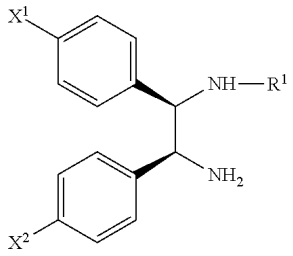
Claims

What is claimed is:

1. A method for chemically synthesizing a cis-imidazoline with an enantiomeric excess (ee) of at least 90%, the method comprising:

(a) obtaining a racemic mixture of a precursor according to Formula (A);



(A)

wherein X^1 and X^2 are both halogen, the first nitrogen is bonded to R^1 having the formula —C(=O)—R^2 where R^2 is an optionally substituted carbocycle or heterocycle group, and the second nitrogen is a primary amine;

(b) combining the racemic mixture of the precursor with a chiral aromatic acid according to Formula (B):

$$HOOC—CH(OH)—R^3 \qquad (B)$$

wherein R^3 is an optionally substituted aryl or heteroaryl group,

whereby a first stereoisomer of the precursor associates with the chiral aromatic acid, and a second stereoisomer of the precursor does not;

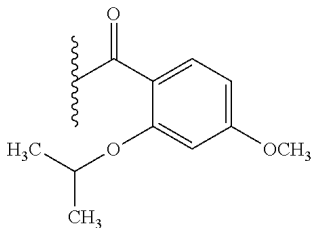
(c) separating and recovering the first stereoisomer from the chiral aromatic acid;

(d) acylating the second nitrogen of the first stereoisomer; and then

(e) performing a ring closing reaction in which the first nitrogen joins with the second nitrogen, thereby forming the cis-imidazoline with an enantiomeric excess (ee) of at least 90%.

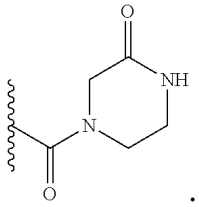
2. The method of claim 1, wherein the acylating of step (d) comprises

(i) converting the second nitrogen to an amide, preferably by substituting the second nitrogen with



, or

(ii) converting the second nitrogen to a urea group, preferably by substituting the second nitrogen with



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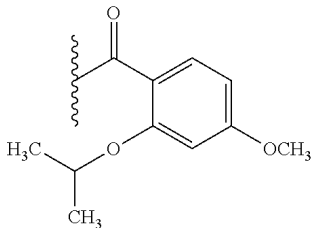
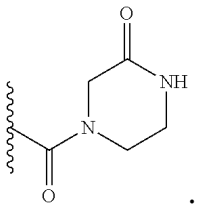
3. The method of claim 1 or 2, wherein R^1 is



or



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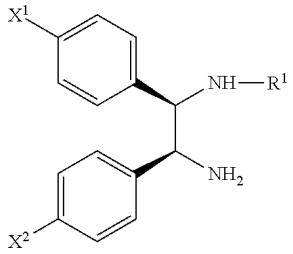
4. A method for chemically synthesizing a cis-imidazoline with an enantiomeric excess (ee) of at least 90%, the method comprising:

(a) obtaining a racemic mixture of a precursor according to Formula (A),



(A)

wherein X^1 and X^2 are both halogen, the first nitrogen is bonded to R^1 which is a nitrogen protecting group, and the second nitrogen is a primary amine;

(b) combining the racemic mixture of the precursor with a chiral aromatic acid according to Formula (B),

$$HOOC—CH(OH)—R^3 \qquad (B)$$

wherein R^3 is an optionally substituted aryl or heteroaryl group,

whereby a first stereoisomer of the precursor associates with the chiral aromatic acid, and a second stereoisomer of the precursor does not;

(c) separating and recovering the first stereoisomer from the chiral aromatic acid;

(d) acylating the second nitrogen of the first stereoisomer ;

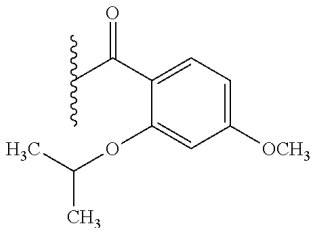
(e) deprotecting the first nitrogen;

(f) acylating the first nitrogen of the first stereoisomer, and then

(g) performing a ring closing reaction on the first stereoisomer in which the first nitrogen joins with the second nitrogen, thereby forming the cis-imidazoline with an enantiomeric excess (ee) of at least 90%.

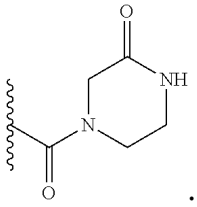
5. The method of claim 4, wherein the acylating of step (d) comprises

(i) converting the second nitrogen to an amide, preferably by substituting the second nitrogen with



, or

(ii) converting the second nitrogen to a urea group, preferably by substituting the second nitrogen with



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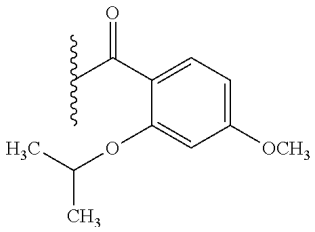
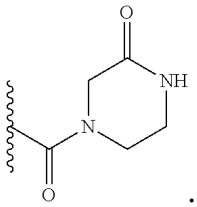
6. The method of claim 4 or 5, wherein the acylating of step (f) comprises

(i) converting the first nitrogen to an amide, preferably by substituting the first nitrogen with



, or

(ii) converting the first nitrogen to a urea group, preferably by substituting the first nitrogen with



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7. The method of any of claims 1 to 6, wherein R^3 is phenyl.

8. The method of any of claims 1 to 7, wherein X^1 and X^2 are both chloride.

9. The method of any of claims 1 to 7, wherein the chiral aromatic acid is D-mandelic acid or L-mandelic acid.

10. The method of any of claims 1 to 9, wherein the separating includes crystallizing molecules of the precursor with the chiral aromatic acid, and recovering the first stereoisomer from crystals formed thereby.

11. The method of any of claims 1 to 10, further comprising separating and recovering the second stereoisomer not associated with the chiral aromatic acid; and derivatizing and cyclizing the second stereoisomer to form a second batch of the same cis-imidazoline.

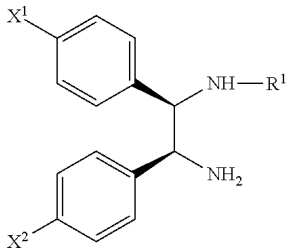
12. The method of any of claims 1 to 11, wherein the ring-closing reaction performed by combining the first stereoisomer with either triphenylphosphine oxide (Ph_3PO) or 2-fluoropyridine, and with either trifluoromethanesulfonic anhydride (Tf_2O) or trifluoroacetic anhydride (TFAA).

13. The method of any of claims 1 to 12, wherein the cis-imidazoline synthesized thereby is 4-[[(4S,5R)-4,5-bis(4-chlorophenyl)-4,5-dihydro-2-[4-methoxy-2-(1-methylethoxy)phenyl]-1H-imidazol-1-yl]carbonyl]-2-piperazinone having an enantiomeric excess (ee) of at least 98%.

14. A method for enantiomerically enriching a cis-imidazoline precursor, comprising:

(a) combining a racemic mixture of a precursor according to Formula (A) with a chiral aromatic acid under conditions whereby crystals selectively form

between a first stereoisomer of the precursor and the chiral aromatic acid, leaving a second stereoisomer of the precursor in solution;



(A)

;

(b) separating the crystals from the solution; and

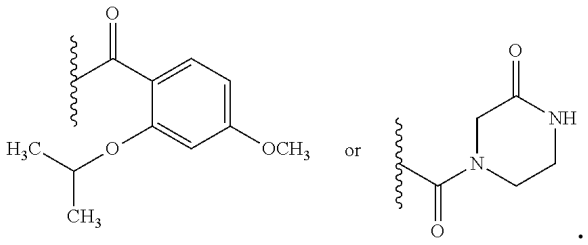
(c) recovering the first stereoisomer from the crystals, thereby enantiomerically enriching the cis-imidazoline precursor;

wherein X^1 and X^2 are both chloride, R^1 is —C(=O)—R^2 or an amine protecting group, and R^2 is an optionally substituted carbocycle or heterocycle group; and

wherein the chiral aromatic acid is HOOC—CH(OH)—R^3 wherein R^3 is a substituted or an unsubstituted aryl or heteroaryl group.

15. The method of claim 14, wherein the chiral aromatic acid is D-mandelic acid or L-mandelic acid.

16. The method of claim 14 or claim 15, wherein R^1 is BOC, another amine protecting group,



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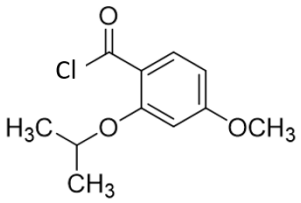
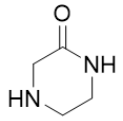
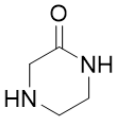
17. The method of any of claims 14 to 16, further comprising reacting the product of step (c) with



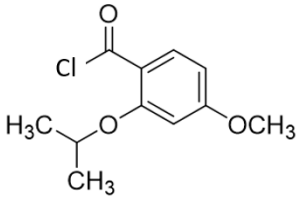
if R^1 is



, or with



if R^1 is



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18. The method of any of claims 14 to 17, whereby the cis-imidazoline prepared from molecules separated in step (c) has an enantiomeric excess (ee) of at least 90%.