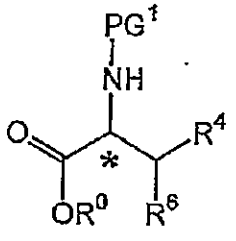
We Claim:

1. A process for the preparation of a compound of formula (I)



(I)

wherein

PG^1 is a nitrogen protecting group;

R^0 is selected from the group consisting of hydrogen, C_{1-4}alkyl and benzyl;

R^6 is selected from the group consisting of hydrogen and C_{1-5}alkyl;

R^4 is aryl or heteroaryl; wherein

the aryl is substituted with two to five substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, arylC_{1-6}alkylcarbonyloxy, heteroaryl C_{1-6}alkylcarbonyloxy, heteroaryl, hydroxyl, halogen, aminosulfonyl, formylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-5}alkyl)aminocarbonyl, heterocyclylcarbonyl, carboxy, and cyano; wherein the C_{1-6}alkyl is optionally substituted with amino, C_{1-6}alkylamino, or $(C_{1-6}alkyl)_2$amino; and wherein the aryl portion of arylC_{1-6}alkylcarbonyloxy is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, cyano, amino and hydroxyl,

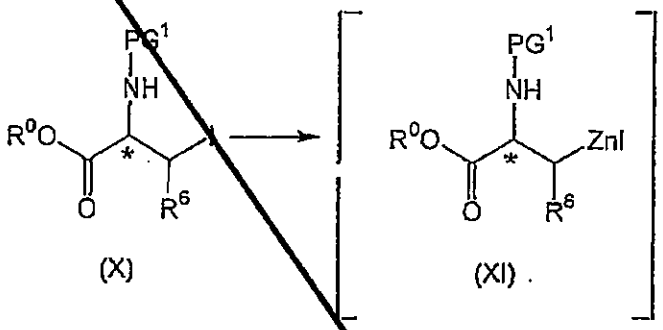
or,

the aryl is substituted with one substituent selected from the group consisting of aryl C_{1-6}alkoxy, aryl C_{1-6}alkylcarbonyloxy, heteroaryl C_{1-6}alkylcarbonyloxy, heteroaryl, hydroxyl, aminosulfonyl, formylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, heterocyclylcarbonyl, carboxy, and cyano; wherein the C_{1-6}alkyl is optionally substituted with amino, C_{1-6}alkylamino, or $(C_{1-6}alkyl)_2$amino; and wherein the aryl portion of aryl C_{1-6}alkylcarbonyloxy is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, cyano, amino and hydroxyl,

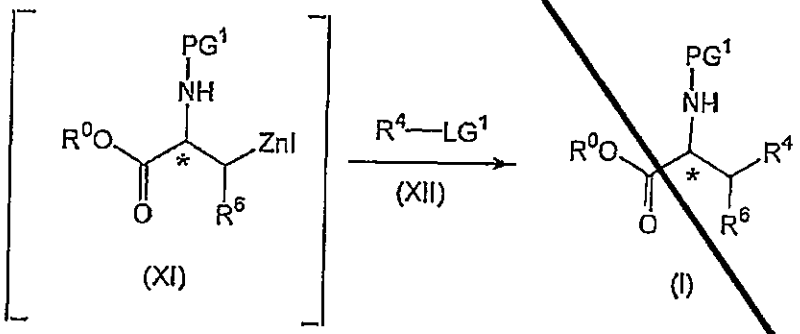
and,

· heteroaryl is optionally substituted with one to five substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, arylC_{1-6}alkoxy, arylC_{1-6}alkylcarbonyloxy, heteroarylC_{1-6}alkylcarbonyloxy, heteroaryl, hydroxy, halogen, aminosulfonyl, formylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, heterocyclylcarbonyl, carboxy, and cyano; wherein the C_{1-6}alkyl is optionally substituted with amino, C_{1-6}alkylamino, or (C_{1-6}alkyl)$_2$amino; and wherein the aryl portion of arylC_{1-6}alkylcarbonyloxy is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, cyano, amino and hydroxy;

and pharmaceutically acceptable enantiomers, pharmaceutically acceptable diastereomers, pharmaceutically acceptable racemates and pharmaceutically acceptable salt thereof; comprising



reacting a compound of formula (X), wherein PG^1 is a nitrogen protecting group, with zinc; in the presence of a source of iodine; in a first organic solvent, or a mixture of organic solvents wherein the first organic solvent is non-reactive to the source iodine; to yield the corresponding compound of formula (XI);



reacting the compound of formula (XI) with a compound of formula (XII), wherein LG^1 is a leaving group; in the presence of a palladium catalyst and phosphine ligand system; in a second organic solvent or a mixture of organic solvents; to yield the corresponding compound of formula (I).

2. A process as in Claim 1 wherein PG^1 is Boc.

3. A process as in Claim 1, wherein R^0 is methyl.

4. A process as in Claim 1, wherein the zinc is zinc powder.

5. A process as in Claim 4, wherein the zinc powder is present in an amount in the range of from about 0.5 to about 1.5 molar equivalents.

6. A process as in Claim 1, wherein the source of iodine is iodine.

7. A process as in Claim 6, wherein the iodine is present in an amount in the range of from about 0.1 to about 0.5 molar equivalents.

8. A process as in Claim 1, wherein the first organic solvent is DMAc.

9. A process as in Claim 1, wherein the compound of formula (X) is reacted with the zinc at a temperature of less than about 10°C.

10. A process as in Claim 1, wherein the zinc and source of iodine are mixed prior to addition to the compound of formula (X).

11. A process as in Claim 1, wherein LG^1 is bromo.

12. A process as in Claim 1, wherein the compound of formula (XII) is present in an amount in the range of from about 0.25 to about 1.0 molar equivalents.

13. A process as in Claim 1, wherein the palladium catalyst and phosphine ligand system is a combination of $Pd_2(dba)_3$ and $P(o\text{-}tol)_3$.

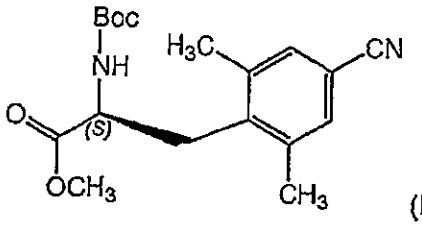
14. A process as in Claim 1, wherein the second organic solvent is DMAc.

15. A process as in Claim 1, wherein the compound of formula (X) is reacted with the compound of formula (XII) at a temperature in the range of from about 50°C to about 100°C.

16. A process as in Claim 1, wherein the compound of formula (XI) is added to a mixture of the compound of formula (XII), the palladium catalyst and phosphine ligand system.

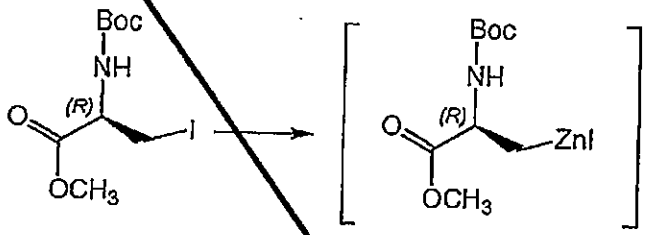
17. A compound prepared according to the process of Claim 1.

18. A process according to claim 1 for the preparation of a compound of formula (I-B)



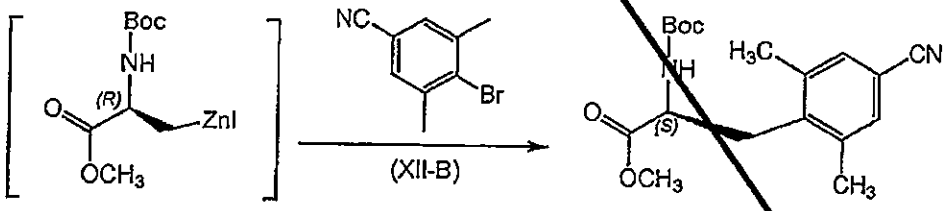
(I-B)

comprising



(X-B) (XI-B)

reacting a compound of formula (X-B) with zinc; in the presence of a source of iodine; in a first organic solvent or a mixture of organic solvents , wherein the first organic solvent is non-reactive to the source iodine; to yield the corresponding compound of formula (XI-B);



(XI-B) (XII-B) (I-B)

reacting the compound of formula (XI-B) with a compound of formula (XII-B); in the presence of a palladium catalyst and phosphine ligand system; in a second organic solvent or a mixture of organic solvents; to yield the corresponding compound of formula (I-B).

19. A process as in Claim 18, wherein the zinc is zinc powder.

20. A process as in Claim 19, wherein the zinc powder is present in an amount in the range of from about 0.5 to about 1.5 molar equivalents.

21. A process as in Claim 18, wherein the source of iodine is iodine.

22. A process as in Claim 21, wherein the iodine is present in an amount in the range of from about 0.1 to about 0.5 molar equivalents.

23. A process as in Claim 18, wherein the first organic solvent is DMAc.

24. A process as in Claim 18, wherein the compound of formula (X-B) is reacted with the zinc at a temperature of less than about 10°C.

25. A process as in Claim 18, wherein the zinc and source of iodine are mixed prior to addition to the compound of formula (X-B).

26. A process as in Claim 18, wherein the compound of formula (XII-B) is present in an amount in the range of from about 0.25 to about 1.0 molar equivalents.

27. A process as in Claim 18, wherein the palladium catalyst and phosphine ligand system is a combination of $Pd_2(dba)_3$ and $P(o\text{-}tol)_3$.

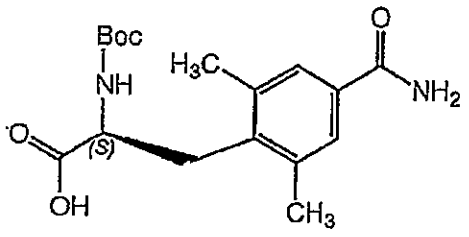
28. A process as in Claim 18, wherein the second organic solvent is DMAc.

29. A process as in Claim 18, wherein the compound of formula (X-B) is reacted with the compound of formula (XII-B) at a temperature in the range of from about 50°C to about 100°C.

30. A process as in Claim 18, wherein the compound of formula (XI) is added to a mixture of the compound of formula (XII), the palladium catalyst and the phosphine ligand system.

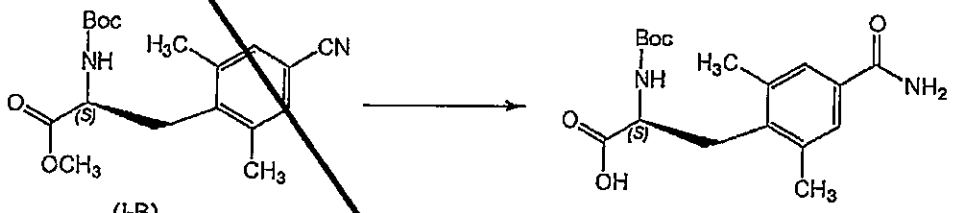
31. A compound prepared according to the process of Claim 18.

32. A process for the using a compound of formula (I-B) according to claim 18 for the preparation of a compound of formula (II-B)



(II-B)

or a pharmaceutically acceptable salt thereof; comprising



(I-B) (II-B)

reacting the compound of formula (I-B) with an oxidizing agent; in the presence of an inorganic base; in a third organic solvent; to yield the corresponding compound of formula (II-B).

33. A process as in Claim 32, wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide, LiOH and LiOOH.

34. A process as in Claim 33, wherein the oxidizing agent is hydrogen peroxide.

35. A process as in Claim 32, wherein the oxidizing agent is 30% hydrogen peroxide and is present in an excess amount.

36. A process as in Claim 32, wherein the inorganic base is potassium carbonate.

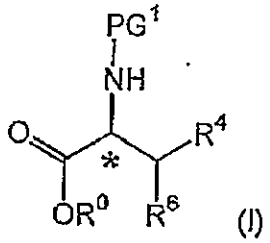
37. A process as in Claim 32, wherein the inorganic base is present in an amount in the range of from about 1.0 to about 3.0 molar equivalents.

38. A process as in Claim 32, wherein the third organic solvent is DMSO.

39. A process as in Claim 32, wherein the compound of formula (I-B) is reacted with the oxidizing agent at a temperature in the range of from about room temperature to about 60°C.

We Claim:

1. A process for the preparation of a compound of formula (I)



(I)

wherein

PG^1 is a nitrogen protecting group;

R^0 is selected from the group consisting of hydrogen, C_{1-4}alkyl and benzyl;

R^6 is selected from the group consisting of hydrogen and C_{1-6}alkyl;

R^4 is aryl or heteroaryl; wherein

the aryl is substituted with two to five substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, arylC_{1-6}alkylcarbonyloxy, heteroaryl C_{1-6}alkylcarbonyloxy, heteroaryl, hydroxyl, halogen, aminosulfonyl, formylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, heterocyclylcarbonyl, carboxy, and cyano; wherein the C_{1-6}alkyl is optionally substituted with amino, C_{1-6}alkylamino, or $(C_{1-6}alkyl)_2$amino; and wherein the aryl portion of arylC_{1-6}alkylcarbonyloxy is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, cyano, amino and hydroxyl,

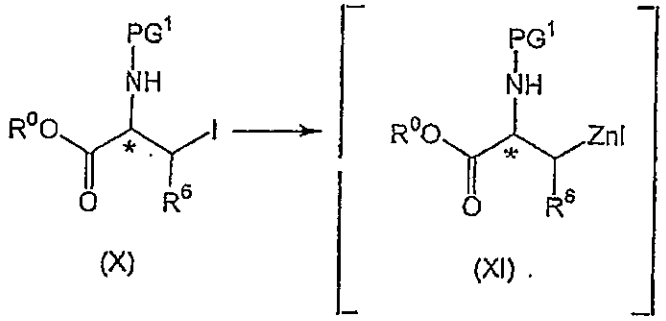
or,

the aryl is substituted with one substituent selected from the group consisting of aryl C_{1-6}alkoxy, aryl C_{1-6}alkylcarbonyloxy, heteroaryl C_{1-6}alkylcarbonyloxy, heteroaryl, hydroxyl, aminosulfonyl, formylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, heterocyclylcarbonyl, carboxy, and cyano; wherein the C_{1-6}alkyl is optionally substituted with amino, C_{1-6}alkylamino, or $(C_{1-6}alkyl)_2$amino; and wherein the aryl portion of aryl C_{1-6}alkylcarbonyloxy is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, cyano, amino and hydroxyl,

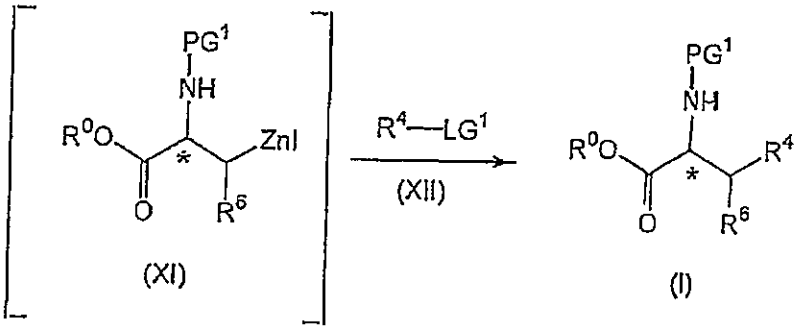
and,

· heteroaryl is optionally substituted with one to five substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, arylC_{1-6}alkoxy, arylC_{1-6}alkylcarbonyloxy, heteroarylC_{1-6}alkylcarbonyloxy, heteroaryl, hydroxy, halogen, aminosulfonyl, formylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, heterocyclylcarbonyl, carboxy, and cyano; wherein the C_{1-6}alkyl is optionally substituted with amino, C_{1-6}alkylamino, or (C_{1-6}alkyl)$_2$amino; and wherein the aryl portion of arylC_{1-6}alkylcarbonyloxy is optionally substituted with one to four substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, cyano, amino and hydroxy;

and pharmaceutically acceptable enantiomers, pharmaceutically acceptable diastereomers, pharmaceutically acceptable racemates and pharmaceutically acceptable salt thereof; comprising



reacting a compound of formula (X), wherein PG^1 is a nitrogen protecting group, with zinc; in the presence of a source of iodine; in a first organic solvent, or a mixture of organic solvents wherein the first organic solvent is non-reactive to the source iodine; to yield the corresponding compound of formula (XI);



reacting the compound of formula (XI) with a compound of formula (XII), wherein LG^1 is a leaving group; in the presence of a palladium catalyst and phosphine ligand system; in a second organic solvent or a mixture of organic solvents; to yield the corresponding compound of formula (I).

2. A process as in Claim 1 wherein PG^1 is Boc.

3. A process as in Claim 1, wherein R^0 is methyl.

4. A process as in Claim 1, wherein the zinc is zinc powder.

5. A process as in Claim 4, wherein the zinc powder is present in an amount in the range of from 0.5 to 1.5 molar equivalents.

6. A process as in Claim 1, wherein the source of iodine is iodine.

7. A process as in Claim 6, wherein the iodine is present in an amount in the range of from 0.1 to 0.5 molar equivalents.

8. A process as in Claim 1, wherein the first organic solvent is DMAc.

9. A process as in Claim 1, wherein the compound of formula (X) is reacted with the zinc at a temperature of less than 10°C.

10. A process as in Claim 1, wherein the zinc and source of iodine are mixed prior to addition to the compound of formula (X).

11. A process as in Claim 1, wherein LG^1 is bromo.

12. A process as in Claim 1, wherein the compound of formula (XII) is present in an amount in the range of from 0.25 to 1.0 molar equivalents.

13. A process as in Claim 1, wherein the palladium catalyst and phosphine ligand system is a combination of $Pd_2(dba)_3$ and $P(o\text{-}tol)_3$.

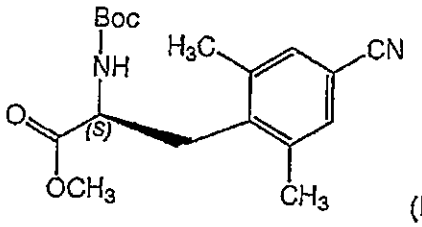
14. A process as in Claim 1, wherein the second organic solvent is DMAc.

15. A process as in Claim 1, wherein the compound of formula (X) is reacted with the compound of formula (XII) at a temperature in the range of from 50°C to 100°C.

16. A process as in Claim 1, wherein the compound of formula (XI) is added to a mixture of the compound of formula (XII), the palladium catalyst and phosphine ligand system.

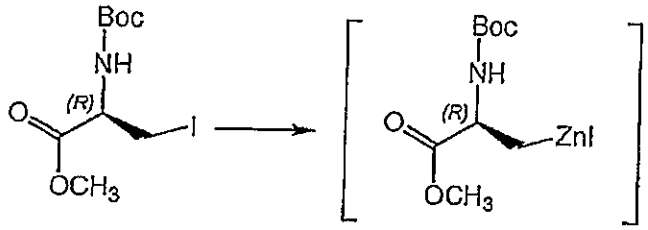
17. A compound prepared according to the process of Claim 1.

18. A process according to claim 1 for the preparation of a compound of formula (I-B)



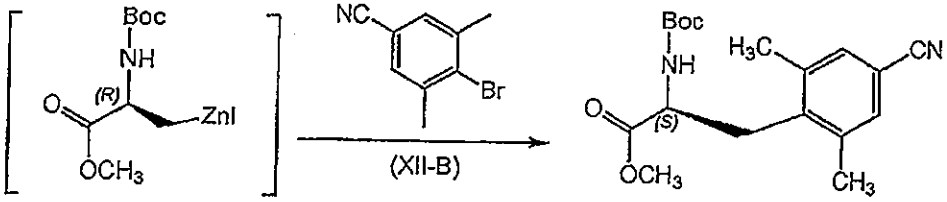
(I-B)

comprising



(X-B) (XI-B)

reacting a compound of formula (X-B) with zinc; in the presence of a source of iodine; in a first organic solvent or a mixture of organic solvents , wherein the first organic solvent is non-reactive to the source iodine; to yield the corresponding compound of formula (XI-B);



(XI-B) (XII-B) (I-B)

reacting the compound of formula (XI-B) with a compound of formula (XII-B); in the presence of a palladium catalyst and phosphine ligand system; in a second organic solvent or a mixture of organic solvents; to yield the corresponding compound of formula (I-B).

19. A process as in Claim 18, wherein the zinc is zinc powder.

20. A process as in Claim 19, wherein the zinc powder is present in an amount in the range of from 0.5 to 1.5 molar equivalents.

21. A process as in Claim 18, wherein the source of iodine is iodine.

22. A process as in Claim 21, wherein the iodine is present in an amount in the range of from 0.1 to 0.5 molar equivalents.

23. A process as in Claim 18, wherein the first organic solvent is DMAc.

24. A process as in Claim 18, wherein the compound of formula (X-B) is reacted with the zinc at a temperature of less than 10°C.

25. A process as in Claim 18, wherein the zinc and source of iodine are mixed prior to addition to the compound of formula (X-B).

26. A process as in Claim 18, wherein the compound of formula (XII-B) is present in an amount in the range of from 0.25 to 1.0 molar equivalents.

27. A process as in Claim 18, wherein the palladium catalyst and phosphine ligand system is a combination of $Pd_2(dba)_3$ and $P(o\text{-}tol)_3$.

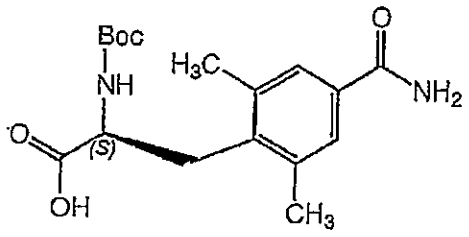
28. A process as in Claim 18, wherein the second organic solvent is DMAc.

29. A process as in Claim 18, wherein the compound of formula (X-B) is reacted with the compound of formula (XII-B) at a temperature in the range of from 50°C to 100°C.

30. A process as in Claim 18, wherein the compound of formula (XI) is added to a mixture of the compound of formula (XII), the palladium catalyst and the phosphine ligand system.

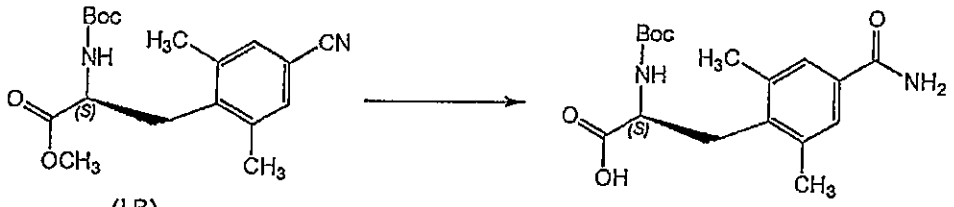
31. A compound prepared according to the process of Claim 18.

32. A process for the using a compound of formula (I-B) according to claim 18 for the preparation of a compound of formula (II-B)



(II-B)

or a pharmaceutically acceptable salt thereof; comprising



(I-B) (II-B)

reacting the compound of formula (I-B) with an oxidizing agent; in the presence of an inorganic base; in a third organic solvent; to yield the corresponding compound of formula (II-B).

33. A process as in Claim 32, wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide, LiOH and LiOOH.

34. A process as in Claim 33, wherein the oxidizing agent is hydrogen peroxide.

35. A process as in Claim 32, wherein the oxidizing agent is 30% hydrogen peroxide and is present in an excess amount.

36. A process as in Claim 32, wherein the inorganic base is potassium carbonate.

37. A process as in Claim 32, wherein the inorganic base is present in an amount in the range of from 1.0 to 3.0 molar equivalents.

38. A process as in Claim 32, wherein the third organic solvent is DMSO.

39. A process as in Claim 32, wherein the compound of formula (I-B) is reacted with the oxidizing agent at a temperature in the range of from room temperature to 60°C.