CLAIMS

1. A method for preparing a composition comprising a plurality of oligonucleotides comprising:

a) a coupling step comprising:

contacting a de-blocked composition comprising a plurality of de-blocked oligonucleotides (a de-blocked oligonucleotide composition) or nucleosides, which is de-blocked in that each independently comprises a free hydroxyl group, with a coupling reagent system comprising a partner compound which comprises a nucleoside unit; and coupling a partner compound with the free hydroxyl groups of a plurality of de-blocked oligonucleotides or nucleosides;

wherein the coupling step provides a coupling product composition comprising a plurality of coupling product oligonucleotides, each of which independently comprises an internucleotidic linkage connecting a hydroxyl group of a de-blocked oligonucleotide with a nucleoside unit of a partner compound;

b) a pre-modification capping step comprising:

contacting a coupling product composition with a pre-modification capping reagent system; and

capping one or more functional groups of the coupling product composition;

wherein the pre-modification capping step provides a pre-modification capping product composition comprising a plurality of pre-modification capping product oligonucleotides;

c) a modification step comprising:

contacting a coupling product composition with a modification reagent system comprising a modification reagent, and modifying one or more internucleotidic linkages of one or more coupling product oligonucleotides; or

contacting a pre-modification capping product composition with a modification reagent system and modifying one or more linkages of one or more pre-modification capping product oligonucleotides;

wherein the modification step provides a modification product composition comprising a plurality of modification product oligonucleotides;

d) a post-modification capping step comprising:

contacting a modification product composition with a post-modification capping reagent system; and

capping one or more functional groups of a plurality of oligonucleotides of the modification product composition;

wherein the post-modification capping step provides a post-modification capping product composition comprising a plurality of post-modification capping product oligonucleotides;

e) optionally a de-blocking step comprising:

contacting a modification product composition, or a post-modification capping product composition, with a de-blocking reagent system;

wherein the deblocking step provides a de-blocking product composition comprising a plurality of de-blocking product oligonucleotides, each of which independently comprises a free hydroxyl group; and

f) optionally repeating steps b) through e) a number of times.

2. A method for preparing a composition comprising a plurality of oligonucleotides comprising one or more cycles, each cycle independently comprises:

a) a coupling step comprising:

contacting a de-blocked composition comprising a plurality of de-blocked oligonucleotides (a de-blocked oligonucleotide composition) or nucleosides, which is de-blocked in that each independently comprises a free hydroxyl group, with a coupling reagent system comprising a partner compound which comprises a nucleoside unit; and coupling a partner compound with the free hydroxyl groups of a plurality of de- blocked oligonucleotides or nucleosides;

wherein the coupling step provides a coupling product composition comprising a plurality of coupling product oligonucleotides, each of which independently comprises an internucleotidic linkage connecting a hydroxyl group of a de-blocked oligonucleotide with a nucleoside unit of a partner compound;

b) a pre-modification capping step comprising:

~~contacting a coupling product composition with a pre-modification capping reagent system; and~~

~~capping one or more functional groups of the coupling product composition;~~

~~wherein the pre-modification capping step provides a pre-modification capping product composition comprising a plurality of pre-modification capping product oligonucleotides;~~

~~c) a modification step comprising:~~

~~contacting a coupling product composition with a modification reagent system comprising a modification reagent, and modifying one or more internucleotidic linkages of one or more coupling product oligonucleotides; or~~

~~contacting a pre-modification capping product composition with a modification reagent system and modifying one or more linkages of one or more pre-modification capping product oligonucleotides;~~

~~wherein the modification step provides a modification product composition comprising a plurality of modification product oligonucleotides;~~

~~d) a post-modification capping step comprising:~~

~~contacting a modification product composition with a post-modification capping reagent system; and~~

~~capping one or more functional groups of a plurality of oligonucleotides of the modification product composition;~~

~~wherein the post-modification capping step provides a post-modification capping product composition comprising a plurality of post-modification capping product oligonucleotides;~~

~~e) optionally a de-blocking step comprising:~~

~~contacting a modification product composition, or a post-modification capping product composition, with a de-blocking reagent system;~~

~~wherein the deblocking step provides a de-blocking product composition comprising a plurality of de-blocking product oligonucleotides, each of which independently comprises a free hydroxyl group.~~

~~3. The method claim 2, wherein there are no steps other than modification steps between the pre-modification capping and post-modification capping steps, wherein a post-modification capping step comprises contacting a modification product composition comprising a plurality of modification product oligonucleotides, each of which independently comprises a linkage phosphorus bonded to an atom that is not oxygen.~~

~~4. The method of claim 3, wherein the pre-modification capping reagent system caps a plurality of non-hydroxyl groups of a plurality of coupling product oligonucleotides, and a modification step that comprises sulfurization, which sulfurization provides a modification product composition comprising a plurality of modification product oligonucleotides, each of which independently comprises a P=S moiety.~~

~~5. The method of claim 4, wherein the method comprises a post-modification capping step, comprising contacting a modification product composition comprising a plurality of modification product oligonucleotide, each of which independently comprises a linkage that comprises at least one chirally controlled chiral center in that at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% oligomeric compounds within the modification product composition comprising the chiral center and having the same constitution share the same stereochemical configuration at the chiral center.~~

~~6. The method of claim 5, wherein the method comprises a post-modification capping step, and a coupling reagent system comprising a chiral partner compound that comprises a monomelic unit of the oligomeric compound, wherein the chiral partner compound comprises a chiral atom that is not within the monomeric unit~~

1.~~.~~

~~7. The method of claim 3, wherein the method comprises a coupling step, a modification step, and one or more pre-modification capping steps between the coupling step and the modification step, wherein for each pre-modification capping step between the coupling step~~

and the modification step, the pre-modification capping step caps amino groups selectively over hydroxyl groups.

8. A method for preparing an oligonucleotide, comprising:

providing a chiral nucleoside phosphoramidite which comprises a chiral atom that is not the phosphorus atom or a sugar carbon atom; and

a post-modification capping step after a modification step but before the next de-blocking step or the next coupling step.

9. A method for preparing an oligonucleotide, comprising one or more cycles, each of which independently comprises:

a pre-modification capping step immediately before a modification step, which comprises sulfurization or oxidation, and a post-modification capping step immediately after a modification step.

10. A method for preparing an oligonucleotide, comprising:

providing an oligonucleotide intermediate comprising a chiral linkage phosphorus atom, which is bonded to a chiral center which is not within a nucleoside unit; and

a post-modification capping step after a modification step but before the next de-blocking step or the next coupling step.

11. The claim of any one of claims 8-10, comprising a coupling step.

12. The claim of claim 11, comprising a pre-modification capping step.

13. The claim of claim 12, comprising a modification step.

14. The claim of claim 13, comprising a de-blocking step.

~~15.~~ A method for preparing an oligonucleotide, comprising one or more cycles, each of which independently comprises the following steps:

(1) coupling;

(2) a pre-modification capping;

(3) a modification step;

(4) a post-modification capping; and

(5) de-blocking~~.~~;

~~16. A method for oligonucleotide synthesis, comprising:~~

~~one or more pre-modification capping steps after a coupling step and before the next modification step,~~

wherein the capping condition of each pre-modification capping step after a coupling step and before the next modification step is independently selective or specific for amidation over esterification.

~~17. A~~2. The method ~~for oligonucleotide synthesis, comprising:~~

~~one or more pre-modification capping steps after a coupling step and before the next modification step,~~

of claim 1, wherein each pre-modification capping step after a coupling step and before the next modification step independently comprises no strong nucleophile, or if it comprises one or more strong nucleophiles, the level of each of the one or more strong nucleophiles is independently no more than ~~no more than about 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, or 1 equivalents~~about 0.1 equivalent relative to the first incorporated nucleoside of the oligonucleotide.

3. The~~18. A~~ method ~~for oligonucleotide synthesis, comprising:~~

~~one or more pre-modification capping steps after a coupling step and before the next modification step,~~

of claim 1, wherein each pre-modification capping step after a coupling step and before the next modification step independently comprises no esterification catalyst, or if it comprises one or more esterification catalysts, the level of each of the one or more esterification catalysts is

independently ~~reduced compared to an appropriate reference capping condition~~no more than about 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, or 1 equivalent relative to the first incorporated nucleoside of the oligonucleotide.

~~19. A~~4. The method ~~for oligonucleotide synthesis, comprising:~~

~~one or more pre-modification capping steps after a coupling step and before the next modification step,~~

~~wherein each pre-modification capping step after a coupling step and before the next modification step independently comprises no esterification catalyst, or if it comprises one or more esterification catalysts, the level~~ of ~~each of the one or more esterification catalysts is independently no more than no more than about 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, or 1 equivalents relative to the first incorporated nucleoside of the oligonucleotide.~~

~~20. The~~ claim ~~of any one of claims 16-19, comprising a post-modification capping step~~1~~.~~

~~21. The claim of claim 20, comprising a de-blocking step.~~

~~22. The method of claim 21, comprising a coupling step wherein the plurality of the de-blocked oligonucleotides or nucleosides is loaded on a support.~~

~~23. The method of claim 22, wherein each oligonucleotide of the plurality of the de-blocked oligonucleotides independently has the structure of formula VIII or a salt thereof.~~

~~24. The method of claim 23, wherein for each coupling step, each oligonucleotide of the plurality of the de-blocked oligonucleotides independently has the structure of formula VIII.~~

~~25. The method of claim 24, wherein each oligonucleotide of the plurality of the de-blocked oligonucleotides independently has the structure of formula VIII or a salt thereof, wherein each L^P is independently of formula VII or a salt form thereof, wherein each P^L is not P, or wherein~~

each oligonucleotide of the plurality of the de-blocked oligonucleotides independently has the structure of formula VIII or a salt thereof, wherein each L^P is independently of formula VII or a salt form thereof, wherein each P^L is independently P(=W), wherein W is O or S, or wherein each oligonucleotide of the plurality of the de-blocked oligonucleotides independently has the structure of formula VIII or a salt thereof, wherein each L^P is independently of formula VII or a salt form thereof, wherein each –X–L^s–R^5 independently contains no free amino group, or

wherein each oligonucleotide of the plurality of the de-blocked oligonucleotides independently has the structure of formula VIII or a salt thereof, wherein each L^P is independently of formula VII or a salt form thereof, wherein each –X–L^s–R^5 is independently –L^7–R^1.

26. The method of claim 25, wherein at least one ofR^5 or R^6 is –C(O)CH_3.

27. The method of claim 24, wherein each oligonucleotide of the plurality of the de-blocked oligonucleotides independently has the structure of formula VIII or a salt thereof, wherein each L^P is independently of formula VII or a salt form thereof, wherein each X is independently –O– or –S–; and/or wherein each oligonucleotide of the plurality of the de-blocked oligonucleotides independently has the structure of formula VIII or a salt thereof, wherein each L^P is independently of formula VII or a salt form thereof, wherein each of Y and Z is –O–; and/or wherein each oligonucleotide of the plurality of the de-blocked oligonucleotides independently has the structure of formula VIII or a salt thereof, wherein each –X–L^s–R^5 independently contains no free amino group; and/or wherein each oligonucleotide of the plurality of the de-blocked oligonucleotides independently has the structure of formula VIII or a salt thereof, wherein each R^{5s} is –OH.

28. The method of claim 24, wherein a de-blocked oligonucleotide composition comprising a plurality of de-blocked oligonucleotides is a chirally controlled oligonucleotide composition, wherein:

oligonucleotides of the plurality share the same constitution; and

~~oligonucleotides of the plurality comprise at least one chirally controlled internucleotidic linkage, which internucleotidic linkage is chirally controlled in that oligonucleotides of the plurality share the same stereochemical configuration at the chiral linkage phosphorus of the internucleotidic linkage; and~~

~~wherein no less than ((DS)^{Nc}*100)% of all oligonucleotides sharing the same base sequence in the de-blocked product composition are oligonucleotides of the plurality, wherein DS is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%, and Nc is the number of chirally controlled internucleotidic linkage.~~

~~29. The method of claim 28, wherein a partner compound is of formula IV, IV-a, IV-b, IV-c-1, IV-c-2, IV-d, IV-e, IVa, IVa-a, IVa-b, IVa-c-1, IVa-c-2, IVa-d, IVa-e, V, V-a, V-b, V-c-1, V-c-2, V-d, V-e, VI, VI-a, VI-b, VI-c-1, VI-c-2, VI-d, or VI-e, or a salt thereof; or wherein a partner compound is a phosphoramidite of formula IV, IV-a, IV-b, IV-c-1, IV-c-2, IV-d, IV-e, IVa, IVa-a, IVa-b, IVa-c-1, IVa-c-2, IVa-d, IVa-e, V, V-a, V-b, V-c-1, V-c-2, V-d, V-e, VI, VI-a, VI-b, VI-c-1, VI-c-2, VI-d, or VI-e, or a salt thereof, wherein P^L is P; or wherein for each coupling step, a partner compound is a phosphoramidite of formula IV, IV-a, IV-b, IV-c-1, IV-c-2, IV-d, IV-e, IVa, IVa-a, IVa-b, IVa-c-1, IVa-c-2, IVa-d, IVa-e, V, V-a, V-b, V-c-1, V-c-2, V-d, V-e, VI, VI-a, VI-b, VI-c-1, VI-c-2, VI-d, or VI-e, or a salt thereof, wherein P^L is P.~~

~~30. The method of claim 29, wherein a coupling reagent system comprises a partner compound and an activator, wherein an activator is an optionally substituted tetrazole, or wherein an activator is selected from cyanomethyl imidazole triflate, cyanomethyl pyrrolidine triflate, ETT, phenyl(2H-tetrazol-5-yl)methanone, 2-(dimethylamino)acetonitrile/trifluorosulfonic acid(2/1), 2-(1H-imidazol-1-yl)acetonitrile/trifluorosulfonic acid(2/1), and 2-(pyrrolidin-1-yl)acetonitrile /trifluorosulfonic acid(2/1) or wherein an activator is CMTMT, or wherein an activator is CMPT, or wherein an activator is ETT.~~

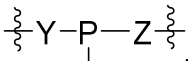
~~31. The method of claim 29~~, wherein each coupling step independently forms an internucleotidic linkage of formula **VII-b**~~, or a salt form thereof.~~:

~~32. The method of claim 31, wherein a coupling product composition comprising a plurality of coupling product oligonucleotides, and the coupling product composition comprising the plurality of oligonucleotides is a chirally controlled oligonucleotide composition wherein:~~

~~oligonucleotides of the plurality share the same constitution; and~~

~~oligonucleotides of the plurality comprise at least one chirally controlled internucleotidic linkage, which internucleotidic linkage is chirally controlled in that oligonucleotides of the plurality share the same stereochemical configuration at the chiral linkage phosphorus of the internucleotidic linkage;~~

~~wherein at least $((DS)^{Nc}*100)$% of all oligonucleotides sharing the same base sequence in the coupling product composition are oligonucleotides of the plurality, wherein DS is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%, and Nc is the number of chirally controlled internucleotidic linkage.~~

~~33. The method of claim 31, comprising~~  ,

VII-b,

or a salt form thereof, wherein:

each of R^1 and R^5 is independently −H, $-L^s-R$, halogen, −CN, $-NO_2$, $-L^s-Si(R)_3$, −OR, −SR, or $-N(R)_2$;

each of X, Y and Z is independently –O–, –S–, $-N(-L^s-R^1)-$, or L^s;

each L^s is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, $-C(R')_2-$, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−,

−P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−, and one or more carbon atoms are optionally and independently replaced with Cy^L;

each −Cy− is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon;

each Cy^L is independently an optionally substituted tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon;

each R' is independently −R, −C(O)R, −C(O)OR, or −S(O)$_2$R;

each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

5. The method of claim 4, wherein a pre-modification capping step comprises utilization of a pre-modification capping reagent system which comprises an acylating agent and a base.

~~34.~~ 6. The method of claim ~~33~~5, wherein a pre-modification capping reagent system comprises an acylating agent, wherein the acylating agent is of formula ~~R'~~ R'−C(O~~)~~)−L^s−−R^s~~.~~, wherein:

each R^s is independently −H, halogen, −CN, $-N_3$, −NO, $-NO_2$, $-L^s-R'$, $-L^s-Si(R)_3$, $-L^s-OR'$, $-L^s-SR'$, $-L^s-N(R')_2$, $-O-L^s-R'$, $-O-L^s-Si(R)_3$, $-O-L^s-OR'$, $-O-L^s-SR'$, or $-O-L^s-N(R')_2$;

each L^s is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, $-C(R')_2-$, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, $-P(OR')[B(R')_3]-$, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or $-OP(OR')[B(R')_3]O-$, and one or more carbon atoms are optionally and independently replaced with Cy^L;

each −Cy− is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-20

membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon;

each Cy^L is independently an optionally substituted tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon;

each R' is independently −R, −C(O)R, −C(O)OR, or $-S(O)_2R$;

each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

7.

~~35.~~ The method of claim ~~34~~6, wherein a base is of formula $N(~~R^3~~)_3$, wherein the nitrogen atom has no alpha-substitution~~.~~, wherein:

each R is independently −H, or an optionally substituted group selected from C_{1-30}

aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

8.

~~36.~~ The method of claim ~~35, wherein a pre-modification capping step is selective for amidation over esterification.~~

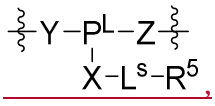
~~37. The method of claim 36, wherein no more than 1%, 5%, 10%, 20%, 30%, 40%, or 50% of free hydroxyl groups is converted into –O–C(O)R.~~

~~38. The method of claim 35, wherein a pre-modification capping step caps at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of free primary and secondary amino groups of a coupling product composition.~~

~~39. The method of claim 38~~7, wherein a pre-modification capping reagent system is a solution of 2,6-Lutidine/Ac_2O.

~~40.~~ ~~9.~~ The method of claim ~~33~~5, comprising a modification step which comprises modifying an internucleotidic linkage formed in the immediate preceding coupling step.

~~41.~~ 10. The method of claim ~~40~~4, wherein a modification step comprises modifying an internucleotidic linkage of formula **VII-b** or a salt form thereof~~, wherein P^L is P~~ to ~~form~~provide an internucleotidic linkage of formula **VII**-:



VII

or a salt form thereof, wherein ~~P^L~~ :

P^L is P(=W) or P→B(R')$_3$;

W is ~~not P.~~O, S or Se;

each of R^1 and R^5 is independently −H, −L^s−R, halogen, −CN, −NO_2, −L^s−Si(R)$_3$, −OR, −SR, or −N(R)$_2$;

each of X, Y and Z is independently –O–, –S–, –N(–L^s–R^1)–, or L^s;

each L^s is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, −C(R')$_2$−, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, −S(O)$_2$−, −S(O)$_2$N(R')−, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−, and one or more carbon atoms are optionally and independently replaced with Cy^L;

each −Cy− is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon;

each Cy^L is independently an optionally substituted tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon;

each R' is independently −R, −C(O)R, −C(O)OR, or $-S(O)_2R$;

each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-30 membered heteroaryl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

11.

42. The method of claim 404, wherein a modification step comprises sulfurization, which sulfurization comprises converting a –P(–)(=O)– linkage phosphorus atom into a –P(=S)(–)– linkage phosphorus atom, or wherein a modification step comprises sulfurization, which sulfurization comprises convertingin an internucleotidic linkage of formula **VII-b** or a salt form thereof, wherein each of X, Y, and Z is –O–, and –X–L^s–R^5 comprises a –$Si(R)_3$ group, into an internucleotidic linkage of formula VII or a salt thereof, wherein P^L is P(=O), and X is –S–, Y is –O–, and Z is –O–. into −P(=S)(−)−.

12.43. The method of claim 4211, wherein a modification reagent system is a sulfurization reagent system comprising one or more sulfurization reagent, wherein wherein a sulfurization reagent system comprises a sulfurization reagent selected from POS (3-phenyl-1,2,4-dithiazolin-5-one), DDTT (((dimethylamino-methylidene)amino)-3H-1,2,4-dithiazaoline-3-thione), DTD (dimethylthiarum disulfide), xanthane hydride (XH), S-(2-cyanoethyl) methanesulfonothioate (MTS-CNE), or phenylacetyl disulfide.

44. 13. The method of claim 4211, comprising a post-modification capping step which caps a plurality of hydroxyl groups.

45. 14. The method of claim 4413, wherein a post-modification capping reagent system is a solution of 2,6-Lutidine/NMI/Ac_2O.

46. 15. The method of claim 4413, comprising a de-blocking step, wherein a de-blocking reagent system comprises a de-blocking reagent, wherein the de-blocking reagent is an acid.

47. 16. The method of claim 4615, comprising a cleavage/deprotection step that comprises:

contacting a plurality of oligonucleotides with one or more cleavage/deprotection reagent systems;

wherein the cleavage/deprotection step provides a final product composition comprising a plurality of final product oligonucleotides.

~~48.~~ 17. The method of claim ~~47, wherein a final product composition comprising a plurality of final product oligonucleotides, each of which is independently an oligonucleotide of formula VIII or a salt thereof.~~

~~49. The method of of claim 48~~16, wherein a final product composition comprising a plurality of final product oligonucleotides is a chirally controlled oligonucleotide composition wherein:

oligonucleotides of the plurality share the same constitution; and

~~oligonucleotides of the plurality comprise at least one chirally controlled internucleotidic linkage, which internucleotidic linkage is chirally controlled in that oligonucleotides of the plurality share the same stereochemical configuration at the chiral linkage phosphorus of the internucleotidic linkage;~~

~~wherein at least ((DS)^{Nc}*100)% of all oligonucleotides sharing the same base sequence in the final product composition are oligonucleotides of the plurality, wherein DS is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%, and Nc is the number of chirally controlled internucleotidic linkage.~~

~~50. The method of any one of the preceding claims, wherein the method provides a final product composition with at least 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75% crude purity, wherein the crude purity is % full-length product.~~

~~51. A crude chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein:~~

~~oligonucleotides of the plurality share the same base sequence;~~

~~oligonucleotides of the plurality share the same pattern of backbone linkages; and~~

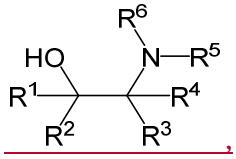
oligonucleotides of the plurality comprise at least one chirally controlled internucleotidic linkage, which internucleotidic linkage is chirally controlled in that oligonucleotides of the plurality share the same stereochemical configuration at the chiral linkage phosphorus of the internucleotidic linkage;

wherein at least ((DS)^{Nc}*100)% of all oligonucleotides sharing the same base sequence in the ~~crude~~final product composition are oligonucleotides of the plurality, wherein DS is at least

80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%, and Nc is the number of chirally controlled internucleotidic linkage~~; or~~.

18. The method of claim 17, wherein the method provides a final product composition with at least 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75% crude purity, wherein the crude purity is % full-length product.

19. The method of claim 4, wherein $-X-L^s-R^5$ is of such a structure that $H-X-L^s-R^5$ is a compound of formula **I-a**:



I-a

or a salt thereof, wherein:

each of R^1 and R^2 is independently $-H$, $-L^s-R$, halogen, $-CN$, $-NO_2$, $-L^s-Si(R)_3$, $-OR$, $-SR$, or $-N(R)_2$;

R^3 is $-H$;

R^4 and R^5 are taken together with their intervening atoms to form an optionally substituted 3-20 membered heterocyclyl ring having 1-5 heteroatoms;

R^6 is –H;

each L^s is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-10 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, $-C(R')_2-$, $-Cy-$, $-O-$, $-S-$, $-S-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-C(O)S-$, $-C(O)O-$, $-P(O)(OR')-$, $-P(O)(SR')-$, $-P(O)(R')-$, $-P(O)(NR')-$, $-P(S)(OR')-$, $-P(S)(SR')-$, $-P(S)(R')-$, $-P(S)(NR')-$, $-P(R')-$, $-P(OR')-$, $-P(SR')-$, $-P(NR')-$, $-P(OR')[B(R')_3]-$, $-OP(O)(OR')O-$, $-OP(O)(SR')O-$, $-OP(O)(R')O-$, $-OP(O)(NR')O-$, $-OP(OR')O-$, $-OP(SR')O-$, $-OP(NR')O-$,

−OP(R')O−, or −OP(OR')[B(R')$_3$]O−, and one or more carbon atoms are optionally and independently replaced with Cy^L;

each −Cy− is independently an optionally substituted bivalent group selected from a C$_{3-20}$ cycloaliphatic ring, a C$_{6-20}$ aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted tetravalent group selected from a C$_{3-20}$ cycloaliphatic ring, a C$_{6-20}$ aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each R' is independently −R, −C(O)R, −C(O)OR, or −S(O)$_2$R;

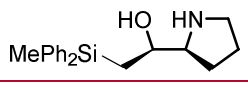
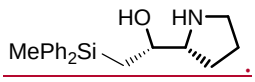
each R is independently −H, or an optionally substituted group selected from C$_{1-30}$ aliphatic, C$_{1-30}$ heteroaliphatic having 1-10 heteroatoms, C$_{6-30}$ aryl, C$_{6-30}$ arylaliphatic, C$_{6-30}$ arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms; or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

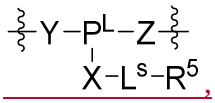
20. The method of claim 19, wherein R^1 is −H and R^2 is −CH$_2$−Si(R)$_3$ wherein each R of −Si(R)$_3$ is independently not −H.

21. The method of claim 20, wherein H−X−L^s−R^5 is  or  .

22.~~a crude chirally controlled oligonucleotide composition comprising a plurality of oligonucleotides, wherein:~~

~~oligonucleotides of the plurality share the same constitution; and~~

~~oligonucleotides of the plurality comprise at least one chirally controlled~~ The method of claim 19, wherein a modification step comprises modifying an internucleotidic linkage~~, which~~ to provide an internucleotidic linkage ~~is chirally controlled in that oligonucleotides of the plurality share the same stereochemical configuration at the chiral linkage phosphorus of the internucleotidic linkage;~~of formula **VII**:



VII

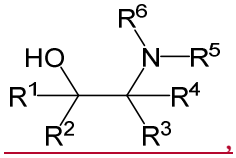
or a salt form thereof, wherein:

P^L is P(=W) or P→B(R')$_3$;

W is O, S or Se;

each of Y and Z is independently –O–, –S–, –N(–L^s–R^1)–, or L^s;

–X–L^s–R^5 is of such a structure that H–X–L^s–R^5 is a compound of formula **I-a**:



I-a

or a salt thereof, wherein:

wherein:

each of R^1 and R^2 is independently –H, –L^s–R, halogen, –CN, –NO_2, –L^s–Si(R)$_3$, –OR, –SR, or –N(R)$_2$;

R^3 is –H;

R^4 and R^5 are taken together with their intervening atoms to form an optionally substituted 3-20 membered heterocyclyl ring having 1-5 heteroatoms;

R^6 is –C(O)R;

each L^s is independently a covalent bond, or a bivalent, optionally substituted, linear or branched group selected from a C_{1-30} aliphatic group and a C_{1-30} heteroaliphatic group having 1-

10 heteroatoms, wherein one or more methylene units are optionally and independently replaced by an optionally substituted group selected from C_{1-6} alkylene, C_{1-6} alkenylene, —C≡C—, a bivalent C_1–C_6 heteroaliphatic group having 1-5 heteroatoms, −C(R')$_2$−, −Cy−, −O−, −S−, −S−S−, −N(R')−, −C(O)−, −C(S)−, −C(NR')−, −C(O)N(R')−, −N(R')C(O)N(R')−, −N(R')C(O)O−, −S(O)−, −S(O)$_2$−, −S(O)$_2$N(R')−, −C(O)S−, −C(O)O−, −P(O)(OR')−, −P(O)(SR')−, −P(O)(R')−, −P(O)(NR')−, −P(S)(OR')−, −P(S)(SR')−, −P(S)(R')−, −P(S)(NR')−, −P(R')−, −P(OR')−, −P(SR')−, −P(NR')−, −P(OR')[B(R')$_3$]−, −OP(O)(OR')O−, −OP(O)(SR')O−, −OP(O)(R')O−, −OP(O)(NR')O−, −OP(OR')O−, −OP(SR')O−, −OP(NR')O−, −OP(R')O−, or −OP(OR')[B(R')$_3$]O−, and one or more carbon atoms are optionally and independently replaced with Cy^L;

each −Cy− is independently an optionally substituted bivalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each Cy^L is independently an optionally substituted tetravalent group selected from a C_{3-20} cycloaliphatic ring, a C_{6-20} aryl ring, a 5-20 membered heteroaryl ring having 1-10 heteroatoms, and a 3-20 membered heterocyclyl ring having 1-10 heteroatoms;

each R' is independently −R, −C(O)R, −C(O)OR, or −S(O)$_2$R;

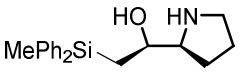
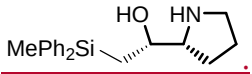
each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 heteroatoms, 5-30 membered heteroaryl having 1-10 heteroatoms, and 3-30 membered heterocyclyl having 1-10 heteroatoms, or

two R groups are optionally and independently taken together to form a covalent bond, or:

two or more R groups on the same atom are optionally and independently taken together with the atom to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the atom, 0-10 heteroatoms; or

two or more R groups on two or more atoms are optionally and independently taken together with their intervening atoms to form an optionally substituted, 3-30 membered, monocyclic, bicyclic or polycyclic ring having, in addition to the intervening atoms, 0-10 heteroatoms.

23. The method of claim 22, wherein R^1 is −H and R^2 is $-CH_2-Si(R)_3$ wherein each R of $-Si(R)_3$ is independently not −H.

24. The method of claim 23, wherein $H-X-L^s-R^5$ is  or  .

25. ~~wherein at least $((DS)^{Nc}*100)$% of all oligonucleotides sharing the same base sequence in the crude composition are oligonucleotides of the plurality, wherein DS is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%, and Nc is the number of chirally controlled internucleotidic linkage;~~

~~wherein the crude chirally controlled oligonucleotide composition has a crude purity of at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75%; or~~

~~a composition~~ The method of claim 1, comprising a ~~plurality of oligonucleotides and a reagent of a reagent system, wherein:~~

~~the plurality of oligonucleotides is a plurality of oligonucleotides~~cycle consisting of ~~a~~ the steps of 1) coupling; 2) capping; 3) modification ~~product composition of any one of the preceding claims;~~; and 4) deblocking.

~~the reagent system is a pre-modification or post-modification capping reagent system of any one of the preceding claims; and~~

~~the post-modification capping reagent system is in contact with the plurality of oligonucleotides.~~

~~52. The method or composition of any one of the preceding claims, wherein oligonucleotides of a plurality have a length of at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleobases, or wherein the final product composition is a chirally controlled oligonucleotide composition of WV-887, WV-892, WV-896, WV-1714, WV-2444, WV-2445, WV-2526, WV-2527, WV-2528, WV-2530, WV-2531, WV-2578, WV-2580, WV-2587, WV-3047, WV-3152, WV-3472, WV-3473, WV-3507, WV-3508, WV-3509, WV-3510, WV-3511,~~

~~WV-3512, WV-3513, WV-3514, WV-3515, WV-3545, WV-3546, WV-2603, WV-2595, WV-1510, WV-2378, WV-2380, WV-1092, WV-1497, WV-1085, WV-1086, or WV-2623.~~

~~53. A method or composition of any one of Example Embodiments 1-464.~~