

CLAIMS

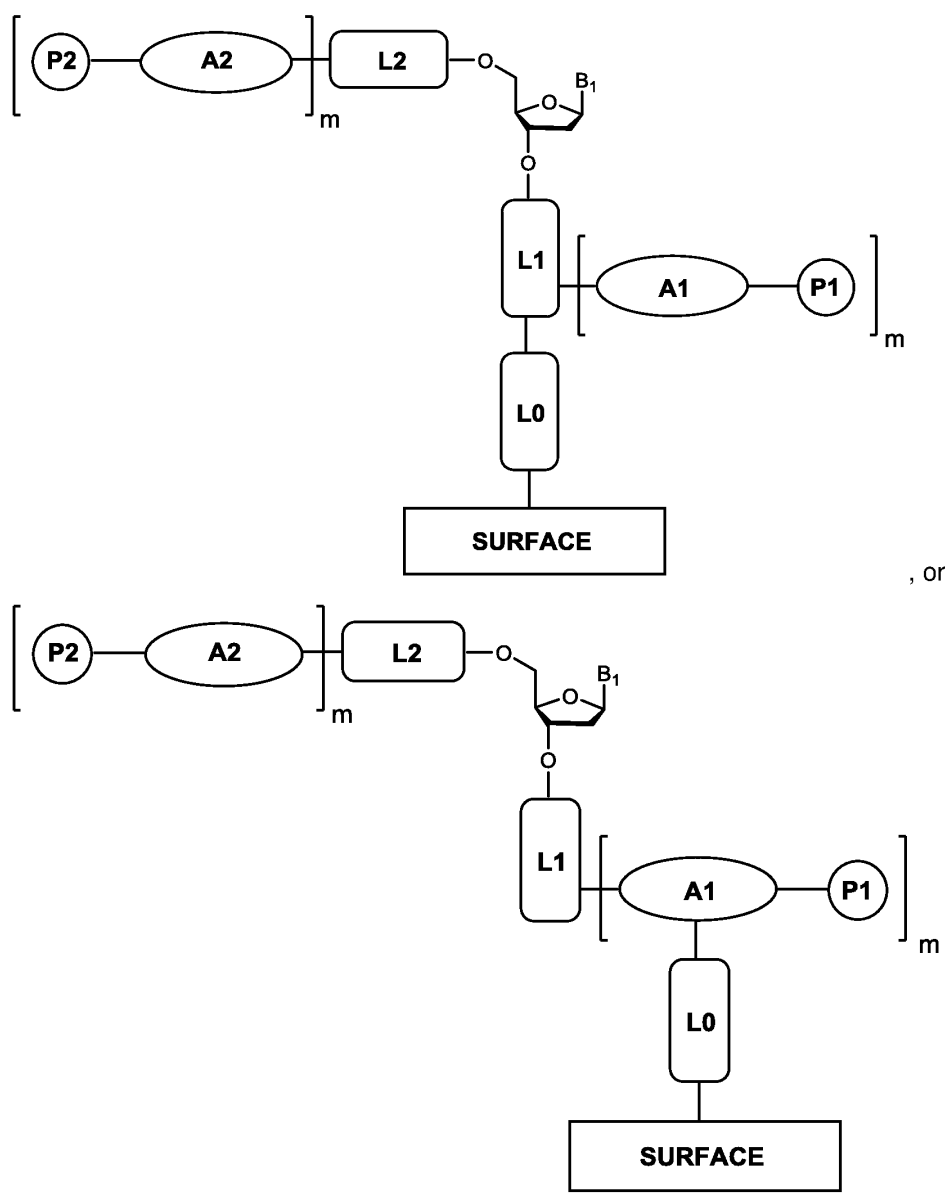
1. A process for the parallel synthesis of one or more oligonucleotides on a plurality of sites on the surface of a solid substrate, said oligonucleotides being the same or different wherein the process comprises:
 - (i) providing each site with a plurality of nucleosides, or nucleotides (preferably wherein the nucleotides are di-nucleotides or tri-nucleotides), wherein each nucleoside or nucleotide comprises a 5'-OH protecting group, and wherein the nucleosides or nucleotides are immobilized on the surface of a solid substrate;
 - (ii) conducting thermally controlled deprotection at the 5'-OH of the nucleosides or nucleotides, at selected sites on the surface of the solid substrate to form, at each of the selected sites, nucleosides or nucleotides having deprotected 5'-OH groups;
 - (iii) at each of the selected sites, coupling onto the deprotected 5'-OH groups: a nucleoside 3'-phosphoramidite, or a di-nucleotide 3'-phosphoramidite, or a tri-nucleotide 3'-phosphoramidite, wherein the nucleoside 3'-phosphoramidite, or di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite comprises a 5'-OH protecting group; and oxidising the resulting phosphite triester group to a phosphate triester group;
 - (iv) conducting thermally controlled deprotection at the 5'-OH of the nucleosides or nucleotides, at selected sites on the surface of the substrate, wherein the selected sites can be the same as, or different from, the selected sites of the preceding step,
 - (v) at each of the selected sites, coupling onto the deprotected 5'-OH groups: a nucleoside 3'-phosphoramidite, or a di-nucleotide 3'-phosphoramidite, or a tri-nucleotide 3'-phosphoramidite, wherein the nucleoside 3'-phosphoramidite, or di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite comprises a 5'-OH protecting group, and oxidising the resulting phosphite triester group to a phosphate triester group; and
 - (vi) repeating steps (iv) and (v) one or more times to obtain the desired oligonucleotides at each site on the surface of a solid substrate.
2. A process according to Claim 1 for the parallel synthesis of one or more oligonucleotides on a plurality of sites on the surface of a solid substrate, said oligonucleotides being the same or different wherein the process comprises:

- (i) providing each site with a plurality of nucleosides, wherein each nucleoside, comprises a 5'-OH protecting group, and wherein the nucleosides are immobilized on the surface of a solid substrate;
 - (ii) conducting thermally controlled deprotection at the 5'-OH of the nucleosides at selected sites on the surface of the solid substrate to form, at each of the selected sites, nucleosides having deprotected 5'-OH groups;
 - (iii) at each of the selected sites, coupling onto the deprotected 5'-OH groups: a nucleoside 3'-phosphoramidite, or a di-nucleotide 3'-phosphoramidite, or a tri-nucleotide 3'-phosphoramidite, wherein the nucleoside 3'-phosphoramidite, or di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite comprises a 5'-OH protecting group; and oxidising the resulting phosphite triester group to a phosphate triester group;
 - (iv) conducting thermally controlled deprotection at the 5'-OH of the nucleosides at selected sites on the surface of the substrate, wherein the selected sites can be the same as, or different from, the selected sites of the preceding step,
 - (v) at each of the selected sites, coupling onto the deprotected 5'-OH groups: a nucleoside 3'-phosphoramidite, or a di-nucleotide 3'-phosphoramidite, or a tri-nucleotide 3'-phosphoramidite, wherein the nucleoside 3'-phosphoramidite, or di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite comprises a 5'-OH protecting group, and oxidising the resulting phosphite triester group to a phosphate triester group; and
 - (vi) repeating steps (iv) and (v) one or more times to obtain the desired oligonucleotides at each site on the surface of a solid substrate.
3. A process according to Claim 1 or Claim 2, for the parallel synthesis of one or more oligonucleotides on a plurality of sites on the surface of a solid substrate, said oligonucleotides being the same or different wherein the process comprises:
- (i) providing each site with a plurality of nucleosides comprising a 5'-OH protecting group, wherein the nucleosides are immobilized on the surface of a solid substrate;
 - (ii) conducting thermally controlled deprotection at the 5'-OH of the nucleosides at selected sites on the surface of the solid substrate to form, at each of the selected sites, nucleosides having deprotected 5'-OH groups;
 - (iii) at each of the selected sites, coupling a nucleoside 3'-phosphoramidite comprising a 5'-OH protecting group, onto the deprotected 5'-OH groups, and oxidising the resulting phosphite triester group to a phosphate triester group;

- (iv) conducting thermally controlled deprotection at the 5'-OH of the nucleosides at selected sites on the surface of the substrate, wherein the selected sites can be the same as, or different from, the selected sites of the preceding step,
 - (v) at each of the selected sites, coupling a nucleoside 3'-phosphoramidite comprising a 5'-OH protecting group onto the deprotected 5'-OH groups, and oxidising the resulting phosphite triester group to a phosphate triester group; and
 - (vi) repeating steps (iv) and (v) one or more times to obtain the desired oligonucleotides at each site on the surface of a solid substrate.
4. A process according to any of Claims 1, 2 or 3, wherein the 5'-OH-protected nucleosides or nucleotides of step (i) comprise a thermally cleavable 5'-OH protecting group.
5. A process according to any of Claims 1, 2, 3 or 4, wherein the thermally cleavable 5'-OH-protecting group comprises an activator moiety and a cleavable linker moiety, that on heating, causes the protecting group to cleave, thereby resulting in deprotection of the 5'-OH group.
6. A process according to Claim 5, wherein the thermally cleavable 5'-OH-protecting group comprises a safety catch protecting group, having one or two activator moieties and a cleavable linker moiety, wherein each activator moiety is protected with a protecting group, wherein the protecting group on each activator moiety is susceptible to deprotection under predetermined conditions, to expose the activator moiety, thereby rendering the activator moiety and cleavable linker moiety susceptible to cleavage on heating.
7. A process according to any preceding claim, wherein the nucleosides or nucleotides in step (i) are attached to the surface of a solid substrate at the 3'-position via a thermally cleavable linker group.
8. A process according to Claim 7, wherein the thermally cleavable linker group comprises one or two activator moieties, and a cleavable linker moiety that on heating, causes the linker group to cleave, thereby causing detachment from the surface of the solid substrate.
9. A process according to Claim 8, wherein the thermally cleavable linker group comprises a safety catch linker, having one or two activator moieties and a cleavable

linker moiety, wherein the activator moiety is protected with a protecting group, wherein the protecting group on each activator moiety is susceptible to deprotection under predetermined conditions, to expose the activator moiety, thereby rendering the activator moiety and cleavable linker moiety susceptible to cleavage on heating.

10. A process according to any preceding claim, wherein the thermally controlled deprotection in steps (ii) and (iv) is achieved by local heating at the selected sites.
11. A process according to Claim 10, wherein there is substantially no deprotection of the 5'-OH protecting groups at sites other than the selected sites.
12. A process according to any preceding claim wherein the coupling steps (iii) and (v) comprise contacting a solution containing the nucleoside 3'-phosphoramidite, or di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite comprising a 5'-OH protecting group with the surface of the substrate, wherein the nucleoside 3'-phosphoramidite, or di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite reacts with the deprotected 5'-OH groups at the selected sites.
13. A process according to Claim 12, wherein there is substantially no reaction at the sites other than the selected sites.
14. A process according to any preceding claim, wherein step (i) comprises providing at each site: a plurality of nucleosides or nucleotides immobilized to the solid surface, represented by:



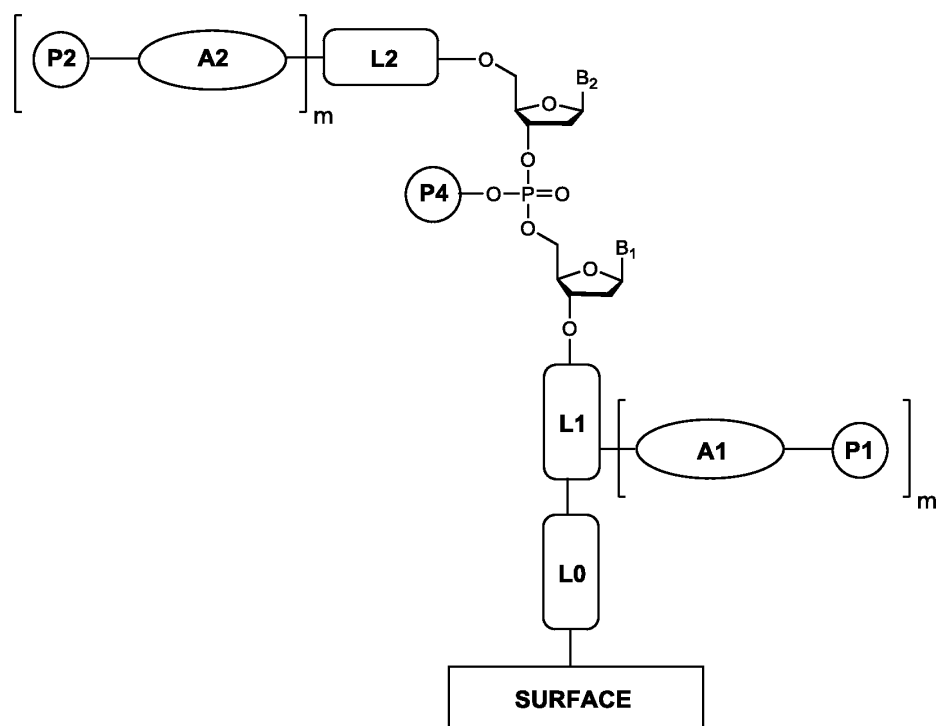
wherein:

- L1-A1-P1 together represents a safety catch linker for attachment at the 3'-OH group of the nucleoside to the surface, wherein:
 - P1 represents a protecting group,
 - L1 represents a thermally cleavable linker moiety,
 - A1 represents an activator moiety that, upon removal of P1, is capable of causing cleavage of the cleavable linker from the solid surface;
- P2-A2-L2 together represents a safety catch 5'-OH-protecting group, wherein:
 - P2 represents a protecting group,

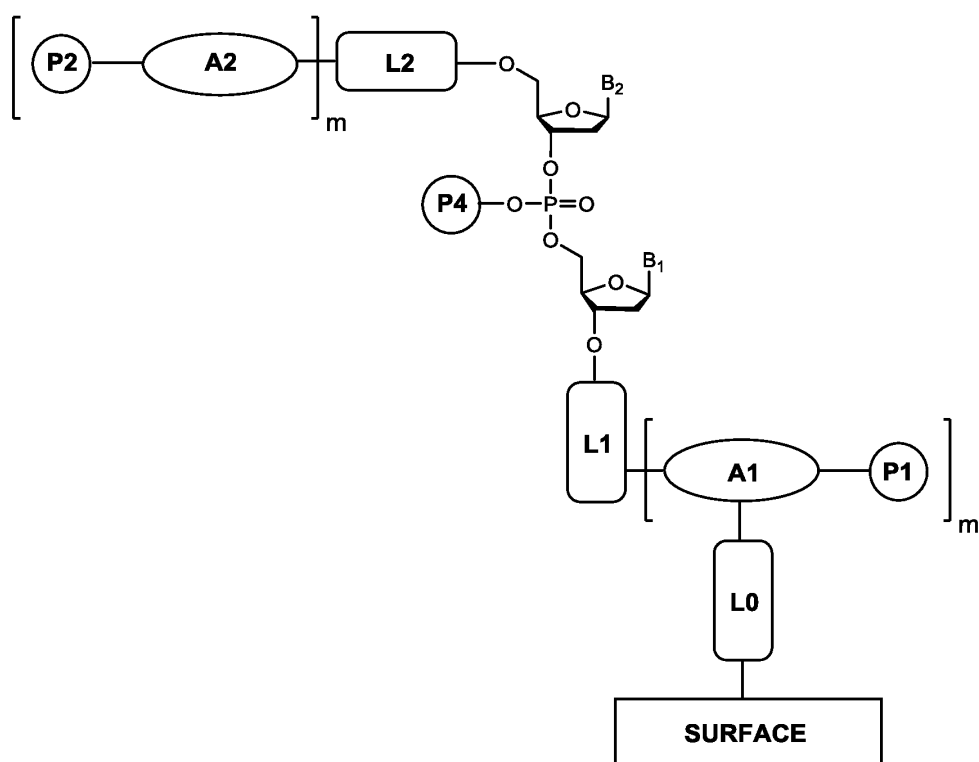
- L2 represents a cleavable linker moiety,
- A2 represents an activator moiety that, upon removal of P2, is capable of causing removal of the 5'-OH protecting group;
- m at each occurrence is the same or different, and represents 1 or 2;
- L0 represents a moiety for attachment of the first nucleoside via the cleavable linker group to the surface; and
- B₁ represents an optionally protected canonical or an optionally protected non-canonical nucleobase,

wherein A1, A2, L1 and L2 can be the same or different, and wherein P1 and P2 are different and are removable under different conditions or reagents;

or



; or

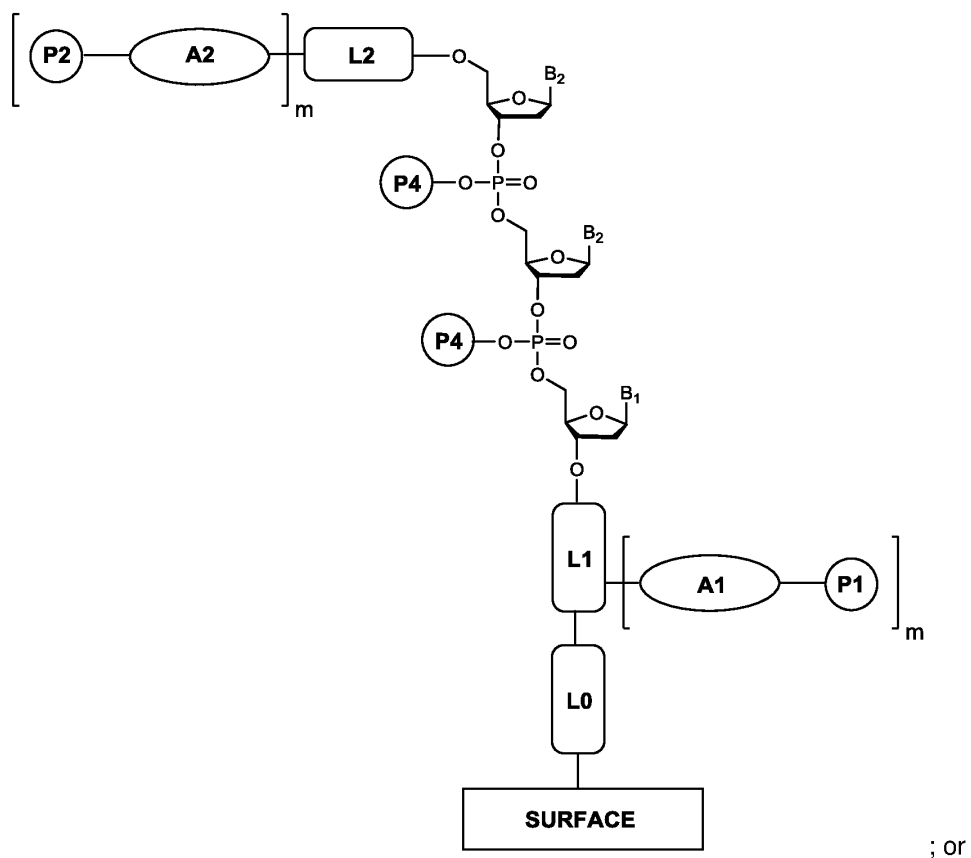


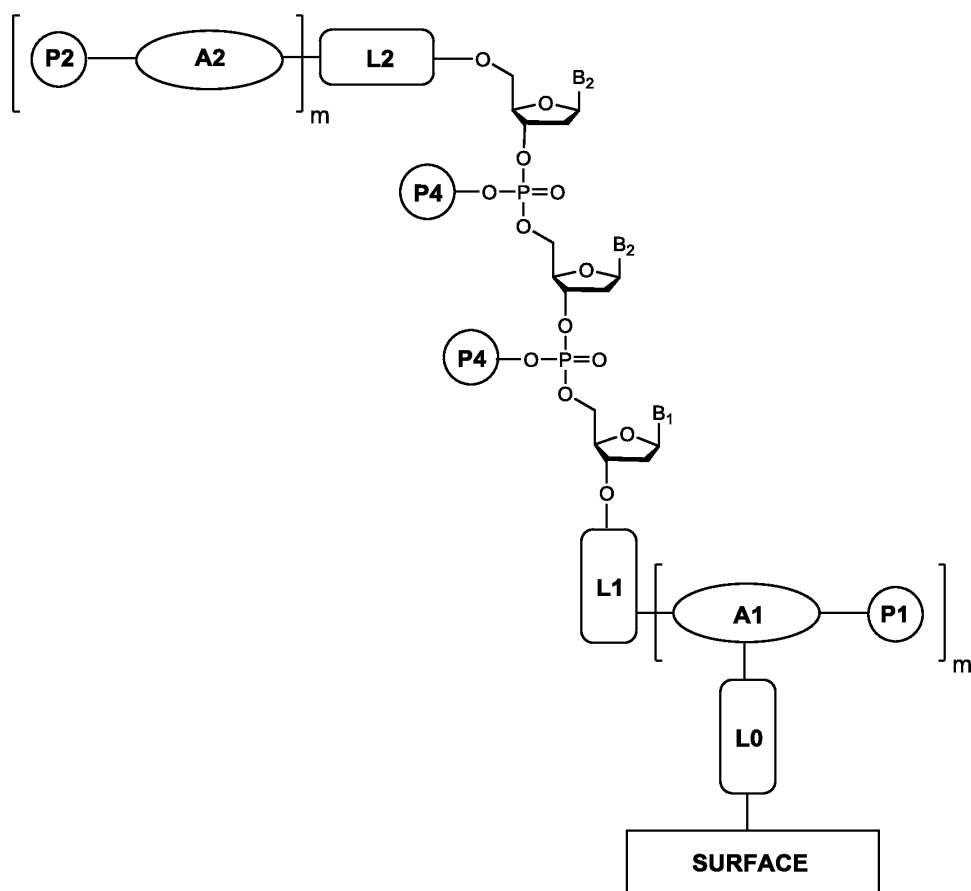
wherein:

- L1-A1-P1 together represents a safety catch linker for attachment at the 3'-OH group of the nucleotide to the surface, wherein:
 - P1 represents a protecting group,
 - L1 represents a thermally cleavable linker moiety,
 - A1 represents an activator moiety that, upon removal of P1, is capable of causing cleavage of the cleavable linker from the solid surface;
- P2-A2-L2 together represents a safety catch 5'-OH-protecting group, wherein:
 - P2 represents a protecting group,
 - L2 represents a cleavable linker moiety,
 - A2 represents an activator moiety that, upon removal of P2, is capable of causing removal of the 5'-OH protecting group;
- P4 represents a phosphate protecting group,
- m at each occurrence is the same or different, and represents 1 or 2;
- L0 represents a moiety for attachment of the first nucleoside via the cleavable linker group to the surface; and
- B_1 and B_2 may be the same or different and each independently represents an optionally protected canonical or an optionally protected non-canonical nucleobase,

wherein A1, A2, L1 and L2 can be the same or different, and wherein P1 and P2 are different and are removable under different conditions or reagents;

or





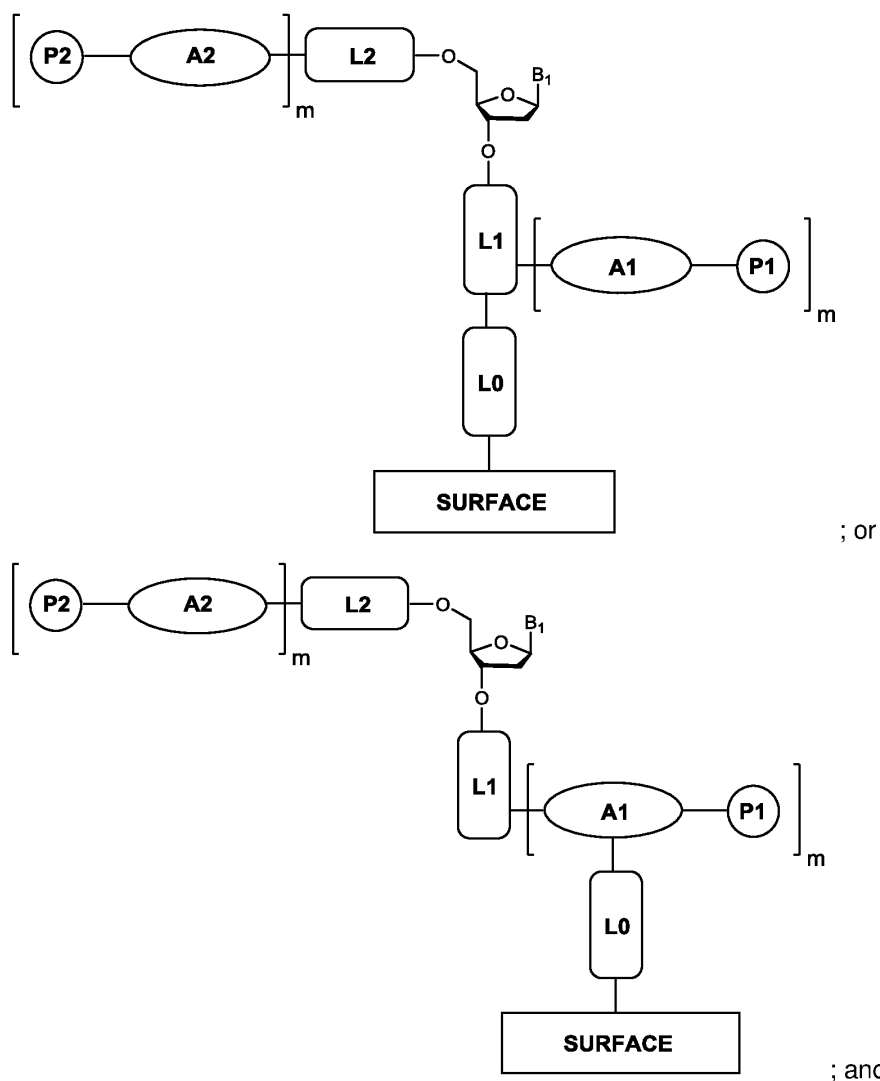
wherein:

- L1-A1-P1 together represents a safety catch linker for attachment at the 3'-OH group of the nucleotide to the surface, wherein:
 - P1 represents a protecting group,
 - L1 represents a thermally cleavable linker moiety,
 - A1 represents an activator moiety that, upon removal of P1, is capable of causing cleavage of the cleavable linker from the solid surface;
- P2-A2-L2 together represents a safety catch 5'-OH-protecting group, wherein:
 - P2 represents a protecting group,
 - L2 represents a cleavable linker moiety,
 - A2 represents an activator moiety that, upon removal of P2, is capable of causing removal of the 5'-OH protecting group;
- each P4 may be the same or different and each independently represents a phosphate protecting group,
- m at each occurrence is the same or different, and represents 1 or 2;
- L0 represents a moiety for attachment of the first nucleoside via the cleavable linker group to the surface; and

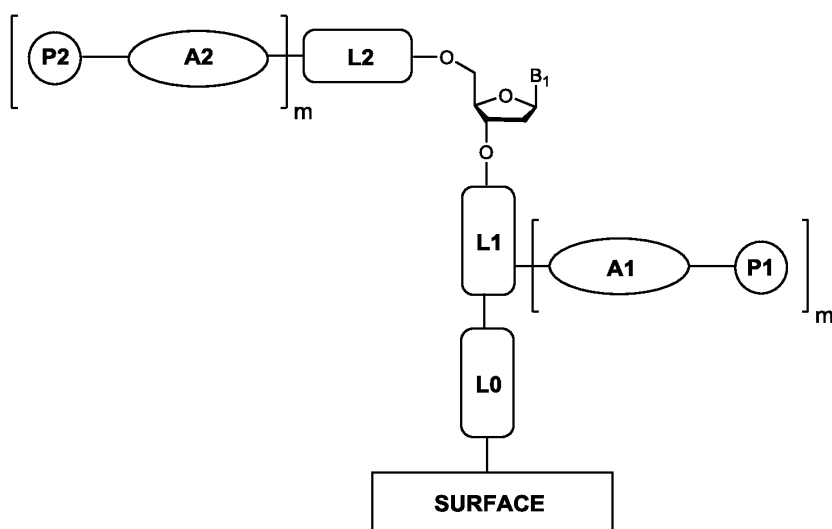
- B₁, B₂ and B₃ may be the same or different and each independently represents an optionally protected canonical or an optionally protected non-canonical nucleobase.

wherein A1, A2, L1 and L2 can be the same or different, and wherein P1 and P2 are different and are removable under different conditions or reagents.

15. A process according to any preceding claim wherein step (i) comprises providing at each site, a plurality of nucleosides immobilized to the solid surface, represented by:



preferably:



wherein:

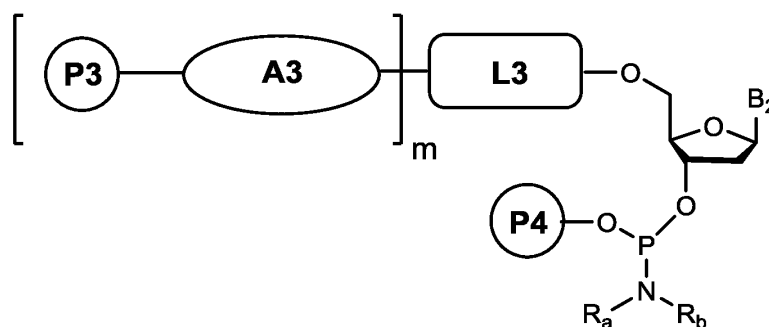
- L1-A1-P1 together represents a safety catch linker for attachment at the 3'-OH group of the nucleoside to the surface, wherein:
 - P1 represents a protecting group,
 - L1 represents a thermally cleavable linker moiety,
 - A1 represents an activator moiety that, upon removal of P1, is capable of causing cleavage of the cleavable linker from the solid surface;
- P2-A2-L2 together represents a safety catch 5'-OH-protecting group, wherein:
 - P2 represents a protecting group,
 - L2 represents a cleavable linker moiety,
 - A2 represents an activator moiety that, upon removal of P2, is capable of causing removal of the 5'-OH protecting group;
- m at each occurrence is the same or different, and represents 1 or 2;
- L0 represents a moiety for attachment of the first nucleoside via the cleavable linker group to the surface; and
- B₁ represents an optionally protected canonical or an optionally protected non-canonical nucleobase,

wherein A1, A2, L1 and L2 can be the same or different, and wherein P1 and P2 are different and are removable under different conditions or reagents.

16. A process according to Claim 14 or Claim 15, wherein step (ii) comprises thermally controlled removal of the safety catch 5'-OH protecting cleavable linker group P2-A2-L2.

17. A process according to any preceding claim, wherein the nucleoside 3'-phosphoramidite, or di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite comprising a 5'-OH protecting group in step (iii) and step (v) is a nucleoside 3'-phosphoramidite or di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite comprising a thermally cleavable 5'-OH protecting group.
18. A process according to Claim 17, wherein the thermally cleavable 5'-OH-protecting group comprises one or two activator moieties and a cleavable linker moiety, that on heating, causes the protecting group to cleave thereby resulting in deprotection of the 5'-OH group.
19. A process according to Claim 18, wherein the thermally cleavable 5'-OH-protecting group comprises a safety catch linker, having one or two activator moieties and a cleavable linker moiety, wherein each activator moiety is protected with a protecting group, wherein the protecting group on each activator moiety is susceptible to deprotection under predetermined conditions, to expose the activator moiety, thereby rendering the activator moiety and cleavable linker moiety susceptible to cleavage on heating.
20. A process according to any preceding claim wherein the nucleoside or nucleotide comprising a 5'-OH-protecting group in step (iii) and step (v) is:

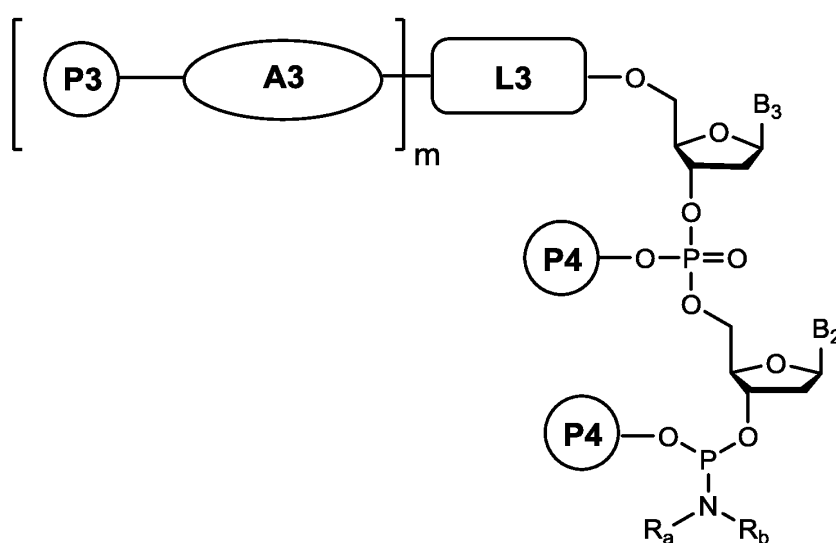
- a nucleoside 3'-phosphoramidite comprising a thermally cleavable 5'-OH protecting group represented by:



wherein:

- $P3-A3-L3$ together represents a safety catch 5'-OH-protecting group, wherein:
- $P3$ represents a protecting group
- $L3$ represents a cleavable linker moiety,

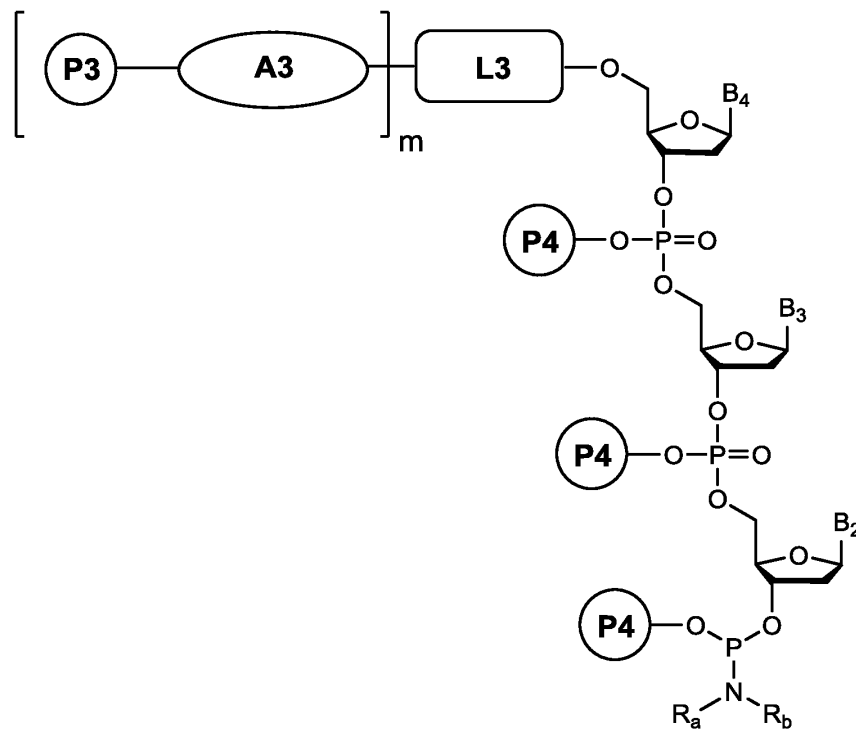
- A3 represents an activator moiety that, upon removal of P3, is capable of causing removal of the 5'-OH protecting group;
 - $m = 1$ or 2 ;
 - P4 represents a phosphoramidite protecting group;
 - B_2 represents an optionally protected canonical or an optionally protected non-canonical nucleobase; and
 - R_a and R_b can be the same or different and each represents alkyl; or
- a di-nucleotide 3'-phosphoramidite comprising a thermally cleavable 5'-OH protecting group represented by:



wherein:

- P3-A3-L3 together represents a safety catch 5'-OH-protecting group, wherein:
 - P3 represents a protecting group
 - L3 represents a cleavable linker moiety,
 - A3 represents an activator moiety that, upon removal of P3, is capable of causing removal of the 5'-OH protecting group;
 - $m = 1$ or 2 ;
 - each P4 may be the same or different and represents a phosphoramidite or phosphate protecting group;
 - B_2 and B_3 may be the same or different and each independently represents an optionally protected canonical or an optionally protected non-canonical nucleobase; and
 - R_a and R_b may be the same or different and each represents alkyl; or

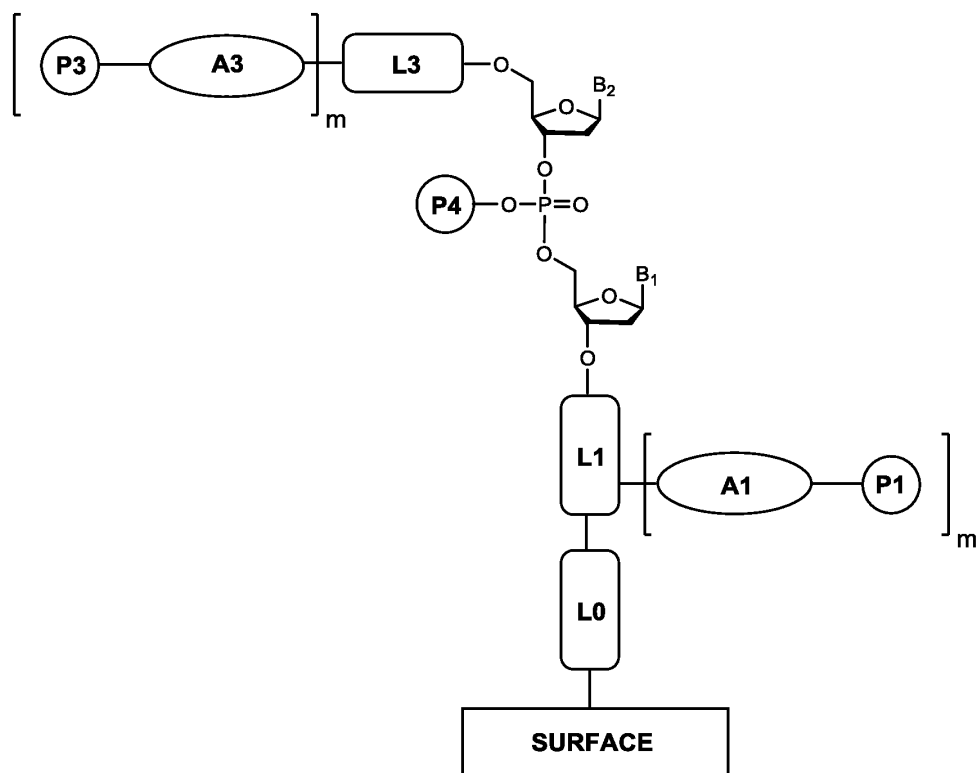
- a tri-nucleotide 3'-phosphoramidite comprising a thermally cleavable 5'-OH protecting group represented by:



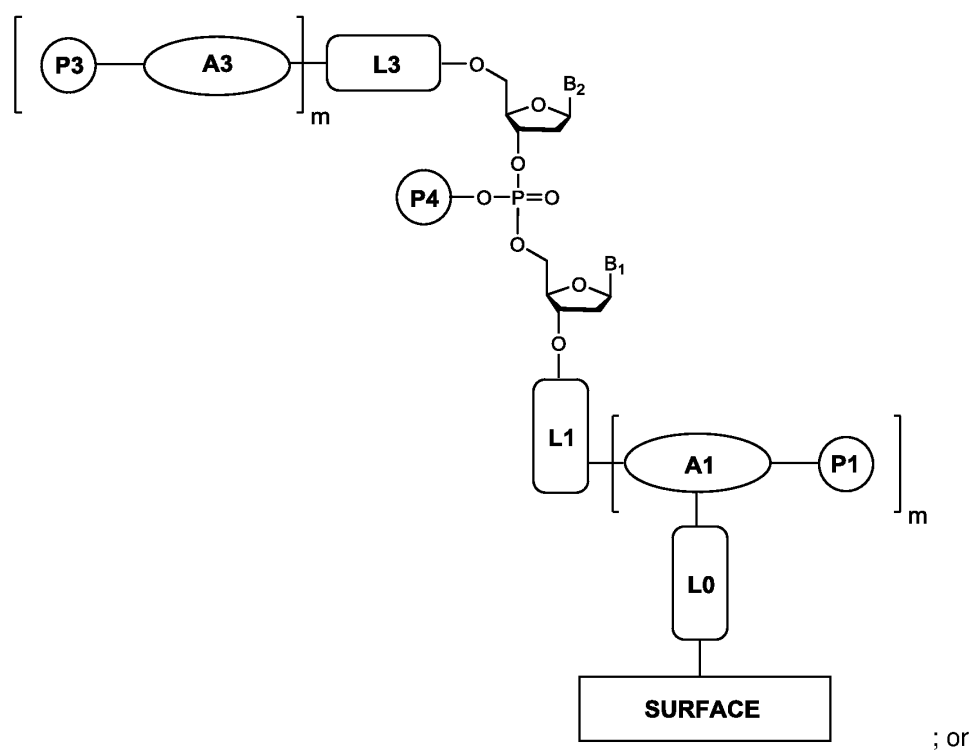
wherein:

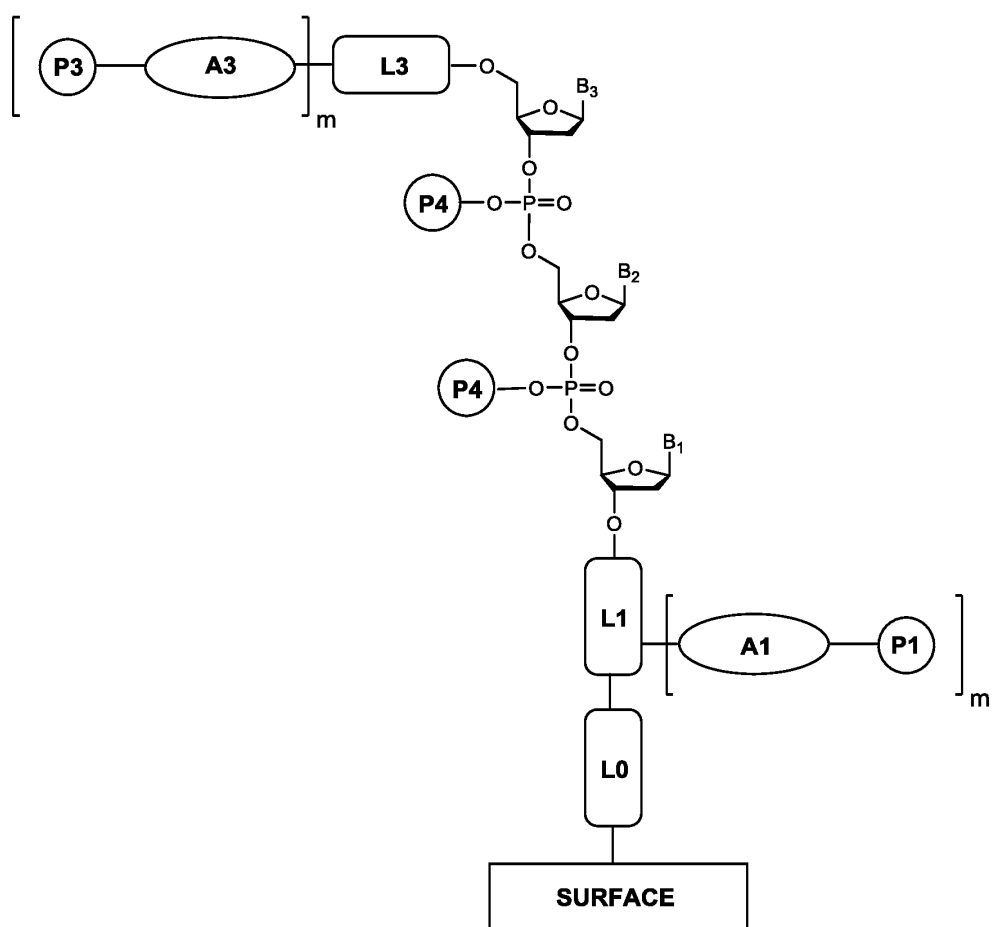
- $P3$ - $A3$ - $L3$ together represents a safety catch 5'-OH-protecting group, wherein:
 - $P3$ represents a protecting group
 - $L3$ represents a cleavable linker moiety,
 - $A3$ represents an activator moiety that, upon removal of $P3$, is capable of causing removal of the 5'-OH protecting group;
 - $m = 1$ or 2 ;
 - each $P4$ may be the same or different and each represents a phosphoramidite or phosphate protecting group;
 - B_2 , B_3 and B_4 may be the same or different and each independently represents an optionally protected canonical or an optionally protected non-canonical nucleobase; and
 - R_a and R_b may be the same or different and each represents alkyl.
21. A process according to any preceding claim wherein the coupling of: the nucleoside 3'-phosphoramidite comprising a 5'-OH protecting group, or the di-nucleotide 3'-

phosphoramidite comprising a 5'-OH protecting group, or the tri-nucleotide 3'-phosphoramidite comprising a 5'-OH protecting group, in step (iii) to a deprotected 5'-OH group of the immobilized nucleoside or nucleotide, followed by oxidation, forms a structure represented by:

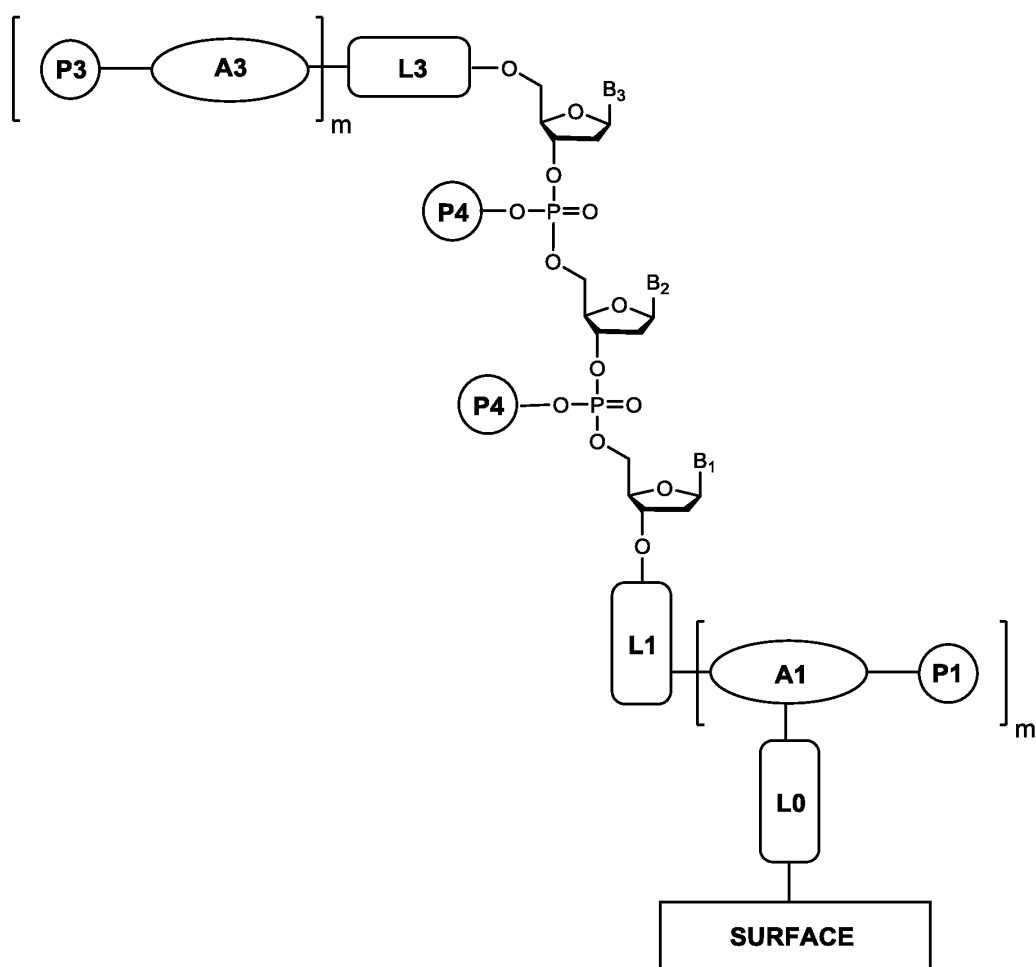


; or





; or

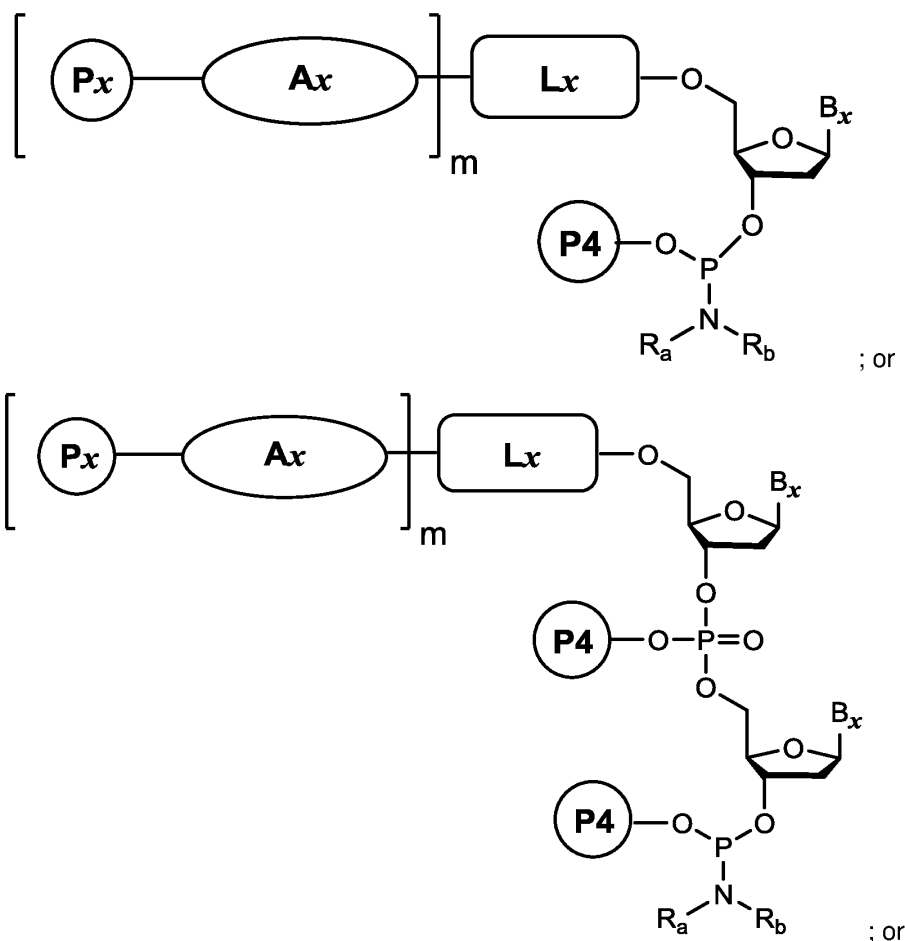


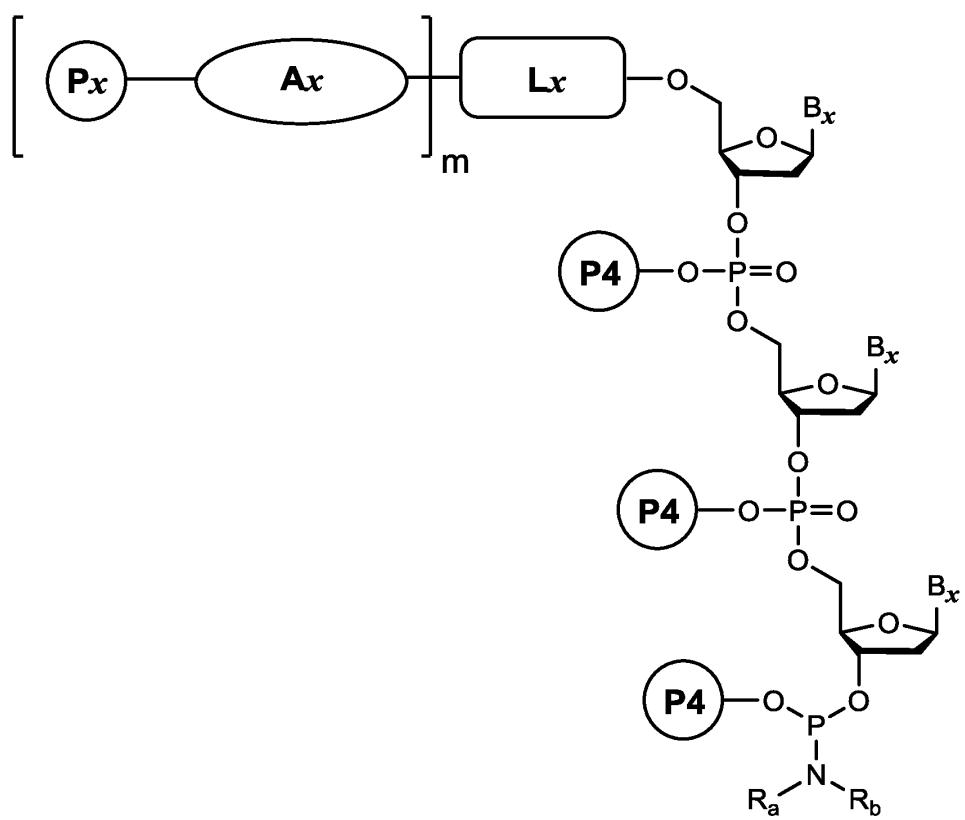
wherein:

- L1-A1-P1 together represents a safety catch linker for attachment at the 3'-OH group of the nucleoside to the surface, wherein:
 - P1 represents a protecting group,
 - L1 represents a thermally cleavable linker moiety,
 - A1 represents an activator moiety that, upon removal of P1, is capable of causing cleavage of the cleavable linker from the solid surface;
- P3-A3-L3 together represents a safety catch 5'-OH protecting group, wherein:
 - P3 represents a protecting group,
 - L3 represents a cleavable linker moiety,
 - A3 represents an activator moiety that, upon removal of P3, is capable of causing removal of the 5'-OH protecting group;
- m at each occurrence is the same or different, and represents 1 or 2;

- L0 represents a moiety for attachment of the first nucleoside via the cleavable linker group to the surface;
 - each B₁, or B₂ or B₃ independently represents an optionally protected canonical or an optionally protected non-canonical nucleobase,
- wherein A1, A3, L1 and L3 can be the same or different, and wherein P1 and P3 are different and are removable under different conditions or reagents; and
- each P4 may be the same or different and each represents a phosphate protecting group.

22. A process according to any preceding claim wherein steps (ii) and (iii) are repeated, to sequentially grow the oligonucleotides at each site by successive thermally controlled deprotection at the 5'-OH of the nucleosides or nucleotides and coupling of an incoming nucleoside or nucleotide represented by:





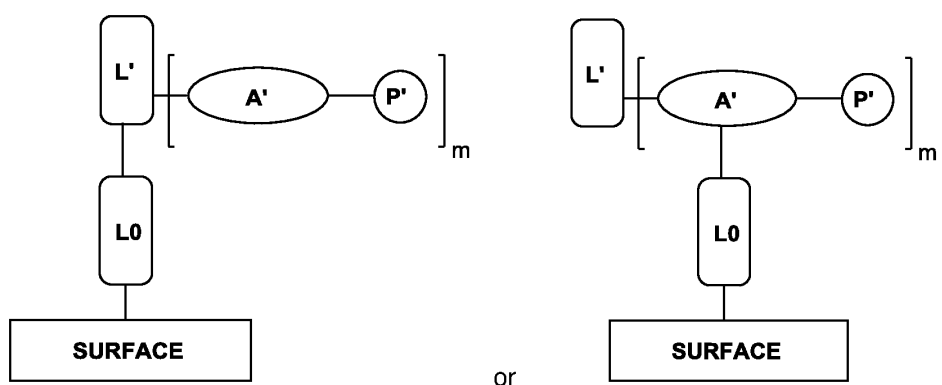
wherein:

- $P_x-A_x-L_x$ together represents a cleavable 5'-OH protecting group which protects the 5'-OH group of the incoming nucleoside or nucleotide, wherein:
 - L_x represents a cleavable linker moiety,
 - P_x represents a protecting group, and
 - A_x represents an activator moiety that, upon removal of P_x , is capable of causing removal of the 5'-OH protecting group;
- $m = 1$ or 2 ;
- each $P4$ can be the same or different and each represents a phosphoramidite or phosphate protecting group;
- each B_x may be the same or different and each independently represents an optionally protected canonical or an optionally protected non-canonical nucleobase; and
- R_a and R_b can be the same or different and each represents alkyl.

23. A process according to any preceding claim, wherein the 5'-OH-protected nucleosides of step (i) comprise a thermally cleavable 5'-OH-protecting group, and are attached to

the surface of a solid substrate at the 3'-position via a thermally cleavable linker group, wherein the thermally cleavable linker attaching the first nucleoside to the surface is stable to removal during the oligonucleotide synthesis steps.

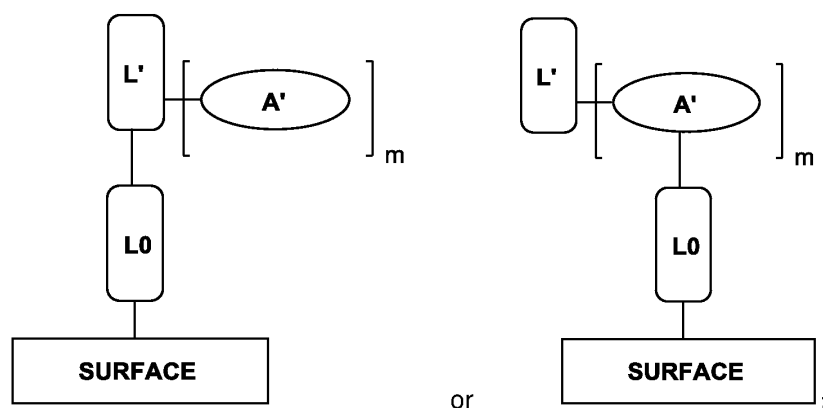
24. A process according to any of Claims 14-23, wherein the protecting groups on the nucleobases, when present, are stable to removal during the oligonucleotide synthesis.
25. A process according to any of Claims 14, 16, 17, 18, 19, or any of Claims 20-24, wherein the protecting groups P4 on the nucleoside 3'-phosphoramidites, or the di-nucleotide 3'-phosphoramidites, or the tri-nucleotide 3'-phosphoramidites, are stable to removal during the oligonucleotide synthesis.
26. A process according to any preceding claim wherein step (i) comprises:
- (a) providing a solid surface comprising a plurality of sites, wherein each site is functionalized with thermally labile linker groups, each of which is represented by:



wherein:

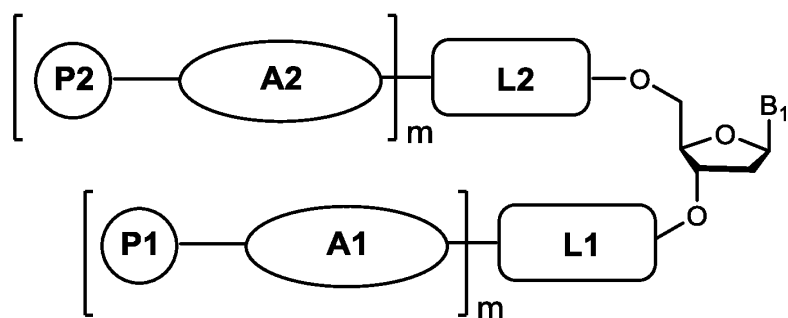
- L'-A'-P' together represents a safety catch linker attached to the surface via L0, wherein:
 - P' represents a protecting group,
 - L' represents a cleavable linker moiety,
 - A' represents an activator moiety that, upon removal of P', is capable of causing cleavage of the cleavable linker group from the solid surface;
- m = 1 or 2;
- L0 represents a moiety for attachment of the cleavable linker group to the surface;

(b) removing the protecting group P', thereby resulting in a solid surface comprising a plurality of sites represented by:



(c) thermally controlled deprotection of the cleavable linker L' via activator moiety A' at selected sites and coupling the deprotected sites with:

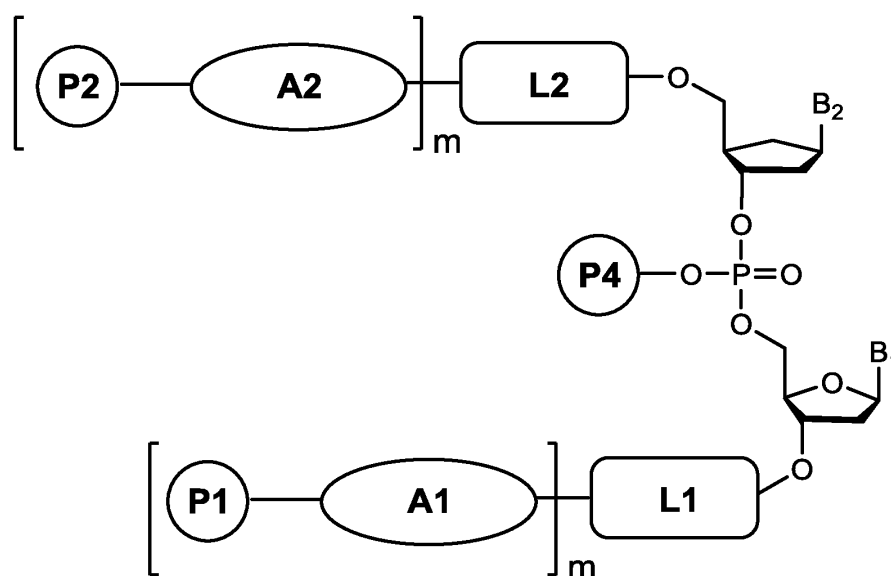
- a nucleoside represented by the formula:



wherein:

- $L1-A1-P1$ together represents a safety catch linker for attachment at the 3'-OH group of the first nucleoside to the surface, wherein:
 - $P1$ represents a protecting group,
 - $L1$ represents a cleavable linker moiety,
 - $A1$ represents an activator moiety that, upon removal of $P1$, is capable of causing cleavage of the cleavable linker from the solid surface;
- $P2-A2-L2$ together represents a safety catch 5'-OH protecting group, wherein:
 - $P2$ represents a protecting group,
 - $L2$ represents a cleavable linker moiety,
 - $A2$ represents an activator moiety that, upon removal of $P2$, is capable of causing removal of the 5'-OH protecting group;

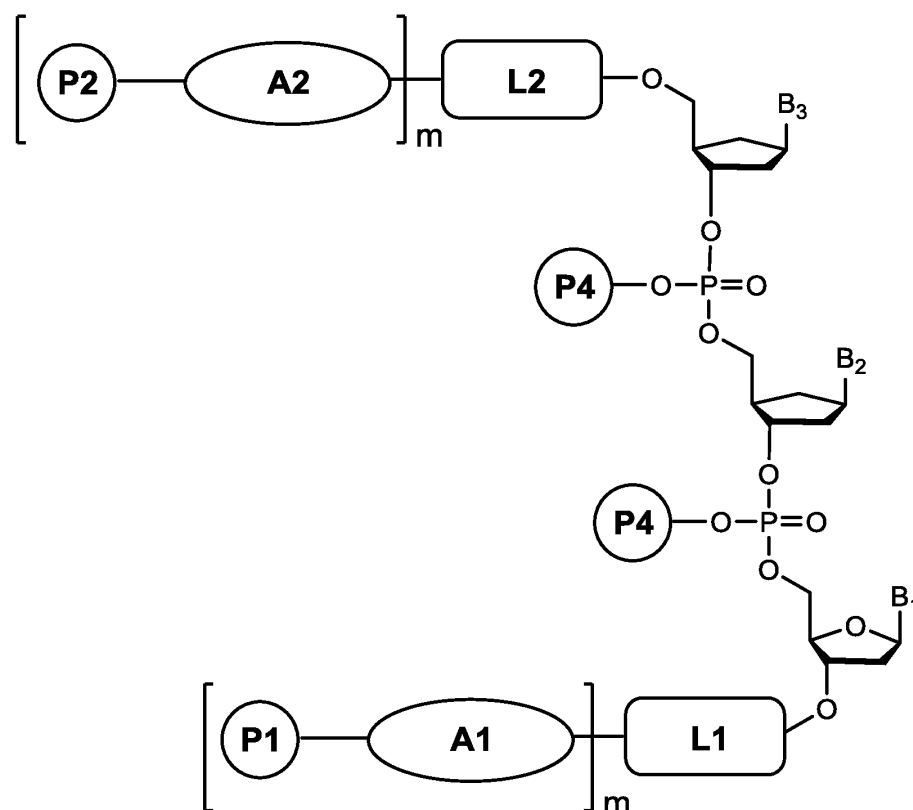
- m at each occurrence is the same or different, and represents 1 or 2; and
 - B₁ represents an optionally protected canonical or an optionally protected non-canonical nucleobase, preferably wherein the nucleobase is one of: adenine (A), cytosine (C), guanine (G) or thymine (T): or
- a di-nucleotide represented by the formula:



wherein:

- L1-A1-P1 together represents a safety catch linker for attachment at the 3'-OH group of the first nucleoside to the surface, wherein:
 - P1 represents a protecting group,
 - L1 represents a cleavable linker moiety,
 - A1 represents an activator moiety that, upon removal of P1, is capable of causing cleavage of the cleavable linker from the solid surface;
- P2-A2-L2 together represents a safety catch 5'-OH protecting group, wherein:
 - P2 represents a protecting group,
 - L2 represents a cleavable linker moiety,
 - A2 represents an activator moiety that, upon removal of P2, is capable of causing removal of the 5'-OH protecting group;
- P4 represents a phosphate protecting group;

- m at each occurrence is the same or different, and represents 1 or 2; and
- B₁ and B₂ may be the same or different, and each independently represents an optionally protected canonical or an optionally protected non-canonical nucleobase, preferably wherein the nucleobase is one of: adenine (A), cytosine (C), guanine (G) or thymine (T); or
- a tri-nucleotide represented by the formula:



wherein:

- L1-A1-P1 together represents a safety catch linker for attachment at the 3'-OH group of the first nucleoside to the surface, wherein:
 - P1 represents a protecting group,
 - L1 represents a cleavable linker moiety,
 - A1 represents an activator moiety that, upon removal of P1, is capable of causing cleavage of the cleavable linker from the solid surface;
- P2-A2-L2 together represents a safety catch 5'-OH protecting group, wherein:
 - P2 represents a protecting group,

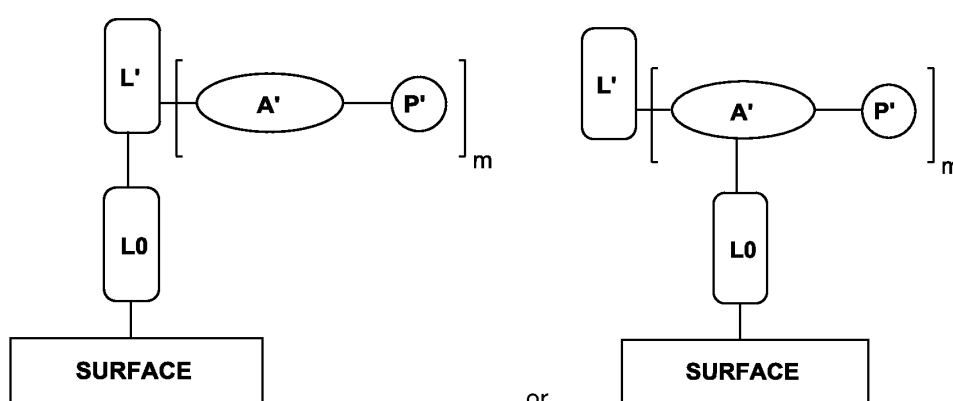
- L2 represents a cleavable linker moiety,
- A2 represents an activator moiety that, upon removal of P2, is capable of causing removal of the 5'-OH protecting group;
- each P4 can be the same or different, and each independently represents a phosphate protecting group;
- m at each occurrence is the same or different, and represents 1 or 2; and
- B₁, B₂ and B₃ may be the same or different, and each independently represents an optionally protected canonical or an optionally protected non-canonical nucleobase, preferably wherein the nucleobase is one of: adenine (A), cytosine (C), guanine (G) or thymine (T);

(d) thermally controlled deprotection of the cleavable linker L' via activator moiety A' at selected sites which were not deprotected in the preceding step, and coupling the deprotected sites with another nucleoside, preferably a nucleoside comprising one of the other three canonical nucleobases; and

(e) repeating step (d) with the other remaining nucleosides; thereby forming a plurality of sites on a solid surface wherein the solid surface comprises a plurality of 5'-OH-protected nucleosides or nucleotides containing nucleobases, wherein the nucleobases are optionally protected canonical or an optionally protected non-canonical nucleobase, and preferably wherein the nucleobases are A, C, G and T, and wherein the nucleosides are each attached at the 3'-OH to the solid surface via a cleavable linker group L1-A1-P1.

27. A process according to any preceding claim wherein step (i) comprises:

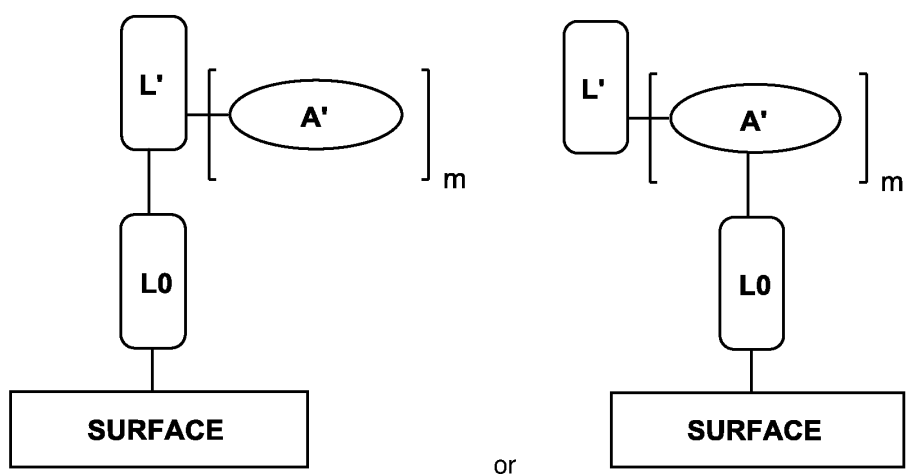
(a) providing a solid surface comprising a plurality of sites, wherein each site is functionalized with thermally labile linker groups, each of which is represented by:



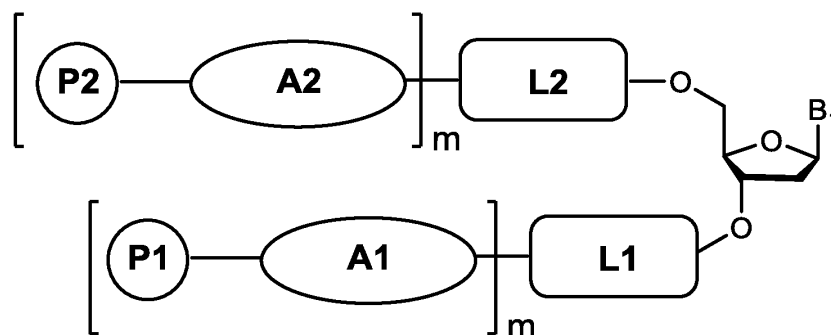
wherein:

- L'-A'-P' together represents a safety catch linker attached to the surface via L0, wherein:
 - P' represents a protecting group,
 - L' represents a cleavable linker moiety,
 - A' represents an activator moiety that, upon removal of P', is capable of causing cleavage of the cleavable linker group from the solid surface;
- m = 1 or 2;
- L0 represents a moiety for attachment of the cleavable linker group to the surface;

(b) removing the protecting group P', thereby resulting in a solid surface comprising a plurality of sites represented by:



(c) thermally controlled deprotection of the cleavable linker L' via activator moiety A' at selected sites and coupling the deprotected sites with a nucleoside represented by the formula:



wherein:

- L1-A1-P1 together represents a safety catch linker for attachment at the 3'-OH group of the first nucleoside to the surface, wherein:
 - P1 represents a protecting group,
 - L1 represents a cleavable linker moiety,
 - A1 represents an activator moiety that, upon removal of P1, is capable of causing cleavage of the cleavable linker from the solid surface;
 - P2-A2-L2 together represents a safety catch 5'-OH protecting group, wherein:
 - P2 represents a protecting group,
 - L2 represents a cleavable linker moiety,
 - A2 represents an activator moiety that, upon removal of P2, is capable of causing removal of the 5'-OH protecting group;
 - m at each occurrence is the same or different, and represents 1 or 2; and
 - B_i represents an optionally protected canonical or an optionally protected non-canonical nucleobase, preferably wherein the nucleobase is one of: adenine (A), cytosine (C), guanine (G) or thymine (T),
 - (d) thermally controlled deprotection of the cleavable linker L' via activator moiety A' at selected sites which were not deprotected in the preceding step, and coupling the deprotected sites with another nucleoside, preferably a nucleoside comprising one of the other three canonical nucleobases; and
 - (e) repeating step (d) with the other remaining nucleosides;
- thereby forming a plurality of sites on a solid surface wherein the solid surface comprises a plurality of 5'-OH-protected nucleosides containing nucleobases, wherein the nucleobases are optionally protected canonical or an optionally protected non-canonical nucleobase, and preferably wherein the nucleobases are A, C, G and T, and wherein the nucleosides are each attached at the 3'-OH to the solid surface via a cleavable linker group L1-A1-P1.

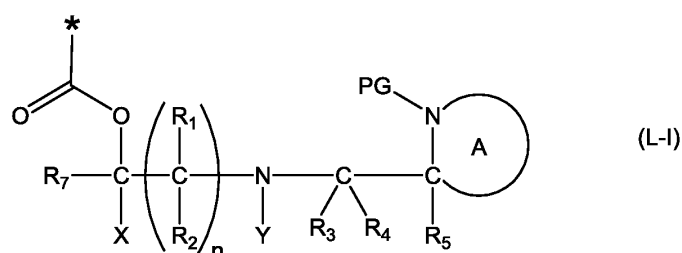
28. A process according to any preceding claim wherein the thermal control of the deprotection of the oligonucleotide is provided by individually thermally addressable sites on a chip.
29. A process according to Claim 1 or Claim 2, for the parallel synthesis of one or more oligonucleotides on a plurality of sites on the surface of solid substrate, wherein the solid substrate comprises a chip, said oligonucleotides being the same or different wherein the process comprises:

- (i) providing each site with a plurality of nucleosides comprising a 5'-OH thermally cleavable protecting group, wherein the nucleosides are attached to the surface of a solid substrate at the 3'-position via a thermally cleavable linker group;
 - (ii) thermally controlled deprotection at the 5'-OH of the nucleosides at selected sites on the surface of the chip to form, at each of the selected sites, nucleosides having deprotected 5'-OH groups;
 - (iii) at each of the selected sites, coupling onto the deprotected 5'-OH groups a nucleoside 3'-phosphoramidite, a di-nucleotide 3'-phosphoramidite, or a tri-nucleotide 3'-phosphoramidite, wherein the nucleoside 3'-phosphoramidite, di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite comprises a thermally cleavable 5'-OH protecting group; , and oxidising the resulting phosphite triester group to a phosphate triester group;
 - (iv) thermally controlled deprotection at the 5'-OH of the nucleosides at selected sites on the surface of the substrate, wherein the selected sites can be the same as, or different from, the selected sites of the preceding step,
 - (v) at each of the selected sites, coupling onto the deprotected 5'-OH groups, a nucleoside 3'-phosphoramidite, a di-nucleotide 3'-phosphoramidite, or a tri-nucleotide 3'-phosphoramidite, wherein the nucleoside 3'-phosphoramidite, di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite comprises a thermally cleavable 5'-OH protecting group; and oxidising the resulting phosphite triester group to a phosphate triester group; and
 - (vi) repeating steps (iv) and (v) one or more times to obtain the desired oligonucleotides at each site on the surface of the chip, wherein the chip comprises individually thermally addressable sites.
30. A process according to Claim 2, for the parallel synthesis of one or more oligonucleotides on a plurality of sites on the surface of solid substrate, wherein the solid substrate comprises a chip, said oligonucleotides being the same or different wherein the process comprises:
- (i) providing each site with a plurality of nucleosides comprising a 5'-OH thermally cleavable protecting group, wherein the nucleosides are attached to the surface of a solid substrate at the 3'-position via a thermally cleavable linker group;
 - (ii) thermally controlled deprotection at the 5'-OH of the nucleosides at selected sites on the surface of the chip to form, at each of the selected sites, nucleosides having deprotected 5'-OH groups;
 - (iii) at each of the selected sites, coupling a nucleoside 3'-phosphoramidite, a di-nucleotide 3'-phosphoramidite, or a tri-nucleotide 3'-phosphoramidite, wherein

the nucleoside 3'-phosphoramidite, di-nucleotide 3'-phosphoramidite, or tri-nucleotide 3'-phosphoramidite comprising a thermally cleavable 5'-OH protecting group, onto the deprotected 5'-OH groups, and oxidising the resulting phosphite triester group to a phosphate triester group;

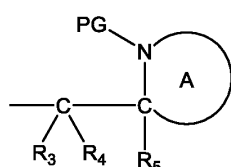
- (iv) thermally controlled deprotection at the 5'-OH of the nucleosides at selected sites on the surface of the substrate, wherein the selected sites can be the same as, or different from, the selected sites of the preceding step,
- (v) at each of the selected sites, coupling a nucleoside 3'-phosphoramidite comprising a thermally cleavable 5'-OH protecting group, onto the deprotected 5'-OH groups, and oxidising the resulting phosphite triester group to a phosphate triester group; and
- (vi) repeating steps (iv) and (v) one or more times to obtain the desired oligonucleotides at each site on the surface of the chip, wherein the chip comprises individually thermally addressable sites.

31. A process according to any preceding claim wherein the solid substrate comprises a temperature control device for controlling temperatures at a plurality of sites of the solid substrate, comprising:
- (i) a plurality of active thermal sites disposed at respective locations on the substrate, each active thermal site comprising a heating element configured to apply a variable amount of heat to a corresponding site of said medium and a thermal insulation layer disposed between the heating element and the substrate; and
 - (ii) one or more passive thermal regions disposed between the plurality of active thermal sites on the substrate, each passive thermal region comprising a thermal conduction layer configured to conduct heat from a corresponding portion of the medium to the substrate;
- wherein the thermal conduction layer of said one or more passive thermal regions has a lower thermal resistance in a direction perpendicular to a plane of the substrate than the thermal insulation layer of said plurality of active thermal sites.
32. A process according to any of Claims 7-31, wherein the thermally cleavable linker group is represented by the formula (L-1):



wherein:

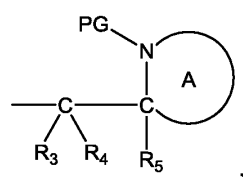
- * represents a point of attachment to the 3'-OH of the nucleoside;
- X represents hydrogen or hydrocarbyl;
- Y represents hydrocarbyl or



- ; each of R_1 , R_2 , R_3 , R_4 , R_5 and R_7 are the same or different and each independently represents hydrogen or hydrocarbyl;
- PG represents a cleavable protecting group for nitrogen;
- n represents 0, 1, 2 or 3; and
- ring A represents a nitrogen-containing heterocyclic group;

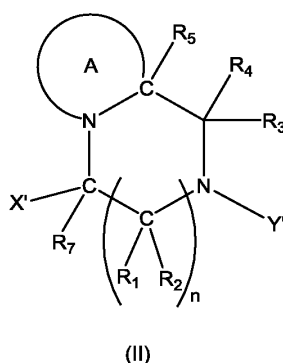
wherein at each occurrence R_1 , R_2 , R_3 , R_4 , R_5 , PG and A may be the same or different,

which is bound to the substrate at one of R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , X, Y or A, preferably which is bound to the substrate at R_7 or Y, and preferably which is bound to the substrate at R_7 when Y is:



or wherein the cleavable linker is bound to the substrate at Y when Y is hydrocarbyl.

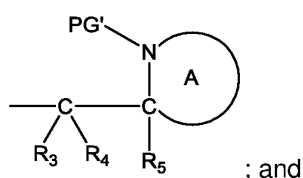
33. A process according to Claim 32, wherein at least one of the protecting groups PG is cleavable under a first reaction condition to produce a deprotected linker, wherein the deprotected linker can undergo intramolecular cyclisation and cleavage with release of carbon dioxide under a second, different, reaction condition, to produce a compound of formula (II):



thereby releasing the oligonucleotide from the surface;

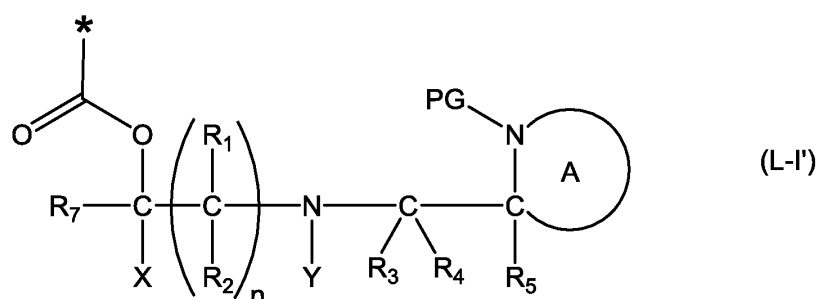
wherein PG' is hydrogen or a cleavable protecting group for nitrogen, provided that at least one PG' is hydrogen;

- Y' represents hydrocarbyl, or



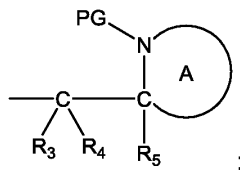
wherein X, R₁-R₅, R₇, A, M and n are as defined in Claim 32.

34. A process according to Claim 32 or Claim 33, wherein Y represents hydrocarbyl, preferably wherein Y represents a C₁₋₂₀ hydrocarbyl or a C₁₋₁₀ or particularly a C₁₋₆ hydrocarbyl, more preferably wherein the C₁₋₂₀ or C₁₋₁₀ or C₁₋₆ hydrocarbyl is alkyl, aryl, alkaryl and arylalkyl, alkenyl, or alkynyl, and most preferably wherein Y is C₁₋₁₀ alkyl or C₆₋₁₀ aryl.
35. A process according to any preceding claim wherein the 5'-OH protecting group is represented by the formula (L-1'):



wherein:

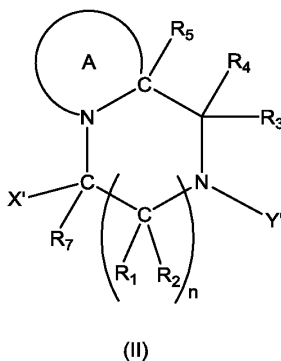
- * represents a point of attachment to the 5'-OH of the nucleoside;
- X represents hydrogen or hydrocarbyl;
- Y represents hydrocarbyl or



- each of R_1 , R_2 , R_3 , R_4 , R_5 and R_7 are the same or different and each independently represents hydrogen or hydrocarbyl;
- PG represents a cleavable protecting group for nitrogen which is different from the PG group in formula L-1;
- n represents 0, 1, 2 or 3; and
- ring A represents nitrogen-containing heterocyclic group;

wherein at each occurrence R_1 , R_2 , R_3 , R_4 , R_5 , PG and A may be the same or different.

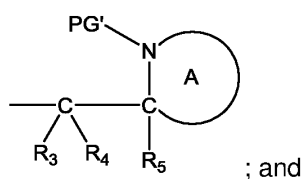
36. A process according to Claim 35, wherein at least one of the protecting groups PG is cleavable under a first reaction condition to produce a deprotected linker, wherein the deprotected linker can undergo intramolecular cyclisation and cleavage with release of carbon dioxide under a second, different, reaction condition, to produce a compound of formula (II):



thereby deprotecting the 5'-OH group of the nucleoside;

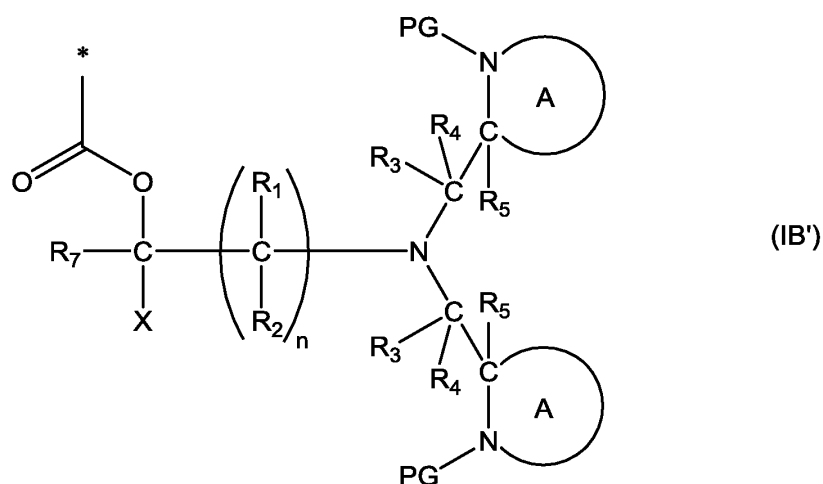
wherein

- PG' is hydrogen or a cleavable protecting group for nitrogen, provided that at least one PG' is hydrogen;
- Y' represents hydrocarbyl, or



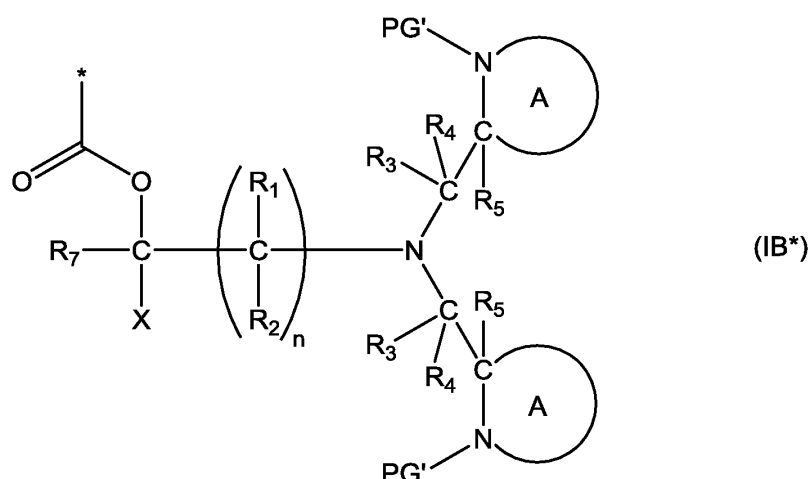
wherein X, R₁-R₅, R₇, A, M and n are as defined in Claim 35.

37. A process according to Claim 35 or Claim 36, wherein the 5'-OH protecting group has the formula (IB'):



wherein *, X, R₁-R₅, R₇, PG, A, M and n are as defined in Claim 35.

38. A process according to Claim 37 wherein R₁-R₅, PG and A at each occurrence in formula (IB), is the same.
39. A process according to Claim 37 or Claim 38, wherein at least one of the protecting groups PG is cleavable under a first reaction condition to produce a compound of formula (IB*):

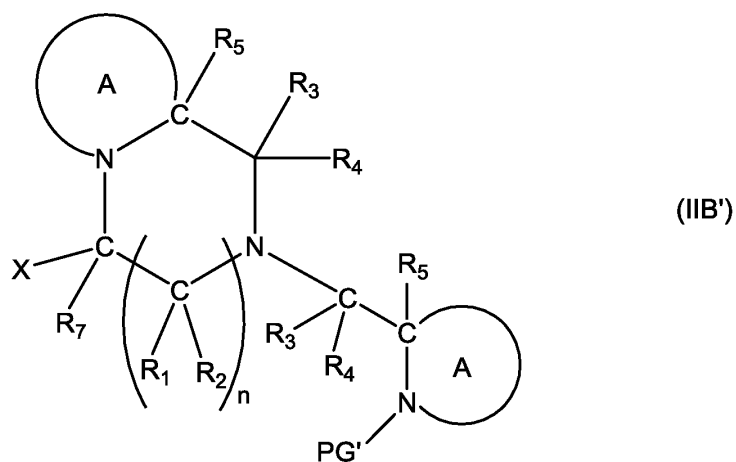


wherein

- PG' is hydrogen or a cleavable protecting group for nitrogen, provided that at least one PG' is hydrogen; and

wherein *, X, R₁-R₅, R₇, A, M and n are as defined in Claim 35;

wherein the compound of Formula (IB*) can undergo intramolecular cyclisation and cleavage with release of carbon dioxide under a second, different reaction condition, to produce a compound of formula (IIB'):



thereby removing the protecting group at 5'-OH.

40. A process according to any of Claims 32-39, wherein ring A represents a 4-12 membered mono-, bi- or tri-cyclic, preferably mono- or bicyclic nitrogen-containing heterocyclic group, and which may contain, in addition to the nitrogen, one or more other heteroatoms selected from N, O or S, preferably O or N.

41. A process according to any of Claims 32-40, wherein ring A represents a 4 to 8-membered monocyclic heterocyclic group.
42. A process according to any of Claims 32-41, wherein ring A represents a 5, 6, or 7-membered monocyclic heterocyclic group.
43. A process according to any of Claims 32-42, wherein ring A represents a heterocycle selected from: piperidyl, morpholinyl, pyrrolidinyl, thiomorpholinyl, and imidazolyl.
44. A process according to any of Claims 32-43, wherein ring A represents piperidyl, pyrrolidinyl or imidazolyl.
45. A process according to any of Claims 32-44, wherein ring A represents piperidyl, or pyrrolidinyl.
46. A process according to any of Claims 32-45, wherein at each occurrence of $-C(R_3)(R_4)$, one of R_3 or R_4 is hydrocarbyl, and the other is H, or wherein R_3 and R_4 at each occurrence, represents H.
47. A process according to any of Claims 32-46, wherein n is 0, 1 or 2; and preferably wherein n is 0 or 1.
48. A process according to any of Claims 32-47, wherein n is 1.
49. A process according to any of Claims 32-48 wherein X is H or hydrocarbyl, wherein the hydrocarbyl is selected from the group consisting of alkyl, aryl or arylalkyl, preferably wherein the alkyl, aryl or arylalkyl is C_{1-20} , C_{1-10} or C_{1-8} and more preferably wherein X is H. C_{1-10} alkyl, C_{6-10} aryl or C_{7-12} arylalkyl; and most preferably wherein X is H. C_{1-6} alkyl, C_{6-10} aryl or C_{7-12} arylalkyl; and particularly wherein X is H.
50. A process according to Claim 49, wherein X is H or aryl, and more preferably wherein X is H or phenyl.
51. A process according to any of Claims 32-50 wherein R_1 and R_2 are independently selected from H, alkyl, aryl or arylalkyl, preferably wherein the alkyl, aryl or arylalkyl is C_{1-20} , C_{1-10} or C_{1-6} , more preferably wherein R is H. C_{1-10} alkyl, C_{6-10} aryl or C_{7-12}

arylalkyl, and most preferably wherein R_1 and R_2 are H.

52. A process according to any of Claims 32-51 wherein R_3 and R_4 are independently selected from H, alkyl, aryl or arylalkyl, preferably wherein the alkyl, aryl or arylalkyl is C_{1-20} , C_{1-10} or C_{1-6} , more preferably wherein R is H. C_{1-10} alkyl, C_{6-10} aryl or C_{7-12} arylalkyl, and most preferably wherein R_1 and R_2 are H.
53. A process according to any of Claims 32-52, wherein R_5 is H.
54. A process according to any of Claims 32-53, wherein cleavage of at least one protecting group PG can be activated by pH, temperature, radiation, or by a chemical activating agent, or by a combination thereof.
55. A process according to any of Claims 32-54, wherein the cleavage of at least one protecting group PG can be activated by pH, temperature, a chemical activation agent, or by a combination thereof.
56. A process according to any of Claims 32-55, wherein at least one protecting group PG is thermally cleavable optionally in the presence of an activating agent.
57. A process according to any of Claims 32-56, wherein at least one protecting group PG is not thermally cleavable in the absence of an activating agent.
58. A process according to any of Claims 32-57, wherein the activating agent is an acid or a base.
59. A process according to any of Claims 32-58, wherein PG is preferably selected from: tert-butyloxycarbonyl (Boc), trityl (Trt), benzyloxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl (Ddz), 2-(4-biphenyl)isopropoxycarbonyl (Bpoc), 2-nitrophenylsulfonyl (Nps), tosyl (Ts), and more preferably wherein the acid cleavable protecting group is selected from Boc and Trt.
60. A process according to any of Claims 32-59, wherein PG is preferably selected from: (1,1-dioxobenzo[*b*]thiophene-2-yl)methyloxycarbonyl (Bsmoc), 9-fluorenylmethoxycarbonyl (Fmoc), (1,1-dioxonaphtho[1,2-*b*]thiophene-2-yl)methyloxycarbonyl (α -Nsmoc), 2-(4-nitrophenylsulfonyl)ethoxycarbonyl (Nsc), 2,7-di-tert-butyl-Fmoc, 2-fluoro-Fmoc, 2-monoisooctyl-Fmoc (mio-Fmoc) and 2,7-

diisooctyl-Fmoc (dio-Fmoc), 2-[phenyl(methyl)sulfonio]ethoxycarbonyl tetrafluoroborate (Pms), ethanesulfonylethoxycarbonyl (Esc), 2-(4-sulfophenylsulfonyl)ethoxycarbonyl (Sps), acetyl (Ac), benzoyl (Bz), $\text{CF}_3\text{C}(=\text{O})$ -trifluoroacetamido, and preferably wherein the base cleavable protecting group is selected from Bsmoc, Fmoc, α -Nsmoc, mio-Fmoc, dio-Fmoc, and more preferably Bsmoc.

61. A process according to any of Claims 32-60, wherein PG is selected from the group consisting of Boc, Fmoc or Bsmoc.
62. A process according to any of Claims 32-61, wherein PG is Alloc.
63. A process according to any of Claims 32-62, wherein at least one Y group is hydrocarbyl, preferably wherein at least one Y is alkyl, alkenyl, aryl, aralkyl, alkaryl, wherein said alkyl, alkenyl, aryl, aralkyl or alkaryl group is substituted with a terminal alkyne group.
64. A process according to any of Claims 32-63, wherein at least one Y group is alkyl, alkenyl, aryl, aralkyl, alkaryl, which is substituted with a terminal alkynyl group, wherein the terminal alkyne group is a C_2 to C_6 alkynyl group, more preferably a C_2 to C_4 alkynyl group, and most preferably ethynyl.
65. A process according to any of Claims 32-64, wherein at least one Y group is aralkyl which is substituted with an alkynyl group and more preferably wherein one Y group is $\text{CH}_2-(\text{C}_6\text{H}_4)\text{CH}\equiv\text{CH}$.
66. A process according to any preceding claim wherein the surface comprises an electrically conductive material, preferably gold or silicon.
67. A process according to any preceding claim wherein the attachment of the nucleoside to the surface is via an association with a functionalised carbene or a functionalised alkyne, preferably via an association with a functionalised alkyne, or preferably wherein the association is with a functionalised carbene and gold, or a functionalised alkyne and silicon, and particularly wherein the association is with a functionalised alkyne and silicon.

68. A process according to any preceding claim which does not involve a capping step.
69. A process according to any preceding claim further comprising: deprotecting the oligonucleotides at the end of the oligonucleotide synthesis to form a plurality of immobilized oligonucleotides at each site, wherein the oligonucleotides are attached to the surface of a solid substrate at the 3'-position via a thermally cleavable linker group.
70. A process according to Claim 69, further comprising cleavage of the thermally cleavable linker group, thereby releasing the oligonucleotide from the surface.
71. A process according to Claim 70, wherein the cleavage of the thermally cleavable linker group is conducted at selected sites on the surface of the solid substrate, thereby providing selective release of oligonucleotides.
72. A process according to any preceding claim, further comprising releasing and hybridising the oligonucleotides to form nucleic acids and releasing the nucleic acids from the surface.
73. A microarray comprising one or more nucleotides, oligonucleotides or nucleic acids on a plurality of sites on the surface of a solid substrate, wherein the nucleotides, oligonucleotides or double stranded nucleic acids are bound to the surface by a thermally cleavable linker.
74. A microarray according to Claim 73, wherein the nucleotides, oligonucleotides or double stranded nucleic acids are bound to the surface by a thermally cleavable linker as defined according to any of Claims 32-34 and 40-65.
75. A microarray according to Claim 73 or 74, which is preparable by the process of any of Claims 1-72.
76. Use of a process according to any of Claim 1-72, or a microarray according to any of Claims 73-75 for preparing an oligonucleotide, a nucleic acid, preferably DNA or XNA.
77. An oligonucleotide or nucleic acid, which is preparable by the process of any of Claims 1-72.