 4.60 (m, 1H), 4.39 (m, 2H), 2.14 (m, 1H), 1.10-1.85 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) 136.7, 129.3, 129.1, 127.3, 86.9, 64.3, 45.3, 31.8, 29.7, 24.8, 24.4; HRMS (EI) calcd. for $C_{13}H_{17}NO_3S$: 267.0929, found: 267.0935.

EXAMPLE 2

[0025] Turnover number refers to the relative number of molecules of product per number of molecules of catalyst prior to the exhaustion of a given reaction and shows a very important aspect of catalyst efficiency. The turnover numbers for the analogous rhodium acetate catalyzed reactions do not exceed 50 (see: Du Bois et al. *J. Am. Chem. Soc.* (2001), 123, 6935). With electron-deficient ruthenium porphyrin 1 as catalyst, intramolecular amidation of 5 and 7 afforded turnover numbers of 290 and 301, respectively (**FIG. 5**). This shows that 1 is more robust catalyst than rhodium (II,II) dimer complexes (the reaction conditions are almost the same as those for EXAMPLE 1, and with a lower catalyst loading in EXAMPLE 2. See **FIG. 5** footnote).

EXAMPLE 3

[0026] Asymmetric Intramolecular Amidation of Sulfamate Ester Catalyzed by Chiral Ruthenium Porphyrin 2

[0027] With chiral ruthenium porphyrin 2 as catalyst (prepared according to: Che et al. *Chem. Commun.* (1997), 1205), sulfamates 5, 8 and 9 undergo enantioselective C—H insertion to give the corresponding cyclic sulfamidates with high ee values (typically 46-87%, **FIG. 6**). As shown in **FIG. 6**, an ee (enantiomeric excess) of 46% or more can be achieved. In order to reduce the amount of by-products, the substrate to $PhI(OAc)_2$ ratio was decreased from 2 to 1.4. Solvent has a very important effect on ee values obtained. For example, reaction of sulfamate ester 5 in CH_2Cl_2 gave 11 with 46% ee (entry 1). In comparison, the analogous reaction carried in C_6H_6 gave 11 with an ee value of 79% (entry 2). Similar outcomes were obtained for substrates 8 and 9.

[0028] Similarly, reaction temperature has an effect on the ee values. With benzene as solvent, lowering the reaction temperature to 4° C. resulted in an increase in ee values (entries 2 and 3: from 79 to 84%; entries 5 and 6: from 82 to 87%; entries 8 and 9: from 81 to 82%).

[0029] The present invention provides an efficient method for the synthesis of chiral cyclic sulfamidates. These compounds are useful synthetic intermediates in the preparation of optically active α - or β -amino alcohols of biological importance. For example, optically active 17 is currently receiving considerable attention as a key component of the HIV protease inhibitor Indinavir 18 (see: Hiyama et al. *Synlett* (1998), 51. **FIG. 7**). Amino alcohol 17 can be prepared from (1S,2R)-14 upon hydrolysis (see: Du Bois et al. *J. Am. Chem. Soc.* (2001), 123, 6935). Using commercially available achiral 2-indanol, amino alcohol 17 can be obtained in 3 steps; optically active 17 requires 8 steps from the chiral amino acid (see: Hiyama et al. *Synlett* (1998), 51).

What is claimed is:

1. A method for synthesizing a cyclic sulfamidate from a sulfamate compound comprising a sulfonylamide functional group comprising the step of catalyzing the reaction of an oxidant with said compound with a catalytic amount of metalloporphyrin as catalyst for producing the cyclic sulfamidate.

2. The method according to claim 1 wherein said compound is a sulfamate ester.

3. The method according to claim 1 wherein the oxidant is selected from the group consisting of $PhI(OAc)_2$, $PhIO$, and NBS.

4. The method according to claim 1 effected in the presence of an organic solvent selected from the group consisting of acetonitrile, DMF, $C_4H_4Cl_2$, CH_2Cl_2 , and benzene.

5. The method according to claim 1 effected in the presence of an inorganic base is selected from the group consisting of Al_2O_3 , MgO, ZnO, K_2CO_3 , and NaOH.

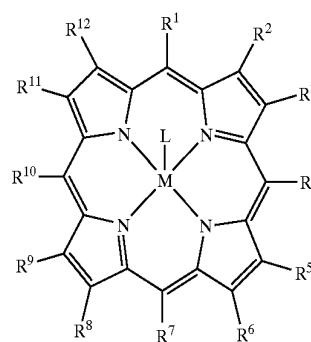
6. The method according to claim 1 wherein the metalloporphyrin is a transition metal metalloporphyrin.

7. The method according to claim 6 wherein the transition metal metalloporphyrin is selected from the group consisting of ruthenium, manganese, iron, cobalt, copper and osmium metalloporphyrin.

8. The method according to claim 7, wherein the metalloporphyrin is ruthenium porphyrin.

9. The method of claim 3 wherein the method is effected in the presence of an inorganic base is selected from the group consisting of Al_2O_3 , MgO, ZnO, K_2CO_3 , and NaOH; the metalloporphyrin is a transition metal metalloporphyrin; and wherein the method is effected in the presence of an organic solvent selected from the group consisting of acetonitrile, DMF, $C_4H_4Cl_2$, CH_2Cl_2 and benzene.

10. The method according to claim 1 wherein the catalyst is represented by the structure:



wherein M is a transition metal;

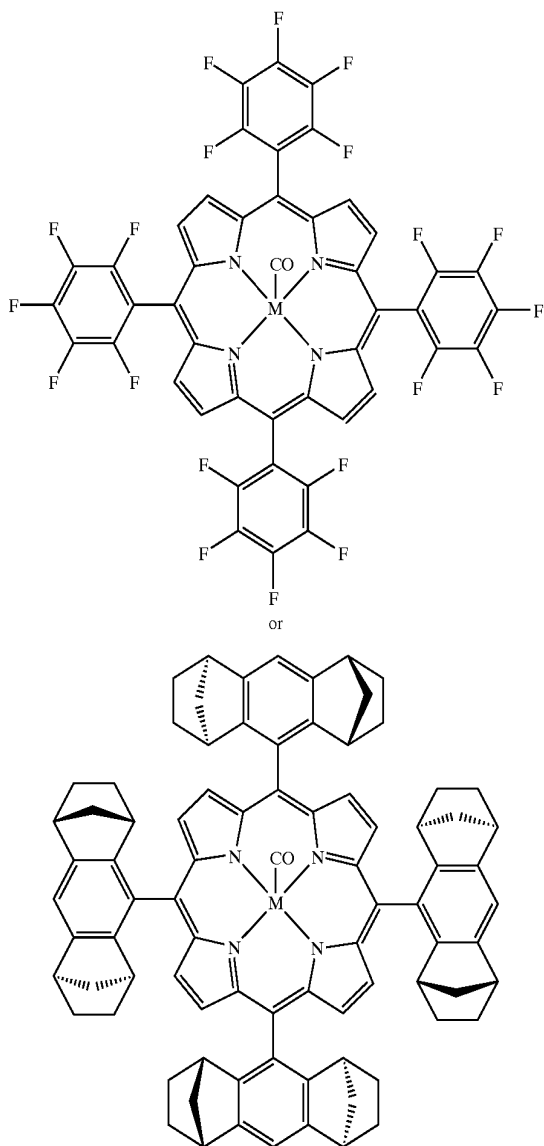
each R^1 - R^{12} is independently selected from the group consisting of —H, —halogen, $-CO_2R^{13}$, —CN, — NO_2 , SR^{13} , SO_2R^3 , optionally substituted hydroxyl, optionally substituted amino, halogen, optionally substituted C_{1-20} alkyl, optionally substituted phenyl;

optionally substituted naphthyl; optionally substituted anthracenyl, and optionally substituted heteroatom-containing aromatic ring, in which the optional substituents are independently selected from the foregoing alkyl, phenyl, naphthyl, anthracenyl and heteroatom-

containing aromatic groups; R^{13} is independently selected from the same groups as R^1 other than $-SR^{13}$ and $-SO_2R^{13}$;

L is CO or as defined as for R^1 ;

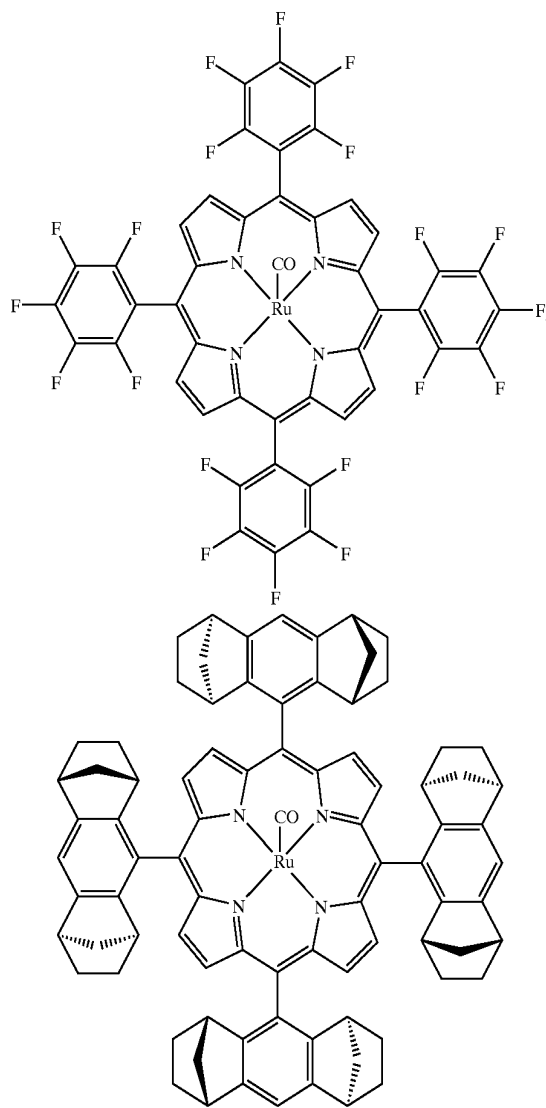
11. The method according to claim 10 wherein the metalloporphyrin catalyst has the structure:



wherein M represents a metal.

12. The method according to claim 11, wherein M represents a transition metal.

13. The method according to claim 12 wherein the catalyst is selected from the group consisting of:



14. The method of claim 9 wherein the catalyst exhibit cis-diastereoselectivity.

15. The method of claim 9 wherein the catalyst exhibits enantioselectivity and yields the corresponding cyclic sulfamidate with an enantiomeric excess value of at least 46.

16. The method of claim 9 wherein the catalyst exhibits a product turnover number of at least 290.

17. The method of claim 9 wherein the catalyst exhibits a product turnover number of at least 290.

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