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(54) **PROCESS FOR THE SYNTHESIS OF OLIGONUCLEOTIDES**

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention discloses novel methods for the synthesis of oligonucleotides with nucleoside phosphoramidites on solid supports. The methods comprise the stepwise chain assembly of oligonucleotides on supports with 5'-acyl phosphoramidites. The synthesis cycles consist of a front end deprotection step which is conducted with a solution of a primary amine or a phenolate, a phosphoramidite coupling step with a 5'-acyl nucleoside phosphoramidite in the presence of an activator, a phosphite oxidation step and an optional capping step. The novel methods improve the quality of synthetic oligonucleotides due to the irreversibility of the front end deprotection step, which prevents the formation of deletion sequences, and due to the avoidance of acidic reagents in the synthesis cycles, which prevent the formation of depurination side products. The invention further discloses novel nucleoside phosphoramidite compositions wherein the phosphoramidites carry acyl front end protective groups which are cleavable with primary amines or phenolates. The invention is applicable to the synthesis of oligodeoxyribonucleotides, oligoribonucleotides and oligonucleotides with modifications in their sugar or phosphate groups.

23 Claims, 6 Drawing Sheets