

CLAIMS

1. A process for coupling amino acid "X" to a protected N-group attached to a peptide synthesis resin comprising:
 - 5 obtaining a first reactor and a second reactor, the first reactor and the second reactor each containing a quantity of a protected N-group attached to a peptide synthesis resin;
 - adding a first quantity of de-protecting reagent to the first reactor;
 - 10 removing the first quantity of de-protecting reagent from the first reactor
 - adding the first quantity of de-protecting reagent to the second reactor;
 - adding a second quantity of de-protecting reagent to the first reactor;
 - removing the first quantity of de-protecting reagent from the second reactor;
 - removing the second quantity of de-protecting reagent from the first reactor;
 - 15 adding the second quantity of de-protecting reagent to the second reactor;
 - removing the second quantity of de-protecting reagent from the second reactor;
 - washing the peptide synthesis resin in both the first and second reactors with a solvent;
 - adding a first quantity amino acid "X" activated ester to the first reactor;
 - 20 removing the first quantity amino acid "X" activated ester from the first reactor;
 - adding the first quantity of amino acid "X" activated ester to the second reactor;
 - adding a second quantity of amino acid "X" activated ester to the first reactor;
 - removing the first quantity of amino acid "X" activated ester from the second reactor;
 - 25 removing the second quantity of amino acid "X" activated ester from the first reactor
 - adding the second quantity of amino acid "X" activated ester to the second reactor;
 - removing the second quantity of amino acid "X" activated ester from the second reactor; and
 - 30 washing the peptide synthesis resin in both the first and second reactors with a solvent.

2. The process of claim 1, wherein the amino acid "X", that is found in the first and second quantity of amino acid "X" activated ester, itself has a protected N-group.
3. The process of any of the preceding claims, further comprising:
 - 5 adding the first quantity of de-protecting reagent to a third reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the second reactor, wherein the third reactor contains a quantity of a protected N-group attached to a peptide synthesis resin; and
 - 10 adding the second quantity of de-protecting reagent to the third reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the second reactor.
4. The process of claim 3, further comprising:
 - 15 adding the first quantity of amino acid "X" activated ester to the third reactor, wherein this adding occurs after the first quantity of amino acid "X" activated ester is removed from the second reactor; and
 - 20 adding the second quantity of amino acid "X" activated ester to the third reactor, wherein this adding occurs after the second quantity of amino acid "X" activated ester is removed from the second reactor.
5. The process of claim 4, further comprising:
 - 25 adding a third quantity of de-protecting reagent to the first reactor, wherein this third quantity of de-protecting reagent is added to the first reactor after the second quantity of de-protecting reagent has been removed from the first reactor; and
 - transferring the third quantity of de-protecting reagent from the first reactor to the second reactor, wherein this transferring occurs after the second quantity of de-protecting reagent is removed from the second reactor; and
 - transferring the third quantity of de-protecting reagent from the second reactor to the third reactor; and
 - 30 removing the third quantity of de-protecting reagent from the third reactor.
6. The process of claim 5, further comprising:

adding a third quantity amino acid "X" activated ester to the first reactor, wherein this adding occurs after the second quantity of amino acid "X" activated ester is removed from the first reactor;

transferring the third quantity of amino acid "X" activated ester to the second
5 reactor, wherein this transferring occurs after the second quantity of amino acid "X" activated ester is removed from the second reactor;

transferring the third quantity of amino acid "X" activated ester from the second reactor to the third reactor; and

removing the third quantity of amino acid "X" activated ester from the third
10 reactor.

7. The process of claim 6, further comprising:

removing the first quantity of amino acid "X" activated ester from the third reactor; and

15 adding the first quantity of amino acid "X" activated ester back to first reactor.

8. The process of claim 7, further comprising:

removing the first quantity of de-protecting reagent from the third reactor; and
adding the first quantity of de-protecting reagent back to the first reactor.

20

9. The process of any of the preceding claims, further comprising swelling the first and second reactors.

10. The process of any of the preceding claims, wherein the first quantity of amino
25 acid "X" activated ester and the second quantity of amino acid "X" activated ester are pre-mixed with a solvent.

11. The process of any of the preceding claims, wherein the washing the first and second reactors with a solvent occurs by adding solvent to the reactors.

30

12. The process of claim 2, wherein after the second quantity of amino acid "X" activated ester has been removed from the first reactor, the method further comprising:
adding a first additional quantity of de-protecting reagent to the first reactor;

transferring the first additional quantity of de-protecting reagent from the first reactor to the second reactor;

adding a second additional quantity of de-protecting reagent to the first reactor;

removing the first additional quantity of de-protecting reagent from the second

5 reactor;

transferring the second additional quantity of de-protecting reagent from the first reactor to the second reactor;

removing the second additional quantity of de-protecting reagent from the second reactor.

10

13. The process of claim 12 wherein after the second additional quantity of de-protecting reagent is removed from the first reactor, further comprising:

adding a first quantity amino acid "Z" activated ester to the first reactor;

transferring the first quantity of amino acid "Z" activated ester to the second

15 reactor;

adding a second quantity of amino acid "Z" activated ester to the first reactor;

removing the first quantity of amino acid "Z" activated ester from the second

reactor;

transferring the second quantity of amino acid "Z" activated ester from the first

20 reactor to the second reactor; and

removing the second quantity of amino acid "Z" activated ester from the second

reactor.

14. The process of claim 13, further comprising:

25 adding the first additional quantity of de-protecting reagent to a third reactor, wherein this adding occurs after the first additional quantity of de-protecting reagent is removed from the second reactor, wherein the third reactor contains a quantity of a protected N-group of amino acid "X" activated ester; and

adding the second additional quantity of de-protecting reagent to the third reactor,

30 wherein this adding occurs after the second quantity of de-protecting reagent is removed from the second reactor.

15. The process of claim 14, further comprising:

adding the first quantity of amino acid "Z" activated ester to the third reactor,
wherein this adding occurs after the first quantity of amino acid "Z" is removed from the
second reactor; and

adding the second quantity of amino acid "Z" activated ester to the third reactor,
5 wherein this adding occurs after the second quantity of amino acid "Z" activated ester is
removed from the second reactor.

16. The process of any of the preceding claims, wherein the peptide synthesis resin in
the first and second reactors are Seiber or Rink resins.

10

17. The process of any of the preceding claims, wherein the peptide synthesis resin in
the first and second reactors are Wang resins or CTC resins.

18. The process of any of the preceding claims, wherein the amount of amino acid X
15 that is added is between 1.1 and 1.6 equivalents.

19. A process for coupling amino acid "X" to a protected N-group that is attached to a
peptide synthesis resin found in a first reactor and a second reactor, comprising:

adding a first quantity of de-protecting reagent to the first reactor;
20 removing the first quantity of de-protecting reagent from the first reactor
adding the first quantity of de-protecting reagent to the second reactor;
adding a second quantity of de-protecting reagent to the first reactor;
removing the first quantity of de-protecting reagent from the second reactor;
removing the second quantity of de-protecting reagent from the first reactor
25 adding the second quantity of de-protecting reagent to the second reactor;
removing the second quantity of de-protecting reagent from the second reactor;
adding a first quantity amino acid "X" activated ester to the first reactor;
removing the first quantity amino acid "X" activated ester from the first reactor;
adding the first quantity of amino acid "X" activated ester to the second reactor;
30 adding a second quantity of amino acid "X" activated ester to the first reactor;
removing the first quantity of amino acid "X" activated ester from the second
reactor;

removing the second quantity of amino acid "X" activated ester from the first reactor;

adding the second quantity of amino acid "X" activated ester to the second reactor; and

5 removing the second quantity of amino acid "X" activated ester from the second reactor.

20. The process of claim 19, wherein the amino acid "X", that is found in the first and second quantity of amino acid "X" activated ester, itself has a protected N-group.

10

21. The process of either claim 18 or 19, further comprising:

adding the first quantity of de-protecting reagent to a third reactor, wherein this adding occurs after the first quantity of de-protecting reagent is removed from the second reactor, wherein the third reactor contains a quantity of a protected N-group attached to a peptide synthesis resin;

15

removing the first quantity of de-protecting reagent from the third reactor;

adding the second quantity of de-protecting reagent to the third reactor, wherein this adding occurs after the second quantity of de-protecting reagent is removed from the second reactor;

20

adding a third quantity of de-protecting reagent to the first reactor, wherein this third quantity of de-protecting reagent is added to the first reactor after the second quantity of de-protecting reagent has been removed from the first reactor; and

transferring the third quantity of de-protecting reagent from the first reactor to the second reactor, wherein this transferring occurs after the second quantity of de-protecting reagent is removed from the second reactor;

25

transferring the third quantity of de-protecting reagent from the second reactor to the third reactor;

adding the first quantity of amino acid "X" activated ester to the third reactor, wherein this adding occurs after the first quantity of amino acid "X" activated ester is removed from the second reactor;

30

removing the first quantity of amino acid "X" activated ester from the third reactor;

adding the second quantity of amino acid "X" activated ester to the third reactor,
wherein this adding occurs after the first quantity of amino acid "X" activated ester is
removed from the third reactor; and

removing the second quantity of amino acid "X" activated ester from the third
5 reactor.

22. The process of claim 21, further comprising:

adding a third quantity amino acid "X" activated ester to the first reactor, wherein
this adding occurs after the second quantity of amino acid "X" activated ester is removed
10 from the first reactor;

transferring the third quantity of amino acid "X" activated ester to the second
reactor, wherein this transferring occurs after the second quantity of amino acid "X"
activated ester is removed from the second reactor;

transferring the third quantity of amino acid "X" activated ester and from the
15 second reactor to the third reactor;

removing the third quantity of amino acid "X" activated ester from the third
reactor;

adding the first quantity of amino acid "X" activated ester back to first reactor,
wherein this adding of the first quantity of amino acid "X" activated ester occurs after the
20 first quantity of amino acid "X" activated ester is removed from the third reactor.

23. A process for coupling amino acid "X" to a de-protected N-group attached to a
peptide synthesis resin comprising:

obtaining a first reactor and a second reactor, the first reactor and the second
25 reactor each containing a quantity of a de-protected N-group attached to a peptide
synthesis resin;

adding a first quantity amino acid "X" activated ester to the first reactor;
removing the first quantity amino acid "X" activated ester from the first reactor;
adding the first quantity of amino acid "X" activated ester to the second reactor,
30 adding a second quantity of amino acid "X" activated ester to the first reactor;
removing the first quantity of amino acid "X" activated ester from the second
reactor;

removing the second quantity of amino acid "X" activated ester from the first reactor;

adding the second quantity of amino acid "X" activated ester to the second reactor; and

5 removing the second quantity of amino acid "X" activated ester from the second reactor.

24. The process of claim 23, further comprising washing the first reactor and a second reactor with solvent.

10

25. The process of claim 22 or 23, further comprising:

adding the first quantity of amino acid "X" activated ester to a third reactor, wherein this adding occurs after the first quantity of amino acid "X" is removed from the second reactor, wherein the third reactor contains a quantity of a protected N-group

15 attached to a peptide synthesis resin;

removing the first quantity of amino acid "X" activated ester from the third reactor; and

adding the second quantity of amino acid "X" to the third reactor.

20 26. The process of claim 25, further comprising:

adding a third quantity of amino acid "X" to the first reactor, wherein this third quantity of amino acid "X" is added to the first reactor after the second quantity of amino acid "X" has been removed from the first reactor; and

25 transferring the third quantity of amino acid "X" from the first reactor to the second reactor, wherein this transferring occurs after the second quantity of amino acid "X" is removed from the second reactor.

27. The process of claim 26, further comprising:

removing the second quantity of amino acid "X" from the third reactor;

30 transferring the third quantity of amino acid "X" from the second reactor to the third reactor;

removing the third quantity of amino acid "X" from the third reactor; and

adding the first quantity of amino acid "X" back to the first reactor, wherein the first quantity of amino acid "X" is added back to the first reactor after the first quantity of amino acid "X" de-protecting reagent has been removed from the third reactor.

- 5 28. A process for de-protecting a protected N-group attached to a peptide synthesis resin comprising:
- obtaining a first reactor and a second reactor, the first reactor and the second reactor each containing a quantity of a protected N-group attached to a peptide synthesis resin;
- 10 adding a first quantity of de-protecting reagent to the first reactor;
- removing the first quantity of de-protecting reagent from the first reactor
- adding the first quantity of de-protecting reagent to the second reactor;
- adding a second quantity of de-protecting reagent to the first reactor;
- removing the first quantity of de-protecting reagent from the second reactor;
- 15 removing the second quantity of de-protecting reagent from the first reactor;
- adding the second quantity of de-protecting reagent to the second reactor; and
- removing the second quantity of de-protecting reagent from the second reactor.
29. The process of claim 28, further comprising washing the first reactor and a second
- 20 reactor with solvent.
30. The process of claim 28 or 29, further comprising:
- adding the first quantity of de-protecting reagent to a third reactor, wherein this
- adding occurs after the first quantity of de-protecting reagent is removed from the second
- 25 reactor, wherein the third reactor contains a quantity of a protected N-group attached to a peptide synthesis resin;
- removing the first quantity of de-protecting reagent from the third reactor; and
- adding the second quantity of de-protecting reagent to the third reactor, wherein
- this adding occurs after the second quantity of de-protecting reagent is removed from the
- 30 second reactor.
31. The process of claim 30, further comprising:

adding a third quantity of de-protecting reagent to the first reactor, wherein this third quantity of de-protecting reagent is added to the first reactor after the second quantity of de-protecting reagent has been removed from the first reactor; and

transferring the third quantity of de-protecting reagent from the first reactor to the second reactor, wherein this transferring occurs after the second quantity of de-protecting reagent is removed from the second reactor.

32. The process of claim 31, further comprising:

removing the second quantity of de-protecting reagent from the third reactor;

transferring the third quantity of de-protecting reagent from the second reactor to the third reactor;

removing the third quantity of de-protecting reagent from the third reactor; and

adding the first quantity of de-protecting reagent back to the first reactor, wherein the first quantity of de-protecting reagent is added back to the first reactor after the first quantity of de-protecting reagent has been removed from the third reactor.

33. A system for de-protecting a protected N-group attached to a peptide synthesis resin comprising a first reactor and a second reactor, the first reactor and the second reactor each containing a quantity of a protected N-group attached to a peptide synthesis resin.

34. A system for coupling amino acid "X" to a de-protected N-group attached to a peptide synthesis resin comprising a first reactor and a second reactor, the first reactor and the second reactor each containing a quantity of a protected N-group attached to a peptide synthesis resin.

35. A system for coupling amino acid "X" to a de-protected N-group attached to a peptide synthesis resin comprising a first reactor and an LCMS device, wherein the system automatically samples slurry from the reactor, and cleaves the peptide from resin and deprotects the functional groups.

36. A system as in claim 35, wherein the sample is sent from the reactor at the beginning, middle, or end of the reaction.

37. A system as in claim 35, wherein the sample is sent from the reactor at the beginning, middle, and end of the reaction.
- 5 38. A system as in claim 35, wherein the reactor is a batch reactor.
39. A system as in claim 35, wherein the system does not use a Kaiser test
40. A system as in claim 35, wherein the system also dilutes the cleaved peptide
10 solution in liquid chromatography diluent, transports solution to the liquid
chromatography injection loop, and flushes the spent resin beads from the cleavage
reactor to waste.
41. The system as in claim 40, wherein the solution liquid liquid chromatography
15 injection loop is free of gas-bubbles.