chain" or other group as part of its structure that may also have to be protected. However, those skilled in the art will appreciate how such side chains or other group may be constructed, protected, and subsequently de-protected during the synthesis process.)

While this SPPS process is used commercially and is still the standard in peptide synthesis, it has a drawback in that it is expensive and time consuming. Each amino acid that is added must be de-protected and coupled, which is difficult and usually results in large quantities of solvents being used. Making matters worse is that many of these solvents are not environmentally friendly.

Accordingly, it would be an improvement to find a new way to use SPPS, that would address one or more of these deficiencies, especially in the commercial manufacturing of peptides. It would be a further advancement if such a system could be more environmentally friendly and reduce manufacturing costs. In fact, the present embodiments will specifically reduce the quantity of waste, and the quantity of solvent and reagents that are used. Such a method and system is disclosed herein.

SUMMARY

In one aspect of the present disclosure, there is provided a process for coupling amino acid "X" to 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;

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;

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

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;

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;

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

washing the peptide synthesis resin in both the first and second reactors with a solvent.

In another aspect of the present disclosure, there is provided 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;

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

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;

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

removing the second quantity of amino acid “X” activated ester from the second reactor.

In a further aspect of the present disclosure, there is provided 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 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,

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

removing the second quantity of amino acid “X” activated ester from the second reactor.

In another aspect of the present disclosure, there is provided 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;

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;

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.

In a further aspect of the present disclosure, there is provided a system for coupling amino acid "X" to a de-protected N-group attached to a peptide synthesis resin comprising a 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.

A process and system for coupling an amino acid "X" activated ester to a protected N-group (such as an NH_2 terminus) of an amino acid that is attached to a SPPS resin. Generally, the system will comprise a collection of reactors that are arranged in series. In some ~~embodiment~~example**s**, two or more reactors are arranged in series. In a preferred ~~embodiment~~example, 3 or more reactors are arranged in series.

Each reactor contains a quantity of a protected N-group affixed to a peptide synthesis resin. This protected N-group may be an NH_2 group of an amino acid or may be an NH_2 group found on or covalently attached to the resin itself such as, but not limited to Sieber amide or Rink Amide resins. Other types of resins, such as Wang resins or CTC (chlorotrityl chloride) resins may also be used.

The first step in the process involves adding a first quantity of de-protecting reagent to the first reactor and allowing this reagent to contact the protected N-group. Then, this first quantity of de-protecting reagent is transferred from the first reactor to the second reactor and a second quantity of de-protecting reagent to the first reactor. The first quantity of de-protecting reagent is removed from the second reactor and the second quantity of de-protecting reagent is transferred from the first reactor to the second reactor. This second quantity of de-protecting reagent is then removed from the second reactor.

The first quantity of amino acid “X” and the first quantity of solvent is removed from the second reactor and the second quantity of amino acid “X” and the second quantity of solvent is transferred from the first reactor to the second reactor. Then the second quantity of amino acid “X” and the second quantity of solvent are removed the from the second reactor. The first and second quantity of amino acid “X”, either separately or collectively, couples the amino acid “X” to the de-protected N group in the second reactor. The first quantity of solvent wash is added to the first reactor then transferred to the second reactor, then to waste. The solvent wash cycle is repeated several times. The second quantity of solvent wash may be in the first reactor simultaneously with the first quantity of solvent wash in the second reactor, and so on. Thus, after performing these steps the amino acid “X” will have been coupled to the de-protected N-group—thereby adding amino acid “X” to the chain. Of course, as with other SPPS systems, amino acid “X” contains a protected NH_2 group, and thus, the process above may be repeated (e.g., de-protecting the NH_2 group and coupling a new amino acid to it, in the manner outlined above). Thus, by repeating this process, the desired amino acid sequence and/or peptide may be constructed. Once the synthesis is finished, the constructed amino acid may be released (de-coupled) to the resin in both the first reactor and the second reactor.

Although the above-recited method uses two reactors in series, each with a supply of resin, other ~~embodiment~~examples may be designed in which a third reactor, also containing a quantity of resin, is put in series with the first two reactors. In this ~~embodiment~~example, the de-protection step must also occur in the third reactor. So once first quantity of de-protecting reagent is removed from the second reactor, it is added to the third reactor. This first quantity of de-protected reagent is removed from the third reactor, and then the second quantity of de-protected agent, once it has been removed from the second reactor, is added to the third reactor. Likewise, a third quantity of de-protecting reagent will be added to the first reactor, moved the second reactor and then moved to the third reactor. The purpose of the first, second and third quantity of de-protecting reagent, either separately or collectively, is to de-protect the protected N-group affixed to the peptide synthesis resin in the third reactor. In like manner, the first quantity of amino acid “X” and the first quantity of solvent to the third reactor will be added to the third reactor after it was removed from the second reactor. Similarly, the second quantity of amino acid “X” and the second quantity of solvent to the third reactor will be added to the third reactor

after it was removed from the second reactor. A third quantity of amino acid "X" and a third third quantity of solvent is sequentially cycled through the first, second and third reactors. The first, second and third quantity of amino acid "X", either separately or collectively, couples the amino acid "X" to the de-protected N group in the third reactor. A washing step, as described above, is then performed. Thus, in this manner, the amino acid sequence may be built in all three reactors iteratively (by repeating these or similar steps for each amino acid) and then released from the resins in each of the three reactors.

Thus, the present ~~embodiment~~example**s** provide various reactors positioned in series and that the reagents will be added to the first reactor and then subsequently and sequentially moved to the second reactor and then the third reactor, etc. By positioning such reactors in series, each reactor can contain a quantity of resin that will be used in SPPS which will be used to construct a peptide sequence. Yet, by positioning the reactors in this manner, lesser amount of solvent (washing material) will be required. Likewise, a lesser amount of coupling reagent may be required, thus resulting in less waste and a more efficient and environmentally-friendly process.

BRIEF DESCRIPTION OF THE DRAWINGS

The features and advantages of the present disclosure will become more apparent to those skilled in the art upon consideration of the following detailed description taken in conjunction with the accompanying figures.

FIG. 1 is a schematic view of the system and method for coupling amino acid "X" to a protected N-group attached to a peptide synthesis resin used herein;

FIG. 2 is a schematic view of the system and method for coupling amino acid "X" to a protected N-group attached to a peptide synthesis resin used herein;

FIG. 3 is a schematic view of the system and method for coupling amino acid "X" to a protected N-group attached to a peptide synthesis resin used herein;

FIG. 4 is a schematic view of the system and method for online LCMS used with the system of Figure 3;

FIG. 5 is a perspective view of three reactors in series as used in the present embodiments;

FIG. 6 shows a peptide that may be made using the present embodiments; and

FIG. 7 shows a peptide that may be made using the present embodiments.

CLAIMS

1. A process for coupling amino acid “X” to 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;

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;

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

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;

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;

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

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 claim 1~~any of the preceding claims~~, 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; 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 second reactor.

4. The process of claim 3, further comprising:

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

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:

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

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 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 reactor.

7. The process of claim 6, further comprising:

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

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.

~~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 acid “X” activated ester and the second quantity of amino acid “X” activated ester are pre-mixed with a solvent.~~

~~11~~9. The process of claim 1~~any of the preceding claims~~, wherein the washing the first and second reactors with a solvent occurs by adding solvent to the reactors.

~~12~~10. 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 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.

~~13~~11. 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 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 reactor to the second reactor; and

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

~~14~~12. The process of claim ~~13~~11, further comprising:

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

~~15~~13. The process of claim ~~14~~12, 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, wherein this adding occurs after the second quantity of amino acid “Z” activated ester is removed from the second reactor.

~~16~~14. The process of claim 1~~any of the preceding claims~~, wherein the peptide synthesis resin in the first and second reactors are Seiber or Rink resins.

~~17~~15. The process of claim 1~~any of the preceding claims~~, wherein the peptide synthesis resin in the first and second reactors are Wang resins or CTC resins.

~~18~~16. The process of claim 1~~any of the preceding claims~~, wherein the amount of amino acid X that is added is between 1.1 and 1.6 equivalents.

~~19~~17. 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;

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

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;

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

removing the second quantity of amino acid “X” activated ester from the second reactor.

~~20~~18. The process of claim ~~19~~17, 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.

~~21~~19. The process of ~~either~~ claim ~~18~~16 or ~~19~~17, 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;

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;

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;

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;

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 reactor.

~~22~~20. The process of claim ~~21~~19, 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 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 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 first quantity of amino acid “X” activated ester is removed from the third reactor.

~~23~~21. 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 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,

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

removing the second quantity of amino acid “X” activated ester from the second reactor.

~~24~~22. The process of claim ~~23~~21, further comprising washing the first reactor and a second reactor with solvent.

~~25~~23. The process of claim ~~22~~20 or ~~23~~21, 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 attached to a peptide synthesis resin;

removing the first quantity of amino acid “X” activated ester from the third reacto;r and

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

~~26~~24. The process of claim ~~25~~23, 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

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~~25. The process of claim ~~26~~24, further comprising:

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

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.

~~28~~26. 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;

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;

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~~27. The process of claim ~~28~~26, further comprising washing the first reactor and a second reactor with solvent.

~~30~~28. The process of claim ~~28~~26 or ~~29~~27, 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;

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 second reactor.

~~31~~29. The process of claim ~~30~~28, 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~~30. The process of claim ~~31~~29, 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~~31. 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.~~

~~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~~32. ~~A~~The system as in claim ~~35~~31, wherein the system ~~also~~ dilutes the cleaved peptide solution in liquid chromatography diluent, ~~transporst~~ transports the solution to ~~the~~a liquid chromatography injection loop of the LCMS device, and flushes the ~~spent~~cleaved resin beads ~~from the cleavage reactor to waste~~.

~~41~~33. The system as in claim ~~40~~32, wherein the solution transported to the~~liquid~~ liquid chromatography injection loop of the LCMS device is free of gas-bubbles.

34. The system as in claim 31, wherein the reactor is a single reactor.

35. The system as in claim 34, wherein the reactor is a batch reactor.

36. The system as in claim 31, wherein the reactor is in series with other reactors.

37. The system as in claim 31, wherein the LCMS is used to monitor the progress of the coupling reaction.

38. The system as in claim 31, wherein the slurry is sampled at regular intervals during the coupling reaction.

39. The system as in claim 38, wherein the regular interval is 45 minutes or 60 minutes.

40. The system as in claim 31, wherein the slurry is sampled during a washing step after coupling.

41. The system as in claim 31, wherein the LCMS is used to identify reactions happening during the coupling reaction.

42. The system as in claim 31, wherein the peptide is cleaved from the resin with TFA.

43. The process of claim 9, wherein multiple washing cycles occur between the addition of each particular amino acid.

44. The process of claim 43, wherein the washing solvent from each washing cycle is collected in a recycle vessel and this recycled washing solvent is used in the next washing cycle.

45. The process of claim 9, wherein the solvent comprises an environmentally friendly or green solvent.

46. The process of claim 45, wherein the environmentally friendly or green solvent is acetonitrile, ethyl acetate, isopropyl acetate, 2-methyltetrahydrofuran, cyclopentyl methyl ether, or N-butylpyrrolidinone, or mixtures thereof.

47. The process of claim 9, wherein the solvent is a mixture of N-butylpyrrolidinone and tetrahydrofuran.

48. The process of claim 9, wherein the solvent is a mixture of N-butylpyrrolidinone and 2-methyltetrahydrofuran.